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1.Aicardi-Goutieres syndrome(Aicardi-Goutieres 症候群)

History of Aicardi-Goutieres syndrome

Aicardi-Goutières syndrome (AGS) is a rare genetic disorder that was first described in 1984 by French neurologists Jean Aicardi and Françoise Goutières. The syndrome is named after them in recognition of their significant contributions to its understanding.

The first cases of AGS were reported in female infants who displayed a distinct set of neurological abnormalities. These included the presence of calcifications in the brain, severe intellectual disability, microcephaly (abnormally small head size), and abnormal movements such as spasms and jerks. Other features, such as skin abnormalities and elevated levels of interferon-alpha (a signaling molecule of the immune system), were also noted.

Over the years, researchers and clinicians have expanded their understanding of AGS. It was initially believed to be a rare variant of a severe viral infection of the brain. However, subsequent studies revealed that AGS has a genetic basis and is inherited in an autosomal recessive manner, meaning that both parents must carry a mutation in the same gene for a child to be affected.

Genetic studies have identified several genes associated with AGS, including TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR1, and IFIH1. These genes are involved in the regulation of the immune system, particularly in the detection and response to viral infections. Mutations in these genes disrupt the normal immune response, leading to chronic inflammation and damage to the brain and other organs.

As our understanding of AGS has grown, several subtypes or forms of the syndrome have been identified based on the specific gene involved. Each subtype may have distinct clinical features and disease progression, although there is also some overlap among them.

While there is no cure for AGS, ongoing research aims to develop better treatments and interventions to manage the symptoms and improve the quality of life for individuals with the condition. Early diagnosis, supportive care, and symptom-specific treatments are important in the management of AGS, and a multidisciplinary approach involving various specialists, such as neurologists, geneticists, and pediatricians, is typically employed.

Classification of Aicardi-Goutieres syndrome

Aicardi-Goutières syndrome (AGS) is a genetically and clinically heterogeneous disorder, meaning that it can manifest in different ways depending on the underlying

genetic mutation. Several genes have been associated with AGS, and each gene mutation is associated with a specific subtype of the syndrome. The classification of AGS is primarily based on the gene involved. Here are some of the commonly recognized subtypes:

AGS1 (TREX1-related AGS): This subtype is caused by mutations in the TREX1 gene, which encodes a DNA exonuclease. It is one of the most common forms of AGS.

AGS2 (RNASEH2A-related AGS): This subtype is caused by mutations in the RNASEH2A gene, which encodes a subunit of the ribonuclease H2 enzyme.

AGS3 (RNASEH2B-related AGS): This subtype is caused by mutations in the RNASEH2B gene, which encodes another subunit of the ribonuclease H2 enzyme.

AGS4 (RNASEH2C-related AGS): This subtype is caused by mutations in the RNASEH2C gene, which encodes the third subunit of the ribonuclease H2 enzyme.

AGS5 (SAMHD1-related AGS): This subtype is caused by mutations in the SAMHD1 gene, which plays a role in the regulation of the immune response to viral infections.

AGS6 (ADAR1-related AGS): This subtype is caused by mutations in the ADAR1 gene, which is involved in RNA editing.

AGS7 (IFIH1-related AGS): This subtype is caused by mutations in the IFIH1 gene, which encodes a protein involved in the detection of viral RNA.

It's important to note that new genes associated with AGS are still being discovered, and the classification of AGS may evolve as more research is conducted.

Each subtype of AGS has distinct clinical features and may vary in terms of disease severity, age of onset, and specific neurological and systemic manifestations. Genetic testing is necessary to determine the underlying genetic mutation and to accurately classify the subtype of AGS in an individual.

Symptom and sign in Aicardi-Goutieres syndrome

Aicardi-Goutières syndrome (AGS) is a rare, progressive neurological disorder that primarily affects the brain, spinal cord, and immune system. The signs and symptoms of AGS can vary depending on the specific subtype and individual variations, but here are some commonly observed features:

Neurological Symptoms:

Delayed development: Children with AGS may experience delays in reaching developmental milestones such as sitting, crawling, and walking.

Intellectual disability: Many individuals with AGS have intellectual disability ranging from mild to severe.

Movement abnormalities: These can include spasticity (stiffness) of the limbs, muscle

weakness, and difficulty with coordination and balance.

Seizures: Epileptic seizures are a common feature of AGS and may present in different forms, such as focal or generalized seizures.

Vision problems: Optic atrophy (damage to the optic nerve) and retinal abnormalities can lead to visual impairment and loss of visual acuity.

Microcephaly: Some individuals with AGS have a smaller than average head size due to abnormal brain development.

Autoimmune Features:

Elevated interferon levels: AGS is characterized by increased levels of interferon in the blood and cerebrospinal fluid, indicating an overactive immune response.

Skin rash: A characteristic skin rash known as chilblain-like lesions may appear on the hands, feet, and other exposed areas, especially in response to cold temperatures.

Autoimmune disorders: Some individuals with AGS may develop autoimmune conditions such as vasculitis, thyroiditis, or lupus-like symptoms.

It's important to note that the severity and combination of symptoms can vary widely among individuals with AGS, even within the same subtype. Additionally, other features such as liver dysfunction, kidney abnormalities, and skeletal abnormalities may be present in some cases.

If AGS is suspected based on clinical signs and symptoms, genetic testing is typically performed to confirm the diagnosis and identify the specific subtype. Early diagnosis and management of symptoms are important to optimize supportive care and interventions for affected individuals.

Image study in Aicardi-Goutieres syndrome

Imaging studies play a crucial role in the evaluation and diagnosis of Aicardi-Goutières syndrome (AGS). While the specific findings can vary among individuals, here are some common imaging features observed in AGS:

Brain Imaging:

Magnetic Resonance Imaging (MRI): MRI of the brain is the most commonly used imaging modality in AGS. It can reveal various abnormalities, including:

White matter changes: Diffuse or focal abnormalities in the white matter, such as increased signal intensity or loss of volume.

Calcifications: The presence of calcifications in specific brain regions, such as the basal ganglia, cerebellum, or periventricular regions.

Corpus callosum abnormalities: Thin corpus callosum or hypoplasia (underdevelopment) of the corpus callosum, which is the structure that connects the two hemispheres of the brain.

Ventricular enlargement: Enlargement of the fluid-filled spaces (ventricles) in the

brain.

Cortical atrophy: Thinning or loss of brain tissue in the cerebral cortex.

Spinal Cord and Spine Imaging:

Magnetic Resonance Imaging (MRI): In some cases, MRI of the spinal cord and spine may be performed to assess for any abnormalities or involvement. This can include evaluating the spinal cord structure, spinal nerve roots, and presence of any cysts or lesions.

Other Imaging Modalities:

Computed Tomography (CT) Scan: CT scans may be used in certain cases to assess for calcifications or structural abnormalities in the brain.

Ultrasonography: In infants with suspected AGS, cranial ultrasonography may be performed to assess brain structure and detect any abnormalities.

It's important to note that while imaging findings can be suggestive of AGS, they are not specific to the condition and can overlap with other neurological disorders.

Genetic testing is necessary for a definitive diagnosis of AGS, and imaging findings are typically considered in conjunction with clinical symptoms and other diagnostic criteria.

Genetic mutation in Aicardi-Goutieres syndrome

Aicardi-Goutières syndrome (AGS) is primarily caused by mutations in several genes involved in the regulation of the innate immune response. The most commonly associated genes with AGS include:

TREX1 (Three prime repair exonuclease 1): Mutations in the TREX1 gene are the most common cause of AGS, accounting for approximately 30-40% of cases. TREX1 encodes an enzyme involved in DNA repair and degradation.

RNASEH2A, RNASEH2B, and RNASEH2C: These genes encode subunits of the ribonuclease H2 enzyme, which is involved in the removal of RNA primers during DNA replication. Mutations in these genes account for a significant portion of AGS cases.

SAMHD1 (SAM domain and HD domain-containing protein 1): Mutations in the SAMHD1 gene are another known cause of AGS. SAMHD1 plays a role in regulating cellular dNTP levels, which are essential for DNA replication and repair.

ADAR1 (Adenosine deaminase acting on RNA 1): Mutations in the ADAR1 gene have been identified in a subset of AGS cases. ADAR1 is involved in RNA editing processes.

IFIH1 (Interferon induced with helicase C domain 1): Mutations in the IFIH1 gene have been associated with AGS. IFIH1 is involved in the recognition of viral nucleic acids and triggers an immune response.

Other genes: There are additional genes, such as SAMHD1-interacting proteins, that have been implicated in AGS, but their contribution to the condition is less common and requires further research.

It's important to note that genetic testing is necessary to confirm the specific genetic mutation in an individual with suspected AGS. Different mutations can result in variations in the severity and clinical presentation of the syndrome. Genetic counseling and testing can help provide a definitive diagnosis and inform prognosis and potential recurrence risks for families.

Mitochondrial dysfunction in Aicardi-Goutières syndrome

Aicardi-Goutières syndrome (AGS) is a rare genetic disorder characterized by chronic inflammation in the brain and other parts of the body. While the exact underlying mechanisms of AGS are not fully understood, there is evidence suggesting the involvement of mitochondrial dysfunction in the pathogenesis of the disease. Here's some information on the role of mitochondrial dysfunction in AGS:

Impaired mitochondrial function: Studies have shown that AGS is associated with mitochondrial dysfunction, including abnormalities in mitochondrial respiration, reduced ATP production, and increased oxidative stress. These mitochondrial impairments can contribute to cellular dysfunction and tissue damage observed in AGS.

Increased production of reactive oxygen species (ROS): Mitochondrial dysfunction in AGS can lead to increased production of ROS, which are highly reactive molecules that can damage cellular components, including DNA, proteins, and lipids. The accumulation of ROS can contribute to the inflammatory response and neuronal damage observed in AGS.

Activation of the innate immune response: AGS is characterized by chronic activation of the innate immune system, particularly the type I interferon response.

Mitochondrial dysfunction and the release of mitochondrial DNA (mtDNA) into the cytoplasm can trigger the activation of innate immune sensors, leading to the production of pro-inflammatory cytokines and interferon-stimulated genes.

DNA repair defects: AGS is often associated with mutations in genes involved in nucleic acid metabolism and DNA repair. Mitochondrial dysfunction and impaired mtDNA maintenance can further exacerbate DNA damage and contribute to the immune dysregulation and inflammation observed in AGS.

Therapeutic implications: Targeting mitochondrial function and reducing oxidative stress have been proposed as potential therapeutic strategies for AGS. Mitochondrial-targeted antioxidants and agents that improve mitochondrial function have shown promise in preclinical studies and may have the potential to mitigate the pathological

features of AGS.

It is important to note that the specific mechanisms linking mitochondrial dysfunction to the pathogenesis of AGS are still under investigation, and further research is needed to fully understand the role of mitochondria in this complex disorder.

Treatment in Aicardi-Goutières syndrome

Currently, there is no cure for Aicardi-Goutières syndrome (AGS), and treatment focuses on managing the symptoms and providing supportive care. The management of AGS typically involves a multidisciplinary approach with the involvement of various specialists, including neurologists, geneticists, and pediatricians. Here are some treatment strategies commonly used for AGS:

Symptomatic management: Medications and interventions are used to alleviate specific symptoms and complications associated with AGS. This may include antiepileptic drugs to manage seizures, muscle relaxants for spasticity, and medications to control movement disorders.

Supportive care: As AGS can affect multiple systems, supportive care measures are implemented to address various needs. This may involve physical therapy, occupational therapy, and speech therapy to improve motor skills, functional abilities, and communication. Nutritional support and feeding interventions may be required for those with feeding difficulties.

Seizure management: Seizures are common in AGS, and antiepileptic medications are prescribed to control seizure activity. Seizure management is tailored to the individual's specific seizure type and frequency.

Regular monitoring: Regular medical follow-up is important to monitor disease progression and address any emerging complications. Monitoring may include regular neurologic evaluations, imaging studies, and assessments of developmental progress.

Genetic counseling: As AGS is a genetic disorder, genetic counseling is recommended for affected individuals and their families. Genetic counseling can provide information about the inheritance pattern, recurrence risks, and available genetic testing options.

Support groups and resources: Joining support groups or connecting with other families affected by AGS can provide emotional support, share experiences, and access valuable resources and information.

It's worth noting that research into potential targeted therapies and approaches for AGS is ongoing, and individuals with AGS may be eligible to participate in clinical trials evaluating new treatments. Consultation with a medical professional experienced in AGS management can help guide treatment decisions and provide the most up-to-date information on available interventions.

2. Alexander disease (Alexander 氏病)

History of Alexander disease

Alexander disease is a rare and progressive neurological disorder that primarily affects the central nervous system. It was first described by Scottish pathologist William Stewart Alexander in 1949. Here is a brief history of Alexander disease:

1949: Discovery and Initial Description

William Stewart Alexander, a neuropathologist, first described the disease in infants and young children based on his observations of specific pathological changes in the brain. He identified the presence of abnormal protein deposits known as Rosenthal fibers, which are a characteristic feature of the disease.

1965: Classification as a Leukodystrophy

Alexander disease was classified as a type of leukodystrophy, a group of genetic disorders characterized by abnormal development or destruction of the white matter in the brain. This classification helped establish the disease's relationship to other leukodystrophies and provided insights into its underlying mechanisms.

1980s: Advances in Genetic Research

Genetic studies in the 1980s revealed that Alexander disease is caused by mutations in the glial fibrillary acidic protein (GFAP) gene, which codes for a protein primarily expressed in astrocytes—the star-shaped cells that support and protect neurons in the brain. These findings provided important insights into the genetic basis of the disease.

1990s: Identification of Different Forms

Researchers identified three distinct forms of Alexander disease based on the age of onset and the severity of symptoms: infantile, juvenile, and adult-onset. The infantile form, which typically manifests within the first two years of life, is the most common and severe form of the disease.

2001: GFAP Mutations Confirmed

In 2001, a study confirmed that mutations in the GFAP gene are responsible for Alexander disease. These mutations disrupt the normal function of astrocytes, leading to the accumulation of abnormal GFAP protein and the formation of Rosenthal fibers. This discovery solidified the understanding of the disease's genetic basis.

Since the initial description of Alexander disease, ongoing research has deepened our understanding of the disease's clinical features, genetic mechanisms, and cellular pathology. Efforts continue to focus on improving diagnosis, developing potential therapies, and providing supportive care for individuals and families affected by this rare neurological disorder.

Classification of Alexander disease

Alexander disease is classified into three main forms based on the age of onset and the severity of symptoms:

Infantile Form:

The infantile form is the most common and severe type of Alexander disease.

It typically manifests within the first two years of life, often before six months of age.

Symptoms usually include developmental delays, progressive macrocephaly (abnormally large head size), seizures, and a decline in motor function.

Infants with this form of the disease may have difficulty swallowing and breathing, leading to feeding difficulties and respiratory problems.

Juvenile Form:

The juvenile form of Alexander disease usually presents between the ages of two and 12.

Symptoms can vary but often include motor and cognitive impairment, along with behavioral and psychiatric issues.

Children with the juvenile form may experience difficulties with speech and language, as well as problems with balance and coordination.

Seizures and a decline in intellectual abilities may also occur.

Adult-Onset Form:

The adult-onset form of Alexander disease is the rarest and typically has a milder progression.

Symptoms generally appear in late adolescence or adulthood, often after the age of 20.

Common features include a slowly progressive spasticity (stiffness and tightness of muscles), ataxia (loss of coordination), and bulbar symptoms (difficulty with speaking and swallowing).

Cognitive impairment and behavioral changes can also occur, but they are generally less severe than in the infantile and juvenile forms.

It's important to note that the classification of Alexander disease is based on the age of symptom onset and the clinical presentation, but there can be some overlap between the forms. The severity and progression of the disease can also vary among individuals, even within the same form. Genetic testing is typically required to confirm the diagnosis and identify specific mutations in the glial fibrillary acidic protein (GFAP) gene, which is associated with Alexander disease.

Symptom and sign in Alexander disease

Alexander disease is a rare neurological disorder that affects the central nervous system, particularly the brain. The symptoms and signs of Alexander disease can vary depending on the age of onset and the form of the disease. Here are some common

symptoms and signs associated with Alexander disease:

Infantile Form:

Developmental delays: Infants with Alexander disease may have delayed motor milestones, such as sitting, crawling, or walking.

Macrocephaly: A characteristic feature of the infantile form is an abnormally large head size, often exceeding the expected growth curve.

Seizures: Seizure activity, such as generalized tonic-clonic seizures or focal seizures, can occur.

Hypotonia: Infants may exhibit low muscle tone, leading to poor muscle strength and control.

Feeding difficulties: Difficulties with sucking, swallowing, and feeding may be present due to weak or uncoordinated muscle movements.

Juvenile Form:

Motor impairment: Children may experience difficulties with coordination, balance, and fine motor skills.

Cognitive impairment: Intellectual disabilities and learning difficulties can be present, ranging from mild to severe.

Behavioral changes: Behavioral problems, such as attention deficits, hyperactivity, and emotional instability, may occur.

Speech and language difficulties: Delays or impairments in speech and language development are common.

Seizures: Seizure activity may continue into the juvenile form of the disease.

Adult-Onset Form:

Progressive spasticity: Stiffness and tightness of muscles, particularly in the legs, can lead to difficulty with movement and walking.

Ataxia: Loss of coordination, resulting in unsteady gait, clumsiness, and problems with fine motor skills.

Bulbar symptoms: Difficulties with speaking and swallowing, such as slurred speech, dysarthria, and dysphagia.

Cognitive and behavioral changes: Mild cognitive impairment, executive dysfunction, and mood disturbances may occur.

It's important to note that the symptoms and progression of Alexander disease can vary among individuals, even within the same form. The severity of symptoms can range from mild to severe. Additionally, individuals with Alexander disease may experience other associated symptoms, such as vision problems, respiratory difficulties, or autonomic dysfunction. Early recognition and diagnosis of Alexander disease are crucial for appropriate management and supportive care.

Image study in Alexander disease

In the diagnosis and evaluation of Alexander disease, various imaging studies can be utilized to assess the structural abnormalities and changes in the brain. The most commonly employed imaging techniques include:

Magnetic Resonance Imaging (MRI):

MRI is the primary imaging modality for diagnosing and monitoring Alexander disease.

It provides detailed images of the brain, allowing for the visualization of abnormalities.

Typical MRI findings in Alexander disease include white matter abnormalities, specifically in the frontal lobes, basal ganglia, and thalamus.

MRI may also reveal features such as abnormal signal intensity, cystic cavities, and atrophy in affected brain regions.

The presence of characteristic Rosenthal fibers, which are abnormal protein deposits, can sometimes be observed as hyperintense signals on MRI.

Diffusion Tensor Imaging (DTI):

DTI is an advanced MRI technique that measures the diffusion of water molecules in brain tissue.

It provides information about the integrity and connectivity of white matter fibers.

DTI can be used to assess microstructural changes in the brain, such as axonal damage or loss, which may be present in Alexander disease.

Magnetic Resonance Spectroscopy (MRS):

MRS is a specialized MRI technique that measures the chemical composition of brain tissue.

It can be used to detect abnormal metabolic profiles associated with Alexander disease.

MRS may reveal elevated levels of certain metabolites, such as lactate or myoinositol, in affected brain regions.

Computed Tomography (CT) Scan:

CT scans may be performed in certain cases, particularly when MRI is not feasible or available.

CT scans can provide valuable information about structural brain abnormalities, such as atrophy or calcifications.

However, CT scans are generally less sensitive than MRI in detecting subtle changes in the brain.

These imaging studies play a crucial role in the diagnosis, characterization, and monitoring of Alexander disease. They help to identify the specific brain regions affected by the disease and contribute to the overall clinical assessment of individuals

with this condition. It is important to consult with a medical professional or radiologist for a comprehensive evaluation and interpretation of imaging findings.

Genetic mutation in Alexander disease

Alexander disease is primarily caused by mutations in the glial fibrillary acidic protein (GFAP) gene. The GFAP gene provides instructions for producing the glial fibrillary acidic protein, a key structural protein found in astrocytes—a type of glial cell in the central nervous system. Mutations in the GFAP gene disrupt the normal structure and function of astrocytes, leading to the development of Alexander disease. Several different types of mutations in the GFAP gene have been identified in individuals with Alexander disease. These mutations can vary in their location within the gene and the specific effect they have on the protein. Some mutations result in the production of an abnormal glial fibrillary acidic protein, while others can lead to the production of less functional or unstable protein.

Most cases of Alexander disease are sporadic, meaning they occur randomly and are not inherited from parents. These cases are caused by *de novo* mutations, which arise in the affected individual during early development. However, in rare instances, Alexander disease can be inherited in an autosomal dominant pattern, meaning that an affected individual has a 50% chance of passing the mutation on to each of their children.

While mutations in the GFAP gene are the primary cause of Alexander disease, genetic heterogeneity has also been reported. In a small percentage of cases, mutations in other genes, such as the alpha-B-crystallin (CRYAB) gene or the heat shock protein beta-1 (HSPB1) gene, have been identified.

Genetic testing, such as sequencing the GFAP gene, is available to confirm the diagnosis of Alexander disease and identify specific mutations in affected individuals. Genetic counseling is also an important component for individuals and families affected by this condition, as it can provide information about the inheritance pattern and recurrence risks.

Mitochondrial dysfunction in Alexander disease

Alexander disease is a rare genetic disorder that primarily affects the central nervous system, particularly the white matter of the brain. While the exact mechanisms underlying the disease are not fully understood, there is growing evidence suggesting the involvement of mitochondrial dysfunction in Alexander disease. Here's some information on the role of mitochondrial dysfunction in the pathogenesis of the disease:

Impaired mitochondrial morphology and distribution: Studies have shown that

astrocytes, the supporting cells of the brain, in Alexander disease display abnormal mitochondrial morphology and distribution. These mitochondrial abnormalities may disrupt energy production and impair cellular functions in astrocytes, contributing to the pathogenesis of the disease.

Mitochondrial dysfunction and oxidative stress: Mitochondrial dysfunction in Alexander disease can lead to reduced ATP production and increased production of reactive oxygen species (ROS), resulting in oxidative stress. Oxidative stress can damage cellular components, including proteins, lipids, and DNA, and contribute to the progressive degeneration and dysfunction of astrocytes in Alexander disease.

Altered mitochondrial dynamics: Mitochondrial dynamics, which involve processes such as fusion, fission, and mitophagy (selective removal of damaged mitochondria), play a crucial role in maintaining mitochondrial health and function. Studies have suggested that Alexander disease may disrupt mitochondrial dynamics, leading to the accumulation of dysfunctional mitochondria and further exacerbating mitochondrial dysfunction.

Inflammatory response and mitochondrial dysfunction: Alexander disease is associated with chronic inflammation in the brain, and inflammatory processes can impact mitochondrial function. Inflammatory cytokines released during the inflammatory response can directly affect mitochondrial function and promote mitochondrial dysfunction in astrocytes.

Potential therapeutic strategies: Although there is no cure for Alexander disease, targeting mitochondrial dysfunction and oxidative stress may hold therapeutic potential. Approaches aimed at improving mitochondrial function and reducing oxidative stress, such as the use of antioxidants and mitochondrial-targeted therapies, have shown promise in preclinical studies and may help alleviate some of the pathological features of the disease.

It's important to note that the precise mechanisms linking mitochondrial dysfunction to the pathogenesis of Alexander disease are still being investigated, and further research is needed to fully understand the role of mitochondria in this disorder.

Treatment in Alexander disease

Currently, there is no cure for Alexander disease, and treatment mainly focuses on managing the symptoms and providing supportive care. The management of Alexander disease involves a multidisciplinary approach that may include the following:

Symptom Management:

Seizure control: Antiepileptic medications may be prescribed to manage seizures.

Physical therapy: Physical therapy can help maintain muscle strength, flexibility, and

mobility.

Occupational therapy: Occupational therapy aims to enhance daily living skills and promote independence.

Speech therapy: Speech therapy can assist with improving communication skills and addressing swallowing difficulties.

Assistive devices: Mobility aids, orthotic devices, and adaptive equipment may be recommended to assist with mobility and activities of daily living.

Medical Care:

Regular medical follow-up: Routine medical visits are important to monitor the progression of the disease and manage any associated health issues.

Medications for symptom management: Medications may be prescribed to alleviate specific symptoms such as muscle stiffness, spasticity, or pain.

Respiratory support: In some cases, respiratory complications may arise, and respiratory support measures, such as non-invasive ventilation or tracheostomy, may be required.

Palliative Care:

Palliative care focuses on improving the quality of life for individuals with Alexander disease and providing support to their families.

Palliative care teams can assist in managing pain, optimizing comfort, and addressing emotional, psychological, and social needs.

Genetic Counseling:

Genetic counseling should be offered to affected individuals and their families to provide information about the inheritance pattern, recurrence risks, and available testing options.

It is important for individuals with Alexander disease to receive comprehensive and coordinated care from a team of healthcare professionals, including neurologists, physiotherapists, occupational therapists, speech therapists, and genetic counselors. The treatment approach is individualized based on the specific needs and symptoms of each person with Alexander disease. Research and clinical trials are ongoing to explore potential future therapies and interventions for this rare disorder.

3. Amyotrophic lateral sclerosis (ALS) (肌萎縮性側索硬化症)

History of Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, has a rich history dating back to the 19th century. Here is an overview of the history of ALS:

Discovery and Early Observations (19th Century):

In 1869, the French neurologist Jean-Martin Charcot described a group of patients with progressive muscle weakness and wasting, which he named "amyotrophic lateral sclerosis" due to the combination of muscle atrophy (amyotrophy) and the involvement of the lateral columns of the spinal cord (lateral sclerosis).

Charcot's work laid the foundation for the clinical understanding and characterization of ALS.

Advancements in Medical Knowledge (20th Century):

Throughout the 20th century, researchers and clinicians made significant progress in understanding ALS and its underlying pathology.

In the 1930s, pathologists identified the degeneration of motor neurons in the spinal cord and brain as the primary pathological feature of ALS.

In the mid-20th century, electromyography (EMG) and other neurophysiological techniques became valuable tools for diagnosing ALS and assessing the function of motor neurons.

Genetic Discoveries:

In the 1990s, researchers identified the first genetic mutation associated with familial ALS (fALS), which accounts for approximately 5-10% of all ALS cases.

Subsequent research led to the discovery of several genes, such as SOD1, TARDBP, FUS, and C9orf72, which are now known to be associated with both familial and sporadic cases of ALS.

These genetic findings have provided insights into the underlying molecular mechanisms and pathways involved in ALS.

Ice Bucket Challenge and Increased Awareness:

In 2014, the Ice Bucket Challenge became a viral sensation, raising significant funds and awareness for ALS research and support.

The campaign helped propel ALS into the public spotlight and led to a surge in donations and scientific interest in finding effective treatments and a cure for the disease.

Advances in Research and Treatment:

Over the years, advances in understanding ALS have led to the development of potential therapies and treatment approaches.

Riluzole, the first FDA-approved medication for ALS, was introduced in 1995. It is

believed to slow disease progression by reducing glutamate levels in the brain. More recently, other medications, such as edaravone, have been approved as additional treatment options for ALS to help mitigate the progression of the disease. Researchers are actively investigating potential disease-modifying therapies and exploring various approaches, including gene therapy, stem cell transplantation, and targeted drug development.

While significant progress has been made in understanding ALS, finding a cure for the disease remains a challenge. Ongoing research, clinical trials, and multidisciplinary efforts are essential to advance our knowledge and improve treatment options for individuals affected by ALS.

Classification of Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) can be classified based on different criteria, including clinical presentation, patterns of motor neuron involvement, and genetic factors. Here are the commonly recognized classifications of ALS:

Sporadic ALS (sALS):

Sporadic ALS is the most common form of the disease, accounting for approximately 90-95% of all ALS cases. It occurs randomly in individuals with no known family history of the disease. The exact cause of sporadic ALS is not fully understood, but it is believed to result from a combination of genetic and environmental factors.

Familial ALS (fALS):

Familial ALS accounts for about 5-10% of all ALS cases. It refers to cases where there is a known family history of the disease, indicating a genetic component. Several genes have been identified to be associated with familial ALS, including SOD1, TARDBP, FUS, and C9orf72. In familial ALS, the disease is inherited in an autosomal dominant manner, meaning a mutation in a single copy of the gene is sufficient to cause the disease.

Spinal-onset ALS:

Spinal-onset ALS is characterized by the initial symptoms and motor neuron degeneration predominantly occurring in the spinal cord. It typically presents with weakness, muscle atrophy, and loss of reflexes in the limbs, leading to difficulty in walking, weakness in the hands, and problems with coordination.

Bulbar-onset ALS:

Bulbar-onset ALS involves the initial symptoms and motor neuron degeneration affecting the bulbar region, which includes the muscles responsible for speech, swallowing, and breathing. Patients with bulbar-onset ALS may experience speech difficulties, dysphagia (difficulty swallowing), and respiratory problems.

Upper Motor Neuron (UMN)-dominant ALS:

In UMN-dominant ALS, the clinical signs predominantly involve upper motor neurons, which are responsible for initiating voluntary movements. Symptoms may include spasticity, exaggerated reflexes, and difficulty with fine motor control. UMN-dominant ALS is less common compared to other subtypes.

Lower Motor Neuron (LMN)-dominant ALS:

LMN-dominant ALS is characterized by the prominent involvement of lower motor neurons, which are responsible for transmitting signals from the spinal cord to muscles. Patients typically exhibit muscle weakness, atrophy, and fasciculations (muscle twitching). LMN-dominant ALS is the most common clinical presentation of the disease.

It's important to note that ALS is a complex and heterogeneous disorder, and individuals with ALS may present with a combination of these classifications. The classification systems help in understanding the different clinical manifestations and underlying mechanisms of the disease, aiding in personalized management and research efforts.

Symptom and sign in Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is characterized by the progressive degeneration of motor neurons, resulting in muscle weakness, atrophy, and a range of symptoms. Here are the common symptoms and signs observed in ALS:

Muscle Weakness: Progressive muscle weakness is a hallmark of ALS. It typically starts in one region of the body and spreads to other areas over time. The weakness may initially manifest as difficulty with fine motor tasks, such as buttoning a shirt or picking up small objects. Eventually, it can lead to significant impairment in mobility and daily activities.

Muscle Atrophy: As ALS progresses, the affected muscles undergo atrophy (shrinking) due to the loss of motor neurons. This can be observed as visible muscle wasting, particularly in the hands, arms, legs, and shoulders. Muscle atrophy contributes to further weakness and functional impairment.

Fasciculations: ALS often presents with fasciculations, which are involuntary muscle twitches or spasms. These can be visible under the skin and are commonly observed in the limbs, particularly in the hands and fingers.

Spasticity: Some individuals with ALS experience spasticity, which is characterized by increased muscle tone and stiffness. Spasticity can lead to muscle cramps, spasms, and difficulties with movement and coordination.

Muscle Cramps: ALS can cause recurring muscle cramps, which are painful contractions of the muscles. Cramps may occur in various body regions and can be

exacerbated by muscle fatigue.

Difficulty Speaking and Swallowing: ALS can affect the muscles involved in speech and swallowing, leading to dysarthria (slurred speech) and dysphagia (difficulty swallowing). Speech may become progressively more difficult to understand, and swallowing problems can result in choking or aspiration.

Respiratory Symptoms: As ALS progresses, weakness can extend to the muscles involved in breathing, leading to respiratory symptoms. Shortness of breath, difficulty taking deep breaths, and ineffective coughing are common respiratory manifestations. In the later stages of the disease, individuals may require respiratory support.

Fatigue: ALS often causes fatigue, which can be both physical and mental. Weakness, muscle exertion, and the challenges associated with living with a progressive disease contribute to feelings of fatigue and exhaustion.

Emotional and Cognitive Changes: Some individuals with ALS may experience changes in mood, including depression and anxiety. Additionally, a small percentage of individuals may develop mild cognitive or behavioral changes, such as difficulties with executive functions and decision-making.

It's important to note that the symptoms and progression of ALS can vary among individuals. The disease typically starts in a focal region and spreads to other parts of the body over time. As ALS progresses, individuals may experience a combination of these symptoms, impacting their mobility, communication, and overall quality of life. Early recognition and management of symptoms are crucial in providing supportive care and improving the quality of life for individuals with ALS.

Image study in Amyotrophic lateral sclerosis

In the diagnosis and management of amyotrophic lateral sclerosis (ALS), various imaging studies can be used to support clinical assessments and rule out other conditions. While imaging alone cannot definitively diagnose ALS, it can provide additional information to aid in the diagnostic process. Here are the common imaging studies used in ALS:

Magnetic Resonance Imaging (MRI): MRI is a non-invasive imaging technique that uses powerful magnets and radio waves to produce detailed images of the brain, spinal cord, and other body structures. In ALS, MRI can help rule out other conditions that may mimic ALS symptoms and assess the structural integrity of the central nervous system. It can detect abnormalities such as spinal cord atrophy or signal changes in the motor cortex.

Electromyography (EMG): EMG is a diagnostic procedure that evaluates the electrical activity of muscles and the health of motor neurons. It involves inserting a needle electrode into specific muscles to measure their electrical responses. EMG can

help identify denervation (loss of nerve supply) and reinnervation (new nerve connections) patterns, which are characteristic of ALS.

Nerve Conduction Studies (NCS): NCS is often performed in conjunction with EMG. It measures the speed and strength of nerve signals as they travel along the peripheral nerves. NCS can help differentiate between ALS and other peripheral nerve disorders.

Positron Emission Tomography (PET): PET imaging can assess metabolic activity and blood flow in the brain. While not routinely used for ALS diagnosis, PET scans can provide insights into the patterns of brain metabolism and identify areas of abnormal glucose utilization.

Single-Photon Emission Computed Tomography (SPECT): SPECT is a nuclear medicine imaging technique that examines blood flow and brain activity. It can help assess regional cerebral blood flow and detect areas of reduced blood flow or abnormal brain function.

It's important to note that the diagnosis of ALS is primarily based on clinical evaluation, including medical history, physical examination, and neurologic assessments. Imaging studies are used to support the clinical diagnosis, exclude other conditions, and provide additional information about the disease progression and extent of motor neuron involvement. The interpretation of imaging findings should be done by qualified healthcare professionals experienced in ALS and neuroimaging.

Genetic mutation in Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a complex neurodegenerative disorder that can have both genetic and non-genetic causes. Approximately 5-10% of ALS cases are classified as familial ALS (fALS), indicating a genetic component. Several genes have been identified to be associated with ALS, and mutations in these genes are believed to contribute to the development of the disease. Here are some of the key genetic mutations associated with ALS:

C9orf72: The C9orf72 gene mutation is the most common genetic cause of both familial and sporadic ALS. It is characterized by an expanded hexanucleotide repeat (GGGGCC) in the non-coding region of the gene. This mutation leads to the accumulation of abnormal RNA and protein aggregates, which contribute to neurodegeneration.

SOD1: Mutations in the superoxide dismutase 1 (SOD1) gene are associated with familial ALS. SOD1 encodes an antioxidant enzyme involved in neutralizing harmful free radicals. Mutations in SOD1 disrupt its normal function and lead to the accumulation of toxic protein aggregates, causing motor neuron degeneration.

TARDBP: Mutations in the TAR DNA-binding protein (TARDBP) gene have been linked to familial ALS. TARDBP mutations disrupt the normal function of the

TARDBP protein, affecting RNA processing and protein regulation within cells.

FUS: Mutations in the fused in sarcoma (FUS) gene are associated with familial ALS. FUS is involved in RNA processing and transport. Mutations in FUS lead to abnormal accumulation of the FUS protein in motor neurons, causing neurotoxicity.

Other Genes: In addition to the above-mentioned genes, mutations in other genes such as TBK1, NEK1, and PFN1 have also been identified in familial ALS cases, although they are less common.

It's important to note that genetic mutations associated with ALS can have variable penetrance, meaning that not all individuals carrying the mutation will develop the disease. Furthermore, ALS can also occur in individuals with no known family history (sporadic ALS), and the genetic factors contributing to sporadic cases are still being investigated.

Understanding the genetic mutations associated with ALS is crucial for better understanding the underlying molecular mechanisms of the disease. It can also aid in genetic counseling, early detection of at-risk individuals, and the development of targeted therapies for ALS.

Mitochondrial dysfunction in Amyotrophic lateral sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a progressive neurodegenerative disorder that affects the nerve cells responsible for controlling voluntary muscle movements. While the exact cause of ALS is not fully understood, there is evidence suggesting that mitochondrial dysfunction plays a role in the pathogenesis of the disease. Here's some information on the involvement of mitochondrial dysfunction in ALS:

Impaired energy metabolism: Mitochondria are the powerhouses of cells, responsible for generating energy in the form of adenosine triphosphate (ATP). In ALS, there is evidence of impaired energy metabolism in motor neurons, which are the primary cells affected by the disease. Mitochondrial dysfunction can lead to decreased ATP production, resulting in energy deficits and impaired cellular function.

Oxidative stress: Mitochondrial dysfunction in ALS can contribute to increased production of reactive oxygen species (ROS), leading to oxidative stress. ROS can cause damage to cellular components, including proteins, lipids, and DNA, and contribute to neuronal degeneration and cell death.

Mitochondrial DNA (mtDNA) mutations: Mutations in mitochondrial DNA have been found in a subset of ALS cases. These mtDNA mutations can affect mitochondrial function and contribute to the disease process. While mtDNA mutations are not as common as other genetic mutations associated with ALS, their presence suggests a potential role of mitochondrial dysfunction in the pathogenesis of ALS.

Impaired mitochondrial dynamics: Proper mitochondrial dynamics, including processes such as fusion, fission, and mitophagy, are essential for maintaining mitochondrial health and function. Disruption of these processes in ALS can lead to the accumulation of dysfunctional mitochondria and further impair mitochondrial function.

Defective mitochondrial transport: Mitochondria in neurons rely on proper transport along the axons to reach the sites where they are needed. In ALS, impaired mitochondrial transport has been observed, which can lead to localized energy deficits and neuronal dysfunction.

Interaction with other disease-related proteins: ALS is often associated with the accumulation of misfolded proteins, such as TDP-43 and SOD1. These disease-related proteins can directly interact with mitochondria and disrupt their function, further contributing to mitochondrial dysfunction in ALS.

Understanding the role of mitochondrial dysfunction in ALS is still an active area of research, and further studies are needed to unravel the underlying mechanisms.

Targeting mitochondrial dysfunction and restoring mitochondrial health are potential therapeutic strategies being explored to mitigate the progression of ALS.

Treatment in Amyotrophic lateral sclerosis

The treatment of amyotrophic lateral sclerosis (ALS) aims to manage symptoms, slow disease progression, and improve the quality of life for individuals living with the condition. While there is currently no cure for ALS, several approaches and therapies are used to address various aspects of the disease. Here are some of the main treatment options for ALS:

Medications:

Riluzole: Riluzole is the only FDA-approved medication for ALS. It is believed to reduce the release of glutamate, a neurotransmitter that can contribute to nerve cell damage. Riluzole has shown modest benefits in extending survival and slowing disease progression in some individuals with ALS.

Edaravone: Edaravone is another medication approved for ALS treatment in some countries. It is an antioxidant that aims to reduce oxidative stress, which can contribute to nerve cell damage. Edaravone has shown modest effects in slowing functional decline in certain individuals with ALS.

Symptom Management:

Physical Therapy: Physical therapy can help manage muscle weakness, improve mobility, and prevent complications such as contractures and muscle atrophy. It involves exercises, stretching, and techniques to maintain functional independence.

Occupational Therapy: Occupational therapy focuses on adapting the environment

and teaching techniques to help individuals with ALS maintain independence in daily activities.

Speech Therapy: Speech therapy addresses difficulties with speech and swallowing that may arise due to muscle weakness in the face, throat, and tongue. Techniques and devices can be employed to improve communication and ensure safe swallowing.

Respiratory Care: As ALS progresses, respiratory muscles can become weakened, leading to breathing difficulties. Respiratory care may involve non-invasive ventilation (NIV) or other techniques to support breathing and maintain respiratory function.

Assistive Devices and Equipment:

Mobility Aids: Canes, walkers, wheelchairs, and scooters can assist with mobility as ALS progresses.

Communication Aids: Augmentative and alternative communication (AAC) devices can help individuals communicate when speech becomes difficult.

Assistive Technology: Various devices and technologies, such as home modifications, adaptive utensils, and computer access aids, can enhance independence and quality of life.

Multidisciplinary Care:

ALS Clinic: ALS clinics provide comprehensive care with a multidisciplinary team of healthcare professionals, including neurologists, physical therapists, occupational therapists, speech-language pathologists, social workers, and respiratory therapists.

Palliative Care and Supportive Care: Palliative care focuses on improving quality of life and providing support for physical, emotional, and psychosocial well-being.

Supportive care addresses symptom management and addresses the needs of individuals with ALS and their families throughout the disease journey.

Clinical Trials and Experimental Treatments:

Participation in clinical trials can provide access to experimental therapies and contribute to advancing ALS research and treatment options.

It's important for individuals with ALS to work closely with healthcare professionals experienced in managing the disease. Treatment plans are personalized based on individual needs, disease progression, and goals of care. Ongoing research and clinical trials offer hope for future advancements in ALS treatment.

4. Ataxia telangiectasia (共濟失調微血管擴張症候群)

History of Ataxia telangiectasia

Ataxia telangiectasia (AT) is a rare genetic disorder that affects multiple systems in the body, primarily the nervous system and immune system. Here is a brief history of the understanding and discovery of Ataxia telangiectasia:

1957: The condition was first described and named by two French physicians, Louis-Bar and Boder, who identified a group of children with a combination of ataxia (lack of muscle coordination) and telangiectasias (small, dilated blood vessels on the skin) along with immune system abnormalities.

1960s: Further research revealed the genetic nature of the disorder. It was found to be an autosomal recessive condition, meaning that affected individuals inherit two copies of the defective gene, one from each parent. The exact genetic cause, however, remained unknown.

1980s: Breakthroughs occurred in the understanding of Ataxia telangiectasia as researchers identified increased sensitivity of AT cells to ionizing radiation. This characteristic became an important diagnostic test for the condition.

1995: Scientists identified the gene responsible for Ataxia telangiectasia, known as ATM (Ataxia Telangiectasia Mutated). Mutations in this gene were found to be the underlying cause of the disorder. The ATM gene is involved in repairing damaged DNA and maintaining the stability of the genome.

2000s: With the discovery of the ATM gene, genetic testing became available for diagnosing Ataxia telangiectasia. This allowed for early identification of affected individuals and genetic counseling for families.

Present: Research on Ataxia telangiectasia continues to explore the underlying mechanisms of the disease and potential treatment options. Efforts are focused on understanding how ATM gene mutations lead to the symptoms and complications of the condition, as well as developing targeted therapies to address the specific genetic abnormalities associated with AT.

Today, Ataxia telangiectasia is still considered a rare disorder with no cure. Treatment focuses on managing symptoms, providing supportive care, and addressing specific complications such as infections and cancer predisposition. Supportive therapies may include physical and occupational therapy, speech therapy, immunoglobulin replacement therapy, and surveillance for potential complications.

Advancements in genetics and ongoing research hold promise for better understanding and potential future treatments for Ataxia telangiectasia, aiming to improve the quality of life for individuals affected by this condition.

Classification of Ataxia telangiectasia

Ataxia telangiectasia (AT) is classified as a rare autosomal recessive genetic disorder. It is characterized by a wide range of symptoms affecting multiple systems in the body. Here is a classification of Ataxia telangiectasia based on its clinical manifestations:

Neurological Features:

Ataxia: Progressive lack of muscle coordination and balance, resulting in unsteady movements.

Dysarthria: Difficulty with articulation and control of speech muscles, leading to slurred speech.

Hypotonia: Reduced muscle tone, resulting in weak muscles.

Nystagmus: Involuntary, rhythmic eye movements, often resulting in reduced visual acuity.

Choreoathetosis: Involuntary, jerky, and writhing movements.

Telangiectasias:

Telangiectasias are small, dilated blood vessels that appear as red clusters on the surface of the skin, typically in the areas of the eyes, ears, and cheeks. These are one of the characteristic features of Ataxia telangiectasia.

Immunodeficiency:

Individuals with Ataxia telangiectasia have an increased susceptibility to infections due to a weakened immune system. This can manifest as frequent respiratory tract infections, sinusitis, and ear infections.

Respiratory Manifestations:

Pulmonary infections and respiratory complications are common in individuals with Ataxia telangiectasia. Recurrent lung infections, such as bronchitis and pneumonia, can occur and lead to respiratory difficulties.

Increased Cancer Risk:

Ataxia telangiectasia is associated with an increased risk of developing certain types of cancer, particularly leukemia and lymphoma. The risk of cancer development increases with age.

Other Features:

Growth retardation: Delayed growth and development, resulting in short stature.

Oculomotor Apraxia: Impaired voluntary eye movements, making it difficult to track objects or move the eyes in specific directions.

Premature Aging: Some individuals with Ataxia telangiectasia may exhibit features of premature aging, such as graying of hair and premature wrinkling.

It's important to note that the severity and specific manifestations of Ataxia telangiectasia can vary among individuals. The classification above provides a general

overview of the common features observed in individuals with AT. Early diagnosis, management of symptoms, and regular medical surveillance are crucial for individuals with Ataxia telangiectasia to optimize their care and quality of life.

Symptom and sign in Ataxia telangiectasia

Ataxia telangiectasia (AT) is a complex genetic disorder that affects multiple systems in the body. It is characterized by a wide range of symptoms and signs that can vary in severity among individuals. Here are the main symptoms and signs associated with Ataxia telangiectasia:

Neurological Symptoms:

Ataxia: Progressive lack of muscle coordination and balance, leading to unsteady movements and difficulties with fine motor skills.

Dysarthria: Impaired control of the muscles involved in speech production, resulting in slurred or difficult-to-understand speech.

Tremors: Involuntary shaking or trembling of the limbs, head, or other body parts.

Hypotonia: Reduced muscle tone or muscle weakness, leading to poor muscle strength and control.

Nystagmus: Involuntary, rhythmic eye movements that can affect vision and coordination.

Telangiectasias:

Telangiectasias are small, red clusters of dilated blood vessels that appear on the surface of the skin, particularly around the eyes, ears, and cheeks. They may become more prominent over time.

Immunodeficiency:

Increased susceptibility to infections due to a weakened immune system. Individuals with AT may experience recurrent respiratory infections, sinusitis, ear infections, and other recurrent infections.

Respiratory Symptoms:

Respiratory issues are common in AT and can include chronic cough, wheezing, and recurrent respiratory tract infections, such as bronchitis and pneumonia.

Growth and Developmental Issues:

Delayed growth and development, resulting in short stature compared to peers.

Delayed onset of puberty.

Increased Cancer Risk:

Individuals with AT have an increased risk of developing certain types of cancer, particularly leukemia and lymphoma. The risk of cancer increases with age.

Other Symptoms:

Oculomotor Apraxia: Difficulty in initiating voluntary eye movements, leading to

problems with eye coordination and tracking objects.

Premature Aging

Image study in Ataxia telangiectasia

In the context of Ataxia telangiectasia (AT), imaging studies are often utilized to evaluate the structural and functional changes in the brain and other affected organs. Here are some of the imaging studies that may be conducted in individuals with Ataxia telangiectasia:

Magnetic Resonance Imaging (MRI): MRI is commonly used to assess the brain structure and detect any abnormalities associated with AT. It can reveal cerebellar atrophy, which is a characteristic finding in AT. MRI can also help identify changes in white matter, cortical thinning, and other structural abnormalities in the brain.

Computed Tomography (CT) Scan: CT scans may be performed to evaluate brain abnormalities, particularly to assess for any signs of cerebellar atrophy, ventricular enlargement, or other structural changes. CT scans are less detailed than MRI but can provide valuable information in certain cases.

Positron Emission Tomography (PET) Scan: PET scans can be used to evaluate the metabolic activity of the brain and identify any functional abnormalities. They may be helpful in assessing brain function and detecting changes associated with AT.

X-rays: X-rays are typically used to evaluate skeletal abnormalities, such as scoliosis, which can occur in individuals with AT. X-rays can also be used to assess lung health and identify any pulmonary complications.

Ultrasonography: Ultrasonography is a non-invasive imaging technique that uses sound waves to create images of internal organs and blood vessels. It may be employed to evaluate the presence of telangiectasias (dilated blood vessels) on the skin and other affected areas.

It's important to note that the choice of imaging studies may vary depending on the specific clinical presentation and concerns of each individual with AT. The primary focus of these imaging studies is to aid in the diagnosis, monitor disease progression, and guide appropriate management strategies for individuals with Ataxia telangiectasia.

Genetic mutation in Ataxia telangiectasia

Ataxia telangiectasia (AT) is caused by mutations in the Ataxia Telangiectasia Mutated (ATM) gene. The ATM gene provides instructions for producing a protein that plays a crucial role in repairing damaged DNA and maintaining the stability of the genome.

The majority of individuals with AT have mutations in both copies of the ATM gene,

resulting in a loss of functional ATM protein. AT follows an autosomal recessive inheritance pattern, meaning that an affected individual inherits one mutated copy of the ATM gene from each parent.

The specific types of mutations within the ATM gene can vary among individuals with AT. These mutations can disrupt the normal functioning of the ATM protein, impairing its ability to repair DNA damage effectively. As a result, cells in various tissues and organs, including the brain, immune system, and other affected areas, become more susceptible to damage and exhibit the characteristic features of AT. The ATM gene mutation can be detected through genetic testing, which typically involves analyzing the DNA of an affected individual. Genetic testing can confirm the diagnosis of AT, identify carriers within families, and provide genetic counseling for individuals and their families.

It's important to note that while most cases of AT are caused by mutations in the ATM gene, there have been rare instances where individuals with clinical features resembling AT do not have identifiable mutations in the ATM gene. In such cases, further genetic testing may be necessary to explore alternative genetic causes of the condition.

Mitochondrial dysfunction in Ataxia telangiectasia

Ataxia telangiectasia (A-T) is a rare genetic disorder characterized by progressive neurodegeneration, immunodeficiency, and increased cancer risk. While A-T primarily affects the cerebellum, which leads to ataxia and movement difficulties, mitochondrial dysfunction has also been implicated in the disease. Here's some information on the involvement of mitochondrial dysfunction in Ataxia telangiectasia:

Oxidative stress: Mitochondrial dysfunction in A-T can contribute to increased oxidative stress. Mitochondria are the primary site of reactive oxygen species (ROS) production, and impaired mitochondrial function can lead to an imbalance between ROS production and antioxidant defense mechanisms. The resulting oxidative stress can damage cellular components, including lipids, proteins, and DNA, and contribute to neurodegeneration.

Energy metabolism impairment: Mitochondria are responsible for generating ATP through oxidative phosphorylation, which is crucial for cellular energy production. In A-T, mitochondrial dysfunction can impair energy metabolism, leading to energy deficits and reduced ATP production. This can contribute to the progressive neurological symptoms seen in the disease.

Mitochondrial DNA (mtDNA) alterations: Studies have shown that individuals with A-T may exhibit mtDNA alterations, including deletions and rearrangements. These mtDNA abnormalities can affect mitochondrial function and contribute to the overall

mitochondrial dysfunction observed in the disease.

Impaired mitochondrial dynamics: Proper mitochondrial dynamics, including processes such as fusion, fission, and mitophagy, are essential for maintaining mitochondrial health and function. Disruption of these processes in A-T can lead to the accumulation of damaged mitochondria and further impair mitochondrial function.

DNA repair defects: A-T is caused by mutations in the ATM (ataxia telangiectasia mutated) gene, which is involved in DNA repair processes. The ATM protein plays a role in maintaining mitochondrial genome integrity, and its dysfunction in A-T can contribute to mitochondrial DNA damage and subsequent mitochondrial dysfunction.

Altered calcium homeostasis: Mitochondria play a crucial role in cellular calcium homeostasis. In A-T, disrupted calcium signaling and handling in mitochondria have been observed, leading to mitochondrial dysfunction. Calcium dysregulation can impair mitochondrial function and contribute to cellular dysfunction and neurodegeneration.

The exact mechanisms linking mitochondrial dysfunction to the pathogenesis of A-T are still being investigated. However, targeting mitochondrial dysfunction and oxidative stress are areas of potential therapeutic interest to mitigate the neurodegenerative processes in A-T.

Treatment in Ataxia telangiectasia

Ataxia telangiectasia (AT) is a complex genetic disorder for which there is currently no cure. Treatment for Ataxia telangiectasia primarily focuses on managing symptoms, preventing complications, and improving the quality of life for affected individuals. Here are some key aspects of treatment for AT:

Multidisciplinary Care:

A team of healthcare professionals, including neurologists, immunologists, physiotherapists, occupational therapists, speech therapists, and genetic counselors, work together to provide comprehensive care and support for individuals with AT.

Symptom Management:

Physical and Occupational Therapy: These therapies aim to improve motor skills, coordination, balance, and daily living activities. They may include exercises, assistive devices, and adaptations to help individuals maintain functional independence.

Speech and Swallowing Therapy: Speech therapy can help address speech difficulties and swallowing problems that may arise due to muscle weakness in the face, throat, and tongue. Techniques and strategies can be taught to enhance communication and ensure safe swallowing.

Supportive Devices: Assistive devices such as wheelchairs, braces, and mobility aids

can assist with mobility and improve independence.

Respiratory Management:

Regular monitoring of respiratory function, including assessment of lung health and breathing capacity.

Pulmonary care and interventions to prevent respiratory complications.

Non-invasive ventilation (NIV) or other respiratory support may be recommended as the disease progresses to assist with breathing.

Immunodeficiency Management:

Regular monitoring of immune function and appropriate management of infections.

Immunoglobulin replacement therapy may be considered to support the immune system.

Surveillance and Early Detection:

Regular check-ups and screening tests to detect and manage potential complications such as cancer, infections, and cardiovascular problems.

Mammograms, colonoscopies, and other screening tests may be recommended depending on individual needs.

Supportive and Palliative Care:

Psychological support, counseling, and resources for individuals and families to cope with the emotional and practical challenges associated with AT.

Palliative care services may be involved to address pain management, symptom control, and support the overall well-being of individuals with AT.

It is important for individuals with Ataxia telangiectasia to have ongoing medical management, regular follow-ups, and individualized care plans tailored to their specific needs. Treatment approaches are aimed at improving quality of life, managing symptoms, and minimizing complications associated with AT. Research efforts continue to explore potential therapeutic interventions for AT, and participation in clinical trials may be considered as an option for eligible individuals.

5. Beta-Propeller Protein-Associated Neurodegeneration (BPAN)

(Beta 螺旋狀蛋白關聯之神經退化疾病)

History of Beta-Propeller Protein-Associated Neurodegeneration

Beta-Propeller Protein-Associated Neurodegeneration (BPAN) is a rare genetic disorder that was first identified and characterized in 2012. The history of BPAN is relatively recent, as it is a relatively newly recognized condition.

The discovery of BPAN is attributed to researchers who conducted genetic studies and identified a specific mutation in the WDR45 gene associated with the disorder.

This gene provides instructions for producing a protein that is involved in the maintenance and function of neurons in the brain.

The clinical features and characteristic symptoms of BPAN were also described in the initial studies. These include developmental delay, intellectual disability, movement abnormalities, seizures, and neurodegeneration. The disorder primarily affects females, as it is inherited in an X-linked dominant pattern.

Since the initial discovery, further research has been conducted to better understand the underlying mechanisms of BPAN and to identify additional cases and associated features. This ongoing research aims to improve diagnostic methods, expand knowledge of the disorder's clinical presentation, and develop potential targeted treatments.

As with many rare diseases, the understanding and awareness of BPAN continue to evolve. More research and clinical studies are needed to fully elucidate the genetic, molecular, and clinical aspects of the disorder and to develop effective therapeutic interventions.

Classification of Beta-Propeller Protein-Associated Neurodegeneration

Beta-Propeller Protein-Associated Neurodegeneration (BPAN) falls under the broader category of neurodegeneration with brain iron accumulation (NBIA). NBIA is a group of inherited neurodegenerative disorders characterized by abnormal accumulation of iron in the brain, leading to progressive neurological symptoms.

BPAN specifically refers to a subtype of NBIA caused by mutations in the WDR45 gene. It is sometimes referred to as "static encephalopathy of childhood with neurodegeneration in adulthood" (SENDA) due to its characteristic features of developmental delay in childhood followed by neurodegenerative symptoms in adulthood.

The classification of BPAN within the NBIA spectrum is based on the underlying genetic cause and the specific clinical features observed in affected individuals. Other subtypes of NBIA include:

Pantothenate Kinase-Associated Neurodegeneration (PKAN) - Caused by mutations in the PANK2 gene and characterized by progressive dystonia, parkinsonism, and cognitive decline.

PLA2G6-Associated Neurodegeneration (PLAN) - Caused by mutations in the PLA2G6 gene and characterized by a range of symptoms including dystonia, parkinsonism, spasticity, and cognitive impairment.

Aceruloplasminemia - Caused by mutations in the CP gene and characterized by iron accumulation in various organs, including the brain, leading to movement disorders, diabetes, and vision and hearing abnormalities.

Coenzyme A (CoA) Synthase Deficiency - Caused by mutations in the COASY gene and characterized by infantile-onset encephalopathy, neurodegeneration, and epileptic seizures.

These subtypes of NBIA share some common features, such as progressive neurological symptoms and abnormal brain iron accumulation, but they also have distinct genetic causes and clinical presentations. Each subtype requires specific genetic testing for accurate diagnosis and management.

Symptom and sign in Beta-Propeller Protein-Associated Neurodegeneration

Beta-Propeller Protein-Associated Neurodegeneration (BPAN) is a rare neurodegenerative disorder that typically presents with a range of symptoms and signs. The symptoms and signs can vary in severity and may change over time. Here are some common features observed in individuals with BPAN:

Developmental Delay: Children with BPAN often experience developmental delays, including delays in reaching developmental milestones such as sitting, walking, and speaking. Intellectual disability is also commonly observed.

Seizures: Epileptic seizures are a common feature of BPAN. The seizures may vary in type and severity, ranging from focal seizures to generalized tonic-clonic seizures.

Movement Disorders: Individuals with BPAN may develop movement abnormalities, including dystonia, which is characterized by involuntary muscle contractions that result in twisting or repetitive movements and abnormal postures. Other movement disorders such as parkinsonism (bradykinesia, rigidity, and tremor) may also be present.

Cognitive Impairment: Progressive cognitive decline is a hallmark of BPAN.

Individuals may experience difficulties with memory, attention, problem-solving, and overall cognitive function.

Behavior and Psychiatric Symptoms: Behavioral changes and psychiatric symptoms can occur in individuals with BPAN. These may include impulsivity, aggression, mood disturbances, and anxiety.

Autonomic Dysfunction: Some individuals with BPAN may exhibit autonomic dysfunction, which can manifest as abnormalities in body temperature regulation, blood pressure control, and gastrointestinal symptoms.

It's important to note that the symptoms and signs of BPAN can vary among affected individuals, and not all individuals will exhibit the complete spectrum of features. Additionally, the onset and progression of symptoms can also vary, with some individuals experiencing more rapid progression than others. A proper diagnosis of BPAN requires genetic testing to confirm the presence of mutations in the WDR45 gene, as the clinical presentation alone may not be sufficient for a definitive diagnosis.

Image study in Beta-Propeller Protein-Associated Neurodegeneration

Imaging studies can help in the evaluation of individuals suspected to have Beta-Propeller Protein-Associated Neurodegeneration (BPAN). However, it's important to note that the specific imaging findings may vary among individuals, and there is no characteristic imaging pattern that is diagnostic of BPAN. Nonetheless, here are some imaging modalities that may be used in the evaluation:

Magnetic Resonance Imaging (MRI): MRI is commonly used to assess the brain structure and detect any abnormalities. In individuals with BPAN, MRI may reveal various findings depending on the stage of the disease. Some possible findings on MRI include:

Progressive brain atrophy: As the disease progresses, there may be a loss of brain tissue, especially in certain regions such as the cerebral cortex and basal ganglia.

White matter abnormalities: MRI may show changes in the white matter, such as hyperintensities or hypointensities, which can indicate degeneration or damage to the myelin sheath.

Delayed myelination: In some cases, delayed myelination, which refers to the delayed maturation of the white matter, may be observed.

Structural abnormalities: Other structural abnormalities, such as malformations or anomalies in specific brain regions, may also be detected in some individuals.

Positron Emission Tomography (PET) and Single-Photon Emission Computed Tomography (SPECT): These imaging techniques are less commonly used in the evaluation of BPAN but may be employed in research settings. They can provide information about the functional activity of the brain and may help in understanding metabolic changes or abnormalities.

It's important to note that imaging findings alone are not sufficient for a definitive diagnosis of BPAN. Genetic testing to identify mutations in the WDR45 gene is the gold standard for confirming the diagnosis. Imaging studies are used as supportive tools to assess the brain structure and provide additional information about the disease

progression and associated changes.

Genetic mutation in Beta-Propeller Protein-Associated Neurodegeneration

Beta-Propeller Protein-Associated Neurodegeneration (BPAN) is primarily caused by mutations in the WDR45 gene, also known as the WIPI4 gene. The WDR45 gene provides instructions for producing a protein called WD repeat-containing protein 45 (WDR45). This protein is involved in the process of autophagy, which is responsible for the degradation and recycling of cellular components.

The most common genetic mutation associated with BPAN is a deletion or loss-of-function mutation in the WDR45 gene. This mutation leads to a deficiency or dysfunction of the WDR45 protein, impairing the autophagy process and resulting in the accumulation of cellular debris and dysfunctional proteins in the brain. This accumulation contributes to the neurodegenerative process seen in BPAN.

It's worth noting that not all individuals with BPAN have a detectable mutation in the WDR45 gene, suggesting that there may be other genetic or molecular mechanisms involved in the development of the condition. Ongoing research is focused on identifying additional genes or genetic factors that may contribute to the development of BPAN.

Mitochondrial dysfunction in Beta-Propeller Protein-Associated Neurodegeneration

Beta-Propeller Protein-Associated Neurodegeneration (BPAN) is a rare genetic disorder characterized by intellectual disability, developmental delay, and neurodegeneration. It is caused by mutations in the WDR45 gene, which encodes a protein involved in autophagy and lysosomal function. While the exact mechanisms of neurodegeneration in BPAN are not fully understood, mitochondrial dysfunction has been implicated in the disease. Here's some information on the involvement of mitochondrial dysfunction in BPAN:

Impaired mitochondrial dynamics: Mitochondrial dynamics, including processes such as fusion, fission, and mitophagy, are essential for maintaining mitochondrial health and function. Disruption of these processes can lead to the accumulation of dysfunctional mitochondria. Studies have shown that mutations in the WDR45 gene can impair mitochondrial dynamics, leading to abnormal mitochondrial morphology and function in BPAN.

Altered oxidative phosphorylation: Mitochondria are responsible for generating ATP through oxidative phosphorylation. Dysfunction in the electron transport chain and oxidative phosphorylation can lead to reduced ATP production and energy deficits. Studies have indicated that BPAN patients may exhibit defects in oxidative

phosphorylation, suggesting mitochondrial dysfunction in energy metabolism. Increased reactive oxygen species (ROS) production: Mitochondria are the primary site of ROS production, and excessive ROS can cause oxidative damage to cellular components. Studies have suggested that mitochondrial dysfunction in BPAN may lead to increased ROS production, contributing to oxidative stress and neuronal damage.

Impaired calcium homeostasis: Mitochondria play a crucial role in regulating intracellular calcium levels. Disrupted calcium signaling and handling in mitochondria can lead to mitochondrial dysfunction. Studies have indicated that altered calcium homeostasis may be involved in the pathogenesis of BPAN, suggesting a potential link to mitochondrial dysfunction.

Altered mitophagy and autophagy: Mitophagy, the selective removal of damaged mitochondria through autophagy, is crucial for maintaining mitochondrial quality control. Impaired autophagy and mitophagy have been observed in BPAN, which can lead to the accumulation of dysfunctional mitochondria and contribute to mitochondrial dysfunction and neurodegeneration.

While the understanding of mitochondrial dysfunction in BPAN is still evolving, these findings highlight the involvement of mitochondrial abnormalities in the disease. Further research is needed to elucidate the precise molecular mechanisms and to explore potential therapeutic strategies targeting mitochondrial dysfunction in BPAN.

Treatment in Beta-Propeller Protein-Associated Neurodegeneration

Currently, there is no specific cure for Beta-Propeller Protein-Associated Neurodegeneration (BPAN) as it is a rare and complex disorder. The treatment of BPAN is mainly focused on managing and alleviating the symptoms experienced by individuals with the condition. The treatment approach is multidisciplinary and may involve a team of healthcare professionals including neurologists, geneticists, physiotherapists, occupational therapists, and speech therapists.

The management of BPAN may include the following:

Symptom-specific treatment: The treatment aims to address specific symptoms and may involve medications to manage seizures, muscle stiffness, sleep disturbances, and other associated symptoms.

Physical and occupational therapy: Physical and occupational therapy can help improve mobility, muscle strength, and coordination. These therapies may involve exercises, stretching, and assistive devices to promote independent functioning and mobility.

Speech and communication therapy: Speech and communication therapy can help

individuals with BPAN improve their communication skills and overcome speech difficulties.

Seizure management: Seizures are a common symptom in BPAN, and antiepileptic medications may be prescribed to manage and control seizures.

Supportive care: Supportive care focuses on providing assistance and support to individuals and their families to improve their quality of life. This may include counseling, educational support, and connecting families with support groups and resources.

It's important to note that the treatment approach may vary based on the individual's specific symptoms and needs. A comprehensive and personalized treatment plan should be developed in collaboration with healthcare professionals experienced in managing rare neurodegenerative disorders like BPAN. Ongoing research is also aimed at identifying potential targeted therapies for BPAN in the future.

6. Cerebro-Costo-Mandibular Syndrome(腦肋小頷症候群)

History of Cerebro-Costo-Mandibular Syndrome

Cerebro-Costo-Mandibular Syndrome (CCMS) is a rare genetic disorder that affects the development of the brain, ribs, and jaw. It was first described in medical literature in 1970 by Hall et al. The condition was initially referred to as "Cerebrocostomandibular Syndrome" due to its characteristic features involving the brain, ribs, and jaw. Over time, the name was modified to Cerebro-Costo-Mandibular Syndrome.

The history of CCMS involves the identification of cases and the understanding of its clinical presentation, genetic causes, and underlying mechanisms. Here is a brief overview of the historical milestones in CCMS:

Initial case reports: The first cases of CCMS were reported in the medical literature in the early 1970s. Researchers observed a pattern of anomalies involving the brain, ribs, and jaw in affected individuals.

Clinical features identification: Through subsequent case reports and studies, researchers identified the common clinical features associated with CCMS. These features include micrognathia (small jaw), rib anomalies such as fused ribs or missing ribs, and cognitive and developmental delays.

Genetic discoveries: Advances in genetic research allowed for the identification of the genetic causes of CCMS. In 2003, mutations in the gene SF3B4 were identified as a common cause of CCMS. SF3B4 is involved in the splicing of RNA molecules, and mutations in this gene disrupt normal development, leading to the characteristic features of CCMS.

Further understanding of the condition: Over time, researchers have gained a deeper understanding of CCMS, including its clinical variability and associated medical complications. This knowledge has helped guide diagnosis, management, and genetic counseling for affected individuals and their families.

While significant progress has been made in understanding CCMS, it remains a rare and complex condition. Ongoing research continues to explore the underlying mechanisms, genotype-phenotype correlations, and potential therapeutic interventions to improve the management and outcomes for individuals with CCMS.

Classification of Cerebro-Costo-Mandibular Syndrome

Cerebro-Costo-Mandibular Syndrome (CCMS) is a rare genetic disorder that affects multiple body systems, primarily involving the brain, ribs, and jaw. The classification of CCMS is primarily based on the clinical features and the severity of the condition. Although there is no universally accepted classification system for CCMS, it can be

broadly categorized as follows:

Type I CCMS: This is the classic form of CCMS characterized by the triad of micrognathia (small jaw), rib anomalies, and brain abnormalities. The rib anomalies can include fused ribs, missing ribs, or other abnormalities of rib development. Brain abnormalities often involve underdevelopment of the brain, such as reduced brain size (microcephaly), abnormalities in the shape of the brain (e.g., simplification of gyri and sulci), and structural defects.

Type II CCMS: This form of CCMS is considered a milder variant, with a less severe presentation compared to Type I. It typically involves a subset of the characteristic features seen in Type I CCMS, such as mild micrognathia, mild rib anomalies, and less pronounced brain abnormalities. The severity of intellectual disability and other associated medical complications may also be less severe in Type II CCMS.

It's important to note that the classification of CCMS is not always straightforward, as there is significant variability in the clinical presentation and severity of the condition among affected individuals. Some individuals may exhibit overlapping features with other syndromes, making precise classification challenging.

In addition to the classification based on the clinical features, CCMS can also be categorized based on the underlying genetic cause. Mutations in the SF3B4 gene have been identified as a common genetic cause of CCMS, although other genetic causes or contributing factors may exist.

It's worth mentioning that the classification and understanding of CCMS may evolve as further research and clinical observations emerge. Therefore, it is important for healthcare professionals to stay updated on the latest findings and diagnostic criteria for CCMS.

Symptom and sign in Cerebro-Costo-Mandibular Syndrome

Cerebro-Costo-Mandibular Syndrome (CCMS) is characterized by a combination of symptoms and signs affecting various body systems. The most common features observed in individuals with CCMS include:

Mandibular (Jaw) Abnormalities:

Micrognathia: The jaw is abnormally small or underdeveloped.

Retrognathia: The lower jaw is positioned further back than normal.

Cleft Palate: A gap or opening in the roof of the mouth.

Rib Abnormalities:

Rib Fusion: Two or more ribs may be fused together.

Rib Gap: One or more ribs may be missing or have gaps.

Short Ribs: The ribs are shorter than usual.

Abnormal Rib Position: The ribs may be misaligned or have other structural

abnormalities.

Central Nervous System (CNS) Abnormalities:

Intellectual Disability: Individuals with CCMS often have varying degrees of intellectual impairment.

Developmental Delay: Delays in achieving developmental milestones, such as sitting, walking, or talking, may be observed.

Brain Abnormalities: Structural anomalies in the brain, including reduced brain size (microcephaly), simplified gyri and sulci, and other malformations.

Hearing Loss: Sensorineural hearing loss, ranging from mild to severe, can occur in some cases.

Other Features:

Respiratory Complications: Difficulties with breathing, recurrent respiratory infections, and respiratory distress may be present.

Growth Retardation: Slowed growth and short stature may be observed.

Facial Dysmorphism: Some individuals may have distinct facial features, such as a high forehead, widely spaced eyes (hypertelorism), or a flat nasal bridge.

Other Skeletal Abnormalities: Additional skeletal abnormalities may be present, including abnormal curvature of the spine (scoliosis) or limb anomalies.

It's important to note that the severity and combination of symptoms can vary among individuals with CCMS. Not all affected individuals will exhibit all the features mentioned above, and the presentation can range from mild to severe. Additionally, some features may be detected prenatally during ultrasound examinations.

If CCMS is suspected, a comprehensive evaluation by a medical geneticist or other healthcare professionals familiar with the condition is necessary to assess and manage the associated symptoms and provide appropriate medical care.

Image study in Cerebro-Costo-Mandibular Syndrome

As Cerebro-Costo-Mandibular Syndrome (CCMS) primarily affects the development of the jaw, ribs, and central nervous system, imaging studies play an important role in its diagnosis and evaluation. The following imaging modalities may be used:

X-ray: X-rays are commonly used to assess the skeletal abnormalities associated with CCMS, particularly the ribs and jaw. X-rays of the chest can reveal rib fusion, rib gaps, and other structural abnormalities. X-rays of the jaw can show micrognathia, retrognathia, and cleft palate.

Computed Tomography (CT) Scan: CT scans provide detailed cross-sectional images of the bones, allowing for a more comprehensive assessment of the jaw, ribs, and other skeletal structures. CT scans can help visualize the extent of rib abnormalities, such as fusion, gaps, or misalignment. They can also reveal jaw abnormalities and

provide information about the structural integrity of the skull and other craniofacial bones.

Magnetic Resonance Imaging (MRI): MRI scans are particularly useful for evaluating the central nervous system (CNS) abnormalities associated with CCMS. They can provide detailed images of the brain, allowing for the detection of structural anomalies, such as reduced brain size (microcephaly), abnormal gyri and sulci, and other malformations. MRI can also assess the integrity of the cranial nerves and help identify any associated brain abnormalities.

Ultrasound: Ultrasound imaging may be used during pregnancy to evaluate the development of the fetus and detect any early signs of CCMS. It can help visualize the jaw, ribs, and other structures, providing valuable information about potential abnormalities.

The specific choice of imaging modality depends on the clinical presentation, age of the individual, and availability of resources. A combination of these imaging techniques is often employed to obtain a comprehensive assessment of the skeletal and CNS abnormalities in individuals suspected of having CCMS. Interpretation of the images is typically performed by a radiologist or other specialists experienced in congenital abnormalities.

Genetic mutation in Cerebro-Costo-Mandibular Syndrome

The genetic basis of Cerebro-Costo-Mandibular Syndrome (CCMS) is associated with mutations in the genes involved in the development and function of the rib, jaw, and central nervous system. The most common genetic mutation associated with CCMS is found in the gene called TBX1.

TBX1 gene mutations are typically responsible for a condition known as 22q11.2 deletion syndrome, which encompasses a range of congenital abnormalities including CCMS. This mutation results in the deletion of a small piece of genetic material on the long arm of chromosome 22. This genetic alteration disrupts normal embryonic development, leading to the characteristic features of CCMS.

Other genes and genetic mutations have also been implicated in CCMS, albeit less frequently. Mutations in the MYH3 gene have been identified in a small number of individuals with CCMS. The MYH3 gene encodes a protein involved in muscle development and contraction. Mutations in this gene can affect the formation and function of the jaw muscles, contributing to the characteristic facial abnormalities observed in CCMS.

It is important to note that CCMS is a genetically heterogeneous disorder, meaning that multiple genes and genetic variations can contribute to its development. Research is ongoing to identify additional genes and mutations associated with CCMS and to

better understand the underlying genetic mechanisms involved in the condition. Genetic testing and counseling are essential for individuals with CCMS and their families to provide accurate diagnosis, inform prognosis, and guide appropriate management strategies.

Mitochondrial dysfunction in Cerebro-Costo-Mandibular Syndrome

Cerebro-Costo-Mandibular Syndrome (CCMS) is a rare genetic disorder characterized by abnormal development of the brain, ribs, and jaw. It is primarily caused by mutations in the gene called SNAP29, which is involved in cellular membrane fusion processes. While the exact mechanisms underlying CCMS are not fully understood, there is evidence suggesting a potential role of mitochondrial dysfunction in the disorder. Here's some information on the involvement of mitochondrial dysfunction in CCMS:

Impaired oxidative phosphorylation: Mitochondria are responsible for generating ATP through oxidative phosphorylation, a process that occurs in the inner mitochondrial membrane. Dysfunction in the electron transport chain and oxidative phosphorylation can lead to reduced ATP production and energy deficits. Studies have shown that mutations in SNAP29 can impair mitochondrial function and disrupt oxidative phosphorylation, leading to energy metabolism dysfunction in CCMS.

Abnormal mitochondrial morphology: Mitochondria have a characteristic tubular morphology, and their shape is regulated by processes such as mitochondrial fusion and fission. Alterations in the balance between fusion and fission can lead to abnormal mitochondrial morphology and function. Studies have indicated that SNAP29 mutations can affect mitochondrial morphology, leading to fragmented or elongated mitochondria in CCMS.

Altered mitochondrial dynamics: Mitochondrial dynamics, including fusion, fission, and mitophagy, play a crucial role in maintaining mitochondrial quality control. Dysfunction in these processes can result in the accumulation of damaged mitochondria and impaired cellular function. Studies have suggested that SNAP29 mutations may affect mitochondrial dynamics, leading to imbalances in fusion and fission and impairing mitophagy, which can contribute to mitochondrial dysfunction in CCMS.

Increased oxidative stress: Mitochondria are a major source of reactive oxygen species (ROS), and excessive ROS production can cause oxidative stress and damage to cellular components. Studies have indicated that mitochondrial dysfunction in CCMS may lead to increased ROS production and oxidative stress, which can contribute to cellular dysfunction and tissue abnormalities observed in the disorder. It's important to note that the understanding of mitochondrial dysfunction in CCMS is

still evolving, and further research is needed to elucidate the precise molecular mechanisms and the extent of mitochondrial involvement in the disorder. Nonetheless, the existing evidence suggests a potential link between mitochondrial dysfunction and the pathogenesis of CCMS.

Treatment in Cerebro-Costo-Mandibular Syndrome

There is no specific cure for Cerebro-Costo-Mandibular Syndrome (CCMS) as it is a congenital disorder caused by genetic mutations. However, the treatment of CCMS focuses on managing the symptoms and providing supportive care to improve the individual's quality of life. The treatment approach may vary depending on the severity and specific symptoms experienced by the individual. Here are some aspects of treatment that are typically considered:

Multidisciplinary care: A team of healthcare professionals, including geneticists, orthopedic surgeons, craniofacial specialists, pulmonologists, and others, work together to provide comprehensive care and address the various aspects of CCMS.

Symptom management: The treatment may involve managing specific symptoms associated with CCMS. This can include surgical interventions for correcting jaw and chest abnormalities, orthopedic interventions for spine and limb deformities, and dental care for addressing dental issues.

Respiratory support: As CCMS can affect the chest wall and respiratory muscles, respiratory support may be necessary in severe cases. This can include the use of assistive devices such as breathing machines (ventilators) or respiratory aids to help with breathing and ensure adequate oxygenation.

Feeding and nutrition support: Some individuals with CCMS may have difficulties with feeding and require specialized techniques or assistance for adequate nutrition. This may involve working with speech therapists, occupational therapists, or dietitians to ensure proper feeding and nutrition.

Rehabilitation and therapy: Physical therapy and occupational therapy may be recommended to improve motor skills, muscle strength, and overall functional abilities. These therapies can help individuals with CCMS to optimize their physical capabilities and enhance independence in daily activities.

Regular monitoring and surveillance: Ongoing medical follow-up and monitoring are important to assess and manage any potential complications or associated health conditions that may arise in individuals with CCMS.

It is crucial for individuals with CCMS to receive personalized care and have a management plan tailored to their specific needs. As CCMS is a rare condition, consultation with medical experts and genetic counseling can be beneficial for individuals and families affected by this syndrome.

7.Charcot Marie Tooth Disease(夏柯-馬利-杜斯氏症)

History of Charcot Marie Tooth Disease

Charcot Marie Tooth (CMT) disease, also known as hereditary motor and sensory neuropathy (HMSN), was first described in 1886 by the French neurologists Jean-Martin Charcot, Pierre Marie, and Howard Henry Tooth. They recognized a hereditary neurological disorder characterized by progressive muscle weakness and wasting, sensory loss, and deformities of the feet.

Since its initial description, significant progress has been made in understanding the different subtypes and genetic basis of CMT disease. Researchers have identified multiple genes that, when mutated, can cause CMT. These genetic mutations affect proteins involved in the structure and function of peripheral nerves, which are responsible for transmitting signals between the brain, spinal cord, and the rest of the body.

Over time, the classification of CMT disease has evolved as new genetic subtypes have been identified. The most common classification system used today is based on the underlying genetic cause and clinical features. CMT disease is categorized into several subtypes, including CMT type 1, CMT type 2, CMT type 4, and others, each associated with specific genetic mutations and clinical characteristics.

The history of CMT disease is also intertwined with advancements in diagnostic techniques and molecular genetics. The discovery of specific genetic mutations has enabled more accurate diagnosis, genetic counseling, and prediction of disease progression. It has also paved the way for potential targeted treatments and therapeutic interventions.

In recent years, there has been increasing research into the pathogenesis of CMT disease and the development of potential therapies. This includes gene therapy approaches, small molecule drug candidates, and other strategies aimed at correcting or mitigating the underlying genetic defects and their effects on peripheral nerve function.

While there is currently no cure for CMT disease, advancements in understanding the genetic and molecular basis of the condition offer hope for future targeted treatments and interventions. Research efforts continue to improve our understanding of CMT disease, with the ultimate goal of improving the quality of life for individuals living with this inherited neurological disorder.

Classification of Charcot Marie Tooth Disease

Charcot Marie Tooth (CMT) disease is a group of inherited peripheral neuropathies that affect the nerves outside the brain and spinal cord. It is classified into several

subtypes based on the underlying genetic cause, clinical features, and nerve conduction study findings. The classification of CMT disease can vary depending on the classification system used, but the following are some commonly recognized subtypes:

CMT Type 1 (CMT1): CMT1 is the most common subtype and is characterized by demyelination, which refers to damage to the myelin sheath that surrounds and insulates the nerves. CMT1 is further divided into subtypes based on the specific genetic mutations involved, including CMT1A (caused by a duplication of the PMP22 gene), CMT1B (caused by mutations in the MPZ gene), and CMT1X (caused by mutations in the GJB1 gene).

CMT Type 2 (CMT2): CMT2 is characterized by axonal degeneration, which involves damage to the nerve fibers themselves. CMT2 is also further classified into subtypes based on the underlying genetic mutations, including CMT2A (caused by mutations in the MFN2 gene), CMT2E (caused by mutations in the NEFL gene), and others.

CMT Type 3 (CMT3), also known as Dejerine-Sottas syndrome: CMT3 is a rare, severe form of CMT disease that presents in early childhood. It is characterized by severe demyelination and more pronounced symptoms compared to other subtypes.

CMT Type 4 (CMT4): CMT4 is a group of rare autosomal recessive forms of CMT disease. It is characterized by both demyelination and axonal degeneration. Different subtypes of CMT4 are associated with specific genetic mutations, such as CMT4A (caused by mutations in the GDAP1 gene) and CMT4B (caused by mutations in the MTMR2 or MTMR13 genes).

CMT Type X (CMTX): CMTX is an X-linked form of CMT disease, meaning it primarily affects males. It is caused by mutations in the GJB1 gene, which is involved in the formation of gap junctions between cells.

Other subtypes: There are additional, less common subtypes of CMT disease, including CMT Type 5 (CMT5), CMT Type 6 (CMT6), and others. These subtypes are associated with specific genetic mutations and may have distinct clinical features. It's important to note that classification systems may vary, and new subtypes of CMT disease continue to be discovered as genetic testing and research advance. A comprehensive evaluation by a medical professional experienced in neuromuscular disorders is necessary to accurately diagnose and classify the specific subtype of CMT disease in an individual.

Symptom and sign in Charcot Marie Tooth Disease

Charcot Marie Tooth (CMT) disease is characterized by a wide range of symptoms and signs that primarily affect the peripheral nerves, leading to progressive muscle

weakness and sensory abnormalities. The severity and specific symptoms can vary depending on the subtype and individual variations. Here are some common symptoms and signs of CMT disease:

Muscle Weakness: CMT disease often presents with muscle weakness, typically starting in the feet and legs and gradually progressing to the hands and arms. The weakness is usually symmetric, meaning it affects both sides of the body equally. It can lead to difficulty with walking, running, climbing stairs, and performing fine motor tasks.

Muscle Atrophy: Over time, the muscles affected by CMT disease may become smaller (atrophy) due to lack of proper nerve stimulation and innervation. This can result in a thinning appearance of the muscles, particularly in the lower legs and feet.

Foot Deformities: CMT disease commonly causes foot deformities such as high arches (pes cavus) and hammertoes. High arches can lead to instability and difficulty with balance, while hammertoes involve abnormal bending of the toes.

Sensory Abnormalities: Individuals with CMT disease may experience sensory abnormalities, including decreased sensation or loss of sensation in the extremities. This can lead to difficulty sensing temperature, pain, and touch.

Balance and Coordination Issues: CMT disease can affect the coordination and balance of individuals, leading to difficulties with walking in a straight line, maintaining balance on uneven surfaces, and performing precise movements.

Nerve Pain: Some individuals with CMT disease may experience neuropathic pain, which is characterized by aching, burning, or shooting pain in the affected limbs.

Reduced Reflexes: CMT disease can cause a decrease or absence of certain reflexes, such as the ankle reflex (Achilles reflex) and knee reflex (patellar reflex).

Progression of Symptoms: CMT disease is generally a progressive condition, meaning that symptoms tend to worsen over time. However, the rate of progression can vary between individuals, even among those with the same subtype of CMT disease.

It's important to note that not all individuals with CMT disease will experience the same combination or severity of symptoms. The specific symptoms and signs can vary widely, even among family members with the same genetic mutation. A thorough evaluation by a healthcare professional specializing in neuromuscular disorders is necessary to diagnose and manage CMT disease.

Image study in Charcot Marie Tooth Disease

Image studies play an important role in the diagnosis and evaluation of Charcot Marie Tooth (CMT) disease. Here are some common imaging techniques used:

Nerve Conduction Studies (NCS): Nerve conduction studies assess the function and conduction speed of peripheral nerves. Electrodes are placed on the skin, and a mild

electrical stimulation is applied to the nerves. The response is recorded, and the conduction speed and amplitude of the nerve signals are measured. NCS can help differentiate between demyelinating and axonal subtypes of CMT disease.

Electromyography (EMG): Electromyography measures the electrical activity of muscles. Thin needles are inserted into the muscles, and the electrical activity is recorded. EMG can help assess the integrity of motor neurons and muscles, as well as identify any abnormal activity that may be indicative of CMT disease.

Magnetic Resonance Imaging (MRI): MRI uses powerful magnets and radio waves to produce detailed images of the body. In the context of CMT disease, MRI can be used to assess the size and structure of nerves, muscles, and other soft tissues. It can help identify any abnormalities or changes associated with CMT, such as muscle atrophy or nerve enlargement.

Ultrasound: Ultrasound imaging uses high-frequency sound waves to create real-time images of the body. It can be used to evaluate the size and structure of peripheral nerves and muscles in individuals with CMT disease. Ultrasound can help detect nerve enlargement, nerve compression, and muscle abnormalities.

Computed Tomography (CT) Scan: CT scan uses a series of X-ray images taken from different angles to create cross-sectional images of the body. It may be used in some cases to assess bony abnormalities or changes in the spinal column that may contribute to symptoms of CMT disease.

Genetic Testing: Although not an imaging study per se, genetic testing plays a crucial role in the diagnosis of CMT disease. It involves analyzing a blood or saliva sample to identify specific genetic mutations associated with CMT. Genetic testing can help confirm the diagnosis, determine the specific subtype of CMT, and provide information about disease prognosis and inheritance patterns.

It's important to note that the choice of imaging studies may vary depending on the individual's clinical presentation, suspected subtype of CMT disease, and the availability of resources and expertise. The results of imaging studies, in conjunction with clinical evaluations and genetic testing, can aid in the diagnosis, classification, and management of CMT disease.

Genetic mutation in Charcot Marie Tooth Disease

Charcot Marie Tooth (CMT) disease is a genetically heterogeneous group of disorders, meaning it can be caused by various genetic mutations. The most common genetic mutations associated with CMT disease affect genes involved in the structure and function of peripheral nerves. Here are some of the key genetic mutations associated with different subtypes of CMT disease:

CMT Type 1: CMT Type 1 is primarily caused by mutations in genes related to

myelin production, which is the fatty substance that forms a protective covering around nerve fibers. The most common genetic mutation associated with CMT Type 1 is a duplication or point mutation in the PMP22 gene. Mutations in the MPZ, GJB1, and EGR2 genes can also cause CMT Type 1.

CMT Type 2: CMT Type 2 is characterized by axonal degeneration, which affects the nerve fibers themselves. Mutations in several genes can cause CMT Type 2, including MFN2, GDAP1, MPZ, NEFL, and HSPB1. The MFN2 gene mutation is the most common cause of CMT Type 2.

CMT Type X: CMT Type X is caused by mutations in the GJB1 gene, which encodes for a protein called connexin 32. This type of CMT is inherited in an X-linked pattern, meaning it is more common in males. Mutations in the GJB1 gene disrupt the normal function of connexin 32, leading to abnormalities in the peripheral nerves.

Other Subtypes: There are additional subtypes of CMT disease that are caused by mutations in less common genes. For example, mutations in the DYNC1H1 gene can cause CMT Type 2O, and mutations in the TRPV4 gene can cause CMT Type 2C.

These subtypes are relatively rare compared to the more common forms of CMT.

It's important to note that the genetic mutations associated with CMT disease can vary between individuals and families. Genetic testing, usually performed through a blood or saliva sample, can help identify the specific genetic mutation causing CMT in an individual. This information is valuable for confirming the diagnosis, determining the subtype of CMT, and providing information about disease prognosis and inheritance patterns.

Mitochondrial dysfunction in Charcot Marie Tooth Disease

Charcot-Marie-Tooth disease (CMT) is a group of inherited peripheral neuropathies that affect the peripheral nerves, leading to muscle weakness and sensory abnormalities. While mitochondrial dysfunction has been implicated in some forms of CMT, it is not a universal feature of the disease.

Certain subtypes of CMT, such as CMT2A and CMT2E, have been associated with mitochondrial dysfunction. In these cases, mutations in specific genes (MFN2 and RAB7A, respectively) can disrupt mitochondrial dynamics and impair mitochondrial function. These mitochondrial abnormalities can contribute to the neurodegenerative process seen in these subtypes of CMT.

However, it is important to note that mitochondrial dysfunction is not a characteristic feature of all types of CMT. CMT is a genetically and clinically heterogeneous disorder, with over 90 different genetic subtypes identified. While mitochondrial dysfunction may play a role in specific subtypes, other genetic mechanisms and cellular processes are also involved in the pathogenesis of CMT.

It is always recommended to consult with a medical geneticist or genetic counselor for comprehensive and up-to-date information about specific subtypes of CMT and their associated genetic and molecular features.

Treatment in Charcot Marie Tooth Disease

Treatment for Charcot Marie Tooth (CMT) disease aims to manage symptoms, improve quality of life, and prevent complications. Since CMT is a progressive and chronic condition, treatment is typically focused on supportive care. Here are some approaches commonly used in the management of CMT:

Physical Therapy: Physical therapy plays a crucial role in managing CMT. It focuses on maintaining and improving strength, mobility, and function. Physical therapists can provide exercises, stretching techniques, and assistive devices to help individuals with CMT optimize their physical abilities and prevent muscle weakness and contractures.

Occupational Therapy: Occupational therapy helps individuals with CMT develop strategies to manage daily activities and improve hand function. Occupational therapists can provide adaptive equipment and techniques to enhance independence and maintain functionality.

Orthopedic Interventions: Orthopedic interventions may be necessary to address musculoskeletal complications associated with CMT, such as foot deformities, scoliosis, or joint contractures. These interventions may include orthotic devices, corrective surgery, or orthopedic bracing to improve stability and mobility.

Pain Management: Some individuals with CMT may experience pain or discomfort due to muscle weakness, nerve damage, or joint abnormalities. Pain management strategies may include over-the-counter pain relievers, physical therapy modalities, and in some cases, prescription medications under the guidance of a healthcare professional.

Assistive Devices: Various assistive devices can aid individuals with CMT in maintaining mobility and independence. Examples include ankle-foot orthoses (AFOs) to improve foot drop, canes or crutches for stability, and mobility aids such as wheelchairs or scooters for individuals with more severe mobility impairments.

Genetic Counseling: Genetic counseling is recommended for individuals with CMT and their families. It can provide information about the specific genetic subtype of CMT, inheritance patterns, and family planning options.

Management of Associated Conditions: CMT can be associated with additional medical conditions, such as neuropathic pain, sensory impairments, and respiratory complications. Managing these conditions in collaboration with appropriate specialists, such as pain specialists, neurologists, and pulmonologists, is an important part of comprehensive care.

It's important for individuals with CMT to work closely with a healthcare team that specializes in neuromuscular disorders. Regular monitoring, ongoing support, and adaptations to treatment plans based on disease progression can help individuals with CMT optimize their overall well-being and maintain the highest level of function and independence possible.

8. Congenital insensitivity to pain with anhidrosis (CIPA) (先天性痛不

敏感症合併無汗症)

History of Congenital insensitivity to pain with anhidrosis

Congenital insensitivity to pain with anhidrosis (CIPA), also known as hereditary sensory and autonomic neuropathy type IV (HSAN IV), is a rare genetic disorder characterized by the inability to feel pain, impaired temperature regulation, and the absence of sweating (anhidrosis). Here is a brief overview of the history of CIPA:

1963: The first documented case of CIPA was reported by Swanson and colleagues. They described a child who exhibited insensitivity to pain, self-mutilating behaviors, and recurrent injuries without appropriate responses.

1983: The term "congenital insensitivity to pain with anhidrosis" was coined by Dyck and Lambert to describe the specific features of this condition.

1996: Using linkage analysis, Indo and colleagues identified the gene responsible for CIPA on chromosome 1q21-q22. They named the gene NTRK1, which encodes the neurotrophic tyrosine kinase receptor 1 (TrkA), a high-affinity receptor for nerve growth factor.

1999: Several mutations in the NTRK1 gene were identified as the underlying cause of CIPA. These mutations disrupt the function of the TrkA receptor, leading to the loss of pain perception and the inability to regulate body temperature and sweat production.

Since the initial identification of the NTRK1 gene mutations, additional studies have further elucidated the genetic basis of CIPA. It has been found that CIPA is an autosomal recessive disorder, meaning that an individual must inherit two copies of the mutated NTRK1 gene (one from each parent) to develop the condition.

Understanding the genetic basis of CIPA has contributed to improved diagnostic capabilities and genetic counseling for affected individuals and their families.

However, due to the rarity of the condition, research and treatment options for CIPA are still limited. The focus of management for individuals with CIPA is centered around preventing injuries, monitoring body temperature, and addressing complications related to anhidrosis and autonomic dysfunction.

It's worth noting that ongoing research is being conducted to explore potential treatments and therapies to alleviate the symptoms and improve the quality of life for individuals with CIPA.

Classification of Congenital insensitivity to pain with anhidrosis

Congenital insensitivity to pain with anhidrosis (CIPA), also known as hereditary

sensory and autonomic neuropathy type IV (HSAN IV), is classified under the broader category of hereditary sensory and autonomic neuropathies (HSAN). HSANs are a group of genetic disorders characterized by abnormalities in the sensory and autonomic nervous systems. Here is a classification of CIPA within the HSAN classification system:

HSAN I: This subtype is known as hereditary sensory neuropathy type I. It is characterized by early-onset progressive sensory loss, particularly affecting pain and temperature sensation. Motor function is typically preserved, and individuals may have a normal life expectancy.

HSAN II: Also referred to as hereditary sensory and autonomic neuropathy type II, this subtype is characterized by impaired pain and temperature sensation, as well as autonomic dysfunction. Features may include gastrointestinal and urinary abnormalities, lack of sweating, and orthostatic hypotension.

HSAN III: Hereditary sensory and autonomic neuropathy type III, also known as familial dysautonomia (FD), is a distinct subtype characterized by severe autonomic dysfunction. Individuals with FD experience multiple symptoms, including insensitivity to pain, impaired temperature regulation, gastrointestinal dysfunction, cardiovascular abnormalities, and other autonomic dysfunctions.

HSAN IV: Congenital insensitivity to pain with anhidrosis (CIPA) falls under this classification. It is characterized by the absence of pain sensation, inability to sweat (anhidrosis), and impaired temperature regulation. Motor and cognitive development is typically normal, but individuals are at high risk of injuries due to the inability to perceive pain.

HSAN V: Hereditary sensory and autonomic neuropathy type V is a rare subtype characterized by early-onset sensory loss, especially affecting pain and temperature sensation. It is often associated with mutations in the NGF (nerve growth factor) or NTRK1 (neurotrophic tyrosine kinase receptor 1) genes.

It's important to note that there may be additional subtypes or variations within the HSAN classification system as new genetic discoveries are made and our understanding of these disorders evolves. Genetic testing and consultation with a healthcare professional experienced in neurogenetics are essential for accurate diagnosis and classification of individuals with congenital insensitivity to pain with anhidrosis or other HSANs.

Symptom and sign in Congenital insensitivity to pain with anhidrosis

Congenital insensitivity to pain with anhidrosis (CIPA), also known as hereditary sensory and autonomic neuropathy type IV (HSAN IV), is characterized by a unique combination of symptoms and signs related to the sensory and autonomic nervous

systems. Here are some of the main symptoms and signs observed in individuals with CIPA:

Insensitivity to Pain: The hallmark feature of CIPA is the inability to perceive pain. Individuals with CIPA do not experience the sensation of pain in response to physical injury, such as cuts, burns, or fractures. This insensitivity to pain can lead to frequent injuries, often without the affected individual being aware of them.

Anhidrosis (Lack of Sweating): CIPA also involves the inability to sweat or regulate body temperature effectively. Sweating plays a crucial role in cooling the body during physical exertion or exposure to heat. In individuals with CIPA, the sweat glands do not function properly, which can result in difficulty in regulating body temperature and increased risk of overheating.

Impaired Temperature Sensation: Besides the lack of sweating, individuals with CIPA may have difficulty perceiving changes in temperature. They may not be able to sense extremes of hot or cold and may not respond appropriately to temperature variations in the environment.

Oral and Dental Problems: CIPA can also affect the oral cavity, leading to dental abnormalities such as delayed tooth eruption, dental caries (cavities), and gum infections. These issues can be due to repeated injuries to the mouth and a lack of pain sensation, which may prevent early detection and appropriate dental care.

Autonomic Dysfunction: In addition to the sensory symptoms, autonomic dysfunction is often observed in CIPA. Autonomic nerves control various involuntary bodily functions, including digestion, heart rate, blood pressure, and bladder function. Individuals with CIPA may experience gastrointestinal problems, cardiovascular abnormalities, and urinary dysfunction.

Delayed Motor Milestones: Some individuals with CIPA may experience delays in motor milestones, such as sitting, standing, and walking. These delays may be due to a lack of pain sensation, which can impact the development of protective reflexes and discourage exploration and physical activities.

It's important to note that the severity and specific manifestations of CIPA can vary among affected individuals. While insensitivity to pain and anhidrosis are consistent features, the presence and severity of other symptoms can differ. Proper medical evaluation and diagnosis by healthcare professionals with expertise in rare genetic disorders are crucial for accurate identification and management of individuals with CIPA.

Image study in Congenital insensitivity to pain with anhidrosis

Imaging studies are not typically used as diagnostic tools for Congenital insensitivity to pain with anhidrosis (CIPA). However, imaging techniques may be employed in

certain cases to assess associated complications or to rule out other potential causes of symptoms. Here are some imaging modalities that may be utilized in the evaluation of individuals with CIPA:

X-ray: X-ray imaging can be useful in assessing skeletal abnormalities or injuries, such as fractures or bone deformities, which may go unnoticed due to the lack of pain sensation. X-rays can help identify any skeletal abnormalities that may be contributing to the individual's symptoms or complications.

Magnetic Resonance Imaging (MRI): MRI scans may be performed to evaluate specific aspects related to CIPA. For example, MRI of the brain may be conducted to investigate any structural abnormalities or developmental issues that could be associated with the condition. Additionally, spinal MRI may be utilized to assess the spinal cord and surrounding structures for any anomalies.

Ultrasound: Ultrasound imaging may be employed in cases where there are concerns about specific organ systems. For instance, abdominal ultrasound can be used to assess the kidneys for any abnormalities, such as renal cysts or tumors. Ultrasound may also be used to evaluate the heart for any structural or functional abnormalities. It's important to note that imaging studies are usually performed based on the individual's specific clinical presentation, symptoms, and suspected complications. The choice of imaging modality will depend on the areas of concern and the information needed to guide further evaluation or treatment. The primary focus in CIPA management is on clinical assessment, genetic testing, and addressing the symptoms and complications associated with the condition.

Genetic mutation in Congenital insensitivity to pain with anhidrosis

Congenital insensitivity to pain with anhidrosis (CIPA), also known as hereditary sensory and autonomic neuropathy type IV (HSAN IV), is caused by mutations in the neurotrophic tyrosine kinase receptor 1 (NTRK1) gene. These mutations disrupt the normal functioning of the NTRK1 gene, leading to the development of CIPA.

The NTRK1 gene provides instructions for producing a protein called TrkA (tyrosine kinase receptor A). TrkA is a receptor protein that plays a crucial role in the development, survival, and function of sensory and sympathetic neurons. It is involved in transmitting signals from nerve growth factor (NGF) to the neurons, which are essential for the proper development and functioning of the sensory and autonomic nervous systems.

In CIPA, various mutations can occur in the NTRK1 gene, leading to a loss of function or abnormal function of the TrkA protein. These mutations can affect the binding ability of TrkA to NGF or interfere with the activation of signaling pathways that are necessary for the normal development and maintenance of sensory and

autonomic neurons.

The inheritance pattern of CIPA is autosomal recessive, meaning that an individual must inherit two copies of the mutated NTRK1 gene (one from each parent) to develop the condition. If an individual inherits only one copy of the mutated gene, they are considered carriers and typically do not exhibit symptoms of CIPA but can pass on the gene to their offspring.

Genetic testing is available to detect mutations in the NTRK1 gene and confirm a diagnosis of CIPA. Identifying the specific genetic mutation in an individual with CIPA can help provide accurate genetic counseling and inform the management and treatment strategies for the condition.

It's important to note that while mutations in the NTRK1 gene are the primary cause of CIPA, there may be rare cases where individuals with clinical features of CIPA do not have identifiable mutations in the NTRK1 gene. This suggests the possibility of involvement of other genes or genetic factors that contribute to the development of the condition. Ongoing research is being conducted to further understand the genetic basis of CIPA and identify any additional genetic factors involved.

Mitochondrial dysfunction in Congenital insensitivity to pain with anhidrosis

Congenital insensitivity to pain with anhidrosis (CIPA), also known as hereditary sensory and autonomic neuropathy type IV (HSAN-IV), is a rare genetic disorder characterized by the inability to feel pain, impaired temperature regulation, and absence of sweating (anhidrosis). While mitochondrial dysfunction has not been directly implicated in CIPA, the condition is primarily caused by mutations in the NTRK1 gene.

The NTRK1 gene provides instructions for producing a protein called TrkA, which is involved in the development and survival of nerve cells. Mutations in the NTRK1 gene can disrupt the normal function of TrkA, leading to abnormal nerve development and function. This ultimately results in the loss of pain and temperature sensation, as well as the inability to sweat.

While mitochondrial dysfunction may not be a primary feature of CIPA, it is worth noting that mitochondrial abnormalities can potentially contribute to the overall pathogenesis of neurodegenerative disorders. However, further research is needed to determine the precise role of mitochondrial dysfunction in CIPA.

Treatment in Congenital insensitivity to pain with anhidrosis

Congenital insensitivity to pain with anhidrosis (CIPA), also known as hereditary sensory and autonomic neuropathy type IV (HSAN IV), is a rare genetic disorder for which there is currently no cure. The treatment approach for individuals with CIPA

focuses on managing symptoms, preventing complications, and ensuring the safety and well-being of the affected individuals. Here are some key aspects of the treatment for CIPA:

Pain Management: Since individuals with CIPA cannot feel pain, they are prone to injuries and may not be aware of wounds or fractures. Caregivers and medical professionals play a crucial role in monitoring and managing any injuries or complications promptly. Regular check-ups and wound care are important to prevent infections and promote healing.

Temperature Regulation: Individuals with CIPA have impaired temperature regulation and cannot sweat, which can lead to overheating. It's important to avoid exposure to extreme temperatures, both hot and cold. Maintaining a comfortable environment and using cooling devices or techniques, such as fans and cooling vests, can help regulate body temperature.

Dental and Oral Care: Regular dental check-ups and oral hygiene are essential for individuals with CIPA. Since they cannot feel pain, routine dental care is crucial to detect and address dental issues, such as cavities or gum infections, in a timely manner.

Protective Measures: Due to the lack of pain sensation, individuals with CIPA need to take extra precautions to avoid injuries. This may involve wearing protective gear, such as helmets or kneepads, and using assistive devices to ensure safety during physical activities.

Supportive Therapies: Occupational and physical therapies can be beneficial in promoting motor development, coordination, and independence in individuals with CIPA. These therapies can help improve functional abilities and enhance overall quality of life.

Genetic Counseling: Genetic counseling is an important aspect of CIPA management, especially for affected individuals and their families. Genetic counselors can provide information about the inheritance pattern, recurrence risks, and family planning options. They can also connect families with support groups and resources for coping with the challenges associated with CIPA.

It's essential for individuals with CIPA to receive comprehensive and multidisciplinary care from healthcare professionals experienced in managing rare genetic disorders. The treatment plan should be tailored to the specific needs of each individual, and regular follow-ups are important to monitor any potential complications and adjust the management strategies accordingly.

9. Dravet Syndrome (DS)(Dravet 症候群)

History of Dravet Syndrome

Dravet Syndrome, also known as Severe Myoclonic Epilepsy of Infancy (SMEI), was first described by Dr. Charlotte Dravet, a French pediatrician, in the 1970s. Dr. Dravet initially observed a group of children with severe, treatment-resistant seizures that began during the first year of life. She noted that these seizures were often triggered by fever and were accompanied by other developmental and neurological abnormalities.

In her initial research and subsequent studies, Dr. Dravet identified a distinct clinical picture and pattern of seizures in these children. She described prolonged seizures (status epilepticus) lasting for more than 30 minutes, myoclonic seizures (brief muscle jerks), atypical absence seizures, and generalized tonic-clonic seizures. Dr. Dravet also noticed that these seizures were often refractory to standard antiepileptic medications, making them difficult to control.

Over the years, further research has expanded our understanding of Dravet Syndrome. In 2001, mutations in the SCN1A gene were identified as the primary cause of the syndrome. The SCN1A gene provides instructions for producing a protein called sodium channel alpha-1 subunit, which is involved in the normal functioning of sodium channels in the brain. Mutations in this gene disrupt the function of sodium channels, leading to abnormal electrical activity and seizures.

Since its initial description, Dravet Syndrome has been recognized as a rare and severe form of epilepsy. It typically presents in the first year of life, with seizures becoming more frequent and severe over time. Children with Dravet Syndrome often experience developmental delays, cognitive impairment, and behavioral challenges. They may also have other medical issues such as sleep disturbances, growth problems, and an increased risk of sudden unexpected death in epilepsy (SUDEP). While there is currently no cure for Dravet Syndrome, ongoing research and advancements in treatment have improved the management of the condition. Early diagnosis, seizure control with antiepileptic medications, and comprehensive care from a multidisciplinary team are key in optimizing the quality of life for individuals with Dravet Syndrome.

Classification of Dravet Syndrome

Dravet Syndrome is classified as a rare and severe form of epilepsy. It falls under the category of developmental and epileptic encephalopathies, which are a group of disorders characterized by early-onset seizures and cognitive and developmental impairments. Specifically, Dravet Syndrome is classified as an ion channelopathy, a

type of genetic disorder that affects the functioning of ion channels in the brain. The primary classification of Dravet Syndrome is based on its clinical features and genetic cause:

Clinical Classification:

Seizure Onset: Dravet Syndrome typically manifests in the first year of life, with seizures often starting before 6 months of age.

Seizure Types: Dravet Syndrome is characterized by a variety of seizure types, including prolonged seizures (status epilepticus), myoclonic seizures (brief muscle jerks), atypical absence seizures, and generalized tonic-clonic seizures.

Seizure Triggers: Seizures in Dravet Syndrome are often triggered by fever or elevated body temperature.

Seizure Resistance: Seizures in Dravet Syndrome are typically resistant to common antiepileptic medications, making them challenging to control.

Genetic Classification:

Genetic Cause: Dravet Syndrome is primarily caused by mutations in the SCN1A gene, which provides instructions for producing a protein called sodium channel alpha-1 subunit. These mutations disrupt the function of sodium channels in the brain, leading to abnormal electrical activity and seizures. However, not all cases of Dravet Syndrome are associated with SCN1A mutations, and other genes may also be involved in a smaller subset of individuals.

It's important to note that the classification of Dravet Syndrome may continue to evolve as our understanding of the condition advances. Ongoing research and genetic testing are helping to identify additional genetic causes and subtypes of the syndrome, leading to a more precise classification and personalized treatment approaches.

Symptom and sign in Dravet Syndrome

Dravet Syndrome is characterized by a range of symptoms and signs that typically become evident during the first year of life. The following are the common features observed in individuals with Dravet Syndrome:

Seizures: Dravet Syndrome is primarily associated with seizures, which are often severe and difficult to control. The seizures typically begin in infancy, frequently occurring within the first year of life. They may be triggered by fever (febrile seizures) or fever-related illnesses. The types of seizures seen in Dravet Syndrome include:

Prolonged Seizures: These seizures, known as status epilepticus, can last for extended periods, requiring emergency medical intervention.

Myoclonic Seizures: These seizures involve brief muscle jerks or twitches, which may affect the arms, legs, or other parts of the body.

Generalized Tonic-Clonic Seizures: These seizures involve loss of consciousness, stiffening of the body (tonic phase), and subsequent rhythmic jerking of the limbs (clonic phase).

Atypical Absence Seizures: These seizures are characterized by brief periods of altered awareness, where the individual may appear to be staring into space.

Developmental and Cognitive Impairment: Children with Dravet Syndrome often experience developmental delays and intellectual disability. This can manifest as delayed motor milestones, speech and language difficulties, learning challenges, and cognitive impairments.

Movement and Balance Problems: Many individuals with Dravet Syndrome have difficulties with movement and coordination. They may experience muscle stiffness (spasticity) or have problems with balance and coordination (ataxia). These motor impairments can affect their ability to walk independently.

Behavioral and Psychiatric Issues: Individuals with Dravet Syndrome may exhibit behavioral problems, such as hyperactivity, impulsivity, and aggression. They may also have difficulties with social interaction and communication skills.

Sleep Disturbances: Sleep disturbances are common in Dravet Syndrome, including disrupted sleep patterns, insomnia, or excessive sleepiness.

It's important to note that the severity and specific combination of symptoms can vary among individuals with Dravet Syndrome. Early diagnosis and comprehensive management by a multidisciplinary team are essential to address the various challenges associated with the condition.

Image study in Dravet Syndrome

Image studies, such as neuroimaging techniques, are often conducted in individuals with Dravet Syndrome to evaluate brain structure and function. These imaging studies can help in the diagnosis and management of the condition. While there is no specific imaging finding that confirms Dravet Syndrome, certain abnormalities may be observed in some individuals. These may include:

Magnetic Resonance Imaging (MRI): MRI scans of the brain are commonly performed in individuals with Dravet Syndrome. Although the findings are typically nonspecific, some individuals may show structural abnormalities, such as cortical atrophy (thinning of the outer layer of the brain), reduced white matter volume, or abnormalities in specific brain regions.

Electroencephalogram (EEG): EEG is a test that measures the electrical activity of the brain. It is a key diagnostic tool for evaluating seizures and epileptic activity in Dravet Syndrome. EEG findings in individuals with Dravet Syndrome often show characteristic patterns, including slow background activity, multifocal or generalized

epileptiform discharges, and focal or generalized slowing of brain waves.

Positron Emission Tomography (PET) Scan: PET scans can provide information about brain metabolism and blood flow. In some cases, PET scans may reveal abnormalities in specific brain regions or changes in glucose metabolism associated with seizures in Dravet Syndrome.

Single-Photon Emission Computed Tomography (SPECT) Scan: SPECT scans involve injecting a radioactive substance into the bloodstream to assess blood flow and brain activity. SPECT scans may show areas of abnormal blood flow or perfusion, which can help identify regions of the brain affected by seizures.

It's important to note that while these imaging studies can provide valuable information, the diagnosis of Dravet Syndrome is primarily based on clinical features, including the presence of characteristic seizures and associated developmental and cognitive impairments. Imaging findings, along with genetic testing and other diagnostic evaluations, help support the diagnosis and guide treatment strategies.

Genetic mutation in Dravet Syndrome

Dravet Syndrome is primarily caused by mutations in the SCN1A gene, which is responsible for producing a protein called sodium channel alpha subunit type 1 (Nav1.1). These mutations lead to dysfunction of the sodium channels in the brain, which play a crucial role in controlling the excitability of neurons and regulating the transmission of electrical signals.

The majority of Dravet Syndrome cases (around 70-80%) are associated with de novo mutations, which means the mutation occurs spontaneously and is not inherited from the parents. In rare cases, Dravet Syndrome can be inherited in an autosomal dominant manner, with affected individuals inheriting the mutated SCN1A gene from an affected parent.

Other rare genetic mutations have also been implicated in a small percentage of Dravet Syndrome cases. These include mutations in other genes such as SCN2A, SCN1B, SCN9A, and PCDH19, among others. However, mutations in SCN1A remain the most common and well-established genetic cause of Dravet Syndrome.

It's important to note that not all individuals with Dravet Syndrome will have an identifiable genetic mutation, as some cases may be caused by genetic changes that are currently unknown or cannot be detected by standard genetic testing methods. Ongoing research continues to uncover additional genetic factors that may contribute to the development of Dravet Syndrome.

Mitochondrial dysfunction in Dravet Syndrome

Dravet Syndrome, also known as severe myoclonic epilepsy of infancy (SMEI), is a

rare and severe form of epilepsy that typically begins in infancy. While the primary cause of Dravet Syndrome is mutations in the SCN1A gene, which encodes a sodium channel in the brain, mitochondrial dysfunction has also been observed in some individuals with the condition.

Research studies have shown that mitochondrial dysfunction, including impaired energy production and oxidative stress, may play a role in the pathogenesis of Dravet Syndrome. Mitochondria are responsible for generating energy in the form of adenosine triphosphate (ATP) through oxidative phosphorylation. Dysfunction in the mitochondria can lead to decreased energy production and impaired cellular function, which may contribute to the development and progression of epilepsy.

The exact mechanisms linking mitochondrial dysfunction to the development of Dravet Syndrome are not fully understood. However, studies have suggested that mitochondrial dysfunction may exacerbate neuronal hyperexcitability and increase susceptibility to seizures. Additionally, mitochondrial dysfunction can further contribute to oxidative stress and inflammation, which are believed to play a role in the progression of the disease.

It is important to note that while mitochondrial dysfunction has been observed in some individuals with Dravet Syndrome, it is not a universal feature of the condition. The primary cause of Dravet Syndrome is still attributed to the mutations in the SCN1A gene. Nevertheless, understanding the potential involvement of mitochondrial dysfunction in Dravet Syndrome may offer insights into novel therapeutic strategies for managing the condition.

Treatment in Dravet Syndrome

The treatment of Dravet Syndrome aims to reduce seizures and improve overall quality of life for individuals with the condition. It typically involves a multidisciplinary approach involving medical management, seizure control, supportive therapies, and lifestyle modifications. Here are some commonly employed treatment strategies:

Antiepileptic Medications: The primary goal of drug treatment is to reduce the frequency and severity of seizures. Sodium channel blockers such as clobazam, valproate, stiripentol, and topiramate are often prescribed to control seizures in Dravet Syndrome. However, individual responses to medications may vary, and a trial-and-error process may be necessary to find the most effective drug regimen.

Seizure Rescue Medications: In some cases, emergency medications such as rectal diazepam or buccal midazolam may be prescribed to halt prolonged or cluster seizures.

Ketogenic Diet: A ketogenic diet, which is high in fats and low in carbohydrates, has

shown promising results in reducing seizures in Dravet Syndrome. It is typically initiated under the guidance of a dietitian and monitored closely by a medical team.

Vagus Nerve Stimulation (VNS): VNS is a surgical procedure where a device is implanted to stimulate the vagus nerve. It can help reduce seizure frequency and severity in some individuals with Dravet Syndrome.

Physical and Occupational Therapy: These therapies can help address motor and developmental delays, improve muscle strength and coordination, and support overall physical and functional abilities.

Speech and Language Therapy: Communication difficulties are common in Dravet Syndrome, and speech therapy can help individuals improve their speech and language skills.

Behavioral and Educational Support: Psychological and behavioral interventions, as well as educational support, are crucial in helping individuals with Dravet Syndrome manage challenges related to cognitive development, behavior, and social interactions.

It's important to note that treatment plans for Dravet Syndrome are highly individualized, and a comprehensive evaluation by a healthcare team experienced in the management of epilepsy and neurological disorders is essential. Regular follow-up visits are necessary to monitor treatment effectiveness, make necessary adjustments, and provide ongoing support for both the individual with Dravet Syndrome and their caregivers.

10. Familial Amyloidotic Polyneuropathy(家族性澱粉樣多發性神經病變)

History of Familial Amyloidotic Polyneuropathy

Familial Amyloidotic Polyneuropathy (FAP), also known as hereditary transthyretin amyloidosis, is a rare genetic disorder characterized by the deposition of abnormal amyloid protein in various tissues of the body, particularly in the peripheral nerves. It was first described in the medical literature in the 1950s.

The history of FAP dates back to the early 20th century when Portuguese neurologist Corino de Andrade first observed and studied the disease in families from northern Portugal. He noticed a pattern of progressive peripheral neuropathy affecting multiple family members across generations, with symptoms such as sensory loss, motor weakness, and autonomic dysfunction. He initially named the condition "corino" after himself but later changed it to familial amyloidotic polyneuropathy to reflect the characteristic amyloid deposition seen in affected individuals.

Further studies and investigations revealed that FAP is an inherited disorder with an autosomal dominant pattern of inheritance. It was found to be associated with mutations in the transthyretin (TTR) gene, which codes for a protein involved in the transport of thyroid hormone and retinol-binding protein.

Over the years, researchers have identified more than 100 different mutations in the TTR gene that can lead to FAP. These mutations affect the stability of the transthyretin protein, causing it to misfold and aggregate into amyloid fibrils. The amyloid fibrils then accumulate in various tissues, including peripheral nerves, heart, kidney, and gastrointestinal tract, leading to progressive damage and dysfunction. FAP has been predominantly observed in certain geographic regions, such as Portugal, Japan, and Sweden, where specific mutations are more prevalent. However, cases have been reported worldwide, and the disease can affect individuals of any ethnic background.

Advances in genetic testing and molecular diagnostics have improved the identification and understanding of FAP. Today, it is recognized as a systemic disorder with diverse clinical manifestations, including peripheral neuropathy, cardiac involvement, gastrointestinal disturbances, and renal dysfunction. The disease is progressive and often leads to significant disability and reduced life expectancy. Treatment options for FAP have evolved over time, including liver transplantation, which has shown to halt or slow down the progression of the disease by replacing the faulty TTR protein with normal protein produced by the transplanted liver. Additionally, there are emerging therapies, such as RNA interference (RNAi) and

gene silencing techniques, that aim to reduce the production of abnormal TTR protein. Research continues to explore novel therapeutic approaches and improve the understanding of the underlying mechanisms of FAP. Efforts are also focused on genetic counseling and early diagnosis to facilitate timely intervention and management of the disease.

Classification of Familial Amyloidotic Polyneuropathy

Familial Amyloidotic Polyneuropathy (FAP), also known as hereditary transthyretin amyloidosis, can be classified based on several factors, including the genetic mutation involved, clinical presentation, and anatomical distribution of amyloid deposition. Here are some common classification approaches used for FAP:

Genetic Mutation:

- a. ATTR Val30Met: This is the most common mutation associated with FAP, particularly in certain geographic regions such as Portugal, Japan, and Sweden. It refers to a substitution of valine (Val) with methionine (Met) at position 30 of the transthyretin protein.
- b. Non-Val30Met Mutations: There are over 100 different mutations identified in the transthyretin (TTR) gene that can cause FAP. These non-Val30Met mutations can result in varying clinical phenotypes and disease severity.

Clinical Presentation:

- a. Classical FAP: This refers to the typical presentation of FAP with peripheral neuropathy as the predominant feature. Symptoms usually start in the lower limbs and progress upwards, affecting both sensory and motor functions.
- b. Late-Onset FAP: This subtype presents later in life, typically after the age of 50, and may have a milder disease course compared to classical FAP.
- c. Cardiac Variant FAP: Some individuals with FAP primarily present with cardiac involvement, including restrictive cardiomyopathy, heart failure, arrhythmias, and conduction abnormalities.
- d. Ocular Variant FAP: This subtype primarily affects the eyes, leading to vitreous opacities, glaucoma, and other ophthalmologic abnormalities.

Anatomical Distribution of Amyloid Deposition:

- a. Neuropathic FAP: In this form, amyloid deposits predominantly accumulate in the peripheral nerves, leading to sensory and motor deficits.
- b. Cardiac FAP: Amyloid deposits are primarily found in the heart, resulting in cardiac dysfunction and related symptoms.
- c. Mixed FAP: This subtype involves amyloid deposition in both peripheral nerves and cardiac tissues, leading to a combination of neurological and cardiac manifestations.

It is important to note that these classification systems may overlap, and individuals with FAP can exhibit a wide range of symptoms and disease severity. Genetic testing and a comprehensive clinical evaluation are essential for accurate diagnosis and classification of FAP. The specific mutation and clinical subtype of FAP can influence the management and treatment strategies for affected individuals.

Symptom and sign in Familial Amyloidotic Polyneuropathy

Familial Amyloidotic Polyneuropathy (FAP) is characterized by the deposition of abnormal amyloid protein in various tissues, particularly in the peripheral nerves. The symptoms and signs of FAP can vary depending on the genetic mutation involved, disease stage, and individual factors. Here are some common symptoms and signs associated with FAP:

Peripheral Neuropathy:

Sensory disturbances: Patients may experience numbness, tingling, or a loss of sensation in the extremities, typically starting in the lower limbs and progressing upwards.

Motor dysfunction: Weakness and muscle wasting can occur, leading to difficulties with coordination, walking, and performing fine motor tasks.

Autonomic dysfunction: Impaired autonomic nerve function can manifest as orthostatic hypotension (low blood pressure upon standing), gastrointestinal disturbances, bladder dysfunction, and sexual dysfunction.

Cardiac Involvement:

Cardiomyopathy: FAP can affect the heart, leading to the thickening and stiffening of the cardiac muscle (restrictive cardiomyopathy). This can result in symptoms such as shortness of breath, fatigue, palpitations, and heart failure.

Arrhythmias: Irregular heart rhythms, including atrial fibrillation, ventricular arrhythmias, and conduction abnormalities, may occur.

Ocular Manifestations:

Vitreous opacities: Deposits of amyloid in the eyes can cause clouding of the vitreous humor, leading to impaired vision and visual disturbances.

Glaucoma: Increased intraocular pressure can develop, potentially resulting in vision loss if left untreated.

Gastrointestinal Involvement:

Gastrointestinal disturbances: FAP can affect the gastrointestinal tract, leading to symptoms such as diarrhea, constipation, and malabsorption.

Swallowing difficulties: Dysphagia (difficulty swallowing) may occur due to muscle weakness and dysfunction.

Renal Involvement:

Kidney dysfunction: In some cases, amyloid deposits can affect the kidneys, leading to proteinuria (presence of excess protein in the urine), renal insufficiency, and eventually renal failure.

It's important to note that the symptoms and signs of FAP can progress over time, and the severity and specific manifestations may vary among individuals. Early recognition and diagnosis are crucial for appropriate management and treatment of FAP. A thorough clinical evaluation, including genetic testing and specialized assessments, is typically required to confirm the diagnosis and guide appropriate care.

Image study in Familial Amyloidotic Polyneuropathy

In Familial Amyloidotic Polyneuropathy (FAP), various imaging studies can be used to aid in the diagnosis and assessment of the disease. Here are some imaging modalities commonly used in FAP:

Nerve Conduction Studies (NCS) and Electromyography (EMG):

NCS measures the electrical activity and conduction velocity of peripheral nerves, assessing the function of both sensory and motor nerves. Abnormalities in nerve conduction can indicate peripheral neuropathy, a hallmark of FAP.

EMG involves the insertion of fine needle electrodes into muscles to record their electrical activity. It helps evaluate muscle function, detect denervation, and assess the extent of motor nerve involvement in FAP.

Magnetic Resonance Imaging (MRI):

MRI scans can provide detailed images of the brain, spinal cord, and peripheral nerves. In FAP, MRI may be performed to evaluate for any structural abnormalities, such as nerve enlargement or compression, and to rule out other causes of neuropathy.

Cardiac Imaging:

Echocardiography: This non-invasive imaging technique uses ultrasound to assess the structure and function of the heart. It can detect signs of cardiomyopathy, such as thickening of the heart walls or impaired ventricular function.

Cardiac MRI: This advanced imaging modality can provide more detailed information about the heart's structure, function, and tissue characterization. It can help assess the presence and extent of cardiac involvement in FAP.

Ocular Examination:

Ophthalmoscopy: A visual examination of the retina and other structures at the back of the eye can be performed to evaluate for vitreous opacities or other ocular abnormalities associated with FAP.

Optical Coherence Tomography (OCT): This imaging technique uses light waves to create detailed cross-sectional images of the retina. OCT can help assess the integrity and thickness of retinal layers and detect any abnormalities related to FAP.

It's important to note that imaging studies alone cannot confirm a diagnosis of FAP but are used in conjunction with clinical evaluation, genetic testing, and other diagnostic measures. The choice of specific imaging modalities depends on the symptoms, suspected areas of involvement, and individual patient characteristics. The interpretation of imaging findings should be done by qualified medical professionals experienced in the evaluation of FAP.

Genetic mutation in Familial Amyloidotic Polyneuropathy

Familial Amyloidotic Polyneuropathy (FAP) is caused by mutations in the transthyretin (TTR) gene. The TTR gene provides instructions for producing a protein called transthyretin, which is primarily produced in the liver and is involved in the transport of thyroid hormone and retinol (vitamin A).

Mutations in the TTR gene can lead to the production of abnormal transthyretin protein that has a tendency to misfold and aggregate. These protein aggregates, known as amyloid fibrils, accumulate in various tissues throughout the body, including the peripheral nerves, heart, kidneys, and gastrointestinal tract. The deposition of amyloid fibrils in peripheral nerves causes the characteristic neuropathy observed in FAP.

Over 100 different mutations in the TTR gene have been identified as causing FAP. The most common mutation associated with FAP is a substitution of the amino acid valine with methionine at position 30 (V30M mutation). However, other mutations, such as substitutions at position 43 (A43G) and position 60 (L60P), among others, have also been identified.

The specific mutation in the TTR gene can influence the age of onset, rate of disease progression, and the organs affected in FAP. Different mutations may have varying degrees of penetrance and expressivity, leading to a wide range of clinical manifestations among affected individuals and families.

Genetic testing, which involves analyzing a person's DNA, can be performed to identify the specific TTR gene mutation responsible for FAP. This testing can help confirm the diagnosis, determine the inheritance pattern, and guide genetic counseling for affected individuals and their families.

It's worth noting that FAP can also occur sporadically, without a known family history, due to de novo mutations in the TTR gene.

Mitochondrial dysfunction in Familial Amyloidotic Polyneuropathy

Familial Amyloidotic Polyneuropathy (FAP), also known as hereditary transthyretin amyloidosis, is a rare genetic disorder characterized by the accumulation of abnormal amyloid protein deposits in various tissues and organs, including the peripheral nerves. While the primary cause of FAP is mutations in the transthyretin (TTR) gene,

which leads to the production of misfolded TTR protein, mitochondrial dysfunction has been implicated in the pathogenesis of the disease.

Mitochondria are responsible for energy production and maintenance of cellular homeostasis. In FAP, mitochondrial dysfunction has been observed in peripheral nerve tissue affected by amyloid deposition. Studies have shown that the accumulation of misfolded TTR protein in the mitochondria can impair mitochondrial function, leading to decreased energy production and increased oxidative stress. The exact mechanisms by which mitochondrial dysfunction contributes to the development and progression of FAP are not fully understood. However, it is believed that impaired mitochondrial function and oxidative stress can lead to nerve cell damage, inflammation, and cell death, contributing to the neurological symptoms and progressive peripheral neuropathy observed in FAP.

Given the involvement of mitochondrial dysfunction in FAP, researchers have explored potential therapeutic strategies aimed at restoring mitochondrial function and reducing oxidative stress. These include the use of mitochondrial-targeted antioxidants and compounds that enhance mitochondrial biogenesis and function. However, further research is needed to better understand the underlying mechanisms of mitochondrial dysfunction in FAP and to develop effective treatments targeting this aspect of the disease.

Treatment in Familial Amyloidotic Polyneuropathy

The treatment approach for Familial Amyloidotic Polyneuropathy (FAP) aims to manage symptoms, slow disease progression, and improve the patient's quality of life. The specific treatment options may vary depending on the individual's symptoms, disease severity, and the organs involved. Here are some common approaches used in the management of FAP:

Liver Transplantation: Liver transplantation is the most effective treatment for FAP. Since the transthyretin (TTR) protein is primarily produced in the liver, replacing the patient's liver with a healthy donor liver can halt the production of abnormal TTR protein and slow down or prevent further disease progression. Liver transplantation is most effective when performed early in the disease course before significant organ damage has occurred.

TTR Stabilizers: TTR stabilizers are medications that help prevent the misfolding and aggregation of TTR protein, thereby reducing the production of amyloid fibrils. Two drugs approved for the treatment of FAP are Tafamidis and Diflunisal. These medications can slow down disease progression and help improve neurological symptoms and quality of life.

Symptomatic Management: Various symptomatic treatments are used to manage

specific symptoms associated with FAP. These may include:

Pain management: Medications such as analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), or antiepileptic drugs (AEDs) may be prescribed to alleviate pain.

Physical therapy: Physical therapy and rehabilitation programs can help maintain mobility, improve muscle strength, and manage gait abnormalities.

Assistive devices: The use of assistive devices such as braces, orthotics, or mobility aids may be recommended to support mobility and reduce the risk of falls.

Symptomatic treatment for autonomic dysfunction: Medications or lifestyle modifications may be used to manage symptoms related to autonomic dysfunction, such as orthostatic hypotension, gastrointestinal disturbances, and urinary problems.

Supportive Care: Providing supportive care and addressing the individual's specific needs are essential in managing FAP. This may involve nutritional support, psychological support, genetic counseling, and regular monitoring of disease progression.

It's important for individuals with FAP to receive care from a multidisciplinary team of healthcare professionals, including neurologists, geneticists, hepatologists, and other specialists, to ensure comprehensive management and personalized treatment approaches.

11. Hereditary spastic paraplegia(遺傳性痙攣性下身麻痺)

History of Hereditary spastic paraplegia

Hereditary spastic paraplegia (HSP) is a group of genetic disorders characterized by progressive weakness and spasticity (stiffness) in the lower limbs. Here is a brief overview of the history of Hereditary spastic paraplegia:

Early observations: The symptoms of spastic paraplegia were first described in medical literature in the 19th century. Neurologists noticed cases of individuals experiencing progressive stiffness and weakness primarily in the legs, leading to difficulties in walking.

Classification and understanding: In the mid-20th century, researchers began to categorize different types of hereditary spastic paraplegia based on the pattern of inheritance and clinical features. They recognized that HSP could be inherited in an autosomal dominant, autosomal recessive, or X-linked manner. Further studies focused on understanding the underlying genetic and molecular mechanisms involved.

Genetic discoveries: With advancements in genetic research techniques, several genes associated with HSP were identified starting in the 1990s. Mutations in these genes were found to play a role in the development of HSP. To date, over 80 genes have been linked to different types of HSP, with varying inheritance patterns and clinical presentations.

Subtypes and classification updates: As more genetic causes of HSP were discovered, the classification system evolved to incorporate the newly identified subtypes.

Classification is now primarily based on the specific gene mutation involved, allowing for more precise diagnosis and genetic counseling.

Advances in molecular understanding: Over the years, research has focused on unraveling the molecular pathways affected in HSP. This has provided insights into the functions of specific proteins and cellular processes involved in maintaining the health and integrity of the nerve cells in the spinal cord and brain.

Treatment approaches: Currently, there is no cure for HSP, and treatment primarily focuses on managing symptoms and improving quality of life. This may involve physical therapy, assistive devices (e.g., braces, walkers), medications to alleviate spasticity and pain, and supportive care.

It is important to note that research into HSP is ongoing, and new genes associated with the condition continue to be discovered. This expanding knowledge contributes to a better understanding of the disease and the potential for future targeted therapies. It is advisable for individuals with HSP to work closely with healthcare professionals experienced in the management of neurological conditions to receive appropriate medical care and support.

Classification of Hereditary spastic paraplegia

Hereditary spastic paraplegia (HSP) is a heterogeneous group of genetic disorders characterized by progressive spasticity and weakness in the lower limbs.

Classification of HSP is primarily based on the mode of inheritance, clinical features, and the specific gene mutations involved. Here is a general classification of Hereditary spastic paraplegia:

Pure Hereditary Spastic Paraplegia (Pure HSP):

Pure HSP is characterized by spasticity and weakness primarily affecting the lower limbs.

There are no significant additional neurological symptoms or findings.

Pure HSP can be further classified into different types based on the inheritance pattern and specific gene mutations involved.

Complex Hereditary Spastic Paraplegia (Complex HSP):

Complex HSP is characterized by spasticity and weakness in the lower limbs, along with additional neurological symptoms or systemic involvement.

These additional features may include cognitive impairment, ataxia (lack of coordination), seizures, peripheral neuropathy, optic neuropathy, intellectual disability, or other neurological manifestations.

Complex HSP can be associated with various genetic mutations and may have different inheritance patterns.

Spastic Paraplegia with Thin Corpus Callosum (SPG11-related HSP):

SPG11-related HSP is a specific subtype of HSP characterized by spasticity and weakness in the lower limbs, along with thinning of the corpus callosum, which is a structure connecting the two cerebral hemispheres.

This subtype is associated with mutations in the SPG11 gene.

X-Linked Hereditary Spastic Paraplegia (X-Linked HSP):

X-Linked HSP is a subtype of HSP that is inherited in an X-linked recessive manner. It predominantly affects males, although females can be carriers.

X-Linked HSP can be caused by mutations in genes such as SPG1 (L1CAM), SPG2 (PLP1), and others.

Autosomal Dominant Hereditary Spastic Paraplegia (AD-HSP):

AD-HSP is a subtype of HSP that is inherited in an autosomal dominant pattern.

Multiple genes have been associated with AD-HSP, including SPG4 (SPAST), SPG3A (ATL1), SPG6 (NIPA1), and others.

Autosomal Recessive Hereditary Spastic Paraplegia (AR-HSP):

AR-HSP is a subtype of HSP that is inherited in an autosomal recessive pattern.

Several genes have been linked to AR-HSP, including SPG7 (paraplegin), SPG15 (ZFYVE26), SPG21 (MASP1), and others.

It is important to note that the classification of HSP is continually evolving as new genes and subtypes are discovered through genetic research. Genetic testing and counseling are crucial for accurate diagnosis and classification of HSP, as it can help guide patient management and provide information about the inheritance pattern and potential risks to family members.

Symptom and sign in Hereditary spastic paraplegia

Hereditary spastic paraplegia (HSP) is characterized by progressive spasticity and weakness in the lower limbs. The symptoms and signs can vary depending on the specific subtype and individual characteristics, but common features of HSP include:

Spasticity: This is the hallmark symptom of HSP, characterized by increased muscle tone and stiffness in the legs. It can lead to difficulty with walking and a stiff, awkward gait.

Weakness: Muscle weakness, particularly in the lower limbs, is another prominent feature of HSP. It can affect the ability to lift the feet, causing a "foot drop" and making walking challenging.

Hyperreflexia: Increased reflexes, such as exaggerated knee-jerk reflexes (patellar reflex), are commonly observed in HSP.

Clonus: Clonus is a rhythmic, involuntary muscle contraction that occurs in response to stretching. It may be present in HSP, particularly in the ankles.

Muscle atrophy: Over time, the muscles in the lower limbs may become progressively weaker and smaller (atrophy) due to lack of use and motor neuron degeneration.

Gait disturbances: HSP can cause various gait abnormalities, including spastic gait with stiff-legged movements, toe walking, difficulty with balance, and a tendency to fall.

Sensory abnormalities: Some individuals with HSP may experience sensory changes, such as decreased sensitivity to pain, temperature, or vibration.

Urinary symptoms: In some cases, individuals with HSP may experience urinary urgency, frequency, or difficulty with bladder control.

Additional neurological features: Depending on the specific subtype of HSP, individuals may present with additional neurological signs and symptoms, such as cognitive impairment, peripheral neuropathy, optic neuropathy, ataxia (lack of coordination), or seizures.

It's important to note that the severity and progression of symptoms can vary widely among individuals with HSP, even within the same subtype. Some individuals may have a mild form of the condition with minimal disability, while others may experience significant impairment in mobility and daily activities. Genetic testing and clinical evaluation are necessary to confirm the diagnosis and determine the specific

subtype of HSP in each case.

Image study in Hereditary spastic paraplegia

In the diagnosis and evaluation of hereditary spastic paraplegia (HSP), various imaging studies can be helpful in assessing the brain and spinal cord for any structural abnormalities. Here are some imaging modalities commonly used in HSP:

Magnetic Resonance Imaging (MRI): MRI is the most commonly used imaging technique in HSP. It provides detailed images of the brain, spinal cord, and surrounding structures. MRI can help identify any structural abnormalities or lesions that may be contributing to the symptoms. It can also help rule out other conditions with similar presentations.

Spinal Cord Imaging: MRI of the spinal cord specifically focuses on evaluating the spinal cord for any abnormalities or lesions. It can help determine if there is any compression, atrophy, or other structural changes that may be contributing to the spasticity and weakness seen in HSP.

Diffusion Tensor Imaging (DTI): DTI is an advanced MRI technique that evaluates the integrity of white matter tracts in the brain and spinal cord. It can provide information about the microstructural integrity and connectivity of nerve fibers. DTI can be used to assess the integrity of the corticospinal tract, which is often affected in HSP, leading to spasticity and weakness.

Magnetic Resonance Spectroscopy (MRS): MRS is a specialized MRI technique that provides information about the biochemical composition of tissues. It can help evaluate the metabolic changes in the brain and spinal cord in individuals with HSP and provide insights into the underlying pathophysiology.

Computed Tomography (CT) Scan: CT scans are less commonly used in the evaluation of HSP but may be used in specific cases. CT scans provide detailed images of the bony structures and can help assess for any structural abnormalities or changes in the spine.

It's important to note that imaging studies alone cannot definitively diagnose HSP. The diagnosis is typically made based on a combination of clinical symptoms, genetic testing, and imaging findings. Imaging studies play a supportive role in assessing for any structural abnormalities and providing additional information about the extent and location of the affected areas in the brain and spinal cord.

Genetic mutation in Hereditary spastic paraplegia

Hereditary spastic paraplegia (HSP) is a genetically heterogeneous condition, meaning that it can be caused by mutations in various genes. To date, more than 80 different genes have been associated with HSP. These genes play a role in the normal

functioning of neurons, particularly in the development, maintenance, and function of the corticospinal tracts, which are responsible for the motor function of the lower limbs. Here are some of the genes commonly associated with HSP:

SPAST (SPG4): Mutations in the SPAST gene are the most common cause of autosomal dominant HSP. SPG4-related HSP accounts for a significant proportion of cases. The SPAST gene encodes spastin, a protein involved in microtubule dynamics.

ATL1 (SPG3A): Mutations in the ATL1 gene cause autosomal dominant HSP. The ATL1 gene encodes atlastin-1, a protein involved in the fusion of endoplasmic reticulum membranes.

REEP1 (SPG31): Mutations in the REEP1 gene cause autosomal dominant HSP. The REEP1 gene encodes receptor expression-enhancing protein 1, which plays a role in shaping and maintaining the endoplasmic reticulum network.

SPG11: Mutations in the SPG11 gene are associated with autosomal recessive HSP and are often characterized by a complicated form of the disease with additional neurological symptoms. The SPG11 gene is involved in regulating endolysosomal trafficking.

SPG7: Mutations in the SPG7 gene cause a form of autosomal recessive HSP known as SPG7-related HSP. The SPG7 gene encodes paraplegin, which is involved in mitochondrial protein quality control.

SPG15 (ZFYVE26): Mutations in the ZFYVE26 gene cause autosomal recessive HSP. The ZFYVE26 gene is involved in the trafficking and regulation of endosomal compartments.

These are just a few examples of the many genes associated with HSP. Each gene mutation leads to specific alterations in the function and structure of neurons, ultimately resulting in the characteristic symptoms of spasticity and weakness in the lower limbs. Genetic testing is essential for confirming the diagnosis and identifying the specific genetic mutation in an individual with HSP.

Mitochondrial dysfunction in Hereditary spastic paraplegia

Hereditary spastic paraplegia (HSP) is a group of inherited neurological disorders characterized by progressive stiffness and weakness in the lower limbs. While the primary genetic cause of HSP is the mutation in various genes involved in neuronal function and axonal transport, mitochondrial dysfunction has been implicated in the pathogenesis of the disease.

Mitochondria are essential organelles responsible for energy production through oxidative phosphorylation and various cellular processes, including calcium homeostasis and apoptosis. In HSP, mitochondrial dysfunction has been observed in affected neurons and axons. Studies have shown abnormalities in mitochondrial

morphology, impaired mitochondrial dynamics, decreased mitochondrial respiration, and increased oxidative stress in HSP patients.

The exact mechanisms by which mitochondrial dysfunction contributes to the development and progression of HSP are not fully understood. However, it is believed that impaired energy production and increased oxidative stress in affected neurons can lead to axonal degeneration and neuronal cell death, contributing to the characteristic motor symptoms observed in HSP.

Mitochondrial dysfunction in HSP suggests that therapeutic strategies targeting mitochondrial function and reducing oxidative stress could be beneficial. These may include the use of mitochondrial-targeted antioxidants, compounds that enhance mitochondrial biogenesis and function, or approaches aimed at restoring mitochondrial dynamics and quality control.

Further research is needed to better understand the specific molecular mechanisms linking mitochondrial dysfunction to HSP and to develop effective treatments targeting this aspect of the disease.

Treatment in Hereditary spastic paraplegia

Treatment for hereditary spastic paraplegia (HSP) focuses on managing symptoms, improving mobility, and enhancing the quality of life for individuals affected by the condition. While there is currently no cure for HSP, there are various approaches and interventions that can be employed to address specific symptoms and provide support. Here are some treatment options commonly used in HSP:

Physical Therapy: Physical therapy plays a crucial role in managing HSP. It involves exercises and techniques to improve strength, flexibility, balance, and mobility.

Physical therapists can create individualized treatment plans and recommend assistive devices such as braces, walkers, or canes to enhance mobility and reduce the risk of falls.

Occupational Therapy: Occupational therapy focuses on maximizing independence in daily activities. Occupational therapists can provide strategies and adaptive equipment to help individuals with HSP manage activities of daily living, such as dressing, bathing, and eating.

Medications: Medications may be prescribed to manage specific symptoms associated with HSP. For example, muscle relaxants or anti-spasticity medications can help alleviate muscle stiffness and reduce spasticity. Pain medications may also be prescribed to manage any discomfort or pain associated with HSP.

Assistive Devices: Various assistive devices can improve mobility and enhance the quality of life for individuals with HSP. These may include orthotic devices, such as ankle-foot orthoses (AFOs) or knee-ankle-foot orthoses (KAFOs), to provide support

and improve walking ability. Mobility aids like canes, walkers, or wheelchairs may also be recommended based on individual needs.

Genetic Counseling: Genetic counseling is crucial for individuals and families affected by HSP. It can provide information about the specific genetic mutation, inheritance patterns, and the likelihood of passing the condition to future generations. Genetic counselors can offer guidance regarding family planning options and discuss available genetic testing.

Symptomatic Management: Additional therapies may be employed to address specific symptoms associated with HSP. This can include speech therapy for individuals with speech or swallowing difficulties, or psychological support to help individuals and families cope with the emotional and psychological impact of living with a chronic condition.

It's important for individuals with HSP to work closely with a multidisciplinary team of healthcare professionals, including neurologists, physical therapists, occupational therapists, and genetic counselors, to develop a comprehensive treatment plan tailored to their specific needs. Regular monitoring and follow-up appointments are essential to track disease progression and adjust treatment strategies as needed.

12.Huntington disease(又稱 Huntington's chorea) (亨丁頓氏舞蹈症)

History of Huntington disease

Huntington's disease (HD) is a hereditary neurodegenerative disorder that affects the central nervous system. Here is a brief history of the understanding and discovery of Huntington's disease:

1872: George Huntington, an American physician, first described the symptoms and progression of the disease in a medical paper titled "On Chorea" published in the medical journal "The Medical and Surgical Reporter."

1918: A genetic link to Huntington's disease was proposed by a British physician, J. M. S. Pearce, who observed the disease's hereditary nature across generations within families.

1983: A major breakthrough occurred when the genetic marker for Huntington's disease was discovered. A team of scientists led by James Gusella and Marcy MacDonald identified the location of the mutant gene responsible for HD on the short arm of chromosome 4. This finding allowed for genetic testing and confirmed the genetic basis of the disease.

1993: The gene mutation responsible for Huntington's disease was identified. An expanded trinucleotide repeat sequence of CAG (cytosine-adenine-guanine) was found in the huntingtin (HTT) gene. The HTT gene provides instructions for the production of the huntingtin protein, and the expanded CAG repeats lead to the production of a mutated, toxic form of the protein.

1990s-Present: Advances in genetic testing have made it possible to accurately diagnose Huntington's disease and determine an individual's risk of developing the condition by analyzing the number of CAG repeats in the HTT gene.

Research continues to deepen our understanding of the underlying mechanisms of Huntington's disease, including the processes by which the mutant huntingtin protein leads to neurodegeneration. Efforts are focused on developing potential treatments to slow the progression of the disease, alleviate symptoms, and ultimately find a cure. Today, there is no cure for Huntington's disease, and treatment primarily focuses on managing symptoms and providing supportive care. Medications, physical therapy, occupational therapy, speech therapy, and psychological support are often utilized to address the motor, cognitive, and psychiatric symptoms associated with HD. Genetic counseling is crucial for individuals and families affected by Huntington's disease to understand the inheritance pattern and make informed decisions regarding family planning and genetic testing.

Classification of Huntington disease

Huntington's disease (HD) can be classified based on several factors, including the age of onset, the pattern of inheritance, and the clinical features. Here are the main classifications of Huntington's disease:

Age of Onset:

Adult-Onset HD: This is the most common form of HD, where symptoms typically appear between the ages of 30 and 50.

Juvenile-Onset HD: In rare cases, symptoms manifest before the age of 20, known as juvenile-onset HD. This form progresses more rapidly and often has distinct clinical features compared to adult-onset HD.

Pattern of Inheritance:

Autosomal Dominant Inheritance: Huntington's disease is inherited in an autosomal dominant pattern, which means that a child of an affected individual has a 50% chance of inheriting the mutated gene and developing the disease.

Clinical Features:

Motor-Onset HD: This form is characterized by prominent motor symptoms, including chorea (involuntary jerking movements), rigidity, and difficulties with coordination and balance.

Non-Motor-Onset HD: Some individuals may present with primarily non-motor symptoms, such as cognitive impairment, psychiatric disturbances (including depression, anxiety, and irritability), and behavioral changes, before or alongside motor symptoms.

Genetic Classification:

HD with Intermediate Alleles: Some individuals may have an intermediate range of CAG repeats in the HTT gene (between 27 and 35 repeats) that does not cause HD but is associated with a small risk of developing motor symptoms or subtle cognitive changes.

HD-Like Syndromes: There are rare genetic conditions that resemble HD but are caused by mutations in genes other than the HTT gene, such as HDL2 (Huntington's disease-like 2) and HDL4 (Huntington's disease-like 4).

It is important to note that these classifications help in understanding the different presentations and characteristics of Huntington's disease. However, the underlying genetic mutation and clinical manifestations can vary between individuals, leading to a spectrum of symptoms and disease progression. Genetic testing and clinical evaluation play a crucial role in accurately diagnosing and classifying Huntington's disease in affected individuals and their families.

Symptom and sign in Huntington disease

Huntington's disease (HD) is a progressive neurodegenerative disorder that affects

various aspects of an individual's physical, cognitive, and psychiatric functioning. The symptoms and signs of Huntington's disease can be grouped into several categories:

Motor Symptoms:

Chorea: Involuntary, random, and jerky movements, often affecting the face, limbs, and trunk. These movements may appear as twitching or fidgeting.

Rigidity: Stiffness and resistance in muscles, leading to decreased range of motion and difficulties with movement.

Bradykinesia: Slowness of voluntary movements, resulting in delayed or reduced ability to initiate and execute motor tasks.

Impaired Coordination: Difficulties with balance, fine motor skills, and coordination, leading to clumsiness and problems with activities requiring precision.

Cognitive Symptoms:

Memory Impairment: Short-term memory loss and difficulties with recall and retention of information.

Executive Dysfunction: Problems with planning, organizing, decision-making, and problem-solving.

Impaired Attention: Difficulty sustaining attention, focusing, and shifting attention between tasks.

Slowed Thinking: Reduced processing speed and cognitive processing.

Psychiatric Symptoms:

Depression: Persistent feelings of sadness, hopelessness, and loss of interest or pleasure in activities previously enjoyed.

Anxiety: Excessive worry, restlessness, and feelings of unease or fear.

Irritability and Aggression: Frequent mood swings, irritability, outbursts of anger, and aggressive behavior.

Psychosis: Delusions, hallucinations, and impaired perception of reality.

Behavioral Changes:

Social Withdrawal: Decreased interest in social interactions, reduced initiation of social contact, and social isolation.

Apathy: Loss of motivation, lack of interest or enthusiasm in activities, and decreased initiative.

Impulsivity: Difficulty controlling impulses, leading to impulsive actions or behaviors.

Other Symptoms:

Speech and Swallowing Difficulties: Slurred speech, changes in voice quality, problems with articulation, and difficulty swallowing.

Weight Loss: Unintentional weight loss due to increased energy expenditure and difficulties with eating and nutrition.

Sleep Disturbances: Insomnia, disrupted sleep patterns, daytime sleepiness, and increased movement during sleep.

It's important to note that the manifestation and progression of symptoms can vary among individuals with Huntington's disease. The age of onset, rate of disease progression, and specific symptom severity may differ. If you or someone you know is experiencing these symptoms associated with Huntington's disease, it is crucial to seek medical evaluation and genetic testing for an accurate diagnosis and appropriate management.

Image study in Huntington disease

Image studies play an important role in the diagnosis and monitoring of Huntington's disease (HD). Here are the main types of imaging studies used in HD:

Magnetic Resonance Imaging (MRI):

MRI scans provide detailed images of the brain's structure and can detect changes associated with HD.

Atrophy: MRI can reveal shrinkage and loss of volume in specific brain regions, such as the striatum (caudate nucleus and putamen), as the disease progresses.

Enlarged Ventricles: The ventricles, fluid-filled spaces within the brain, may appear enlarged due to the loss of surrounding brain tissue.

White Matter Changes: MRI can detect abnormalities in the white matter tracts, which are responsible for transmitting signals between different brain regions.

Functional MRI (fMRI):

fMRI measures brain activity by detecting changes in blood flow and oxygenation in response to specific tasks or stimuli.

fMRI can help assess brain function in individuals with HD and detect abnormal patterns of activation compared to healthy individuals.

It can provide insights into how different brain regions are affected by the disease and how functional connectivity is altered.

Positron Emission Tomography (PET) Scan:

PET scans use radioactive tracers to measure brain metabolism and blood flow, providing information about brain function.

In HD, PET scans can reveal decreased glucose metabolism in specific brain regions, particularly the striatum and frontal cortex.

PET imaging can also help differentiate HD from other neurodegenerative conditions with similar symptoms.

Single-Photon Emission Computed Tomography (SPECT):

SPECT scans use radioactive tracers to measure blood flow and brain activity.

SPECT imaging can demonstrate reduced blood flow in the striatum and other

affected brain regions in HD.

These imaging studies help in confirming the diagnosis of Huntington's disease, assessing disease progression, and monitoring the effects of potential treatments. They provide valuable information about structural and functional brain changes associated with the disease, aiding in understanding the underlying pathology and guiding patient management. It's important to consult with healthcare professionals who specialize in HD to determine the most appropriate imaging modality and interpretation for each individual case.

Genetic mutation in Huntington disease

Huntington's disease (HD) is caused by a specific genetic mutation in the huntingtin (HTT) gene. The mutation involves an abnormal expansion of a trinucleotide repeat sequence of cytosine-adenine-guanine (CAG) in the HTT gene. The normal range of CAG repeats is between 10 and 35, but in individuals with HD, this repeat sequence expands beyond the normal range.

The expanded CAG repeat leads to the production of an abnormal form of the huntingtin protein, known as mutant huntingtin (mHTT). The mHTT protein has toxic effects on brain cells, particularly in the basal ganglia and cortex, leading to the progressive neurodegeneration observed in HD.

The length of the CAG repeat expansion correlates with the age of onset and severity of HD symptoms. Individuals with fewer than 40 CAG repeats typically have a later onset and milder form of the disease, known as late-onset or adult-onset HD. Those with 40 or more CAG repeats usually have an earlier onset and more severe form of the disease. In rare cases, individuals with 60 or more CAG repeats may develop juvenile-onset HD, which manifests before the age of 20.

The HTT gene mutation follows an autosomal dominant pattern of inheritance. This means that an affected individual has a 50% chance of passing the mutated gene to each of their children. As a result, HD can be inherited from an affected parent or can occur spontaneously due to a new mutation in the HTT gene.

Genetic testing, such as DNA analysis, can detect the presence of the expanded CAG repeat in the HTT gene. This testing is used to confirm the diagnosis of HD, predict the likelihood of developing the disease in at-risk individuals, and provide information for family planning and genetic counseling.

It's important to note that the expansion of the CAG repeat is the primary genetic cause of HD, but other genetic and environmental factors may influence the age of onset and progression of the disease. Ongoing research aims to better understand the mechanisms of the mutation and develop potential treatments to target the underlying genetic defect in Huntington's disease.

Mitochondrial dysfunction in Huntington disease

Huntington's disease (HD) is a genetic neurodegenerative disorder characterized by the progressive loss of neurons in the brain, particularly in the basal ganglia. While the primary cause of HD is a mutation in the huntingtin (HTT) gene, which leads to the production of a mutant huntingtin protein, mitochondrial dysfunction has been implicated in the pathogenesis of the disease.

Studies have demonstrated several mitochondrial abnormalities in HD, including impaired mitochondrial bioenergetics, altered mitochondrial dynamics, disrupted mitochondrial quality control mechanisms, and increased oxidative stress. These dysfunctions are thought to contribute to the neurodegenerative process in HD.

One key aspect of mitochondrial dysfunction in HD is the impaired energy production. Mitochondria play a crucial role in generating adenosine triphosphate (ATP), the energy currency of the cell. In HD, there is a decline in mitochondrial ATP production, which can lead to energy deficits and impaired cellular function.

Mitochondrial dynamics, which involve the processes of mitochondrial fusion, fission, and transport, are also disrupted in HD. Studies have shown abnormalities in mitochondrial morphology and impaired mitochondrial movement in HD cells and animal models. These defects can impair the distribution of healthy mitochondria throughout neurons and compromise cellular function.

Furthermore, increased oxidative stress is observed in HD, which can result from mitochondrial dysfunction. The mutant huntingtin protein and dysfunctional mitochondria generate reactive oxygen species (ROS), leading to oxidative damage to cellular components such as proteins, lipids, and DNA. Oxidative stress can further exacerbate mitochondrial dysfunction and contribute to neuronal degeneration.

While the precise mechanisms linking mitochondrial dysfunction to the pathogenesis of HD are still being investigated, it is clear that restoring mitochondrial function and reducing oxidative stress hold potential as therapeutic strategies. Approaches targeting mitochondrial biogenesis, enhancing mitochondrial quality control mechanisms, and modulating mitochondrial dynamics have shown promise in preclinical studies and may offer avenues for future treatment development.

However, it's important to note that mitochondrial dysfunction is just one aspect of the complex pathology of HD, and additional research is needed to fully understand its contribution to the disease and to develop effective therapeutic interventions.

Treatment in Huntington disease

Currently, there is no cure for Huntington's disease (HD), but there are various treatment approaches aimed at managing the symptoms and improving the quality of life for individuals with the condition. The treatment plan for HD is typically tailored

to the specific needs and symptoms of each patient and may involve a multidisciplinary approach involving neurologists, psychiatrists, physical therapists, occupational therapists, and other healthcare professionals. Here are some common treatment strategies for HD:

Medications:

Tetrabenazine and Deutetrabenazine: These drugs help to reduce chorea, one of the primary motor symptoms of HD, by depleting dopamine in the brain.

Antipsychotic Medications: Certain antipsychotic drugs may be prescribed to help manage psychiatric symptoms, such as psychosis, aggression, and irritability.

Antidepressants and Anxiolytics: These medications can be used to address depression and anxiety symptoms associated with HD.

Physical and Occupational Therapy:

Physical therapy aims to maintain mobility, improve balance, and manage movement difficulties.

Occupational therapy focuses on strategies to maintain independence in daily activities, adapt to changes in motor skills, and enhance quality of life.

Speech and Swallowing Therapy:

Speech therapy helps individuals with HD improve their speech clarity, swallowing abilities, and communication skills as the disease progresses.

Supportive Care:

Nutrition and Diet: A balanced diet and adequate nutrition are essential for maintaining overall health and managing weight loss or swallowing difficulties.

Assistive Devices: Assistive devices, such as mobility aids or adaptive tools, can help individuals with HD maintain independence and perform daily activities more easily.

Psychological and Social Support: HD can have a significant impact on mental health and social well-being. Support groups, counseling, and resources for patients and their families can provide emotional support and coping strategies.

Experimental Therapies:

Several ongoing clinical trials and research studies are investigating potential disease-modifying treatments and symptom management approaches for HD. These may include gene therapies, neuroprotective agents, and targeted therapies aimed at modifying the underlying disease processes.

It is crucial for individuals with HD and their families to work closely with a knowledgeable healthcare team to develop a comprehensive treatment plan that addresses their specific needs. Regular monitoring and adjustments to the treatment approach are typically necessary as the disease progresses. Genetic counseling is also recommended for affected individuals and their families to understand the hereditary aspects of HD and make informed decisions regarding family planning.

13. Infantile-Onset Ascending Hereditary Spastic Paralysis,

IAHSP(嬰兒型上行性遺傳性痙攣性麻痺)

History of Infantile-Onset Ascending Hereditary Spastic Paralysis

Infantile-Onset Ascending Hereditary Spastic Paralysis (IAHSP) is a rare genetic disorder characterized by progressive muscle weakness and stiffness in the lower limbs, leading to difficulty in walking and other motor impairments. Here is a brief overview of the history of IAHSP:

IAHSP was first described in the medical literature in 1893 by a French neurologist named Maurice Londe. He reported a case of a young child with progressive weakness and spasticity in the legs, which started in infancy and gradually progressed upwards to involve the upper limbs and other body parts. Londe referred to the condition as "paraplegie spasmodique ascendante familiale" in French, which translates to "familial ascending spastic paraplegia."

In the following years, several other cases of IAHSP were reported in the medical literature, further expanding the understanding of the clinical features and inheritance pattern of the disease. However, it was not until the late 20th century that the genetic basis of IAHSP was elucidated.

In 1993, a landmark study led by Finkenstedt and colleagues identified the genetic mutation associated with IAHSP. They found that the disease is caused by mutations in the SPG4 gene, also known as the SPAST gene. This gene encodes a protein called spastin, which is involved in the regulation of microtubules in nerve cells. Mutations in the SPG4 gene lead to a dysfunction of spastin, resulting in the characteristic motor impairments seen in IAHSP.

Since the discovery of the genetic mutation, further research has been conducted to understand the underlying mechanisms of IAHSP and to explore potential treatment options. However, there is currently no cure for IAHSP, and treatment mainly focuses on managing the symptoms and improving the quality of life for affected individuals. The history of IAHSP highlights the progress made in understanding the genetic basis of the disease and provides a foundation for ongoing research and the development of potential therapies in the future.

Classification of Infantile-Onset Ascending Hereditary Spastic Paralysis

Infantile-Onset Ascending Hereditary Spastic Paralysis (IAHSP), also known as Strümpell-Lorrain syndrome or Hereditary Spastic Paraplegia type 4 (HSP4), is classified as a subtype of Hereditary Spastic Paraplegia (HSP). HSP is a group of genetic disorders characterized by progressive weakness and spasticity (muscle stiffness) in the lower limbs, resulting from degeneration or dysfunction of the upper

motor neurons.

IAHSP is specifically classified as a pure form of HSP, meaning that it primarily affects the lower limbs without significant involvement of other body systems. It is inherited in an autosomal dominant manner, which means that an affected individual has a 50% chance of passing the condition on to each of their children.

The classification of IAHSP is based on its clinical features, genetic mutation, and mode of inheritance. It is important to note that HSP is a genetically heterogeneous condition, and different subtypes of HSP can have overlapping clinical features.

However, the identification of specific genetic mutations can help in distinguishing between different subtypes.

The most common genetic mutation associated with IAHSP is a mutation in the SPG4 gene, also known as the SPAST gene. Other rare genetic mutations have also been reported in association with IAHSP, such as mutations in the SPG3A, SPG31, and SPG7 genes. These mutations disrupt the normal function of proteins involved in neuronal cell processes, leading to the characteristic motor symptoms observed in IAHSP.

It is important to consult with a medical professional or genetic specialist for a comprehensive evaluation and accurate classification of Infantile-Onset Ascending Hereditary Spastic Paralysis, as further advancements in genetic testing and research may refine the classification in the future.

Symptom and sign in Infantile-Onset Ascending Hereditary Spastic Paralysis

Infantile-Onset Ascending Hereditary Spastic Paralysis (IAHSP), also known as Strümpell-Lorrain syndrome or Hereditary Spastic Paraplegia type 4 (HSP4), is characterized by specific symptoms and signs. These may include:

Progressive spasticity: The hallmark symptom of IAHSP is progressive spasticity, which refers to muscle stiffness and increased muscle tone. This spasticity primarily affects the lower limbs, leading to difficulty with walking, abnormal gait, and increased muscle resistance.

Muscle weakness: Along with spasticity, muscle weakness is a common feature of IAHSP. The weakness typically starts in the lower limbs and may progress to involve the upper limbs as the condition advances. Muscle weakness can contribute to difficulties with mobility and motor coordination.

Babinski sign: The presence of the Babinski sign is a characteristic feature of IAHSP. This sign refers to the upward extension of the big toe and fanning of the other toes when the sole of the foot is stimulated. It is an indication of upper motor neuron dysfunction.

Hyperreflexia: IAHSP often presents with hyperreflexia, which means that the

reflexes, such as the knee-jerk reflex, are exaggerated. This is another manifestation of the dysfunction of the upper motor neurons.

Clonus: Clonus, which is characterized by rhythmic muscle contractions and relaxations, can occur in individuals with IAHSP. It is commonly observed in the ankles and may be elicited by certain movements or stimuli.

Developmental delay: In some cases, individuals with IAHSP may exhibit developmental delay, particularly in motor milestones such as sitting, standing, and walking. The severity of developmental delay can vary among affected individuals. It's important to note that the symptoms and signs of IAHSP can vary in their severity and progression among affected individuals. Additionally, the presence and severity of symptoms can also be influenced by the specific genetic mutation and other individual factors. Consulting with a healthcare professional or genetic specialist is crucial for accurate diagnosis and management of Infantile-Onset Ascending Hereditary Spastic Paralysis.

Image study in Infantile-Onset Ascending Hereditary Spastic Paralysis

Infantile-Onset Ascending Hereditary Spastic Paralysis (IAHSP) is primarily diagnosed based on clinical presentation and genetic testing. However, certain imaging studies can be useful in supporting the diagnosis and assessing the extent of involvement. The following imaging modalities may be used:

Magnetic Resonance Imaging (MRI): MRI is the most commonly used imaging modality for evaluating individuals with suspected IAHSP. It provides detailed images of the brain and spinal cord, allowing for the assessment of structural abnormalities. In IAHSP, MRI may reveal features such as thinning of the corpus callosum (the structure that connects the two hemispheres of the brain), atrophy (shrinkage) of the brain, and abnormalities in the spinal cord.

Diffusion Tensor Imaging (DTI): DTI is an advanced MRI technique that measures the diffusion of water molecules in the brain's white matter tracts. It provides information about the integrity and connectivity of nerve fibers. DTI can be helpful in detecting abnormalities in the white matter tracts associated with IAHSP, such as reduced fiber density or altered fiber orientation.

Electromyography (EMG) and Nerve Conduction Studies (NCS): While not imaging studies per se, EMG and NCS are electrophysiological tests that can be performed to assess the function of nerves and muscles. In IAHSP, these tests may reveal signs of peripheral neuropathy, such as abnormal nerve conduction velocities or muscle denervation.

It's important to note that imaging studies alone are not sufficient to diagnose IAHSP, and they are typically used in conjunction with clinical findings and genetic testing for

a comprehensive evaluation. The specific imaging studies ordered may vary based on the individual's symptoms, clinical presentation, and the preferences of the healthcare provider.

Genetic mutation in Infantile-Onset Ascending Hereditary Spastic Paralysis

Infantile-Onset Ascending Hereditary Spastic Paralysis (IAHSP) is associated with mutations in the ALS2 gene. The ALS2 gene provides instructions for producing the alsin protein, which is involved in the maintenance and function of nerve cells. Mutations in the ALS2 gene disrupt the normal functioning of alsin protein, leading to the development of IAHSP.

IAHSP is inherited in an autosomal recessive manner, which means that an affected individual must inherit two copies of the mutated ALS2 gene, one from each parent. The ALS2 gene mutations in IAHSP can vary in their specific location and effect, leading to some variability in the severity and presentation of the condition.

Genetic testing, such as DNA sequencing or targeted gene panel testing, can be used to detect mutations in the ALS2 gene and confirm the diagnosis of IAHSP. Genetic counseling is also recommended for individuals with a family history of IAHSP or those who are considering having children, as it can provide information about the inheritance pattern and the risk of passing on the condition.

Mitochondrial dysfunction in Infantile-Onset Ascending Hereditary Spastic Paralysis

Infantile-Onset Ascending Hereditary Spastic Paralysis (IAHSP), also known as Strümpell-Lorrain syndrome, is a rare genetic disorder characterized by progressive weakness and spasticity of the lower limbs. While IAHSP primarily involves dysfunction of the upper motor neurons, mitochondrial dysfunction has also been implicated in the disease.

Several studies have reported evidence of mitochondrial abnormalities in IAHSP, suggesting a potential role in the pathogenesis of the condition. These abnormalities include defects in mitochondrial morphology, impaired mitochondrial function, and altered mitochondrial dynamics.

One study identified mitochondrial fragmentation and abnormal distribution in fibroblast cells derived from individuals with IAHSP. These mitochondrial abnormalities could impact the energy production and overall function of the cells. Additionally, alterations in mitochondrial respiratory chain complexes have been observed in IAHSP. These complexes are responsible for generating ATP, the energy currency of the cell. Dysfunction in these complexes can result in energy deficits and compromised cellular function.

Furthermore, disturbances in mitochondrial dynamics, including impaired mitochondrial fusion and fission, have been reported in IAHSP. Proper mitochondrial dynamics are essential for maintaining mitochondrial health and function. Disrupted dynamics can lead to defective mitochondrial turnover and accumulation of damaged mitochondria, further contributing to cellular dysfunction.

The exact mechanisms by which mitochondrial dysfunction contributes to the pathogenesis of IAHSP are not fully understood. It is likely that impaired energy production, increased oxidative stress, and compromised cellular function play a role in the development and progression of the disease.

While there is currently no specific treatment targeting mitochondrial dysfunction in IAHSP, therapies aimed at improving mitochondrial function and reducing oxidative stress may hold potential. These may include approaches such as antioxidant supplementation, promoting mitochondrial biogenesis, and enhancing mitochondrial quality control mechanisms. However, further research is needed to elucidate the specific mitochondrial defects in IAHSP and to develop targeted therapeutic interventions.

Treatment in Infantile-Onset Ascending Hereditary Spastic Paralysis

Unfortunately, there is currently no cure for Infantile-Onset Ascending Hereditary Spastic Paralysis (IAHSP), and treatment focuses on managing the symptoms and providing supportive care. The treatment approach may vary depending on the specific symptoms and needs of the individual.

Some of the treatment options that may be considered for individuals with IAHSP include:

Physical and occupational therapy: These therapies can help improve mobility, muscle strength, and coordination. They may involve exercises, stretching, and assistive devices to enhance functional abilities and independence.

Medications: Certain medications may be prescribed to manage specific symptoms associated with IAHSP, such as muscle stiffness, spasticity, or seizures. These medications may include muscle relaxants, anti-spasticity drugs, or anti-seizure medications, among others.

Assistive devices: Depending on the severity of motor impairments, assistive devices such as braces, splints, orthotics, or wheelchairs may be recommended to improve mobility and support daily activities.

Management of associated conditions: Individuals with IAHSP may have other medical conditions or complications, such as respiratory problems, gastrointestinal issues, or swallowing difficulties. These may require specific management approaches, including medication, dietary modifications, or other interventions.

Multidisciplinary care: Given the complex nature of IAHSPP, a multidisciplinary approach involving a team of healthcare professionals, including neurologists, physical and occupational therapists, speech therapists, and other specialists, may be beneficial in providing comprehensive care and support.

It's important for individuals with IAHSPP to have regular follow-up appointments with their healthcare team to monitor their condition, manage symptoms, and make adjustments to the treatment plan as needed. Genetic counseling may also be helpful in providing information about the condition and addressing any concerns related to inheritance or family planning.

14.Joubert syndrome(Joubert氏症候群(家族性小腦蚓部發育不全))

History of Joubert syndrome

Joubert syndrome is a rare genetic disorder characterized by a specific brain malformation called the "molar tooth sign," which can be seen on brain imaging studies. The syndrome was first described by Marie Joubert and colleagues in 1969. Here is a brief history of Joubert syndrome:

1969: Discovery of Joubert Syndrome

Joubert syndrome was first described by Marie Joubert and colleagues in a French medical journal in 1969. They reported on four siblings who presented with a unique combination of symptoms, including abnormal eye movements, intellectual disability, and the characteristic brainstem and cerebellar malformation.

1984: Expanded Understanding of Joubert Syndrome

In 1984, Maria Joubert and Daniel D'Agostino expanded the understanding of Joubert syndrome by identifying additional clinical features and defining the characteristic "molar tooth sign" on brain imaging studies. The molar tooth sign refers to the shape of the midbrain and hindbrain structures on axial brain imaging, resembling the shape of a molar tooth.

1995: Genetic Basis of Joubert Syndrome

In 1995, the first genetic cause of Joubert syndrome was discovered. The gene AHI1 (Abelson Helper Integration Site 1) was identified as a causative gene in some cases of Joubert syndrome. This finding opened the door to further genetic research and the identification of additional genes associated with the syndrome.

2003-2006: Discovery of More Genes

Between 2003 and 2006, several more genes associated with Joubert syndrome were discovered. These genes include NPHP1, ARL13B, CEP290, RPGRIP1L, TMEM216, and others. These discoveries have provided valuable insights into the underlying molecular mechanisms of Joubert syndrome.

Present: Advances in Research and Clinical Management

In recent years, research on Joubert syndrome has expanded, leading to a better understanding of the genetic and cellular mechanisms involved. Advances in genetic testing techniques have facilitated the identification of additional causative genes. There has also been progress in the clinical management of individuals with Joubert syndrome, including the development of multidisciplinary care teams and the implementation of supportive therapies to address the various symptoms and challenges associated with the condition.

It's important to note that the history of Joubert syndrome is ongoing, with ongoing research and discoveries continuing to deepen our understanding of the syndrome and

improve clinical care for affected individuals.

Classification of Joubert syndrome

Joubert syndrome (JS) is a genetically and clinically heterogeneous disorder. It is classified as a ciliopathy, a group of disorders characterized by dysfunction of cellular structures called cilia. Several classification systems have been proposed for Joubert syndrome based on different criteria, including genetic factors and clinical features.

Here are two commonly used classification systems:

Clinical Classification:

Based on the clinical presentation and associated features, Joubert syndrome is classified into different subtypes. The clinical classification system takes into account the specific symptoms and additional features observed in affected individuals. Some of the recognized subtypes of Joubert syndrome include:

Pure Joubert syndrome (JS): This subtype refers to individuals who meet the diagnostic criteria for Joubert syndrome without any additional major organ involvement or significant developmental delay.

Joubert syndrome with ocular involvement: This subtype includes individuals with Joubert syndrome who have additional eye abnormalities, such as retinal dystrophy, colobomas, or cataracts.

Joubert syndrome with renal involvement: This subtype refers to individuals with Joubert syndrome who also have kidney abnormalities, such as cystic kidney disease or nephronophthisis.

Joubert syndrome with hepatic involvement: This subtype includes individuals with Joubert syndrome who have liver involvement, such as hepatic fibrosis or liver cysts.

Genetic Classification:

Joubert syndrome is genetically heterogeneous, meaning it can be caused by mutations in various genes. Genetic classification of Joubert syndrome involves identifying the specific gene mutations associated with the condition. Some of the genes commonly associated with Joubert syndrome include:

NPHP1

AHI1

CEP290

TMEM216

TMEM67

RPGRI1L

Genetic testing can help determine the underlying genetic cause of Joubert syndrome in an individual, which can provide valuable information for prognosis, genetic counseling, and personalized management.

It's important to note that the classification systems for Joubert syndrome continue to evolve as new genes and clinical features are discovered. Classification can help guide diagnosis, inform prognosis, and aid in clinical management and genetic counseling for affected individuals and their families.

Symptom and sign in Joubert syndrome

Joubert syndrome (JS) is characterized by a distinctive set of symptoms and signs. While the severity and specific features can vary among individuals, there are several common manifestations associated with Joubert syndrome. Here are some of the typical symptoms and signs:

Hypotonia: Infants with Joubert syndrome often present with low muscle tone (hypotonia), which can affect their ability to control their movements and posture. This may lead to floppiness or difficulty with maintaining muscle tone and coordination.

Abnormal Respiratory Patterns: Many individuals with Joubert syndrome exhibit abnormal breathing patterns, such as episodes of rapid breathing (hyperpnea) followed by periods of shallow or irregular breathing (apnea). These breathing irregularities may occur during sleep or wakefulness.

Ataxia: Ataxia refers to a lack of coordination and balance control. People with Joubert syndrome often have difficulty with voluntary movements, including walking, reaching, and fine motor tasks.

Eye Movement Abnormalities: Joubert syndrome is frequently associated with abnormal eye movements, including oculomotor apraxia. This condition affects voluntary control of eye movements, leading to difficulties in tracking objects or controlling eye gaze.

Intellectual Disability: Many individuals with Joubert syndrome experience some degree of intellectual disability. The severity can vary widely, ranging from mild to severe cognitive impairment.

Facial Dysmorphism: Some individuals with Joubert syndrome may exhibit distinctive facial features, such as a prominent forehead, wide-set eyes, and a broad nasal bridge. However, these facial characteristics are not present in all cases.

Kidney and Liver Involvement: Certain subtypes of Joubert syndrome may involve additional organ systems. Kidney abnormalities, such as cystic kidney disease or nephronophthisis, and liver involvement, such as liver fibrosis or liver cysts, can occur in some individuals.

Developmental Delay: Children with Joubert syndrome often experience delays in reaching developmental milestones, such as sitting, crawling, walking, and speaking. It's important to note that the symptoms and signs of Joubert syndrome can vary

among individuals, and not all features may be present in every case. The severity of the condition can also vary, from mild to severe. Early diagnosis, comprehensive medical evaluation, and individualized care management are essential for individuals with Joubert syndrome to optimize their quality of life and provide appropriate support for their specific needs.

Image study in Joubert syndrome

Several imaging studies can be used to support the diagnosis of Joubert syndrome (JS) and visualize the characteristic brain abnormalities associated with the condition.

These imaging techniques help identify the "molar tooth sign," which is a key diagnostic feature of Joubert syndrome. Here are the main imaging studies used in Joubert syndrome:

Magnetic Resonance Imaging (MRI): MRI is the primary imaging modality used in Joubert syndrome. It provides detailed images of the brain structures and helps identify the characteristic features of the molar tooth sign. The molar tooth sign refers to the appearance of the midbrain and hindbrain structures on axial or sagittal MRI images, resembling the shape of a molar tooth. This sign is due to the abnormal development of the cerebellar vermis and the brainstem.

Diffusion Tensor Imaging (DTI): DTI is a specialized MRI technique that measures the movement of water molecules within brain tissues. It provides information about the integrity and connectivity of white matter tracts in the brain. DTI can be used to assess abnormalities in the cerebellar vermis, corpus callosum, and other white matter tracts in individuals with Joubert syndrome.

Magnetic Resonance Spectroscopy (MRS): MRS is an advanced MRI technique that measures the levels of certain chemicals in the brain. It can provide information about brain metabolism and detect any abnormalities in certain metabolites. MRS can be used to evaluate the chemical composition of the brain in Joubert syndrome.

Computed Tomography (CT): CT scans may be used to visualize the brain structures in individuals with Joubert syndrome, particularly in cases where MRI is contraindicated or unavailable. CT scans can provide detailed images of the brain, including the cerebellum, brainstem, and ventricles.

Ultrasonography: In infants with suspected Joubert syndrome, cranial ultrasonography may be performed to evaluate the brain structures. Ultrasonography can provide a preliminary assessment of the cerebellar vermis and other brain abnormalities, although it may not be as detailed as MRI.

These imaging studies, particularly MRI, play a crucial role in the diagnosis of Joubert syndrome by visualizing the characteristic brain abnormalities associated with the condition. They help differentiate Joubert syndrome from other disorders with

similar clinical features and contribute to a comprehensive evaluation of affected individuals.

Genetic mutation in Joubert syndrome

Joubert syndrome (JS) is a genetically heterogeneous disorder, meaning it can be caused by mutations in various genes. To date, mutations in more than 30 genes have been identified as associated with Joubert syndrome. These genes are involved in the structure and function of the primary cilium, a cellular structure essential for normal development and signaling in various organs and tissues.

Here are some of the genes commonly associated with Joubert syndrome:

AHI1 (Abelson Helper Integration Site 1): Mutations in the AHI1 gene are one of the most common causes of Joubert syndrome. The AHI1 gene plays a role in ciliary function and is involved in brain development.

CEP290 (Centrosomal Protein 290): Mutations in the CEP290 gene are also a common cause of Joubert syndrome. The CEP290 gene is important for ciliary structure and function.

TMEM216 (Transmembrane Protein 216): Mutations in the TMEM216 gene are found in a subset of individuals with Joubert syndrome. The TMEM216 gene is involved in ciliary trafficking and signaling.

TMEM67 (Transmembrane Protein 67): Mutations in the TMEM67 gene are associated with Joubert syndrome as well as other ciliopathies. The TMEM67 gene is involved in ciliary assembly and function.

RPGRIP1L (Retinitis Pigmentosa GTPase Regulator-Interacting Protein 1-Like): Mutations in the RPGRIP1L gene have been found in individuals with Joubert syndrome and related disorders. The RPGRIP1L gene is involved in ciliary transport and signaling.

It's important to note that Joubert syndrome can also be caused by mutations in other less common genes, and there may be additional genes yet to be discovered. Genetic testing, such as targeted gene sequencing or whole exome sequencing, can help identify the specific genetic mutation responsible for Joubert syndrome in an affected individual. Understanding the genetic basis of Joubert syndrome is important for accurate diagnosis, prognosis, genetic counseling, and potential future therapeutic interventions.

Mitochondrial dysfunction in Joubert syndrome

Joubert syndrome is a rare genetic disorder characterized by a distinctive brain malformation called the "molar tooth sign," which can be observed on brain imaging studies. While Joubert syndrome primarily affects the development of the cerebellum

and brainstem, mitochondrial dysfunction has also been implicated in the disease. Several studies have reported evidence of mitochondrial abnormalities in Joubert syndrome, suggesting a potential role of mitochondrial dysfunction in its pathogenesis. These abnormalities include impaired mitochondrial morphology, altered mitochondrial function, and disruptions in mitochondrial dynamics. Studies using patient-derived cells and animal models of Joubert syndrome have shown abnormalities in mitochondrial structure and distribution. These abnormalities can impact the energy production and overall function of the cells. Specifically, alterations in mitochondrial cristae morphology, reduced mitochondrial density, and abnormal mitochondrial distribution have been observed. Furthermore, defects in mitochondrial function have been reported in Joubert syndrome. Studies have shown impaired mitochondrial respiration and decreased ATP production in patient-derived cells. These functional deficits can lead to energy deficits and compromised cellular function. Mitochondrial dynamics, including mitochondrial fusion and fission, are crucial for maintaining mitochondrial health and function. Disruptions in mitochondrial dynamics have been observed in Joubert syndrome. Studies have shown abnormalities in proteins involved in mitochondrial fusion and fission, which can result in defective mitochondrial turnover and accumulation of damaged mitochondria. The exact mechanisms by which mitochondrial dysfunction contributes to the pathogenesis of Joubert syndrome are not fully understood. It is likely that impaired energy production, increased oxidative stress, and compromised cellular function play a role in the development and progression of the disease. Although there is currently no specific treatment targeting mitochondrial dysfunction in Joubert syndrome, therapies aimed at improving mitochondrial function and reducing oxidative stress may hold potential. These may include approaches such as antioxidant supplementation, promoting mitochondrial biogenesis, and enhancing mitochondrial quality control mechanisms. However, further research is needed to understand the specific mitochondrial defects in Joubert syndrome and to develop targeted therapeutic strategies.

Treatment in Joubert syndrome

As of my knowledge cutoff in September 2021, there is currently no cure for Joubert syndrome (JS), and treatment focuses on managing the specific symptoms and providing supportive care. The treatment approach for Joubert syndrome involves a multidisciplinary team of healthcare professionals who work together to address the individual needs of each affected person. Here are some aspects of treatment for Joubert syndrome:

Management of Symptoms: Specific symptoms and complications associated with Joubert syndrome, such as breathing abnormalities, movement disorders, and developmental delays, may require targeted interventions. For example, respiratory support may be provided to manage breathing irregularities, physical therapy and assistive devices may be used to improve motor function and mobility, and early intervention programs may be recommended to address developmental delays.

Neurological and Developmental Monitoring: Regular neurological and developmental assessments are important to monitor the progression of the condition, identify any new symptoms or complications, and provide appropriate interventions and support. Close monitoring allows for timely adjustments to treatment plans and early detection of potential issues.

Supportive Care: People with Joubert syndrome may require ongoing supportive care to manage their overall health and well-being. This can include regular check-ups with various specialists, such as neurologists, geneticists, ophthalmologists, and physiotherapists. Supportive care also involves addressing any associated medical conditions, such as kidney or liver abnormalities, through appropriate medical interventions.

Symptomatic Management: Treatment may involve managing specific symptoms and complications associated with Joubert syndrome. For example, medications may be prescribed to alleviate seizures or to control certain movement disorders. Physical and occupational therapy can help improve motor skills and enhance independence.

Early Intervention and Educational Support: Early intervention programs that incorporate physical, occupational, and speech therapy can be beneficial for children with Joubert syndrome to promote their overall development and functional abilities. Educational support, including special education services and individualized educational plans (IEPs), can help optimize learning and academic progress.

It's important to note that treatment approaches may vary depending on the specific needs and challenges of each individual with Joubert syndrome. As research continues to advance, there is hope for potential future therapies targeting the underlying genetic causes of Joubert syndrome. Genetic counseling is also an essential component of treatment to provide families with information about the inheritance pattern and to support family planning decisions. Consulting with a healthcare professional familiar with Joubert syndrome can provide the most up-to-date and individualized treatment recommendations.

15.Kennedy Disease(甘迺迪氏症(脊髓延髓性肌肉萎縮症))

History of Kennedy Disease

Kennedy Disease, also known as spinal and bulbar muscular atrophy (SBMA), is a rare genetic disorder that primarily affects males. Here is a brief history of the discovery and understanding of Kennedy Disease:

1950s: Kennedy Disease was first described by Dr. William R. Kennedy, an American neurologist, in the late 1950s. Dr. Kennedy observed a group of male patients who exhibited a specific set of symptoms, including muscle weakness, atrophy, and twitching, as well as problems with speech and swallowing.

1968: The genetic basis of Kennedy Disease was not understood until several years later. In 1968, Dr. Andrew Engel and his colleagues discovered that the disease was inherited in an X-linked recessive pattern, meaning that the mutated gene responsible for the disorder is located on the X chromosome.

1991: In 1991, the gene responsible for Kennedy Disease was identified and named the androgen receptor (AR) gene. Mutations in the AR gene result in an abnormal expansion of a specific sequence of DNA called the CAG repeat, which leads to the production of a toxic protein that causes damage to motor neurons.

1992: The name "spinal and bulbar muscular atrophy" (SBMA) was introduced as an alternative term for Kennedy Disease to better reflect the characteristic involvement of the spinal cord and the bulbar region (which controls speech and swallowing).

Present: Over the years, our understanding of Kennedy Disease has continued to expand. Advances in genetic testing have allowed for more accurate diagnosis and identification of individuals at risk of developing the disease. Researchers are actively investigating potential treatments and therapies to alleviate symptoms and slow down disease progression.

Kennedy Disease remains a relatively rare condition, and as of now, there is no cure. However, ongoing research and advancements in the field of genetics and neurology hold promise for improved understanding and management of this condition in the future.

Classification of Kennedy Disease

Kennedy Disease, also known as spinal and bulbar muscular atrophy (SBMA), is classified as a neuromuscular disorder. It is specifically categorized under motor neuron diseases, which are a group of disorders that affect the function of motor neurons, the nerve cells responsible for controlling voluntary muscle movement. Within the classification of motor neuron diseases, Kennedy Disease is considered a subtype known as lower motor neuron disease.

Kennedy Disease is characterized by the progressive degeneration and loss of lower motor neurons, which are located in the spinal cord and brainstem. These neurons are responsible for transmitting signals from the brain to the muscles, enabling voluntary movement. The degeneration of motor neurons in Kennedy Disease leads to muscle weakness, atrophy, and various symptoms related to motor dysfunction.

It is important to note that Kennedy Disease primarily affects males, as it is inherited in an X-linked recessive pattern. This means that the mutated gene responsible for the disease is located on the X chromosome. Females can be carriers of the mutated gene but are typically unaffected or may exhibit mild symptoms.

The classification of Kennedy Disease as a motor neuron disease helps distinguish it from other neurological disorders with similar symptoms. However, it is important for healthcare professionals to conduct a thorough evaluation, including genetic testing, to confirm the diagnosis and rule out other potential causes of motor dysfunction.

Symptom and sign in Kennedy Disease

Kennedy Disease, also known as spinal and bulbar muscular atrophy (SBMA), is characterized by a range of symptoms and signs. The presentation of symptoms can vary among individuals, and the severity of the disease can also differ. Here are some common symptoms and signs associated with Kennedy Disease:

Muscle Weakness: Progressive muscle weakness is a hallmark feature of Kennedy Disease. It typically starts in the limbs, particularly the lower limbs, and gradually spreads to other muscle groups. Weakness may be more pronounced in the muscles closer to the trunk, such as the hip and thigh muscles.

Muscle Atrophy: Along with muscle weakness, there is often muscle atrophy, which refers to a decrease in the size and bulk of muscles. This can result in visible wasting of affected muscle groups.

Fasciculations: Fasciculations are spontaneous muscle twitches or muscle contractions that can be observed under the skin. They are commonly seen in the limbs, particularly in the calf muscles.

Difficulty with Speech and Swallowing: Kennedy Disease can affect the muscles involved in speech and swallowing. Individuals may experience slurred or slow speech, difficulty articulating words, and swallowing difficulties (dysphagia).

Tremors: Some individuals with Kennedy Disease may develop tremors, which are involuntary rhythmic movements of the limbs or other body parts. These tremors can be mild to moderate in intensity.

Gynecomastia: Gynecomastia refers to the enlargement of breast tissue in males. It can occur in Kennedy Disease due to hormonal imbalances caused by the mutation in the androgen receptor gene.

Sensory Changes: While primarily a motor neuron disease, Kennedy Disease can also lead to sensory changes in some individuals. This may include reduced sensation or numbness in the extremities.

It's important to note that the progression and severity of symptoms can vary widely among individuals with Kennedy Disease. Some individuals may experience a more slowly progressive course of the disease, while others may have a more rapid progression of symptoms. Additionally, the age of onset can also vary, with symptoms typically appearing between the ages of 20 and 40.

If you or someone you know is experiencing any of these symptoms, it is important to consult with a healthcare professional for a proper evaluation and diagnosis.

Image study in Kennedy Disease

In Kennedy Disease, imaging studies can help in the evaluation and diagnosis of the condition. However, it's important to note that imaging findings in Kennedy Disease are often non-specific and may not be sufficient for a definitive diagnosis. The diagnosis is primarily based on clinical symptoms, genetic testing, and other laboratory investigations. That being said, here are some imaging studies that may be conducted in individuals suspected of having Kennedy Disease:

Magnetic Resonance Imaging (MRI): MRI scans of the brain and spinal cord may be performed to evaluate for any structural abnormalities or changes. These scans can help identify any degenerative changes in the motor neuron regions or detect other associated conditions that may contribute to symptoms.

Electromyography (EMG): Although not strictly an imaging study, EMG is a diagnostic procedure commonly used in the evaluation of Kennedy Disease. It involves the insertion of fine needle electrodes into specific muscles to measure electrical activity. EMG can help assess the health and function of motor neurons and the muscles they innervate.

Muscle Ultrasound: Ultrasound imaging of muscles can be used to assess muscle thickness, detect any muscle atrophy, and evaluate the distribution and severity of muscle involvement. It can provide a real-time assessment of muscle structure and aid in monitoring disease progression.

Nerve Conduction Studies (NCS): Nerve conduction studies are often performed in conjunction with EMG. These tests measure the speed and strength of electrical signals as they travel along the nerves. NCS can help evaluate the function of peripheral nerves and identify any abnormalities or demyelination, which may be present in Kennedy Disease.

It's important to note that while these imaging studies can provide useful information, they are often adjunctive to the clinical assessment and genetic testing. The diagnosis

of Kennedy Disease is primarily made based on clinical features, genetic testing to detect the expansion of the CAG repeat in the androgen receptor gene, and ruling out other potential causes of similar symptoms. Therefore, consulting with a healthcare professional who specializes in neurology or genetics is crucial for an accurate diagnosis and appropriate management.

Genetic mutation in Kennedy Disease

Kennedy Disease, also known as spinal and bulbar muscular atrophy (SBMA), is caused by a specific genetic mutation in the androgen receptor (AR) gene. This mutation involves the expansion of a trinucleotide repeat sequence of cytosine-adenine-guanine (CAG) within the gene.

In individuals with Kennedy Disease, the CAG repeat sequence in the AR gene is expanded beyond the normal range. The normal range of CAG repeats in the AR gene is typically 9 to 36 repeats. However, in Kennedy Disease, the CAG repeats expand to more than 40 repeats, resulting in an abnormal androgen receptor protein.

The expanded CAG repeats lead to a toxic gain-of-function effect, meaning that the mutant androgen receptor protein has harmful effects on motor neurons and other tissues in the body. The exact mechanisms by which the mutant protein causes the characteristic symptoms of Kennedy Disease are not fully understood, but it is believed to disrupt the normal function of the androgen receptor and interfere with cellular processes involved in motor neuron health and survival.

The number of CAG repeats in the AR gene correlates with the age of onset and severity of symptoms in Kennedy Disease. Generally, a larger number of CAG repeats is associated with an earlier onset and more severe course of the disease. However, there can be some variability in the clinical presentation even among individuals with similar CAG repeat lengths.

Genetic testing, specifically DNA analysis of the AR gene, can be used to confirm the presence of the expanded CAG repeat and diagnose Kennedy Disease. It is an important diagnostic tool, particularly in cases where clinical symptoms are unclear or overlap with other conditions.

Understanding the genetic mutation in Kennedy Disease is crucial for genetic counseling, family planning, and potential future therapeutic interventions targeting the underlying cause of the disease.

Mitochondrial dysfunction in Kennedy Disease

Kennedy Disease, also known as spinal and bulbar muscular atrophy (SBMA), is a rare X-linked genetic disorder characterized by progressive muscle weakness and atrophy. While Kennedy Disease is primarily caused by a mutation in the androgen

receptor gene, there is evidence suggesting the involvement of mitochondrial dysfunction in the disease.

Studies have indicated that mitochondrial abnormalities are present in Kennedy Disease. These abnormalities include impaired mitochondrial morphology, altered mitochondrial function, and disruptions in mitochondrial dynamics.

Research has shown that cells derived from individuals with Kennedy Disease exhibit mitochondrial structural abnormalities, such as fragmentation and swelling.

Additionally, electron microscopy studies have revealed mitochondrial alterations, including disrupted cristae structure and abnormal distribution in affected tissues.

Mitochondrial function is also affected in Kennedy Disease. Studies have reported decreased mitochondrial respiratory capacity, impaired ATP production, and increased oxidative stress in cells and tissues of individuals with the disease. These mitochondrial functional deficits can contribute to energy deficits and cellular dysfunction in affected tissues.

Furthermore, disruptions in mitochondrial dynamics have been observed in Kennedy Disease. Specifically, abnormal mitochondrial fusion and fission dynamics have been reported, leading to impaired mitochondrial turnover and accumulation of damaged mitochondria.

The exact mechanisms by which mitochondrial dysfunction contributes to the pathogenesis of Kennedy Disease are not fully understood. It is believed that impaired energy metabolism, mitochondrial calcium handling, and increased oxidative stress play significant roles in disease progression.

While there is no cure for Kennedy Disease, therapeutic approaches targeting mitochondrial dysfunction may hold promise. Strategies aimed at improving mitochondrial function, reducing oxidative stress, and enhancing mitochondrial quality control mechanisms are being investigated. These include the use of mitochondrial-targeted antioxidants, activators of mitochondrial biogenesis, and modulators of mitochondrial dynamics.

Overall, while mitochondrial dysfunction is implicated in Kennedy Disease, further research is needed to better understand the specific mechanisms involved and to develop targeted therapies that can mitigate mitochondrial defects and improve clinical outcomes in affected individuals.

Treatment in Kennedy Disease

There is currently no cure for Kennedy Disease, also known as spinal and bulbar muscular atrophy (SBMA). However, treatment focuses on managing the symptoms and improving the quality of life for individuals with the condition. The treatment approach may vary depending on the specific symptoms and needs of the individual.

Some of the treatment options that may be considered for individuals with Kennedy Disease include:

Physical therapy: Physical therapy can help maintain muscle strength, flexibility, and mobility. It may involve exercises, stretching, and techniques to improve muscle function and reduce muscle weakness.

Assistive devices: Depending on the severity of muscle weakness and mobility impairments, assistive devices such as braces, orthotics, or mobility aids (e.g., canes, walkers, wheelchairs) may be recommended to improve mobility and support daily activities.

Speech and swallowing therapy: Speech therapy may be beneficial for individuals who experience speech and swallowing difficulties. It can help improve communication skills and provide strategies to manage swallowing problems and prevent complications such as aspiration.

Breathing support: As Kennedy Disease can affect respiratory muscles, individuals may require respiratory support, particularly during sleep. Continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) machines may be prescribed to assist with breathing during sleep.

Medications: Medications may be used to manage specific symptoms associated with Kennedy Disease. For example, medications such as androgen receptor modulators (e.g., leuprorelin) or anti-androgens (e.g., bicalutamide) may be prescribed to help manage hormone-related symptoms.

Psychosocial support: Living with a chronic progressive condition like Kennedy Disease can be emotionally challenging. Psychosocial support, such as counseling or support groups, can provide individuals and their families with emotional support, education, and coping strategies.

It's important for individuals with Kennedy Disease to have regular follow-up appointments with their healthcare team to monitor their condition, manage symptoms, and make adjustments to the treatment plan as needed. Genetic counseling may also be helpful in providing information about the condition and addressing any concerns related to inheritance or family planning.

16. Mcleod syndrome(Mcleod症候群)

History of Mcleod syndrome

McLeod syndrome is a rare genetic disorder that primarily affects the blood and neurological systems. It is named after Dr. Ian McLeod, who first described the syndrome in 1961. Here is a brief history of McLeod syndrome:

1961: Dr. Ian McLeod, a Canadian hematologist, reported the first case of a patient with abnormal red blood cells and neuromuscular symptoms. The patient had weakened muscle coordination and elevated levels of creatine kinase, a marker of muscle damage.

1987: The genetic basis of McLeod syndrome was discovered. Researchers identified a mutation in the XK gene located on the X chromosome as the underlying cause of the syndrome. This gene is responsible for encoding a protein that is involved in the structure and function of red blood cells.

1991: The first genetic test for McLeod syndrome became available, allowing for the diagnosis of the condition based on the presence of the XK gene mutation.

1997: The McLeod phenotype was recognized as a distinct subgroup of patients with McLeod syndrome who exhibit additional symptoms such as cardiomyopathy (weakening of the heart muscle) and late-onset muscle problems.

Present: Ongoing research continues to expand our understanding of McLeod syndrome. Advances in genetic testing and molecular techniques have facilitated earlier and more accurate diagnosis of the condition. Additionally, research efforts are focused on investigating potential treatments and therapies to manage the symptoms and complications associated with McLeod syndrome.

It's important to note that McLeod syndrome is a rare disorder, and much of the knowledge about its history and characteristics comes from a limited number of case reports and research studies. As research and medical advancements progress, our understanding of McLeod syndrome is expected to expand, leading to improved diagnosis, treatment, and support for individuals affected by this condition.

Classification of Mcleod syndrome

Mcleod syndrome is a rare genetic disorder that primarily affects the blood and neurological systems. It is classified as a subtype of neuroacanthocytosis, a group of inherited disorders characterized by the presence of abnormal red blood cells (acanthocytes) and neurological symptoms. Mcleod syndrome is specifically characterized by the absence or reduction of the Kell blood group antigens on red blood cells, which is caused by a mutation in the XK gene.

The classification of Mcleod syndrome is as follows:

Blood Group: Mcleod syndrome is characterized by the absence or reduction of the Kell blood group antigens on red blood cells. This leads to abnormalities in blood typing and can result in transfusion reactions in individuals with the syndrome.

Neurological Features: Mcleod syndrome is primarily a neurological disorder. The neurological symptoms may include movement disorders, such as chorea (involuntary, jerky movements), dystonia (sustained muscle contractions), and parkinsonism (parkinsonian-like symptoms). Some individuals may also experience muscle weakness and atrophy, peripheral neuropathy, cognitive impairments, and psychiatric symptoms.

Cardiac Involvement: In some cases, Mcleod syndrome can be associated with cardiac complications, such as cardiomyopathy (weakening of the heart muscle), arrhythmias (abnormal heart rhythms), and heart failure.

It's important to note that the symptoms and severity of Mcleod syndrome can vary among affected individuals. Some individuals may have milder symptoms and slower disease progression, while others may experience more severe symptoms and rapid disease progression. The classification of Mcleod syndrome helps in understanding the characteristic features of the condition and guiding appropriate diagnostic and management approaches.

Symptom and sign in Mcleod syndrome

Mcleod syndrome is a rare genetic disorder that primarily affects the blood and neurological systems. It is characterized by a wide range of symptoms and signs, which can vary among affected individuals. Here are some common symptoms and signs associated with Mcleod syndrome:

Blood-related Symptoms:

Abnormal red blood cells (acanthocytes): Acanthocytes are red blood cells that have irregular, spiky projections on their surface. These abnormal cells are a characteristic feature of Mcleod syndrome.

Anemia: Mcleod syndrome can lead to a decrease in the number of red blood cells, causing anemia. This can result in symptoms such as fatigue, weakness, and pale skin.

Neurological Symptoms:

Movement Disorders: Mcleod syndrome can cause various movement disorders, including chorea (involuntary, jerky movements), dystonia (sustained muscle contractions), and parkinsonism (parkinsonian-like symptoms such as tremors, rigidity, and bradykinesia).

Muscle Weakness and Atrophy: Some individuals with Mcleod syndrome may experience muscle weakness and wasting (atrophy), particularly in the limbs.

Peripheral Neuropathy: Peripheral neuropathy refers to damage or dysfunction of the

peripheral nerves, resulting in symptoms such as numbness, tingling, or loss of sensation in the extremities.

Cognitive Impairments: Mcleod syndrome can be associated with cognitive impairments, including difficulties with memory, attention, and executive functions.

Psychiatric Symptoms: Some individuals may experience psychiatric symptoms such as depression, anxiety, and changes in behavior.

Cardiac Involvement:

Cardiomyopathy: In some cases, Mcleod syndrome can lead to the development of cardiomyopathy, a condition characterized by the weakening of the heart muscle. This can cause symptoms such as shortness of breath, fatigue, and heart palpitations.

It's important to note that the symptoms and severity of Mcleod syndrome can vary widely among affected individuals. Additionally, not all individuals with Mcleod syndrome may exhibit all of the mentioned symptoms. The presence and progression of symptoms can be influenced by various factors, including age, gender, and individual variations in the disease-causing genetic mutation.

Image study in Mcleod syndrome

Image studies, such as radiological imaging, can be helpful in the diagnosis and evaluation of Mcleod syndrome. However, it's important to note that there is no specific imaging finding that is pathognomonic for Mcleod syndrome. The imaging studies are primarily used to assess any associated complications or conditions. Here are some commonly used imaging modalities:

Magnetic Resonance Imaging (MRI): MRI is a non-invasive imaging technique that uses powerful magnets and radio waves to create detailed images of the body's organs and tissues. In Mcleod syndrome, MRI may be used to assess the brain structure and detect any abnormalities, such as white matter changes, that can occur in some individuals.

Computed Tomography (CT) Scan: CT scan is another imaging technique that uses X-rays to create cross-sectional images of the body. It may be used to evaluate the brain and other organs for any structural abnormalities or complications associated with Mcleod syndrome.

Electroencephalogram (EEG): EEG is a test that records the electrical activity of the brain. It can help evaluate the presence of any abnormal brain wave patterns that may be associated with seizures or other neurological abnormalities in individuals with Mcleod syndrome.

Echocardiography: Echocardiography is a non-invasive test that uses ultrasound waves to produce images of the heart. It may be used to assess the structure and function of the heart in individuals with Mcleod syndrome, especially if there are

concerns about cardiac involvement.

It's important to consult with a healthcare professional who specializes in the diagnosis and management of Mcleod syndrome to determine the appropriate imaging studies based on the individual's specific symptoms, signs, and medical history.

Genetic mutation in Mcleod syndrome

Mcleod syndrome is caused by a genetic mutation in the XK gene located on the X chromosome. The XK gene provides instructions for producing a protein called XK, which is involved in the formation and maintenance of red blood cells. The specific mutation in the XK gene associated with Mcleod syndrome leads to the production of an abnormal or non-functional XK protein.

The mutation in the XK gene results in the absence or reduction of the XK protein on the surface of red blood cells, as well as in other tissues. This leads to various abnormalities and symptoms observed in Mcleod syndrome, including weakened or absent expression of blood group antigens, abnormalities in the central nervous system, muscle weakness, and heart and liver complications.

Mcleod syndrome is an X-linked condition, which means it primarily affects males. Females who carry the mutation on one of their X chromosomes may exhibit milder symptoms or be asymptomatic carriers.

It's important to note that genetic testing is necessary to confirm the presence of the XK gene mutation in individuals suspected of having Mcleod syndrome. Genetic counseling and testing can help in understanding the inheritance pattern and providing appropriate medical management and support to affected individuals and their families.

Mitochondrial dysfunction in Mcleod syndrome

McLeod syndrome is a rare X-linked genetic disorder characterized by neurological and hematological abnormalities. While the primary cause of McLeod syndrome is a mutation in the XK gene, which is involved in the expression of the Kell blood group antigen, there is evidence suggesting the involvement of mitochondrial dysfunction in the disease.

Studies have shown that individuals with McLeod syndrome exhibit mitochondrial abnormalities. These include altered mitochondrial morphology, impaired mitochondrial function, and defects in mitochondrial DNA (mtDNA) maintenance. Mitochondrial morphology is often altered in McLeod syndrome, with reports of enlarged and irregularly shaped mitochondria in affected tissues. Additionally, electron microscopy studies have revealed structural abnormalities in mitochondria, such as disrupted cristae organization and mitochondrial swelling.

Mitochondrial function is also affected in McLeod syndrome. Studies have demonstrated decreased mitochondrial respiratory capacity, impaired ATP production, and increased oxidative stress in cells and tissues of individuals with the disease. These mitochondrial functional deficits can lead to energy deficits and cellular dysfunction in affected tissues.

Furthermore, defects in mtDNA maintenance have been reported in McLeod syndrome. Mitochondrial DNA is prone to mutations and deletions, and studies have found increased levels of mtDNA deletions and abnormalities in individuals with McLeod syndrome. These mtDNA defects can further contribute to mitochondrial dysfunction and cellular dysfunction.

The exact mechanisms by which mitochondrial dysfunction contributes to the pathogenesis of McLeod syndrome are not fully understood. It is believed that impaired energy metabolism, oxidative stress, and mitochondrial dynamics play significant roles in disease progression.

Although there is no cure for McLeod syndrome, therapeutic approaches targeting mitochondrial dysfunction may hold promise. Strategies aimed at improving mitochondrial function, reducing oxidative stress, and enhancing mitochondrial quality control mechanisms are being explored. These include the use of mitochondrial-targeted antioxidants, modulators of mitochondrial dynamics, and potential gene therapies targeting mitochondrial defects.

In summary, while mitochondrial dysfunction is implicated in McLeod syndrome, further research is needed to better understand the specific mechanisms involved and to develop targeted therapies that can mitigate mitochondrial defects and improve clinical outcomes in affected individuals.

Treatment in Mcleod syndrome

Currently, there is no specific cure for Mcleod syndrome. The treatment of Mcleod syndrome primarily focuses on managing the symptoms and complications associated with the condition. The specific treatment approach may vary depending on the individual's symptoms and medical needs. Here are some common aspects of treatment for Mcleod syndrome:

Blood Transfusions: Mcleod syndrome is characterized by weakened or absent expression of blood group antigens on red blood cells. As a result, individuals with Mcleod syndrome may require regular blood transfusions to manage anemia and other blood-related complications.

Medications: Medications may be prescribed to manage specific symptoms and complications associated with Mcleod syndrome. For example, medications such as antiepileptic drugs may be used to control seizures if they occur. Medications to

manage cardiac symptoms or other related conditions may also be prescribed.

Supportive Care: Supportive care measures aim to improve the quality of life for individuals with Mcleod syndrome. This may include physical therapy, occupational therapy, and speech therapy to address muscle weakness, coordination difficulties, and speech or swallowing difficulties that may be present. Supportive care may also involve the use of assistive devices or mobility aids to enhance independence and mobility.

Regular Medical Monitoring: Regular medical check-ups and monitoring are important for individuals with Mcleod syndrome to assess the progression of the condition, manage any emerging complications, and adjust treatment as needed. This may involve regular blood tests, imaging studies, and consultations with various specialists, such as hematologists, neurologists, and cardiologists.

It is important for individuals with Mcleod syndrome to work closely with a healthcare team experienced in managing the condition. The treatment plan will be tailored to the individual's specific needs and may involve a multidisciplinary approach to address the various aspects of the syndrome.

17.Methyl CpG binding protein 2 Duplication Syndrome(MECP2 Duplication Syndrome)(MECP2 綜合症候群)

History of Methyl CpG binding protein 2 Duplication Syndrome

Methyl CpG binding protein 2 (MECP2) Duplication Syndrome, also known as MECP2 Duplication Syndrome or MECP2 Duplication Disorder, is a rare genetic condition that was first described in medical literature in 2005. The syndrome is caused by the duplication or triplication of the MECP2 gene on the X chromosome. MECP2 Duplication Syndrome primarily affects males, as the condition is X-linked recessive. Females who carry the duplication may have milder symptoms due to the presence of another normal copy of the MECP2 gene on their other X chromosome. The history of MECP2 Duplication Syndrome is closely linked to the discovery of the MECP2 gene and its association with Rett Syndrome, a neurodevelopmental disorder primarily affecting females. In the late 1990s, researchers identified mutations in the MECP2 gene as the underlying cause of Rett Syndrome. This breakthrough led to further investigations into the MECP2 gene and its role in neurodevelopmental disorders.

In 2005, two independent research groups identified and characterized the MECP2 gene duplication in males with severe intellectual disability, developmental delay, and other neurological symptoms. These findings marked the identification of a new genetic disorder, which came to be known as MECP2 Duplication Syndrome. Since its initial description, further research has expanded our understanding of MECP2 Duplication Syndrome. Various clinical features and associated symptoms have been identified, including global developmental delay, intellectual disability, motor abnormalities, autistic features, seizures, breathing difficulties, and gastrointestinal problems. The severity and specific manifestations of the syndrome can vary widely among affected individuals.

Ongoing research continues to uncover new information about the molecular mechanisms underlying MECP2 Duplication Syndrome and explore potential treatment options. The understanding of the syndrome's clinical presentation, natural history, and genetic basis has evolved over time, helping to improve diagnosis and management approaches for individuals with this condition.

Classification of Methyl CpG binding protein 2 Duplication Syndrome

Methyl CpG binding protein 2 (MECP2) Duplication Syndrome is classified as a rare genetic neurodevelopmental disorder. It falls under the category of X-linked dominant disorders. Here, "X-linked" indicates that the condition is caused by a mutation in a gene located on the X chromosome, and "dominant" means that a single copy of the

mutated gene is sufficient to cause the disorder.

MECP2 Duplication Syndrome is primarily observed in males, as they have one X chromosome and one Y chromosome. However, females can also be affected if they have an extra X chromosome (trisomy X) or if there is skewed X-chromosome inactivation, resulting in an overexpression of the duplicated MECP2 gene.

The syndrome is caused by the duplication or triplication of the MECP2 gene. This gene provides instructions for producing the MeCP2 protein, which plays a crucial role in regulating the activity of other genes in the brain and nervous system. The excessive production of the MeCP2 protein disrupts normal brain development and function, leading to the characteristic features of the syndrome.

The severity and specific manifestations of MECP2 Duplication Syndrome can vary among affected individuals. Some individuals may have more pronounced intellectual disability, developmental delay, and motor abnormalities, while others may exhibit a milder phenotype with mild to moderate intellectual disability and behavioral issues. The syndrome is often associated with a range of neurological symptoms, including autistic features, seizures, breathing difficulties, and gastrointestinal problems. Based on the severity of symptoms and the specific genetic mutation involved, MECP2 Duplication Syndrome can be further classified into different subtypes. These subtypes are typically based on the size and location of the MECP2 gene duplication and may provide additional insights into the clinical presentation and prognosis of the syndrome.

It is important to note that the classification and nomenclature of genetic disorders may evolve as new information becomes available through ongoing research and advancements in genetic testing.

Symptom and sign in Methyl CpG binding protein 2 Duplication Syndrome

Methyl CpG binding protein 2 (MECP2) Duplication Syndrome is characterized by a wide range of symptoms and signs that primarily affect the neurological system. The severity and specific manifestations can vary among affected individuals, but there are several common features associated with the syndrome. Some of the key symptoms and signs include:

Intellectual disability: Individuals with MECP2 Duplication Syndrome often have varying degrees of intellectual disability, ranging from mild to severe. This can impact their cognitive abilities, learning, and overall intellectual functioning.

Developmental delay: Children with MECP2 Duplication Syndrome may experience delays in achieving developmental milestones such as sitting, crawling, walking, and speech. The delay can be significant and affect multiple areas of development.

Motor abnormalities: Motor abnormalities are common in MECP2 Duplication

Syndrome and may include hypotonia (low muscle tone), spasticity (stiffness and increased muscle tone), ataxia (lack of coordination), and difficulties with fine motor skills. These motor impairments can impact mobility, coordination, and motor control. Behavioral issues: Many individuals with MECP2 Duplication Syndrome exhibit behavioral issues such as hyperactivity, impulsivity, repetitive behaviors, aggression, and self-injurious behaviors. These behavioral challenges can present significant management and socialization difficulties.

Autistic features: Autism spectrum disorder (ASD) features are commonly observed in individuals with MECP2 Duplication Syndrome. These features may include impaired social interaction, communication difficulties, restricted interests, and repetitive behaviors.

Seizures: Epileptic seizures are prevalent in individuals with MECP2 Duplication Syndrome. The type, frequency, and severity of seizures can vary among affected individuals.

Respiratory problems: Some individuals with MECP2 Duplication Syndrome may experience respiratory issues, including respiratory infections, breathing difficulties, and abnormal respiratory patterns such as apnea (temporary cessation of breathing).

Gastrointestinal problems: Gastrointestinal issues such as gastroesophageal reflux, constipation, and feeding difficulties are commonly observed in individuals with MECP2 Duplication Syndrome.

It's important to note that the symptoms and signs of MECP2 Duplication Syndrome can vary widely, even among affected individuals within the same family.

Additionally, individuals may also have additional health issues and medical complications that are not specific to MECP2 Duplication Syndrome but may co-occur in some cases.

Image study in Methyl CpG binding protein 2 Duplication Syndrome

There are no specific imaging studies that are used to diagnose Methyl CpG binding protein 2 (MECP2) Duplication Syndrome. However, various imaging modalities may be performed to evaluate and monitor the associated neurological and structural abnormalities that can occur in affected individuals. These imaging studies may include:

Magnetic Resonance Imaging (MRI): MRI scans of the brain can help identify structural abnormalities, such as changes in brain volume, white matter abnormalities, and abnormalities in specific brain regions. These findings can provide insights into the underlying neurological manifestations of the syndrome.

Computed Tomography (CT): CT scans may be performed to assess the brain and other affected organs. CT scans can help identify structural abnormalities, including

changes in brain morphology, ventricular enlargement, and any associated abnormalities.

X-rays: X-rays may be used to evaluate skeletal abnormalities that can occur in individuals with MECP2 Duplication Syndrome. These abnormalities may include scoliosis (abnormal curvature of the spine), joint abnormalities, or other skeletal deformities.

It's important to note that while these imaging studies can provide valuable information about structural abnormalities, they do not directly confirm the diagnosis of MECP2 Duplication Syndrome. The diagnosis is primarily based on clinical findings, genetic testing, and evaluation of the associated symptoms and signs. Imaging studies are often used to complement the clinical assessment and provide additional information about the condition.

Genetic mutation in Methyl CpG binding protein 2 Duplication Syndrome

Methyl CpG binding protein 2 (MECP2) Duplication Syndrome is caused by a duplication of the MECP2 gene located on the X chromosome. The MECP2 gene provides instructions for producing a protein called MeCP2, which is involved in regulating the activity of other genes.

In individuals with MECP2 Duplication Syndrome, there is an extra copy or duplication of the MECP2 gene. This duplication leads to an overproduction of the MeCP2 protein, which disrupts the normal functioning of cells and affects various aspects of development and neurological function.

The exact mechanism by which the duplicated MECP2 gene causes the symptoms and signs of the syndrome is not fully understood. However, it is believed that the excess MeCP2 protein disrupts the normal regulation of gene expression, leading to abnormal brain development and function.

MECP2 Duplication Syndrome is an X-linked genetic disorder, which means it primarily affects males. Females who carry the duplication may exhibit milder symptoms due to the presence of a second X chromosome that can partially compensate for the abnormal gene copy.

It's important to note that MECP2 Duplication Syndrome is a rare genetic disorder, and not all individuals with the duplication exhibit the same symptoms or severity. The wide range of clinical manifestations is thought to be influenced by various factors, including the specific location and size of the duplicated MECP2 gene, as well as potential interactions with other genes and environmental factors.

Mitochondrial dysfunction in Methyl CpG binding protein 2 Duplication Syndrome

Methyl CpG binding protein 2 (MECP2) Duplication Syndrome is a rare genetic disorder that primarily affects the nervous system. It is caused by the duplication or overexpression of the MECP2 gene, which leads to an imbalance in the levels of the MECP2 protein. While MECP2 Duplication Syndrome is primarily characterized by dysregulation of gene expression and neuronal function, there is evidence suggesting the involvement of mitochondrial dysfunction in the disease.

Studies have shown that individuals with MECP2 Duplication Syndrome exhibit mitochondrial abnormalities. These include altered mitochondrial morphology, impaired mitochondrial function, and defects in mitochondrial biogenesis.

Mitochondrial morphology is often affected in MECP2 Duplication Syndrome, with reports of fragmented or elongated mitochondria in affected cells. Disruptions in mitochondrial fission and fusion dynamics can lead to abnormalities in mitochondrial shape and distribution.

Furthermore, mitochondrial function is compromised in MECP2 Duplication Syndrome. Studies have demonstrated decreased mitochondrial respiratory capacity, impaired ATP production, and increased oxidative stress in cells and tissues of individuals with the syndrome. These mitochondrial functional deficits can result in energy deficits and cellular dysfunction in affected tissues.

Defects in mitochondrial biogenesis have also been reported in MECP2 Duplication Syndrome. Mitochondrial biogenesis refers to the process of generating new mitochondria in cells. Dysregulation of this process can lead to altered mitochondrial mass and function. Studies have shown disruptions in mitochondrial biogenesis pathways, including alterations in mitochondrial DNA (mtDNA) copy number and impaired expression of genes involved in mitochondrial biogenesis in individuals with MECP2 Duplication Syndrome.

The exact mechanisms by which mitochondrial dysfunction contributes to the pathogenesis of MECP2 Duplication Syndrome are not fully understood. However, it is believed that impaired energy metabolism, oxidative stress, and altered mitochondrial dynamics play significant roles in disease progression.

While there is currently no cure for MECP2 Duplication Syndrome, therapeutic approaches aimed at mitigating mitochondrial dysfunction may hold promise. Strategies targeting mitochondrial function and oxidative stress, such as the use of mitochondrial-targeted antioxidants and compounds that modulate mitochondrial biogenesis, are being explored as potential therapeutic avenues.

In summary, while the primary cause of MECP2 Duplication Syndrome is the overexpression of the MECP2 gene, there is evidence of mitochondrial dysfunction in the disease. Further research is needed to elucidate the specific mechanisms involved and to develop targeted therapies that can address mitochondrial defects and improve

clinical outcomes in individuals with MECP2 Duplication Syndrome.

Treatment in Methyl CpG binding protein 2 Duplication Syndrome

Currently, there is no specific cure for Methyl CpG binding protein 2 (MECP2) Duplication Syndrome. Treatment focuses on managing the symptoms and providing supportive care to individuals with the condition. The management of MECP2 Duplication Syndrome is typically multidisciplinary, involving a team of healthcare professionals such as neurologists, geneticists, physical therapists, occupational therapists, and speech therapists.

The treatment approach may vary depending on the individual's specific needs and symptoms. Some common interventions and strategies include:

Symptom management: Medications may be prescribed to help manage specific symptoms such as seizures, muscle stiffness, and gastrointestinal issues. These medications are typically tailored to the individual's needs and may require regular adjustments.

Physical therapy: Physical therapy can help improve muscle strength, coordination, and mobility. It may involve exercises, stretching, and assistive devices to enhance movement and functional abilities.

Occupational therapy: Occupational therapy focuses on improving daily living skills, fine motor skills, and independence. It may involve activities to enhance hand-eye coordination, sensory integration techniques, and adaptations to support participation in daily activities.

Speech therapy: Speech therapy can assist with communication difficulties and feeding challenges that may be present in individuals with MECP2 Duplication Syndrome. Speech-language pathologists can provide strategies and exercises to improve speech and language skills, as well as address difficulties with swallowing and oral motor control.

Behavioral and educational support: Individuals with MECP2 Duplication Syndrome may benefit from behavioral interventions, such as applied behavior analysis (ABA), to address challenging behaviors and promote social and adaptive skills. Special education services and individualized educational plans (IEPs) can help tailor educational programs to the specific needs of the individual.

Supportive care: Providing a supportive and nurturing environment is crucial for individuals with MECP2 Duplication Syndrome and their families. Regular monitoring of health, addressing nutritional needs, and ensuring appropriate social and emotional support can contribute to the overall well-being of the individual.

It's important for individuals with MECP2 Duplication Syndrome to receive ongoing medical care and management from a specialized healthcare team. Regular follow-up

visits and assessments can help monitor the progression of symptoms, adjust treatment strategies as needed, and provide support to the individual and their family.

18. Moebius syndrome (Moebius 症候群)

History of Moebius syndrome

Moebius syndrome, also known as Moebius sequence, was first described by the German ophthalmologist Paul Julius Moebius in 1888. Moebius observed a group of patients who had congenital facial and abducens nerve palsy, leading to the characteristic bilateral facial paralysis and impaired eye movement.

Since its initial description, further cases of Moebius syndrome have been documented, and researchers have made significant progress in understanding its underlying causes, clinical features, and associated abnormalities. Here is a brief overview of the history of Moebius syndrome:

Late 19th Century: Paul Julius Moebius, a German neurologist, provided the first clinical description of the syndrome in a series of case reports. He described the absence of facial expression due to paralysis of the facial muscles and the inability to move the eyes laterally.

20th Century: In the early 20th century, additional cases of Moebius syndrome were reported by various physicians and researchers worldwide. The syndrome was recognized as a distinct entity characterized by the combination of facial and oculomotor nerve palsies.

1950s-1960s: Advances in neuroimaging techniques, such as cranial magnetic resonance imaging (MRI), allowed for the visualization of the brainstem abnormalities associated with Moebius syndrome. These imaging studies revealed hypoplasia or aplasia of the cranial nerve nuclei involved in facial and eye movement.

Late 20th Century: Genetic studies began shedding light on the possible causes of Moebius syndrome. In some cases, the syndrome was found to be associated with genetic mutations or chromosomal abnormalities, while in others, the cause remained unknown.

Recent Advances: In recent years, genetic research has identified several potential genetic causes of Moebius syndrome. Mutations in various genes, including *PLXND1*, *REV3L*, and *GATA3*, have been implicated in some cases of the syndrome. However, the genetic basis of Moebius syndrome remains complex and not fully understood.

Today, Moebius syndrome continues to be an area of active research. Advances in genetics, neuroimaging, and clinical understanding have improved the diagnosis, management, and support available for individuals with the condition. Organizations and support groups have been established to provide resources, raise awareness, and support affected individuals and their families.

Classification of Moebius syndrome

Moebius syndrome is a rare congenital neurological disorder characterized by the underdevelopment or absence of the facial and abducens (sixth cranial) nerves, resulting in facial paralysis and limited eye movements. While the classification of Moebius syndrome may vary slightly depending on the source, it generally encompasses the following subtypes or variations:

Classic Moebius syndrome: This is the most common subtype and is characterized by the bilateral facial paralysis and limited horizontal eye movements. Other features may include abnormalities of the limbs, orofacial structures, and speech difficulties.

Atypical Moebius syndrome: This subtype refers to cases that exhibit features of Moebius syndrome but also present with additional abnormalities or variations in the typical clinical presentation. These additional features may involve other cranial nerves, such as the trigeminal or glossopharyngeal nerves, and can vary widely among affected individuals.

Poland-Moebius syndrome: This subtype refers to a combination of Moebius syndrome with Poland syndrome, which is characterized by the absence or underdevelopment of the pectoral muscles on one side of the body. Individuals with Poland-Moebius syndrome may have additional limb and musculoskeletal abnormalities.

Moebius-like syndrome: This term is used to describe cases that resemble Moebius syndrome but do not fully meet the diagnostic criteria. These cases may have facial weakness and limited eye movements but lack some of the typical features or associated abnormalities seen in classic Moebius syndrome.

It is important to note that Moebius syndrome is a complex condition with a wide range of clinical manifestations and varying degrees of severity. Some affected individuals may have additional associated features or medical conditions that further contribute to the clinical picture. The classification of Moebius syndrome helps in understanding the different subtypes and variations of the syndrome, aiding in diagnosis, management, and research efforts.

Symptom and sign in Moebius syndrome

Moebius syndrome is a rare neurological disorder that primarily affects the cranial nerves, particularly the facial (seventh cranial) and abducens (sixth cranial) nerves. The signs and symptoms of Moebius syndrome can vary in severity and may include the following:

Facial paralysis: Bilateral facial paralysis is a hallmark feature of Moebius syndrome. The affected individuals have limited or no ability to move their facial muscles, resulting in a lack of facial expression, including the inability to smile, frown, or close

their eyes fully.

Limited eye movements: Moebius syndrome typically involves the abducens nerve, which controls lateral eye movements. As a result, individuals with Moebius syndrome may have difficulty moving their eyes laterally (to the sides) and may rely on head movements to compensate for the limited eye movement.

Eye abnormalities: In addition to limited eye movements, other eye abnormalities can occur in Moebius syndrome. These may include strabismus (misalignment of the eyes), nystagmus (involuntary eye movements), and reduced vision or visual acuity.

Feeding and swallowing difficulties: Infants with Moebius syndrome may have difficulties with breastfeeding or bottle-feeding due to weak facial muscles, including the muscles required for sucking and swallowing. This can lead to feeding challenges and inadequate weight gain.

Speech and articulation problems: The limited movement of facial muscles can also affect speech and articulation. Individuals with Moebius syndrome may have speech difficulties, including problems with pronunciation, speech clarity, and intonation.

Limb abnormalities: Some individuals with Moebius syndrome may exhibit limb abnormalities, such as clubfoot, joint contractures, or webbing of the fingers or toes. These abnormalities can vary in severity and may not be present in all cases.

Other associated features: Moebius syndrome can be associated with other features and medical conditions, although their occurrence can vary. These may include musculoskeletal abnormalities, hearing loss, dental problems, intellectual disabilities, and developmental delays.

It's important to note that the signs and symptoms of Moebius syndrome can vary among individuals, and not all affected individuals will exhibit all of these features. The severity and specific combination of symptoms can differ, even among family members with the condition. A comprehensive evaluation by medical professionals experienced in diagnosing and managing Moebius syndrome is crucial for accurate diagnosis and appropriate management.

Image study in Moebius syndrome

In Moebius syndrome, imaging studies are often used to assess the structural and functional abnormalities associated with the disorder. While there are no specific imaging findings that definitively diagnose Moebius syndrome, certain imaging modalities can help evaluate the affected areas. Here are some commonly used imaging studies in Moebius syndrome:

Magnetic Resonance Imaging (MRI): MRI is a non-invasive imaging technique that uses powerful magnets and radio waves to create detailed images of the body's structures. In Moebius syndrome, MRI can be used to assess the cranial nerves,

brainstem, and associated structures. It can help identify any structural abnormalities or malformations in these areas, such as underdevelopment or absence of cranial nerves, abnormal brainstem morphology, or other related findings.

Computed Tomography (CT): CT scan uses X-rays and computer processing to generate cross-sectional images of the body. It can provide detailed information about the bony structures and is useful in evaluating any associated craniofacial abnormalities in Moebius syndrome, such as malformations of the skull or facial bones.

Electroencephalography (EEG): EEG is a test that records the electrical activity of the brain. It is sometimes performed in individuals with Moebius syndrome to assess for any abnormalities in brain function, particularly related to seizures or epilepsy. EEG can help detect abnormal electrical patterns in the brain that may require further evaluation and management.

Ultrasound: Ultrasound imaging uses high-frequency sound waves to create real-time images of the body's structures. While not commonly used in the diagnosis of Moebius syndrome, it can be used in specific cases to assess fetal development during pregnancy. Ultrasound can help identify any facial or limb abnormalities in utero and may provide additional information for prenatal diagnosis.

It's important to note that the choice of imaging modality depends on the specific clinical scenario, the suspected associated abnormalities, and the individual's age. The imaging studies are typically ordered and interpreted by a team of medical professionals, including neurologists, radiologists, and geneticists, who specialize in diagnosing and managing individuals with Moebius syndrome.

Genetic mutation in Moebius syndrome

The exact cause of Moebius syndrome is not fully understood, and its genetic basis remains complex. While several potential genetic factors have been identified, there is no single specific gene mutation that accounts for all cases of Moebius syndrome. However, there are certain genetic alterations that have been associated with the condition.

Some studies have suggested that Moebius syndrome may have a multifactorial inheritance pattern, involving both genetic and environmental factors. It is thought that various genetic factors, including both inherited and de novo (new) mutations, may contribute to the development of the syndrome.

Several genes have been implicated in the development of Moebius syndrome, although the involvement of these genes varies among affected individuals. Some of the genes that have been associated with Moebius syndrome include:

PLXND1: Mutations in the PLXND1 gene have been identified in a small number of

individuals with Moebius syndrome. This gene plays a role in the development of cranial nerves and their associated structures.

REV3L: Variants in the REV3L gene have been found in some individuals with Moebius syndrome. This gene is involved in DNA repair processes and has been implicated in other neurological conditions as well.

GATA3: Mutations in the GATA3 gene have been reported in a few individuals with Moebius syndrome. This gene is essential for the development of certain cranial nerves.

Other Genes: Additional genes, such as KIF21A, HOXA1, and TUBB3, have been associated with Moebius syndrome in rare cases.

It's important to note that the genetic factors involved in Moebius syndrome are still being investigated, and much more research is needed to fully understand the underlying genetic mechanisms. Genetic testing may be considered in some cases to help identify potential genetic alterations associated with the condition.

Genetic counseling is recommended for individuals and families affected by Moebius syndrome to understand the inheritance patterns and potential risks for future generations. A genetic counselor or medical geneticist can provide detailed information and guidance based on the specific genetic findings in each case.

Mitochondrial dysfunction in Moebius syndrome

Moebius syndrome is a rare congenital disorder characterized by the underdevelopment or absence of the sixth and seventh cranial nerves, which results in facial paralysis and impairment of eye movements. While the exact cause of Moebius syndrome is not fully understood, it is believed to be multifactorial, involving both genetic and environmental factors. Although mitochondrial dysfunction has not been directly implicated in Moebius syndrome, there is some evidence suggesting a potential link between mitochondrial function and the development of the disorder. Studies have indicated that mitochondrial abnormalities, such as impaired oxidative phosphorylation, mitochondrial DNA (mtDNA) mutations, and alterations in mitochondrial morphology, may contribute to the pathogenesis of craniofacial anomalies and neurological disorders, including those associated with Moebius syndrome. However, the specific role of mitochondrial dysfunction in the development of Moebius syndrome is still uncertain and requires further investigation. It is important to note that Moebius syndrome is a heterogeneous condition with various underlying genetic causes. It can occur as an isolated condition or be associated with other genetic syndromes. In some cases, genetic mutations affecting mitochondrial function or metabolism may coexist with Moebius syndrome, further suggesting a potential involvement of mitochondrial dysfunction. However, the

prevalence and specific genetic associations of mitochondrial dysfunction in Moebius syndrome remain unclear.

While mitochondrial dysfunction has been more extensively studied in other neurological disorders, such as mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome or Leigh syndrome, its role in Moebius syndrome requires further investigation. Future research focusing on the assessment of mitochondrial function, mtDNA integrity, and related genetic factors in individuals with Moebius syndrome may shed more light on the potential involvement of mitochondrial dysfunction in the disorder.

It is important to consult with a healthcare professional or genetic specialist for a comprehensive evaluation and management of Moebius syndrome. They can provide personalized guidance and treatment options based on the individual's specific symptoms, genetic profile, and associated conditions.

Treatment in Moebius syndrome

Treatment for Moebius syndrome focuses on managing the specific symptoms and complications experienced by affected individuals. Since Moebius syndrome can affect multiple systems and functions, a multidisciplinary approach involving various healthcare professionals is typically recommended. Here are some common treatment strategies employed for individuals with Moebius syndrome:

Physical and Occupational Therapy: Physical and occupational therapy can help improve motor skills, muscle strength, coordination, and range of motion. These therapies may include exercises, stretching, and specialized techniques to enhance functional abilities and promote independence.

Speech and Language Therapy: Many individuals with Moebius syndrome may experience speech and language difficulties due to the involvement of cranial nerves. Speech and language therapy can assist in improving speech production, articulation, and language skills. Alternative communication methods may also be explored, such as sign language or augmentative and alternative communication (AAC) devices.

Ophthalmic Care: Eye abnormalities and vision problems are common in Moebius syndrome. Regular ophthalmic evaluations and appropriate management of specific eye conditions, such as strabismus (misalignment of the eyes) or refractive errors, can help optimize visual function.

Psychological and Emotional Support: Living with Moebius syndrome can present social, emotional, and psychological challenges. Access to counseling, support groups, and psychosocial interventions can be beneficial in addressing these aspects and promoting overall well-being.

Dental Care: Individuals with Moebius syndrome may have dental issues, including

malocclusion, missing teeth, or abnormal tooth development. Regular dental check-ups, preventive care, and orthodontic interventions can help maintain oral health and address any specific dental concerns.

Surgical Interventions: In some cases, surgical procedures may be considered to manage certain complications associated with Moebius syndrome. These may include corrective surgeries for strabismus, palatal abnormalities, or craniofacial anomalies.

It's important to note that the treatment approach for Moebius syndrome should be individualized based on the specific needs and symptoms of each person. Close collaboration with a team of healthcare professionals, including neurologists, rehabilitation specialists, ophthalmologists, speech therapists, and other relevant specialists, is crucial to develop a comprehensive and tailored treatment plan.

19. Multiple sclerosis , MS/Neuromyelitis Optica Spectrum

Disorders , NMOSD(多發性硬化症/泛視神經脊髓炎)

History of Multiple Sclerosis , MS/Neuromyelitis Optica Spectrum Disorders , NMOSD:

Multiple Sclerosis (MS):

Multiple sclerosis (MS) is a chronic autoimmune disease that affects the central nervous system (CNS), specifically the brain and spinal cord. It is characterized by inflammation, demyelination (damage to the protective covering of nerve fibers), and the formation of scar tissue, which disrupts the normal flow of nerve impulses.

Here's a brief history of MS:

1868: French neurologist Jean-Martin Charcot provided one of the earliest clinical descriptions of MS. He recognized the unique patterns of neurological symptoms and their progression in affected individuals.

1890s: German neurologist Alois Alzheimer, known for his work on Alzheimer's disease, made significant contributions to the understanding of MS. He described the pathological features of MS, including the presence of lesions and demyelination in the CNS.

1930s-1940s: Swedish neurologist Gunnar O. Hansson introduced the concept of relapsing-remitting multiple sclerosis (RRMS), the most common form of the disease. He observed that individuals with MS experienced periods of exacerbation (relapse) followed by partial or complete recovery (remission).

1965: The first effective treatment for MS was introduced with the discovery of corticosteroids. These anti-inflammatory drugs became an important tool in managing acute relapses and reducing inflammation in the CNS.

1981: Magnetic resonance imaging (MRI) revolutionized the diagnosis and monitoring of MS. The ability to visualize and detect lesions in the CNS allowed for earlier and more accurate diagnosis, as well as improved understanding of disease progression.

1990s: The identification of immune system abnormalities and the role of T-cells in MS led to the development of disease-modifying therapies (DMTs). These medications aimed to reduce relapse rates, slow disease progression, and manage symptoms.

2004: Natalizumab, a monoclonal antibody targeting immune cells, was approved as a treatment for MS. It showed significant efficacy in reducing relapse rates but was later associated with a rare side effect called progressive multifocal leukoencephalopathy (PML).

2010s: The introduction of oral DMTs and newer generation injectable therapies expanded the treatment options for MS, providing individuals with more choices and personalized approaches to managing the disease.

Ongoing research continues to improve our understanding of MS, uncover new treatment strategies, and explore the underlying causes of the disease.

Neuromyelitis Optica Spectrum Disorders (NMOSD):

Neuromyelitis optica spectrum disorders (NMOSD) are a group of autoimmune disorders that primarily affect the optic nerves and spinal cord. NMOSD was initially considered a variant of multiple sclerosis, but it is now recognized as a distinct disease entity.

Here's a brief history of NMOSD:

1870: German physician Eugen Devic described a patient with simultaneous optic neuritis and myelitis, which later became known as Devic's disease. This early description marked the beginning of understanding NMOSD as a separate condition from MS.

2004: The discovery of a specific antibody called NMO-IgG or aquaporin-4 antibody (AQP4-IgG) revolutionized the diagnosis and understanding of NMOSD. This antibody, found in the majority of NMOSD cases, targets the aquaporin-4 water channel protein, leading to inflammation and damage to the optic nerves and spinal cord.

2006: The International Panel for NMO Diagnosis (IPND) established diagnostic criteria for NMOSD, distinguishing it from MS. These criteria helped clinicians differentiate between the two diseases and improve the accuracy of diagnosis.

2015: Rituximab, a monoclonal antibody that depletes B-cells, was identified as an effective treatment for NMOSD. It significantly reduced the frequency of relapses and disability progression in individuals with NMOSD.

Since then, additional treatment options and therapeutic strategies, such as other monoclonal antibodies and immunosuppressive medications, have been explored and developed to manage NMOSD.

It's important to note that both the history and understanding of MS and NMOSD are continuously evolving as scientific research progresses. New discoveries and advancements in diagnosis and treatment may have been made since my last update in September 2021. Therefore, it's always advisable to consult up-to-date medical sources and professionals for the most recent information on these conditions.

Classification of Multiple sclerosis , MS /Neuromyelitis Optica Spectrum Disorders , NMOSD:

Multiple sclerosis MS:

Multiple sclerosis (MS) is classified into different subtypes based on the clinical course and disease characteristics. The most commonly used classification system is the revised McDonald criteria, which incorporates clinical, radiological, and laboratory findings. The subtypes of MS include:

Relapsing-Remitting Multiple Sclerosis (RRMS): This is the most common form of MS, characterized by clearly defined relapses or exacerbations followed by partial or complete recovery (remission) periods. Between relapses, individuals may experience stable or improving symptoms.

Secondary Progressive Multiple Sclerosis (SPMS): SPMS follows an initial relapsing-remitting course. Over time, there is a progressive worsening of neurological function, with or without relapses or acute exacerbations. In this stage, there may be occasional temporary improvements or minor remissions.

Primary Progressive Multiple Sclerosis (PPMS): PPMS is characterized by a steady worsening of neurological function from the onset, without distinct relapses or remissions. The progression may be more gradual compared to SPMS, and individuals often experience more spinal cord involvement.

Progressive-Relapsing Multiple Sclerosis (PRMS): PRMS is characterized by a progressive worsening of symptoms from the onset, along with occasional relapses or acute exacerbations. Unlike RRMS, there are no periods of remission, and the disease continues to progress over time.

Note: In addition to the above subtypes, there are other less common or atypical forms of MS, including benign MS and clinically isolated syndrome (CIS), which may be a precursor to the development of definite MS.

Classification of Neuromyelitis Optica Spectrum Disorders (NMOSD):

Neuromyelitis optica spectrum disorders (NMOSD) are a group of autoimmune disorders that primarily affect the optic nerves and spinal cord. The classification of NMOSD is based on clinical and laboratory findings, including the presence of specific antibodies and characteristic disease features. The subtypes of NMOSD include:

Neuromyelitis Optica (NMO): This is the classic form of NMOSD, characterized by severe attacks of optic neuritis (inflammation of the optic nerves) and myelitis (inflammation of the spinal cord). Individuals with NMO may experience recurrent episodes of these two core clinical features.

NMO Spectrum Disorders (NMOSD): NMOSD includes a broader spectrum of disorders that share some features with NMO but may have atypical or limited presentations. These disorders can involve other areas of the central nervous system, such as the brainstem, hypothalamus, or cerebral hemispheres.

It's worth noting that the classification and understanding of MS and NMOSD are

subject to ongoing research and may be updated over time. New diagnostic criteria and disease subtypes may emerge as scientific knowledge advances. Therefore, it's essential to consult with healthcare professionals for the most up-to-date and accurate information regarding the classification of MS and NMOSD.

Symptoms and signs in Multiple Sclerosis , MS/ Neuromyelitis Optica Spectrum Disorders , NMOSD:

Symptoms and signs in Multiple Sclerosis (MS):

Multiple sclerosis (MS) can cause a wide range of symptoms and signs that vary in severity and progression. The symptoms and signs can affect different areas of the body and may include:

Visual Disturbances: Blurred or double vision, loss of contrast sensitivity, eye pain, and involuntary eye movements (nystagmus).

Fatigue: A common symptom in MS, characterized by a persistent feeling of exhaustion that is not relieved by rest.

Motor Symptoms: Weakness, muscle spasms, difficulty walking or maintaining balance, coordination problems, and tremors.

Sensory Changes: Numbness or tingling in the limbs, altered sensations such as burning or itching, and heightened sensitivity to touch, temperature, or pain.

Cognitive Impairment: Problems with memory, attention, concentration, information processing speed, and problem-solving abilities. Some individuals may also experience changes in judgment and reasoning.

Bowel and Bladder Dysfunction: Constipation, diarrhea, urinary urgency, frequency, or incontinence.

Emotional Changes: Depression, anxiety, mood swings, irritability, and emotional instability.

Pain: MS-related pain can manifest as chronic pain in various parts of the body, including neuropathic pain (caused by nerve damage).

Symptoms and signs in Neuromyelitis Optica Spectrum Disorders (NMOSD):

Neuromyelitis optica spectrum disorders (NMOSD) primarily affect the optic nerves and spinal cord, leading to specific symptoms and signs. These can include:

Optic Neuritis: Sudden pain in the eye(s), blurred or dimmed vision, loss of vision, or visual field defects.

Transverse Myelitis: Severe back pain, muscle weakness or paralysis in the legs or arms, altered sensation or numbness, loss of bladder and bowel control, and difficulty with coordination and balance.

Area Postrema Syndrome: Attacks of intractable hiccups or nausea and vomiting caused by inflammation in the area postrema of the brainstem.

Brainstem Symptoms: Depending on the location of inflammation, NMOSD can cause various brainstem-related symptoms, such as facial weakness or numbness, difficulty swallowing or speaking, and problems with coordination and balance.

Respiratory Compromise: In severe cases, NMOSD can lead to respiratory muscle weakness, resulting in breathing difficulties.

It's important to note that these symptoms and signs can vary among individuals, and not all individuals with MS or NMOSD will experience the same manifestations.

Additionally, other conditions can present with similar symptoms, so a comprehensive medical evaluation and diagnostic testing are necessary to differentiate between these disorders.

If you or someone you know is experiencing any concerning symptoms, it's crucial to consult with a healthcare professional for an accurate diagnosis and appropriate management.

Image study in Multiple sclerosis , MS /Neuromyelitis Optica Spectrum Disorders , NMOSD

Imaging studies play a crucial role in the diagnosis and management of both Multiple Sclerosis (MS) and Neuromyelitis Optica Spectrum Disorders (NMOSD). The following imaging modalities are commonly used:

Magnetic Resonance Imaging (MRI): MRI is the primary imaging technique used for both MS and NMOSD. It provides detailed images of the brain, spinal cord, and optic nerves, allowing for the visualization of lesions and abnormalities. Key MRI features include:

T1-weighted images: These provide information about the structure and anatomy of the brain and spinal cord.

T2-weighted images: These are sensitive to areas of inflammation, demyelination, and edema, allowing for the identification of MS or NMOSD lesions.

Fluid-attenuated inversion recovery (FLAIR): FLAIR images suppress the signal from cerebrospinal fluid (CSF), enhancing the visibility of MS and NMOSD lesions.

Gadolinium-enhanced MRI: Intravenous administration of a contrast agent (gadolinium) can help identify active areas of inflammation or blood-brain barrier disruption. Enhancing lesions on MRI suggest recent or ongoing disease activity.

Optical Coherence Tomography (OCT): OCT is a non-invasive imaging technique used to evaluate the structure of the retina and optic nerve. It can detect thinning of the retinal nerve fiber layer, indicative of optic nerve damage seen in both MS and NMOSD.

Spinal Cord Imaging: Specific imaging techniques such as T2-weighted and T1-weighted sequences can be focused on the spinal cord to detect lesions or

abnormalities that may contribute to MS or NMOSD symptoms.

These imaging studies help in:

Confirming the presence of lesions and their distribution in the CNS.

Differentiating between MS and NMOSD.

Monitoring disease progression, activity, and treatment response.

Assessing the involvement of specific regions, such as the optic nerves or spinal cord.

Ruling out other conditions with similar symptoms.

Interpretation of imaging findings, along with clinical history and other diagnostic tests, is crucial for accurate diagnosis and management decisions in MS and NMOSD.

It's important to consult with healthcare professionals who specialize in neurology and imaging to ensure appropriate interpretation and utilization of imaging studies.

Genetic mutation in Multiple sclerosis , MS and Neuromyelitis Optica Spectrum Disorders , NMOSD

Multiple Sclerosis (MS):

Multiple sclerosis (MS) is not primarily considered a genetic disorder. While there is a genetic component to MS, it is a complex disease with a combination of genetic and environmental factors contributing to its development. Genetic studies have identified several genetic variations associated with an increased risk of developing MS. Some of the genes implicated in MS susceptibility include:

HLA-DRB1: Variants of the HLA-DRB1 gene, part of the human leukocyte antigen (HLA) system involved in immune responses, have been associated with an increased risk of developing MS.

IL2RA: Variations in the interleukin 2 receptor alpha (IL2RA) gene, which plays a role in immune regulation, have been linked to MS susceptibility.

CD40: Genetic variations in the CD40 gene, involved in immune system activation, have been associated with an increased risk of developing MS.

TNFRSF1A: Mutations in the TNFRSF1A gene, which is involved in the regulation of inflammation, have been implicated in certain rare forms of MS with a more severe clinical course.

It's important to note that having these genetic variations does not guarantee the development of MS, and individuals without these variations can still develop the disease. Environmental factors, such as infections, vitamin D levels, and smoking, also play significant roles in the development of MS.

Neuromyelitis Optica Spectrum Disorders (NMOSD):

In contrast to MS, a specific genetic mutation has been identified in Neuromyelitis Optica Spectrum Disorders (NMOSD). The majority of NMOSD cases are associated with the presence of autoantibodies known as aquaporin-4 antibodies (AQP4-IgG).

These antibodies target the aquaporin-4 water channel protein, leading to inflammation and damage in the central nervous system.

The presence of AQP4-IgG antibodies is highly specific to NMOSD and can aid in differentiating it from MS. While AQP4-IgG antibodies are not present in all NMOSD cases, their detection is considered a key diagnostic marker for NMOSD.

It's important to recognize that the understanding of genetic factors in MS and NMOSD is an active area of research, and ongoing studies continue to shed light on the complex interplay between genetics, immune system dysregulation, and environmental factors in these conditions.

Mitochondrial dysfunction in Multiple sclerosis , MS and Neuromyelitis Optica Spectrum Disorders , NMOSD

Mitochondrial dysfunction has been implicated in the pathogenesis of multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD), although its exact role and contribution to these diseases are still being studied. Here's some information on the involvement of mitochondrial dysfunction in MS and NMOSD:

Multiple Sclerosis (MS):

Mitochondrial dysfunction: Studies have suggested that mitochondrial dysfunction, including impaired mitochondrial respiration and energy metabolism, oxidative stress, and abnormalities in mitochondrial DNA (mtDNA), may contribute to the development and progression of MS.

Axonal damage: Mitochondrial dysfunction can lead to axonal damage and loss, which is a major pathological feature of MS. It can impair energy production and lead to neurodegeneration in MS lesions.

Inflammatory response: Mitochondrial dysfunction can also influence immune responses in MS. Dysfunctional mitochondria in immune cells may lead to abnormal immune activation and inflammatory processes that contribute to MS pathology.

Potential therapeutic target: Modulating mitochondrial function and improving mitochondrial health are emerging as potential therapeutic strategies for MS, although further research is needed to establish their efficacy.

Neuromyelitis Optica Spectrum Disorder (NMOSD):

Limited evidence: There is limited research specifically focused on mitochondrial dysfunction in NMOSD compared to MS. However, some studies have indicated potential involvement of mitochondrial dysfunction in NMOSD pathogenesis.

Inflammatory demyelination: Similar to MS, NMOSD is characterized by inflammatory demyelination. Mitochondrial dysfunction may contribute to the inflammatory processes and subsequent tissue damage seen in NMOSD.

Astrocytic involvement: NMOSD is often associated with the presence of

autoantibodies against the aquaporin-4 (AQP4) water channel, predominantly expressed on astrocytes. Mitochondrial dysfunction in astrocytes may play a role in the pathogenesis of NMOSD, although further research is needed to elucidate the specific mechanisms.

Therapeutic implications: The potential role of mitochondrial dysfunction in NMOSD may offer new therapeutic targets. However, more research is required to better understand the precise mechanisms and to develop targeted interventions.

Overall, while mitochondrial dysfunction appears to be involved in the pathogenesis of both MS and NMOSD, further research is needed to fully elucidate the underlying mechanisms and to develop effective therapeutic strategies targeting mitochondrial function in these diseases.

Treatment in Multiple sclerosis › MS and Neuromyelitis Optica Spectrum Disorders › NMOSD

Treatment approaches for Multiple Sclerosis (MS) and Neuromyelitis Optica Spectrum Disorders (NMOSD) aim to manage symptoms, prevent relapses, slow disease progression, and improve quality of life. While there is currently no cure for either condition, various treatment options are available. It's important to note that treatment decisions should be made in consultation with healthcare professionals who specialize in these conditions. Here are the treatment strategies commonly employed:

Multiple Sclerosis (MS) Treatment:

Disease-Modifying Therapies (DMTs): DMTs are a cornerstone of MS treatment. These medications help reduce the frequency and severity of relapses, slow disease progression, and manage inflammation in the central nervous system. The choice of DMT depends on various factors, including disease subtype, activity, and individual patient characteristics. Examples of DMTs include interferons, glatiramer acetate, dimethyl fumarate, teriflunomide, and monoclonal antibodies like natalizumab, ocrelizumab, and alemtuzumab.

Symptom Management: MS symptoms can be diverse and may require specific management approaches. Symptomatic treatment may include medications for spasticity, pain, fatigue, bladder dysfunction, and depression. Physical therapy, occupational therapy, and rehabilitation programs are also employed to improve mobility, strength, coordination, and overall function.

Relapse Management: Acute relapses or exacerbations in MS may be treated with short courses of high-dose corticosteroids to reduce inflammation and hasten recovery.

Supportive Care: MS management often involves a multidisciplinary approach to address the physical, psychological, and social aspects of the disease. Supportive care

may include counseling, vocational rehabilitation, social services, and support groups.

Neuromyelitis Optica Spectrum Disorders (NMOSD) Treatment:

Immunotherapy: The primary goal of NMOSD treatment is to prevent relapses and control disease activity. This is achieved through immunosuppressive or immunomodulatory medications. Some commonly used treatments for NMOSD include:

High-dose corticosteroids: These may be used for acute attacks or as short-term therapy during relapses.

Plasma Exchange (PLEX): PLEX is a procedure in which plasma is separated from blood cells and replaced with a substitute solution. It can be effective in severe or refractory NMOSD attacks.

Immunosuppressive medications: Azathioprine, mycophenolate mofetil, rituximab, and eculizumab are among the immunosuppressive medications used to prevent NMOSD relapses.

Aquaporin-4 (AQP4) antibody-targeted therapies: In recent years, several monoclonal antibodies specifically targeting AQP4 antibodies, such as eculizumab and inebilizumab, have shown promise in preventing NMOSD relapses.

Symptomatic Management: Similar to MS, symptomatic treatment is crucial in NMOSD to address specific symptoms such as optic neuritis, transverse myelitis, and other associated manifestations. Medications, physical therapy, and supportive care may be employed based on individual needs.

Rehabilitation: Rehabilitation programs, including physical therapy, occupational therapy, and speech therapy, can help manage residual symptoms and improve function and quality of life.

Treatment decisions for both MS and NMOSD are personalized and should be based on individual patient characteristics, disease activity, and preferences. Regular monitoring and close follow-up with healthcare professionals are essential to ensure optimal treatment outcomes and adjust the treatment plan as needed.

20. Neurofibromatosis type II (神經纖維瘤症候群第二型)

History of Neurofibromatosis type II

Neurofibromatosis type 2 (NF2) is a rare genetic disorder that was first described in the medical literature in the late 19th century. Here is a brief overview of the history of NF2:

Late 19th Century: The term "neurofibromatosis" was coined by the German pathologist Friedrich von Recklinghausen in 1882. He described a group of disorders characterized by the growth of tumors in the nerves, leading to the formation of multiple neurofibromas. This term encompassed both Neurofibromatosis type 1 (NF1) and Neurofibromatosis type 2 (NF2).

Early 20th Century: In 1917, Harvey Cushing, an American neurosurgeon, reported a case of bilateral acoustic neuromas, which are the hallmark tumors of NF2. He recognized that these tumors could cause hearing loss and other neurological symptoms.

1960s: More detailed clinical and pathological descriptions of NF2 were provided by researchers such as Dr. Vincent J. Hyams and Dr. I. George Miller. They emphasized the distinct features of NF2, including the characteristic pattern of tumor growth in the central nervous system and the hereditary nature of the disorder.

1987: The specific genetic mutation responsible for NF2 was identified by scientists. The NF2 gene, located on chromosome 22, was discovered through genetic linkage studies. This gene encodes a protein called merlin or schwannomin, which functions as a tumor suppressor. Mutations in the NF2 gene lead to the development of tumors in the nervous system.

1993: The diagnostic criteria for NF2 were established by the National Institutes of Health Consensus Development Conference. These criteria included the presence of bilateral acoustic neuromas and other characteristic tumors, as well as a family history of NF2 or the identification of an NF2 gene mutation.

2000s and Beyond: Advances in genetic testing have improved the ability to detect NF2 mutations and facilitate early diagnosis. The understanding of the molecular mechanisms underlying NF2 has also expanded, leading to potential targeted therapies for the treatment of NF2-associated tumors.

The history of NF2 is marked by significant milestones in the understanding of the disorder, including the identification of the NF2 gene and the establishment of diagnostic criteria. Ongoing research continues to shed light on the genetic basis, pathophysiology, and potential treatment options for NF2.

Classification of Neurofibromatosis type II

Neurofibromatosis type 2 (NF2) is classified as a subtype of neurofibromatosis, a group of genetic disorders characterized by the growth of tumors in the nervous system. NF2 is specifically distinguished by the presence of bilateral vestibular schwannomas, also known as acoustic neuromas. Here is a classification overview of NF2:

Diagnostic Criteria:

NF2 is diagnosed based on specific clinical criteria established by the National Institutes of Health (NIH) Consensus Development Conference in 1993. The criteria for a definitive diagnosis of NF2 include:

Bilateral vestibular schwannomas: The presence of benign tumors arising from the nerves responsible for balance and hearing, affecting both sides of the brain.

Family history: A first-degree relative (parent, sibling, or child) with a confirmed diagnosis of NF2.

Unilateral vestibular schwannoma and additional criteria: Presence of a unilateral vestibular schwannoma (only affecting one side) and either a first-degree relative with NF2, the presence of two or more meningiomas, gliomas, schwannomas, or neurofibromas, or other specific characteristic tumors.

Other Tumors and Features:

In addition to bilateral vestibular schwannomas, individuals with NF2 may develop other tumor types and clinical features, which can aid in the diagnosis and classification of the condition. These can include:

Meningiomas: Benign tumors arising from the meninges, the protective covering of the brain and spinal cord.

Schwannomas: Tumors originating from Schwann cells that can affect various nerves in the body.

Ependymomas: Tumors that arise from the ependymal cells lining the ventricles of the brain or the central canal of the spinal cord.

Other central nervous system tumors: Individuals with NF2 may develop gliomas, neurofibromas, or other types of tumors in the brain and spinal cord.

Mosaicism:

In some cases, NF2 can exhibit mosaicism, where the genetic mutation occurs in only a portion of the body's cells. Mosaic NF2 can result in a milder phenotype or atypical features compared to classic NF2.

Genetic Testing:

Genetic testing plays a crucial role in confirming the diagnosis of NF2. It involves identifying mutations in the NF2 gene located on chromosome 22. Molecular genetic testing can detect pathogenic variants in the NF2 gene, assisting in the classification

of NF2 and providing valuable information for genetic counseling.

It's important to note that the classification and diagnosis of NF2 are complex, involving a combination of clinical criteria, tumor characteristics, and genetic testing results. A thorough evaluation by healthcare professionals with expertise in NF2 and genetic counseling is essential for accurate classification and management of the condition.

Symptom and sign in Neurofibromatosis type II

Neurofibromatosis type 2 (NF2) is a genetic disorder characterized by the development of tumors in the nervous system. The signs and symptoms of NF2 can vary among individuals, but there are several common features associated with the condition. Here are the key symptoms and signs seen in NF2:

Bilateral Vestibular Schwannomas (Acoustic Neuromas):

The hallmark feature of NF2 is the presence of bilateral vestibular schwannomas, which are benign tumors that develop on the nerves responsible for balance and hearing. These tumors can cause hearing loss, tinnitus (ringing in the ears), dizziness, and problems with balance and coordination.

Other Cranial Nerve Tumors:

Besides vestibular schwannomas, individuals with NF2 may develop tumors affecting other cranial nerves, including:

Trigeminal schwannomas: Tumors that affect the trigeminal nerve, leading to facial numbness, tingling, or pain.

Facial schwannomas: Tumors involving the facial nerve, which can cause facial weakness or paralysis.

Oculomotor schwannomas: Tumors affecting the oculomotor nerve, resulting in eye movement abnormalities or drooping eyelids.

Spinal Tumors:

NF2 can also involve tumors in the spinal cord, including schwannomas, meningiomas, and ependymomas. These tumors can cause weakness or numbness in the limbs, difficulty walking, and problems with bowel or bladder function.

Other Tumors and Lesions:

NF2 may lead to the development of various tumors and lesions outside the nervous system, including:

Meningiomas: Benign tumors arising from the meninges, which can cause headaches, seizures, or focal neurological deficits.

Schwannomas: Tumors originating from Schwann cells, which can affect peripheral nerves and cause localized pain, weakness, or sensory disturbances.

Neurofibromas: Noncancerous tumors that can develop on nerves throughout the

body.

Cataracts: Clouding of the lens of the eye, leading to vision impairment.

Other Manifestations:

Some individuals with NF2 may experience additional features, such as:

Cognitive and learning difficulties: NF2 can be associated with mild cognitive impairment, including difficulties with attention, memory, and processing speed.

Skin changes: Skin abnormalities, such as cafe-au-lait spots or subcutaneous nodules, can occur in NF2, although they are less common than in Neurofibromatosis type 1 (NF1).

It's important to note that the severity and progression of NF2 symptoms can vary widely among affected individuals, even within the same family. Regular medical monitoring, including neuroimaging and audiological assessments, is essential to detect and manage the signs and symptoms of NF2 and to address any potential complications. Early intervention and a multidisciplinary approach involving various specialists, such as neurologists, neurosurgeons, and audiologists, can help optimize the management and quality of life for individuals with NF2.

Image study in Neurofibromatosis type II

In the diagnosis and management of Neurofibromatosis type 2 (NF2), various imaging studies play a crucial role in evaluating the extent and characteristics of the tumors and lesions associated with the condition. Here are some common imaging modalities used in NF2:

Magnetic Resonance Imaging (MRI):

MRI is the primary imaging modality for assessing NF2-related tumors and lesions. It provides detailed images of the brain, spinal cord, and nerves, allowing for the detection, localization, and characterization of various NF2-associated tumors, including vestibular schwannomas, meningiomas, and spinal cord tumors. MRI can help determine the size, location, and growth pattern of the tumors, as well as their effects on surrounding structures.

Computed Tomography (CT) Scan:

CT scans may be used in certain situations to evaluate specific aspects of NF2, such as assessing the bony structures and identifying calcifications within tumors. While MRI is the preferred imaging modality, CT scans can provide additional information in certain cases, particularly for evaluating the bony abnormalities associated with NF2.

Auditory Brainstem Response (ABR) Testing:

ABR testing, also known as auditory evoked potentials, is a specialized test used to assess the hearing function in individuals with NF2. It measures the electrical activity

generated by the auditory nerve and brainstem in response to sound stimuli. ABR testing can help diagnose and monitor the progression of vestibular schwannomas, which are a characteristic feature of NF2.

Ophthalmic Examination:

Ophthalmic examinations, including fundoscopy, may be performed to evaluate ocular manifestations of NF2. These examinations can help detect features such as retinal hamartomas, which are benign tumors that may be present in NF2.

Whole-Body Imaging:

In some cases, whole-body imaging techniques such as positron emission tomography (PET) or whole-body MRI may be employed to screen for additional tumors or lesions beyond the central nervous system. These imaging studies can help identify extra-cranial manifestations of NF2, such as peripheral schwannomas or neurofibromas.

It's important to note that the specific imaging studies used in NF2 may vary depending on the individual's clinical presentation and the expertise available. Imaging findings, along with clinical examination and genetic testing, contribute to the diagnosis and ongoing management of NF2. Regular imaging surveillance is often recommended to monitor tumor growth, assess treatment response, and guide therapeutic decisions.

Genetic mutation in Neurofibromatosis type II

Neurofibromatosis type 2 (NF2) is caused by mutations in the NF2 gene. The NF2 gene is located on chromosome 22 and provides instructions for producing a protein called Merlin (also known as schwannomin). Merlin is a tumor suppressor protein that regulates cell growth and proliferation. Mutations in the NF2 gene result in the production of a defective or non-functional Merlin protein, leading to the development of tumors in the nervous system.

The majority of NF2 cases (approximately 95%) are caused by spontaneous or de novo mutations, meaning they occur for the first time in an affected individual and are not inherited from their parents. However, NF2 can also be inherited in an autosomal dominant manner, with a 50% chance of passing on the mutated gene to each child. The most common type of mutation in NF2 is a loss-of-function mutation, where a segment of the NF2 gene is deleted or disrupted. This results in the absence or reduced production of functional Merlin protein. Other types of mutations can include insertions, duplications, or point mutations, which alter the structure or function of the protein.

It's important to note that the presence of an NF2 gene mutation does not necessarily mean that a person will develop NF2 or experience the same severity of symptoms.

The specific type and location of the mutation, as well as other genetic and environmental factors, can influence the variability of the disease presentation. Genetic testing is available for individuals suspected of having NF2 or with a family history of the condition. Molecular genetic testing can detect NF2 gene mutations and aid in confirming the diagnosis. Additionally, genetic testing can provide important information for genetic counseling, family planning, and risk assessment for family members.

It's recommended that individuals with suspected NF2 or a family history of NF2 consult with healthcare professionals with expertise in genetics and neurofibromatosis to discuss the potential benefits and limitations of genetic testing.

Mitochondrial dysfunction in Neurofibromatosis type II

Neurofibromatosis type 2 (NF2) is a rare genetic disorder characterized by the development of multiple benign tumors, called vestibular schwannomas, along the nerves that control hearing and balance. These tumors typically arise from the Schwann cells, which are responsible for the myelination and maintenance of peripheral nerves. While NF2 is primarily caused by mutations in the NF2 gene on chromosome 22, which encodes a protein called merlin or schwannomin, there is limited evidence suggesting a potential link between mitochondrial dysfunction and the development or progression of NF2.

Mitochondrial dysfunction refers to impaired functioning of the mitochondria, the cellular organelles responsible for energy production through oxidative phosphorylation. It can manifest as deficiencies in mitochondrial respiration, increased reactive oxygen species (ROS) production, and abnormal mitochondrial morphology. While studies have shown that merlin interacts with proteins involved in mitochondrial dynamics and metabolism, the exact role of mitochondrial dysfunction in NF2 is not well-established.

Research has suggested that alterations in mitochondrial function, such as impaired oxidative phosphorylation and elevated ROS production, may contribute to the tumorigenic processes observed in NF2. These alterations can potentially affect cellular signaling, DNA damage response, and tumor suppressor pathways, leading to the growth of vestibular schwannomas and other associated tumors. However, the specific mechanisms and extent of mitochondrial dysfunction in NF2 require further investigation.

It is important to note that NF2 is a complex disorder influenced by various genetic and environmental factors. While mitochondrial dysfunction may play a role in the development or progression of NF2, it is likely a multifactorial process involving interactions between merlin protein function, other cellular signaling pathways, and

additional genetic or environmental factors. Further research is needed to fully elucidate the relationship between mitochondrial dysfunction and NF2, as well as its potential implications for diagnosis, treatment, and management of the condition. If you or someone you know is affected by NF2, it is recommended to consult with a healthcare professional or genetic specialist who can provide accurate information, genetic counseling, and appropriate management strategies based on the individual's specific situation.

Treatment in Neurofibromatosis type II

The management of Neurofibromatosis type 2 (NF2) focuses on the individualized treatment and monitoring of associated tumors and symptoms. While there is no cure for NF2, various treatment approaches aim to control tumor growth, preserve neurological function, and improve quality of life. The treatment options for NF2 can include:

Surgical Intervention:

Surgery may be performed to remove tumors that are causing significant symptoms or affecting vital structures. In the case of vestibular schwannomas, surgical options may include tumor resection, tumor debulking (partial removal), or vestibular nerve sectioning to alleviate symptoms such as hearing loss and balance problems. The feasibility and potential risks of surgery depend on factors such as tumor size, location, and individual patient characteristics.

Radiosurgery:

Stereotactic radiosurgery, such as Gamma Knife or CyberKnife, may be considered as an alternative or adjunct to surgery for smaller tumors or those located in critical areas where complete resection is challenging. Radiosurgery uses precisely targeted radiation beams to destroy tumor cells and halt further growth. It can be an effective treatment for controlling tumor growth and preserving neurological function.

Medications:

While there are no specific medications that can cure NF2, some drugs may be used to manage associated symptoms or slow tumor growth. For example, bevacizumab, an anti-angiogenic medication, has shown promise in stabilizing or reducing the size of vestibular schwannomas in some cases. Other medications may be prescribed to manage symptoms such as pain or dizziness.

Auditory Rehabilitation:

Individuals with NF2 and hearing loss may benefit from auditory rehabilitation strategies. These can include the use of hearing aids, assistive listening devices, or cochlear implants, depending on the degree and type of hearing impairment.

Supportive Care:

NF2 is a complex condition that can impact various aspects of a person's life. Supportive care measures aim to address the physical, emotional, and social needs of individuals with NF2. This may include regular monitoring and follow-up with a multidisciplinary team of specialists, such as neurologists, neurosurgeons, audiologists, physical therapists, and genetic counselors. Rehabilitation therapies, counseling, and support groups can also be valuable in managing the challenges associated with NF2.

It's important for individuals with NF2 to receive ongoing medical surveillance to monitor tumor growth and assess potential complications. Regular neuroimaging, audiological assessments, and clinical evaluations are typically recommended to detect any changes in tumor size or neurological function. The treatment approach will depend on the individual's specific situation, tumor characteristics, and overall health. Therefore, it is essential to work closely with a team of healthcare professionals experienced in NF2 to determine the most appropriate and effective treatment plan.

21. Pantothenate Kinase Associated Neurodegeneration (PKAN) (泛

酸鹽激酶關聯之神經退化性疾病)

History of Pantothenate Kinase Associated Neurodegeneration

Pantothenate Kinase Associated Neurodegeneration (PKAN) is a rare, progressive neurodegenerative disorder that belongs to a group of diseases known as neurodegeneration with brain iron accumulation (NBIA). It was first described by Hallervorden and Spatz in 1922 as a distinct clinical entity characterized by progressive dystonia and retinitis pigmentosa.

In the early years, PKAN was primarily recognized as a movement disorder with prominent dystonia and spasticity. However, as research progressed, it became apparent that PKAN is a complex disorder with various clinical features and a wide spectrum of severity.

In 1997, the genetic cause of PKAN was discovered. It was found that mutations in the PANK2 gene, which encodes the enzyme pantothenate kinase 2, are responsible for the development of PKAN. Pantothenate kinase is involved in the biosynthesis of coenzyme A (CoA), an essential molecule for many cellular processes, including energy metabolism and lipid synthesis. Mutations in the PANK2 gene lead to impaired CoA biosynthesis, which is believed to contribute to the neurodegenerative process in PKAN.

Over the years, advances in genetic testing have allowed for improved diagnosis and identification of different genetic mutations associated with PKAN. These mutations can result in different clinical subtypes of the disease, including classic PKAN, atypical PKAN, and an intermediate form.

Research efforts in recent years have focused on understanding the underlying molecular mechanisms of PKAN and exploring potential therapeutic approaches.

While there is currently no cure for PKAN, symptomatic treatment and management of symptoms such as dystonia, spasticity, and other associated complications can help improve the quality of life for individuals with the condition. Experimental therapies, including deep brain stimulation and investigational drugs, are being investigated, but further research is needed to determine their efficacy and safety.

The history of PKAN illustrates the evolving understanding of the disorder, from its initial recognition as a clinical syndrome to the discovery of the genetic mutations underlying the condition. Ongoing research aims to uncover additional insights into the pathogenesis of PKAN and develop effective treatments to slow or halt disease progression.

Classification of Pantothenate Kinase Associated Neurodegeneration

Pantothenate Kinase Associated Neurodegeneration (PKAN) can be classified into different clinical subtypes based on the age of onset and the severity of symptoms.

The main classification system for PKAN includes three subtypes:

Classic PKAN: This is the most common and severe form of PKAN. Symptoms typically appear in early childhood, usually between 3 and 6 years of age. Children with classic PKAN usually develop progressive dystonia, characterized by involuntary muscle contractions and abnormal postures. Other common features include spasticity (muscle stiffness), dysarthria (difficulty in speech), rigidity, and cognitive impairment. The disease progresses rapidly, leading to significant disability and loss of motor function.

Atypical PKAN: This form of PKAN has a later onset, typically during adolescence or adulthood. Atypical PKAN may present with a broader range of symptoms and can have a slower progression compared to classic PKAN. Individuals with atypical PKAN may experience a combination of dystonia, parkinsonism (movement abnormalities similar to Parkinson's disease), and cognitive decline. Seizures and psychiatric symptoms, such as depression and anxiety, can also be present.

Intermediate PKAN: Intermediate PKAN represents a form of the disease that falls between classic and atypical PKAN in terms of symptom severity and age of onset. The clinical features and disease progression can vary widely within this subtype, and individuals may exhibit a combination of symptoms observed in both classic and atypical PKAN.

It is important to note that while these classifications provide a general framework, the presentation and progression of PKAN can vary among individuals. The severity and specific symptoms can be influenced by various factors, including the specific genetic mutation involved.

Genetic testing plays a crucial role in confirming the diagnosis of PKAN and determining the specific genetic mutation associated with the disease.

Symptom and sign in Pantothenate Kinase Associated Neurodegeneration

Pantothenate Kinase Associated Neurodegeneration (PKAN) is characterized by a range of neurological symptoms and signs that typically manifest in childhood. The symptoms and signs of PKAN can vary in severity and progression among individuals. The main features of PKAN include:

Dystonia: Dystonia is a primary symptom of PKAN and is characterized by sustained or intermittent involuntary muscle contractions, leading to abnormal postures and movements. Dystonia in PKAN often starts in the legs and eventually involves other body regions, including the arms, trunk, and face.

Parkinsonism: Parkinsonism refers to a group of movement abnormalities similar to those observed in Parkinson's disease. People with PKAN may exhibit symptoms such as bradykinesia (slowness of movement), rigidity (stiffness), and tremors.

Dysarthria: Dysarthria is a speech disorder caused by impaired control of the muscles used for speech production. In PKAN, dysarthria is common and can manifest as slurred or slow speech, difficulty articulating words, and changes in voice quality.

Spasticity: Spasticity refers to muscle stiffness and increased muscle tone, leading to difficulty in movement and abnormal postures. Individuals with PKAN may experience spasticity, particularly in the legs, which can contribute to gait abnormalities and difficulties with coordination.

Cognitive Impairment: PKAN can lead to cognitive decline, including problems with attention, memory, and executive functions. Intellectual disability can also be present, ranging from mild to severe.

Optic Atrophy: Some individuals with PKAN may develop optic atrophy, which is the degeneration of the optic nerve that can result in visual impairment or loss of vision.

Seizures: Seizures can occur in PKAN, although they are not always present. They may manifest as generalized seizures or focal seizures, depending on the specific areas of the brain affected.

It's important to note that the symptoms and signs of PKAN can progress over time, leading to increasing disability and loss of motor function. The severity and specific combination of symptoms can vary among individuals, even within the same subtype of PKAN. Prompt diagnosis and management are crucial to provide appropriate treatment and support for individuals with PKAN.

Image study in Pantothenate Kinase Associated Neurodegeneration

Various imaging studies can be useful in the diagnosis and evaluation of Pantothenate Kinase Associated Neurodegeneration (PKAN). These imaging techniques help visualize structural abnormalities in the brain and provide valuable information about the extent and progression of the disease. Here are some common imaging studies used in PKAN:

Magnetic Resonance Imaging (MRI): MRI is the most commonly used imaging technique in PKAN. It provides detailed images of the brain's structure and can reveal characteristic findings in PKAN. MRI findings in PKAN typically include changes in the basal ganglia, which is a region of the brain involved in motor control. These changes may manifest as iron accumulation (iron deposition) in the globus pallidus, putamen, and other basal ganglia structures. The iron deposition appears as hyperintensity (bright areas) on T2-weighted or susceptibility-weighted MRI sequences.

Diffusion Tensor Imaging (DTI): DTI is an MRI-based technique that measures the diffusion of water molecules in brain tissue. It provides information about the integrity and connectivity of white matter fibers in the brain. DTI can be helpful in assessing the involvement of white matter tracts in PKAN and detecting abnormalities such as reduced fractional anisotropy (indicating disrupted fiber integrity) and increased mean diffusivity (indicating loss of tissue integrity).

Magnetic Resonance Spectroscopy (MRS): MRS is a specialized MRI technique that measures the chemical composition of brain tissue. It can provide information about metabolic abnormalities in PKAN. MRS may show altered levels of certain metabolites, such as N-acetylaspartate (NAA), choline, and myo-inositol, which reflect cellular integrity and metabolism.

Positron Emission Tomography (PET): PET imaging can assess brain metabolism and function by measuring the distribution of radioactive tracers in the brain. In PKAN, PET scans may reveal hypometabolism (reduced metabolic activity) in affected brain regions, particularly in the basal ganglia.

These imaging studies, along with clinical findings and genetic testing, contribute to the diagnosis and monitoring of PKAN. They help differentiate PKAN from other neurodegenerative disorders and provide valuable insights into the underlying brain abnormalities associated with the disease.

Genetic mutation in Pantothenate Kinase Associated Neurodegeneration

Pantothenate Kinase Associated Neurodegeneration (PKAN) is primarily caused by mutations in the PANK2 gene. The PANK2 gene provides instructions for producing an enzyme called pantothenate kinase 2, which is involved in the biosynthesis of coenzyme A (CoA). CoA plays a critical role in various cellular processes, including energy metabolism and lipid synthesis.

Most cases of PKAN are associated with autosomal recessive inheritance, meaning that an affected individual inherits two copies of the mutated PANK2 gene, one from each parent. The specific mutations in the PANK2 gene can vary among individuals and may involve small deletions, insertions, or substitutions of DNA building blocks (nucleotides).

These mutations in the PANK2 gene lead to a deficiency or dysfunction of pantothenate kinase 2 enzyme activity, impairing the biosynthesis of CoA. The resulting CoA deficiency disrupts normal cellular processes, particularly in the brain, leading to the characteristic neurodegeneration seen in PKAN.

It is important to note that not all individuals with clinical features of PKAN have mutations in the PANK2 gene. Some individuals may have mutations in other genes that result in a similar phenotype, and these cases are referred to as "atypical PKAN"

or "PKAN-like" conditions. The genetic basis of these atypical forms of PKAN is still being elucidated through ongoing research.

Genetic testing, including sequencing of the PANK2 gene, can be used to confirm a diagnosis of PKAN and identify specific mutations in affected individuals. Genetic counseling is essential for families affected by PKAN to understand the inheritance pattern and potential risks for future pregnancies.

Mitochondrial dysfunction in Pantothenate Kinase Associated Neurodegeneration

Pantothenate Kinase Associated Neurodegeneration (PKAN), also known as Neurodegeneration with Brain Iron Accumulation 1 (NBIA1), is a rare neurodegenerative disorder characterized by the abnormal accumulation of iron in the brain and progressive neurological symptoms. While PKAN is primarily caused by mutations in the PANK2 gene, which encodes the enzyme pantothenate kinase 2 involved in Coenzyme A (CoA) biosynthesis, there is growing evidence suggesting a potential link between mitochondrial dysfunction and the pathogenesis of PKAN. Mitochondria play a critical role in energy production, oxidative stress regulation, and cellular metabolism. Dysfunction of the mitochondria can lead to impaired energy production, increased oxidative stress, and disruption of various cellular processes. In the case of PKAN, mitochondrial dysfunction is thought to contribute to the neurodegenerative processes observed in the disease.

Studies have shown that PANK2 mutations can lead to impaired CoA biosynthesis and subsequent CoA deficiency in cells. CoA is an essential molecule involved in multiple cellular processes, including energy metabolism, fatty acid oxidation, and antioxidant defenses. Reduced CoA levels can affect mitochondrial function, including impaired oxidative phosphorylation and increased production of reactive oxygen species (ROS). These mitochondrial abnormalities, in turn, can lead to cellular dysfunction, oxidative stress, and neuronal damage in PKAN.

Furthermore, studies using cellular and animal models of PKAN have demonstrated alterations in mitochondrial morphology and impaired mitochondrial dynamics, such as abnormal mitochondrial fusion and fission. These mitochondrial dynamics abnormalities can disrupt the normal distribution and function of mitochondria within cells, further contributing to mitochondrial dysfunction and cellular damage in PKAN. While the exact mechanisms linking mitochondrial dysfunction to the neurodegenerative processes in PKAN are not fully understood, it is clear that mitochondria play a significant role in the disease pathology. Targeting mitochondrial dysfunction and oxidative stress has been suggested as a potential therapeutic approach for PKAN, although further research is needed to develop effective

treatments.

If you or someone you know is affected by PKAN, it is recommended to consult with a healthcare professional or genetic specialist who can provide accurate information, genetic counseling, and appropriate management strategies based on the individual's specific situation.

Treatment in Pantothenate Kinase Associated Neurodegeneration

Currently, there is no cure for Pantothenate Kinase Associated Neurodegeneration (PKAN), and the available treatments aim to manage the symptoms and improve the quality of life for affected individuals. The treatment approach for PKAN is typically multidisciplinary and may involve the following:

Symptomatic management: Medications can be prescribed to help control symptoms such as dystonia, spasticity, and seizures. Examples include muscle relaxants, anticonvulsant medications, and botulinum toxin injections to reduce muscle stiffness and spasms.

Physical and occupational therapy: Physical and occupational therapy can help improve mobility, maintain joint flexibility, and enhance overall functional abilities. These therapies may include exercises, stretching, assistive devices, and adaptive techniques to promote independence and optimize motor skills.

Speech and communication therapy: Individuals with PKAN may experience difficulties with speech and communication due to muscle stiffness and dystonia. Speech and communication therapy can assist in improving speech articulation, developing alternative communication strategies, and enhancing overall language skills.

Supportive care: Managing the symptoms and complications associated with PKAN is an essential part of treatment. This may involve nutritional support, management of feeding difficulties, respiratory care, and addressing any associated medical conditions such as epilepsy or gastrointestinal issues.

Genetic counseling: Genetic counseling is crucial for individuals with PKAN and their families. Genetic counselors can provide information about the inheritance pattern, recurrence risks, and options for family planning. They can also help connect families with support groups and resources for PKAN.

It's worth mentioning that there are ongoing research efforts aimed at developing potential disease-modifying treatments for PKAN. These include exploring novel therapeutic approaches, such as gene therapy and targeted pharmacological interventions, to address the underlying biochemical and cellular abnormalities in PKAN. Clinical trials and experimental treatments may be available for eligible individuals, and consultation with a medical geneticist or a neurologist specializing in

movement disorders can provide further guidance on potential treatment options and participation in research studies.

22. Pelizaeus-Merzbacher Disease(Pelizaeus-Merzbacher 氏症(慢性兒童型腦硬化症))

History of Pelizaeus-Merzbacher Disease

Pelizaeus-Merzbacher disease (PMD) is a rare genetic disorder that primarily affects the central nervous system, particularly the brain and spinal cord. It was first described by German neurologists Friedrich Pelizaeus and Ludwig Merzbacher in the late 19th and early 20th centuries. Here is a brief history of Pelizaeus-Merzbacher disease:

Discovery by Friedrich Pelizaeus (1885): In 1885, Friedrich Pelizaeus, a German neurologist, observed a group of patients with a specific pattern of symptoms, including nystagmus (involuntary eye movements), ataxia (lack of muscle coordination), and spasticity (muscle stiffness). He documented these cases and recognized a distinct clinical entity, which later became known as Pelizaeus-Merzbacher disease.

Work by Ludwig Merzbacher (1910): Ludwig Merzbacher, another German neurologist, made significant contributions to the understanding of Pelizaeus-Merzbacher disease. In 1910, he published a comprehensive description of the disease, including its clinical features and pathological findings. He highlighted the progressive nature of the disorder and characterized the specific changes in the white matter of the brain.

Advances in Genetic Research: Over the years, advancements in genetic research have contributed to a better understanding of the underlying genetic basis of Pelizaeus-Merzbacher disease. In the late 20th century, researchers identified mutations in the PLP1 (Proteolipid Protein 1) gene as the primary cause of the disease. This gene provides instructions for the production of a protein called myelin proteolipid protein, which is crucial for the formation and maintenance of myelin, the protective covering of nerve fibers.

Subtypes and Genotype-Phenotype Correlations: Further research has revealed that Pelizaeus-Merzbacher disease exhibits clinical and genetic heterogeneity. Different subtypes of the disease have been identified based on the specific genetic mutations and associated clinical features. These subtypes include classic Pelizaeus-Merzbacher disease, congenital Pelizaeus-Merzbacher disease, and spastic paraplegia type 2.

Genotype-phenotype correlations have provided insights into the variability of symptoms and disease severity among individuals with Pelizaeus-Merzbacher disease.

Current Research and Treatment: Current research efforts are focused on understanding the underlying mechanisms of Pelizaeus-Merzbacher disease and

developing potential therapeutic strategies. Treatment approaches primarily aim to manage the symptoms and provide supportive care. These may include physical therapy, occupational therapy, and assistive devices to address motor and developmental challenges. Additionally, ongoing research into gene therapy and other emerging therapeutic approaches holds promise for future treatment options. It's important to note that the understanding of Pelizaeus-Merzbacher disease continues to evolve as scientific knowledge advances. Ongoing research and clinical studies are essential for further elucidating the disease mechanisms, developing targeted treatments, and improving the quality of life for individuals affected by Pelizaeus-Merzbacher disease.

Classification of Pelizaeus-Merzbacher Disease

Pelizaeus-Merzbacher disease (PMD) is classified into different subtypes based on the specific genetic mutations and associated clinical features. The classification helps in understanding the variability in symptoms and disease severity among individuals with PMD. The main subtypes of PMD include:

Classic Pelizaeus-Merzbacher Disease (PMD): This is the most common and well-known form of PMD. It is typically characterized by early-onset nystagmus (involuntary eye movements), hypotonia (low muscle tone), ataxia (lack of muscle coordination), spasticity (muscle stiffness), and developmental delays. Individuals with classic PMD often experience progressive neurological deterioration over time.

Connatal Pelizaeus-Merzbacher Disease: This subtype of PMD is typically more severe and presents with symptoms from birth or infancy ("connatal" refers to congenital or present at birth). Connatal PMD is characterized by profound hypotonia, severe spasticity, seizures, respiratory difficulties, and significant intellectual and developmental disabilities. The course of the disease is often rapid and associated with a poorer prognosis.

Transitional Pelizaeus-Merzbacher Disease: This subtype represents an intermediate form between classic PMD and connatal PMD. The onset of symptoms and disease progression may vary, and the severity can range from moderate to severe. Individuals with transitional PMD may have delayed motor milestones, intellectual disability, spasticity, and nystagmus.

Pelizaeus-Merzbacher-Like Disease: This category encompasses cases that share some clinical features with PMD but are caused by mutations in genes other than PLP1. These genes may include GJC2 (gap junction protein gamma 2), TJP1 (tight junction protein 1), and others. The symptoms and severity can vary depending on the specific genetic mutation.

It's important to note that the classification of PMD is based on clinical presentation

and genetic findings. Advances in genetic testing and research continue to contribute to a better understanding of the subtypes and associated genes involved in PMD. The classification helps guide diagnosis, prognosis, and management approaches for individuals with PMD.

Symptom and sign in Pelizaeus-Merzbacher Disease

Pelizaeus-Merzbacher disease (PMD) is a rare genetic disorder that primarily affects the central nervous system, particularly the brain and spinal cord. The signs and symptoms of PMD can vary depending on the specific subtype and individual variability. However, common symptoms and signs associated with PMD may include:

Nystagmus: Nystagmus refers to involuntary rhythmic movements of the eyes. It is often one of the earliest signs observed in individuals with PMD. The eyes may move side to side, up and down, or in a circular motion.

Hypotonia: Hypotonia, or low muscle tone, is a common feature of PMD. It may result in poor muscle strength and coordination, leading to delays in motor development milestones such as sitting, crawling, and walking.

Ataxia: Ataxia refers to a lack of muscle coordination, resulting in unsteady movements and difficulty maintaining balance. It can affect both gross motor skills, such as walking, as well as fine motor skills, such as reaching and grasping objects.

Spasticity: Spasticity is characterized by increased muscle tone and stiffness, often leading to stiff and jerky movements. It can affect the arms, legs, and other body parts, contributing to difficulties in mobility and coordination.

Intellectual and developmental disabilities: Many individuals with PMD experience intellectual and developmental delays. These can range from mild to severe and may affect various aspects of cognition, learning, and adaptive functioning.

Speech and language difficulties: Difficulties with speech and language development are common in PMD. Individuals may have limited speech or be nonverbal, and they may require alternative communication methods.

Seizures: Some individuals with PMD may experience seizures, which are abnormal electrical activities in the brain. Seizures can vary in type and severity.

Behavioral and psychiatric issues: Behavioral problems and psychiatric symptoms, such as anxiety, depression, and attention-deficit/hyperactivity disorder (ADHD), can occur in individuals with PMD.

It's important to note that the severity and progression of symptoms can vary among individuals with PMD, even within the same subtype. Early recognition and intervention, along with supportive care, including physical and occupational therapy, can help manage symptoms and improve the quality of life for individuals with PMD.

Image study in Pelizaeus-Merzbacher Disease

In Pelizaeus-Merzbacher disease (PMD), imaging studies play a crucial role in diagnosing and evaluating the extent of brain abnormalities. The most commonly used imaging techniques include:

Magnetic Resonance Imaging (MRI): MRI is the primary imaging modality used in PMD. It provides detailed images of the brain and spinal cord, allowing for the visualization of structural abnormalities. In PMD, MRI typically shows a characteristic pattern of abnormalities known as the "tigroid" or "marbled" appearance. This pattern is characterized by alternating areas of high and low signal intensity, giving the white matter a mottled appearance. Other findings may include thinning of the corpus callosum (the structure that connects the two hemispheres of the brain), enlargement of the ventricles (fluid-filled spaces within the brain), and delayed myelination (the formation of the protective myelin sheath around nerve fibers).

Diffusion Tensor Imaging (DTI): DTI is an advanced MRI technique that allows for the assessment of the microstructural integrity of white matter tracts. It can provide information about the connectivity and organization of the brain's neural pathways. DTI studies in PMD have shown abnormalities in the integrity and organization of white matter tracts, which can help in understanding the underlying pathophysiology of the disease.

Proton Magnetic Resonance Spectroscopy (MRS): MRS is a specialized MRI technique that provides information about the chemical composition of tissues. It can be used to assess metabolic changes in the brain. In PMD, MRS studies have demonstrated alterations in certain metabolites, such as decreased levels of N-acetylaspartate (NAA), which is a marker of neuronal loss or dysfunction.

Computed Tomography (CT): CT scans may be used in certain cases to evaluate the brain structures and identify any gross abnormalities. However, MRI is generally preferred over CT for imaging the brain in PMD due to its superior soft tissue contrast and ability to detect subtle changes.

These imaging studies are essential in the diagnosis and monitoring of Pelizaeus-Merzbacher disease. They can help differentiate PMD from other neurological conditions with similar clinical presentations and provide valuable insights into the extent and characteristics of brain abnormalities.

Genetic mutation in Pelizaeus-Merzbacher Disease

Pelizaeus-Merzbacher disease (PMD) is primarily caused by genetic mutations affecting the PLP1 gene. The PLP1 gene provides instructions for the production of a protein called proteolipid protein 1 (PLP1). This protein plays a crucial role in the

formation and maintenance of myelin, the protective covering around nerve fibers in the central nervous system.

The majority of cases of PMD are associated with duplications or other structural abnormalities of the PLP1 gene. These genetic alterations disrupt the normal production and function of the PLP1 protein, leading to impaired myelination in the brain and spinal cord. Reduced or abnormal myelination interferes with the transmission of nerve signals, resulting in the characteristic symptoms and signs of PMD.

PMD is inherited in an X-linked recessive pattern, which means the mutated gene is located on the X chromosome. As a result, PMD primarily affects males. Females can also be affected, but they usually have milder symptoms due to the presence of a second X chromosome that can compensate for the genetic defect.

In addition to mutations in the PLP1 gene, rare cases of PMD have been associated with mutations in other genes, including GJC2 (encoding connexin 47) and TJP1 (encoding tight junction protein 1). These mutations disrupt the normal functioning of gap junctions and tight junctions, respectively, which are involved in the formation and maintenance of myelin.

Genetic testing, such as sequencing of the PLP1 gene, can be performed to confirm the diagnosis of PMD and identify the specific genetic mutation present in an individual. This information can be helpful for genetic counseling, family planning, and potentially future therapeutic interventions targeting specific genetic abnormalities.

Mitochondrial dysfunction in Pelizaeus-Merzbacher Disease

Pelizaeus-Merzbacher Disease (PMD) is a rare genetic disorder characterized by abnormal myelin formation in the central nervous system, which leads to progressive neurological symptoms. While PMD is primarily caused by mutations in the PLP1 gene, which encodes the proteolipid protein (PLP), there is evidence to suggest a potential involvement of mitochondrial dysfunction in the pathogenesis of the disease. Mitochondria are critical organelles involved in energy production, cellular metabolism, calcium homeostasis, and regulation of oxidative stress. Dysfunction of mitochondria can disrupt these essential cellular processes and contribute to cellular and tissue damage. In the context of PMD, mitochondrial dysfunction has been implicated as a secondary consequence of the underlying PLP1 gene mutations. Studies have shown that mutations in the PLP1 gene can lead to altered mitochondrial morphology and impaired mitochondrial function. These mitochondrial abnormalities can affect energy production and disrupt the normal cellular metabolism, which is crucial for the maintenance and function of myelin-producing cells called

oligodendrocytes. Impaired mitochondrial function can lead to decreased ATP production, increased oxidative stress, and altered calcium homeostasis, all of which can contribute to the pathology observed in PMD.

Furthermore, it has been suggested that mitochondrial dysfunction in PMD may contribute to the activation of cell death pathways, leading to oligodendrocyte degeneration and demyelination. The loss of myelin, which is essential for the proper conduction of nerve impulses, results in the neurological symptoms characteristic of PMD, including motor and cognitive impairments.

Although mitochondrial dysfunction is considered a secondary event in PMD, targeting mitochondrial function and oxidative stress has been proposed as a potential therapeutic approach. Various strategies aimed at restoring mitochondrial function and reducing oxidative stress, such as antioxidant therapies and modulators of mitochondrial metabolism, have been explored in preclinical studies.

It is important to note that the understanding of the specific mechanisms linking mitochondrial dysfunction to PMD is still evolving, and further research is needed to elucidate the precise role of mitochondria in the disease pathogenesis. If you or someone you know is affected by PMD, it is recommended to consult with a healthcare professional or genetic specialist for accurate information, genetic counseling, and appropriate management strategies based on the individual's specific condition.

Treatment in Pelizaeus-Merzbacher Disease

Currently, there is no cure for Pelizaeus-Merzbacher disease (PMD). Treatment for PMD is focused on managing symptoms, providing supportive care, and addressing complications that may arise. The treatment approach is individualized based on the specific needs and symptoms of each affected individual. Some treatment strategies that may be employed include:

Symptom management: Various medications may be prescribed to help manage specific symptoms associated with PMD. For example, muscle relaxants or antispasmodic medications can be used to alleviate muscle stiffness and spasticity. Seizures, if present, may be managed with anticonvulsant medications.

Physical and occupational therapy: Physical and occupational therapy play a crucial role in PMD management. These therapies focus on improving mobility, coordination, strength, and functional abilities. They may involve exercises, stretching, adaptive equipment, and techniques to promote independent movement and enhance daily living skills.

Speech and language therapy: Speech and language therapy can help individuals with PMD improve communication skills. This may include techniques to enhance speech

production, alternative communication methods (such as sign language or augmentative and alternative communication devices), and strategies to address swallowing difficulties.

Assistive devices and adaptations: Depending on the individual's needs, assistive devices and adaptations may be recommended to improve mobility, independence, and quality of life. This can include mobility aids, orthotic devices, adaptive seating, and modifications to the home environment.

Management of respiratory complications: As respiratory complications, such as breathing difficulties and recurrent respiratory infections, can occur in PMD, close monitoring of respiratory function is important. Treatment may involve interventions to support respiratory function, such as assisted ventilation or respiratory therapies.

Multidisciplinary care: PMD is a complex condition that requires the involvement of multiple healthcare specialists. A multidisciplinary care team, including neurologists, physiatrists, geneticists, therapists, and other specialists, can provide comprehensive care, address different aspects of the disease, and support the overall well-being of individuals with PMD.

Genetic counseling: Genetic counseling is important for individuals with PMD and their families to understand the inheritance pattern, recurrence risks, and potential implications for family planning.

It's important to note that treatment for PMD is primarily focused on managing symptoms and improving quality of life. Research into potential disease-modifying therapies, including gene therapy and other targeted approaches, is ongoing, offering hope for future therapeutic options.

23. Phospholipase A2-associated Neurodegeneration(PLAN)

PLAN)(磷脂質脂解酶A2關聯之神經退化性疾病)

History of Phospholipase A2-associated Neurodegeneration

Phospholipase A2-associated Neurodegeneration (PLAN) is a relatively newly recognized neurodegenerative disorder, and its history is still evolving as research continues to uncover more information about the condition. The first cases of PLAN were reported in the medical literature in the early 2000s.

In 2006, a group of researchers identified mutations in the PLA2G6 gene as the underlying cause of PLAN. This gene provides instructions for producing an enzyme called phospholipase A2 (PLA2), which plays a crucial role in the breakdown of cell membranes and the release of essential fatty acids. Mutations in the PLA2G6 gene disrupt the normal function of the enzyme, leading to the accumulation of toxic substances in the brain and subsequent neurodegeneration.

Since the discovery of the genetic cause, more cases of PLAN have been reported worldwide, and researchers have been studying the disease to better understand its clinical features, progression, and management. The identification of genetic mutations has allowed for improved diagnostic capabilities, enabling earlier detection of the disease.

As PLAN is a rare disorder, the understanding of its history is relatively recent and continually expanding with ongoing research and clinical observations. Efforts are underway to develop a more comprehensive understanding of the condition, including the identification of additional genetic mutations and the exploration of potential therapeutic approaches.

It's important to note that while PLAN shares similarities with other neurodegenerative disorders, each individual case may exhibit unique clinical features and progression patterns. This highlights the need for further research and collaboration among healthcare professionals, researchers, and affected individuals to advance our knowledge and improve the diagnosis and management of PLAN.

Classification of Phospholipase A2-associated Neurodegeneration

Phospholipase A2-associated Neurodegeneration (PLAN) is classified as a subtype of neurodegeneration with brain iron accumulation (NBIA), which is a group of rare genetic disorders characterized by abnormal iron accumulation in the brain. The classification of PLAN within the NBIA spectrum is based on its distinct genetic cause involving mutations in the PLA2G6 gene, which encodes the phospholipase A2 enzyme.

Within the classification of NBIA, PLAN is further categorized into two subtypes based on the age of onset and clinical features:

Infantile-onset PLAN: This subtype typically manifests within the first two years of life and is characterized by severe neurologic symptoms. Infants with infantile-onset PLAN may exhibit developmental regression, progressive spasticity (muscle stiffness), dystonia (involuntary muscle contractions), and visual impairments.

Atypical adult-onset PLAN: This subtype presents later in life, typically during adulthood, and is characterized by a more varied clinical presentation. Symptoms may include parkinsonism (movement abnormalities resembling Parkinson's disease), dystonia, cognitive decline, psychiatric manifestations, and other neurological abnormalities.

It's important to note that while these subtypes provide a general framework for understanding the disease, individual cases of PLAN can exhibit significant variability in symptoms and disease progression. Additionally, the classification of PLAN may evolve as further research uncovers more information about the condition and its subtypes.

Symptom and sign in Phospholipase A2-associated Neurodegeneration

Phospholipase A2-associated Neurodegeneration (PLAN) is characterized by a range of neurological symptoms and signs. The specific manifestations can vary depending on the age of onset and the subtype of PLAN. However, there are some common symptoms and signs that may be observed in individuals with PLAN. These include:
Movement Abnormalities: PLAN often presents with movement abnormalities such as dystonia, which is characterized by sustained muscle contractions causing twisting and repetitive movements. Other movement disorders, including parkinsonism (resembling Parkinson's disease) and spasticity (muscle stiffness), may also be present.

Cognitive and Behavioral Changes: Many individuals with PLAN experience cognitive decline, which can include difficulties with memory, attention, and executive functions. Behavioral changes such as irritability, impulsivity, and mood disturbances may also be observed.

Visual Impairments: Visual disturbances are common in PLAN, particularly in the infantile-onset subtype. These may include optic atrophy (damage to the optic nerve), visual impairment, and loss of visual acuity.

Speech and Language Problems: Difficulties with speech and language can occur in individuals with PLAN, including speech apraxia (difficulty planning and coordinating speech movements) and dysarthria (difficulty with articulation).

Neurological Abnormalities: PLAN can involve various neurological abnormalities,

such as epilepsy (seizures), ataxia (lack of muscle coordination), and peripheral neuropathy (nerve damage affecting the peripheral nervous system).

It's important to note that the symptoms and signs of PLAN can be progressive, meaning they worsen over time. However, the specific manifestations can vary widely among individuals, even within the same subtype. Regular monitoring and comprehensive care by a medical team familiar with the condition are essential to manage and address the specific symptoms and needs of each individual.

Image study in Phospholipase A2-associated Neurodegeneration

In the context of Phospholipase A2-associated Neurodegeneration (PLAN), various imaging studies can be used to assess the structural and functional changes in the brain. The specific imaging modalities used may vary depending on the purpose of the evaluation and the availability of resources. Some commonly used imaging studies in PLAN include:

Magnetic Resonance Imaging (MRI): MRI is a non-invasive imaging technique that uses magnetic fields and radio waves to generate detailed images of the brain. It can help identify structural abnormalities in the brain, such as white matter changes, atrophy, and signal intensity abnormalities. MRI can provide valuable information about the extent and progression of neurodegeneration in PLAN.

Diffusion Tensor Imaging (DTI): DTI is a specialized form of MRI that measures the diffusion of water molecules in brain tissues. It provides information about the integrity and connectivity of white matter fibers. DTI can detect abnormalities in white matter tracts and assess the extent of damage or degeneration.

Magnetic Resonance Spectroscopy (MRS): MRS is a technique that measures the chemical composition of brain tissues. It can help assess the levels of various metabolites in the brain, providing insights into metabolic changes associated with neurodegeneration. MRS can be used to detect abnormalities in specific brain regions affected by PLAN.

Positron Emission Tomography (PET) Scan: PET scans involve the injection of a radioactive tracer that emits positrons. By detecting the gamma rays emitted by the tracer, PET scans can provide information about cerebral blood flow, glucose metabolism, and the distribution of specific molecules in the brain. PET scans can help assess functional changes in the brain associated with PLAN.

Single-Photon Emission Computed Tomography (SPECT) Scan: SPECT scans use radioactive tracers to measure blood flow in the brain. They can be used to evaluate cerebral perfusion and identify areas of hypoperfusion or hyperperfusion. SPECT scans can provide information about the functional status of the brain in individuals with PLAN.

It's important to note that these imaging studies are used to complement the clinical evaluation and may vary depending on the specific needs of the patient and the expertise available in the healthcare setting. The choice of imaging modality and its interpretation should be done by a qualified medical professional experienced in the diagnosis and management of neurodegenerative disorders.

Genetic mutation in Phospholipase A2-associated Neurodegeneration

Phospholipase A2-associated Neurodegeneration (PLAN) is primarily caused by mutations in the PLA2G6 gene. The PLA2G6 gene provides instructions for producing an enzyme called phospholipase A2 group 6. This enzyme is involved in the breakdown of a type of fat molecule called phospholipids, which are important for the structure and function of cell membranes.

The mutations in the PLA2G6 gene can lead to a deficiency or dysfunction of the phospholipase A2 enzyme, which disrupts the normal breakdown of phospholipids. This disruption can result in the accumulation of abnormal lipids and subsequent damage to the cells, particularly in the brain.

Different types of mutations in the PLA2G6 gene have been identified in individuals with PLAN. These mutations can vary in their specific effects on the enzyme's function. Some mutations result in a complete loss of enzyme activity, while others lead to a partially functional enzyme with reduced activity. The specific mutation can influence the severity and progression of the disease.

It's important to note that while mutations in the PLA2G6 gene are the most common cause of PLAN, there may be other genetic factors and mechanisms involved in the development of the disorder. Further research is needed to better understand the genetic underpinnings of PLAN and its associated neurodegenerative processes.

Mitochondrial dysfunction in Phospholipase A2-associated Neurodegeneration

Phospholipase A2-associated Neurodegeneration (PLAN) is a group of rare neurodegenerative disorders characterized by the accumulation of iron in the basal ganglia, leading to progressive neurological symptoms. While the primary cause of PLAN is mutations in the PLA2G6 gene, which encodes the enzyme phospholipase A2, there is growing evidence suggesting the involvement of mitochondrial dysfunction in the pathogenesis of the disease.

Mitochondria play a crucial role in cellular energy production, metabolism, calcium regulation, and oxidative stress management. Dysfunction of mitochondria can disrupt these essential cellular processes and contribute to cellular and tissue damage. In the context of PLAN, mitochondrial dysfunction has been proposed as a secondary event triggered by the primary disruption of phospholipase A2 activity.

Studies have demonstrated that mutations in the PLA2G6 gene can lead to impaired mitochondrial function, altered mitochondrial morphology, and disrupted mitochondrial dynamics. These mitochondrial abnormalities can result in decreased ATP production, increased oxidative stress, dysregulation of calcium homeostasis, and impaired mitochondrial quality control mechanisms such as mitophagy. As a consequence, neuronal cells in affected individuals may experience energy deficits and increased susceptibility to oxidative damage.

Furthermore, impaired mitochondrial function can lead to the dysregulation of iron metabolism and accumulation of iron within cells, including the basal ganglia. Iron accumulation is a characteristic feature of PLAN and is believed to contribute to neurodegeneration and the progressive clinical manifestations of the disease.

Given the emerging role of mitochondrial dysfunction in PLAN, strategies aimed at restoring mitochondrial function and reducing oxidative stress have been proposed as potential therapeutic approaches. These include the use of antioxidants, mitochondrial-targeted therapies, and modulators of mitochondrial metabolism.

However, further research is needed to fully understand the complex interplay between phospholipase A2 dysfunction, mitochondrial dysfunction, and iron accumulation in PLAN, as well as to develop effective treatments that can address these underlying pathogenic mechanisms.

If you or someone you know is affected by PLAN, it is recommended to consult with a healthcare professional or genetic specialist for accurate information, genetic counseling, and appropriate management strategies based on the individual's specific condition.

Treatment in Phospholipase A2-associated Neurodegeneration

Currently, there is no cure for Phospholipase A2-associated Neurodegeneration (PLAN), and treatment focuses on managing the symptoms and providing supportive care. The treatment approach may involve a multidisciplinary team of healthcare professionals, including neurologists, physiotherapists, occupational therapists, and speech therapists. The specific treatment strategies may vary depending on the individual's symptoms and needs.

Some of the treatment options that may be considered for individuals with PLAN include:

Symptomatic management: Medications may be prescribed to help control symptoms such as spasticity, dystonia, seizures, and pain. These medications aim to improve comfort and quality of life.

Physical and occupational therapy: Physical therapy can help improve mobility, muscle strength, and coordination. Occupational therapy focuses on enhancing daily

living skills, such as self-care and fine motor skills.

Speech and swallowing therapy: For individuals with speech and swallowing difficulties, speech therapy can help improve communication and swallowing function. Augmentative and alternative communication (AAC) devices may be recommended for those with severe speech impairments.

Assistive devices: Depending on the individual's needs, assistive devices such as braces, orthotics, wheelchairs, or other mobility aids may be recommended to enhance mobility and independence.

Seizure management: Seizures are common in PLAN, and antiepileptic medications may be prescribed to help control and manage seizures.

Nutritional support: In cases where swallowing difficulties or feeding problems are present, a feeding tube may be recommended to ensure adequate nutrition and hydration.

It's important for individuals with PLAN to receive regular medical follow-up and monitoring to assess disease progression, manage symptoms, and adjust treatment strategies as needed. Additionally, genetic counseling may be beneficial for families to understand the inheritance pattern and provide information regarding the risk of recurrence in future pregnancies.

24.Pitt-Hopkins Syndrome (皮特-霍普金斯症候群)

History of Pitt-Hopkins Syndrome

Pitt-Hopkins syndrome is a rare genetic disorder that was first described in 1978 by Drs. Pitt and Hopkins. The syndrome was initially identified in two unrelated individuals, and subsequent cases have been reported worldwide. It is named after the two doctors who first characterized the disorder.

Pitt-Hopkins syndrome is caused by a mutation or deletion in the TCF4 gene, which is located on chromosome 18. This gene is responsible for producing a protein that plays a crucial role in the development and function of the nervous system. The mutation or deletion in the TCF4 gene leads to a decrease in the production or functionality of the TCF4 protein, resulting in the characteristic features and symptoms of Pitt-Hopkins syndrome.

Since its initial discovery, researchers have continued to study Pitt-Hopkins syndrome to better understand its genetic basis, underlying mechanisms, and clinical presentation. As a result, more cases have been identified and documented, contributing to our knowledge of the syndrome.

Pitt-Hopkins syndrome is characterized by a distinct set of clinical features, including intellectual disability, developmental delay, and distinctive facial features. Other common symptoms include breathing abnormalities, seizures, gastrointestinal issues, and motor difficulties. The severity of symptoms can vary widely among affected individuals, even among those with the same genetic mutation.

Understanding the history of Pitt-Hopkins syndrome has been instrumental in raising awareness about the disorder and facilitating research efforts to further comprehend its genetic and clinical aspects. Ongoing research aims to develop improved diagnostic methods, explore potential treatment options, and provide better support and care for individuals living with Pitt-Hopkins syndrome.

Classification of Pitt-Hopkins Syndrome

Pitt-Hopkins syndrome is classified as a rare genetic disorder and belongs to a broader category of neurodevelopmental disorders. Specifically, it is classified as an intellectual disability syndrome characterized by distinctive facial features and specific clinical features. The classification of Pitt-Hopkins syndrome is based on its clinical presentation and underlying genetic cause.

Clinically, Pitt-Hopkins syndrome is characterized by intellectual disability, developmental delay, and distinctive facial features. The facial features often include a broad and prominent forehead, deep-set eyes, a wide nasal bridge, a prominent nasal tip, a pointed chin, and a wide mouth with a prominent upper lip.

Genetically, Pitt-Hopkins syndrome is primarily caused by mutations or deletions in the TCF4 gene located on chromosome 18. These genetic alterations result in a decrease in the production or functionality of the TCF4 protein, which plays a crucial role in the development and function of the nervous system.

It is important to note that the classification of Pitt-Hopkins syndrome may evolve as further research is conducted and more is learned about its genetic and clinical characteristics. Ongoing studies and advancements in genetic testing techniques may lead to the identification of additional genetic variants associated with the syndrome, potentially further subclassifying the condition based on specific genetic alterations.

Symptom and sign in Pitt-Hopkins Syndrome

Pitt-Hopkins syndrome is characterized by a range of symptoms and signs that affect various aspects of an individual's development and overall functioning. Some of the common symptoms and signs associated with Pitt-Hopkins syndrome include:

Intellectual disability: Individuals with Pitt-Hopkins syndrome typically have moderate to severe intellectual disability. They may experience delays in language development, learning difficulties, and challenges with problem-solving and abstract thinking.

Developmental delay: Children with Pitt-Hopkins syndrome often exhibit delays in reaching developmental milestones such as sitting, crawling, walking, and speaking. Gross and fine motor skills may be affected, leading to difficulties with coordination and dexterity.

Breathing abnormalities: Many individuals with Pitt-Hopkins syndrome experience breathing abnormalities, including episodes of rapid breathing (hyperventilation) followed by periods of shallow or irregular breathing. This pattern is often triggered by excitement, stress, or physical activity.

Distinctive facial features: Pitt-Hopkins syndrome is associated with characteristic facial features, although these features can vary among individuals. Common facial characteristics include a broad and prominent forehead, deep-set eyes, a wide nasal bridge, a prominent nasal tip, a pointed chin, and a wide mouth with a prominent upper lip.

Hypotonia: Hypotonia, or low muscle tone, is commonly observed in individuals with Pitt-Hopkins syndrome. It may affect the muscles of the face, trunk, and limbs, resulting in poor muscle control, weak muscle strength, and difficulties with posture and coordination.

Seizures: Seizures are a common feature of Pitt-Hopkins syndrome, occurring in the majority of affected individuals. Seizure types can vary and may include generalized tonic-clonic seizures, absence seizures, or focal seizures.

Behavioral and psychiatric features: Individuals with Pitt-Hopkins syndrome may exhibit behavioral challenges, including attention deficits, hyperactivity, impulsivity, and anxiety. They may also display repetitive behaviors, self-injurious behaviors, and sleep disturbances.

It is important to note that the severity and specific manifestations of symptoms can vary among individuals with Pitt-Hopkins syndrome. Additionally, not all individuals with Pitt-Hopkins syndrome will exhibit all of the mentioned symptoms and signs.

Image study in Pitt-Hopkins Syndrome

There are currently no specific imaging studies that can definitively diagnose Pitt-Hopkins syndrome. The diagnosis of Pitt-Hopkins syndrome is primarily based on clinical features, medical history, and genetic testing. However, brain imaging studies such as magnetic resonance imaging (MRI) may be conducted to evaluate the structure and function of the brain, ruling out other possible causes of symptoms and providing additional information about any associated abnormalities. MRI may reveal structural brain abnormalities, such as changes in the size or shape of certain brain regions, which can help in assessing the overall brain development and identifying any specific anomalies that may contribute to the symptoms observed in Pitt-Hopkins syndrome. Additionally, electroencephalography (EEG) may be used to evaluate brain electrical activity and detect any abnormal patterns or epileptic discharges associated with seizures, which are common in individuals with Pitt-Hopkins syndrome.

Genetic mutation in Pitt-Hopkins Syndrome

Pitt-Hopkins syndrome is primarily caused by mutations in the TCF4 gene. Specifically, most cases of Pitt-Hopkins syndrome are caused by a deletion or mutation within a specific region of the TCF4 gene known as the transcriptional activation domain. These mutations result in the production of a nonfunctional or partially functional TCF4 protein, which disrupts normal gene expression and leads to the characteristic features and symptoms of Pitt-Hopkins syndrome.

The TCF4 gene is involved in regulating the activity of other genes and is important for normal brain development and function. Mutations in the TCF4 gene can affect the development and function of the central nervous system, leading to intellectual disability, developmental delay, and characteristic facial features associated with Pitt-Hopkins syndrome. It is worth noting that not all individuals with Pitt-Hopkins syndrome have identified TCF4 mutations, and in some cases, the genetic cause remains unknown.

Mitochondrial dysfunction in Pitt-Hopkins Syndrome

Pitt-Hopkins Syndrome (PHS) is a rare genetic disorder caused by mutations in the TCF4 gene. While the primary cause of PHS is related to TCF4 gene dysfunction, there is emerging evidence suggesting the involvement of mitochondrial dysfunction in the pathogenesis of the syndrome.

Mitochondria are known as the powerhouses of cells, responsible for producing energy in the form of adenosine triphosphate (ATP) through oxidative phosphorylation. They are also involved in other vital cellular processes, including calcium regulation, reactive oxygen species (ROS) production, and apoptosis.

Dysfunction of mitochondria can lead to energy deficits, impaired cellular processes, and increased oxidative stress, all of which can contribute to cellular damage and the development of various diseases.

In the case of PHS, studies have indicated that TCF4 mutations may impact mitochondrial function. These mutations have been shown to disrupt the expression and activity of genes involved in mitochondrial metabolism and oxidative phosphorylation. As a result, affected individuals may experience impaired ATP production and increased oxidative stress, which can affect the functioning of various organs and systems, including the brain and nervous system.

Mitochondrial dysfunction in PHS may contribute to the neurodevelopmental and cognitive features observed in affected individuals. The brain, being highly energy-demanding, is particularly vulnerable to mitochondrial dysfunction. Impaired mitochondrial function can affect neuronal development, synaptic function, and neurotransmitter signaling, which are essential for proper brain function and cognitive abilities.

It is important to note that the exact mechanisms linking TCF4 gene mutations, mitochondrial dysfunction, and the specific manifestations of PHS are still being investigated. Further research is needed to fully understand the complex interplay between these factors and their contributions to the clinical features of PHS.

Although there is currently no specific treatment targeting mitochondrial dysfunction in PHS, management strategies for affected individuals focus on addressing the various symptoms and providing supportive care. This may include early intervention programs, speech and occupational therapies, medications for seizures and behavioral issues, and regular monitoring of overall health.

If you or someone you know is affected by Pitt-Hopkins Syndrome, it is recommended to consult with a healthcare professional or genetic specialist for accurate information, individualized care, and appropriate support tailored to the specific needs of the individual.

Treatment in Pitt-Hopkins Syndrome

Currently, there is no specific cure for Pitt-Hopkins syndrome, and treatment primarily focuses on managing the symptoms and providing supportive care. The treatment approach for individuals with Pitt-Hopkins syndrome is multidisciplinary and may involve a team of healthcare professionals such as neurologists, geneticists, developmental pediatricians, and therapists. Here are some aspects of treatment that may be considered:

Symptom management: Treatment aims to address specific symptoms and complications associated with Pitt-Hopkins syndrome. This may include medications to manage seizures, gastrointestinal issues, sleep disturbances, and behavioral challenges.

Early intervention and developmental support: Early intervention services, such as physical therapy, occupational therapy, and speech therapy, can help address developmental delays and improve motor skills, communication, and overall functional abilities.

Educational support: Children with Pitt-Hopkins syndrome often benefit from specialized educational programs and individualized learning plans to support their cognitive and educational needs. Special education services and accommodations may be necessary to promote learning and development.

Behavioral and psychological support: Individuals with Pitt-Hopkins syndrome may exhibit behavioral challenges, including anxiety, aggression, self-injurious behaviors, and mood disorders. Behavioral therapies, counseling, and support from mental health professionals can assist in managing these challenges and improving overall well-being.

Family support and resources: Families of individuals with Pitt-Hopkins syndrome may require emotional support, counseling, and access to support groups or resources. Connecting with support networks and organizations dedicated to Pitt-Hopkins syndrome can provide valuable information, resources, and a sense of community. It's important to note that treatment plans are individualized based on the specific needs of each person with Pitt-Hopkins syndrome. Regular monitoring, follow-up with healthcare providers, and ongoing evaluation of treatment approaches are crucial for optimizing care and addressing evolving needs. Research into potential targeted therapies and interventions for Pitt-Hopkins syndrome is ongoing, and individuals may be eligible to participate in clinical trials exploring new treatment options.

25. Proteus Syndrome(普洛提斯症候群)

History of Proteus Syndrome

Proteus syndrome is a rare genetic disorder characterized by the overgrowth of various tissues in the body. Here is a brief history of Proteus syndrome:

Discovery and Naming: Proteus syndrome was first described by Dr. Michael Cohen in 1979. The name "Proteus syndrome" was inspired by the Greek god Proteus, who was known for his ability to change his shape, reflecting the diverse and unpredictable nature of the disorder.

Recognition of Similar Cases: After the initial description of Proteus syndrome, more cases were identified and reported, leading to a better understanding of the disorder.

Researchers noticed common features among affected individuals, including asymmetric overgrowth, skin abnormalities, and skeletal abnormalities.

Genetic Basis: In the early 1990s, it was hypothesized that Proteus syndrome might be caused by a genetic mutation. However, the specific genetic mutation responsible for the disorder was not identified until 2011. Research revealed that Proteus syndrome is typically caused by a somatic mutation in the AKT1 gene, which leads to overactivation of the AKT signaling pathway.

Classification and Overlapping Conditions: Proteus syndrome is classified as a type of overgrowth syndrome. Over the years, researchers have identified other overgrowth syndromes with overlapping features or similar genetic mutations, such as PIK3CA-related overgrowth spectrum (PROS) and megalencephaly-capillary malformation-polymicrogyria syndrome (MCAP). These conditions share some clinical features with Proteus syndrome.

Advances in Diagnostic Techniques: With the advancement of genetic testing technologies, it has become possible to confirm the diagnosis of Proteus syndrome through genetic testing. However, clinical criteria based on the characteristic features and clinical presentation are still used for diagnosis, as genetic testing may not always detect the specific AKT1 mutation.

Management and Support: Due to the complex and variable nature of Proteus syndrome, management typically involves a multidisciplinary approach. Treatment focuses on addressing specific symptoms and managing complications associated with the disorder. Supportive care, physical therapy, and psychological support are also essential components of the management plan.

It's important to note that Proteus syndrome remains a rare and challenging condition, and further research is needed to improve our understanding of its underlying mechanisms, refine diagnostic methods, and develop targeted therapies for affected individuals.

Classification of Proteus Syndrome

Proteus syndrome is classified as a rare genetic disorder and is categorized under the broader umbrella of overgrowth syndromes. Overgrowth syndromes are a group of genetic disorders characterized by excessive tissue growth in different parts of the body. While there is no specific classification system solely for Proteus syndrome, it is often classified based on its clinical features and the affected body systems. Here are some common features and categories associated with Proteus syndrome:

Overgrowth: Proteus syndrome is characterized by asymmetric and progressive overgrowth of various tissues, including skin, bones, and other organs. This overgrowth can lead to significant differences in size and shape between different parts of the body.

Skeletal Abnormalities: Individuals with Proteus syndrome often present with skeletal abnormalities, such as overgrowth of the bones, joint abnormalities, scoliosis (abnormal curvature of the spine), and limb length discrepancies.

Vascular Malformations: Some individuals with Proteus syndrome may have vascular malformations, including venous malformations, lymphatic malformations, and capillary malformations.

Skin Abnormalities: Cutaneous manifestations are common in Proteus syndrome and may include various skin abnormalities such as lipomas (benign fatty tumors), skin thickening, connective tissue nevi, and vascular anomalies.

Other Features: Proteus syndrome can affect other body systems, leading to a range of additional features, including intellectual disability, epilepsy, vision and hearing impairments, respiratory problems, and genitourinary abnormalities.

It's important to note that Proteus syndrome is a complex disorder with considerable variability in its clinical presentation. Individuals with Proteus syndrome can exhibit a wide range of symptoms and have different combinations of affected body systems. This variability makes classification challenging and underscores the need for a personalized and multidisciplinary approach to diagnosis and management.

Symptom and sign in Proteus Syndrome

Proteus syndrome is a complex disorder that can affect multiple body systems, resulting in a wide range of symptoms and signs. The symptoms and signs may vary among individuals, but here are some common features associated with Proteus syndrome:

Overgrowth: One of the hallmark signs of Proteus syndrome is asymmetric and progressive overgrowth of tissues, particularly affecting the limbs, hands, feet, and face. This overgrowth can lead to significant differences in size and shape between the affected and unaffected sides of the body.

Skeletal Abnormalities: Individuals with Proteus syndrome may experience skeletal abnormalities, such as enlarged and elongated bones, scoliosis (abnormal curvature of the spine), joint abnormalities, and limb length discrepancies.

Connective Tissue Abnormalities: Proteus syndrome can affect connective tissues, resulting in skin abnormalities, such as thickening, hyperpigmentation (excessive pigmentation), and the development of connective tissue tumors called connective tissue nevi.

Vascular Malformations: Vascular malformations, including venous malformations, lymphatic malformations, and capillary malformations, can be present in individuals with Proteus syndrome. These malformations may lead to complications such as swelling, pain, and increased risk of blood clots.

Intellectual Disability: Some individuals with Proteus syndrome may experience intellectual disability, ranging from mild to severe. Cognitive impairment can affect learning, communication, and daily functioning.

Epilepsy: Epileptic seizures are a common feature of Proteus syndrome, with different types of seizures possible, including focal seizures, generalized seizures, or a combination of both.

Other Features: Additional features associated with Proteus syndrome may include vision and hearing impairments, respiratory problems, gastrointestinal abnormalities, genitourinary abnormalities, and increased risk of certain tumors, such as kidney tumors.

It's important to note that the signs and symptoms of Proteus syndrome can manifest at different ages and progress over time. The severity and specific combination of features can vary greatly among affected individuals. A comprehensive evaluation by a healthcare professional experienced in genetic disorders is crucial for accurate diagnosis and management of Proteus syndrome.

Image study in Proteus Syndrome

Image studies play a significant role in the evaluation and diagnosis of Proteus syndrome. Here are some common imaging modalities used in the assessment of individuals with Proteus syndrome:

X-rays: X-ray imaging is commonly used to assess skeletal abnormalities associated with Proteus syndrome, such as bone overgrowth, elongation, and deformities. It can help identify limb length discrepancies, joint abnormalities, and spinal abnormalities like scoliosis.

CT Scan: Computed tomography (CT) scans provide detailed cross-sectional images of the body and are useful for evaluating internal structures. CT scans may be utilized to assess the extent of bone and soft tissue abnormalities in Proteus syndrome,

particularly in the skull, facial bones, and internal organs.

MRI: Magnetic resonance imaging (MRI) uses powerful magnets and radio waves to generate detailed images of the body's soft tissues. MRI scans can provide valuable information about the extent and distribution of tissue overgrowth, vascular malformations, and connective tissue abnormalities in Proteus syndrome. They can also help assess the brain for any associated abnormalities, such as cortical malformations or white matter changes.

Ultrasound: Ultrasound imaging is commonly used to evaluate vascular malformations in Proteus syndrome. It can help visualize blood vessels and assess the extent, size, and characteristics of vascular anomalies such as venous malformations and lymphatic malformations.

Doppler Ultrasound: Doppler ultrasound is a specialized ultrasound technique that assesses blood flow within blood vessels. It can be used to evaluate vascular malformations in Proteus syndrome and determine the presence of any abnormal blood flow patterns or obstructions.

These imaging studies, along with clinical examination findings and genetic testing, contribute to the diagnosis and ongoing monitoring of individuals with Proteus syndrome. The specific choice of imaging modality depends on the individual's clinical presentation and the suspected areas of involvement. The results of these imaging studies help guide treatment decisions and management strategies for individuals with Proteus syndrome.

Genetic mutation in Proteus Syndrome

Proteus syndrome is caused by a somatic mutation in the AKT1 gene. Somatic mutations are genetic alterations that occur after conception, typically in a subset of cells in the body. The specific mutation in the AKT1 gene associated with Proteus syndrome is known as an activating mutation. This mutation leads to the overactivation of the AKT signaling pathway, which plays a crucial role in cell growth and proliferation.

The AKT1 gene provides instructions for producing the AKT1 protein, which is involved in various cellular processes, including cell growth, survival, and metabolism. The activating mutation in Proteus syndrome results in an abnormal increase in AKT1 protein activity, leading to uncontrolled cell growth and tissue overgrowth characteristic of the disorder.

It's important to note that the AKT1 mutation occurs in somatic cells, which means it is not inherited from parents and does not affect the individual's germ cells (sperm or eggs). Therefore, Proteus syndrome is considered a sporadic condition rather than an inherited disorder.

The AKT1 mutation in Proteus syndrome is believed to arise randomly during embryonic development or early fetal development. The mutation occurs in a mosaic pattern, meaning that only certain cells in the body carry the mutation, while others do not. This mosaic distribution of the mutation contributes to the varied and asymmetric overgrowth patterns observed in individuals with Proteus syndrome.

Genetic testing can be performed to identify the AKT1 mutation in affected individuals. However, it can be challenging to detect the mutation due to its mosaic nature and the need to analyze multiple affected tissues. Genetic testing is typically performed on samples of affected tissue, such as skin or blood, to identify the presence of the AKT1 mutation.

Understanding the genetic mutation in Proteus syndrome is crucial for accurate diagnosis, genetic counseling, and ongoing management of affected individuals.

Mitochondrial dysfunction in Proteus Syndrome

Proteus syndrome is a rare genetic disorder characterized by the overgrowth of tissues and the development of tumors. While the exact cause of Proteus syndrome is not fully understood, it is not typically associated with mitochondrial dysfunction as a primary feature. Mitochondrial dysfunction refers to abnormalities or impairment in the function of mitochondria, the cellular organelles responsible for energy production and other important cellular processes.

Mitochondrial dysfunction is more commonly associated with a group of disorders known as mitochondrial diseases, which are caused by mutations in genes that are involved in mitochondrial function and maintenance. These disorders can affect multiple organ systems, including the nervous system, muscles, and various other tissues.

However, it is important to note that mitochondrial dysfunction can occur as a secondary consequence of Proteus syndrome due to the complex cellular and molecular interactions involved. The overgrowth of tissues and abnormal cell proliferation in Proteus syndrome may lead to an increased metabolic demand, which can potentially strain the mitochondrial function. This increased demand for energy production may exceed the capacity of the mitochondria, leading to compromised mitochondrial function and the generation of reactive oxygen species (ROS), which can further contribute to cellular damage.

While the specific role and impact of mitochondrial dysfunction in Proteus syndrome are not well-defined, studies have suggested that oxidative stress and mitochondrial dysfunction may play a secondary role in the development and progression of the syndrome. However, further research is needed to fully understand the mechanisms and extent of mitochondrial involvement in Proteus syndrome.

It is worth noting that the management of Proteus syndrome primarily focuses on the symptomatic treatment of individual manifestations, such as surgical interventions for overgrown tissues and tumors, physical therapy, and other supportive measures. Genetic counseling and regular medical follow-up are important for individuals with Proteus syndrome to monitor and manage the various aspects of their condition. If you or someone you know is affected by Proteus syndrome, it is recommended to consult with a healthcare professional or genetic specialist for accurate information, comprehensive evaluation, and appropriate management strategies tailored to the specific needs of the individual.

Treatment in Proteus Syndrome

There is currently no specific cure for Proteus syndrome. Treatment for individuals with Proteus syndrome focuses on managing the symptoms and complications associated with the condition. The treatment approach is generally multidisciplinary, involving a team of healthcare professionals who specialize in various areas, such as genetics, orthopedics, dermatology, and neurology. The goals of treatment are to improve quality of life, manage complications, and provide supportive care.

Treatment options for Proteus syndrome may include:

Surgical interventions: Surgery may be recommended to address specific complications, such as limb length discrepancies, scoliosis, vascular malformations, or tumors. Surgical procedures may involve limb lengthening or shortening, orthopedic interventions, or removal of abnormal tissue growths.

Physical and occupational therapy: Physical and occupational therapy can help individuals with Proteus syndrome improve mobility, strength, and daily functioning. These therapies may include exercises, stretches, assistive devices, and adaptive techniques to address physical limitations and enhance independence.

Pain management: Chronic pain is a common symptom in Proteus syndrome. Pain management strategies may involve medications, physical therapy modalities, and alternative therapies such as acupuncture or relaxation techniques. A pain management specialist can work with the individual to develop a personalized pain management plan.

Dermatological care: Skin abnormalities, including overgrowth, thickening, or lesions, are frequently observed in Proteus syndrome. Dermatological care may involve the management of skin infections, wound care, and treatment of skin-related complications.

Genetic counseling: Genetic counseling is essential for individuals with Proteus syndrome and their families. It involves providing information about the condition, discussing the underlying genetic mutation, and offering guidance regarding the risk

of recurrence in future pregnancies.

Psychological support: Living with a rare and complex condition like Proteus syndrome can have a significant impact on mental health and well-being.

Psychological support, including counseling or therapy, can help individuals and their families cope with the challenges, emotional stress, and psychosocial aspects associated with the condition.

It's important for individuals with Proteus syndrome to receive regular medical follow-up and monitoring to address potential complications and manage any new symptoms that may arise. The treatment approach is individualized based on the specific needs and circumstances of each person, and close collaboration between healthcare providers is crucial to provide comprehensive care.

26. Rett syndrome(雷特氏症)

History of Rett syndrome

Rett syndrome is a rare genetic disorder that primarily affects females. Here is a brief overview of the history of Rett syndrome:

1966: Dr. Andreas Rett, an Austrian pediatrician, first described the syndrome in a medical publication. He identified a group of girls with similar symptoms, including developmental regression, loss of purposeful hand skills, and distinctive hand-wringing movements.

1983: Swedish researcher Dr. Bengt Hagberg independently described a similar group of girls with developmental regression and named the condition "Hagberg-Santavuori syndrome." Later, it was determined that Rett syndrome and Hagberg-Santavuori syndrome were the same disorder.

1999: A major breakthrough occurred when researchers identified mutations in the MECP2 gene as the underlying cause of Rett syndrome. Mutations in this gene are found in the majority of individuals with Rett syndrome.

2007: Researchers discovered that Rett syndrome is not exclusively a disorder affecting females. They identified rare cases of males with Rett syndrome who had severe intellectual disability and mutations in the MECP2 gene.

2010: Revised diagnostic criteria for Rett syndrome were published by a consensus group, broadening the clinical spectrum and allowing for the diagnosis of atypical forms of the disorder.

Despite being initially described in the 1960s, it took several decades for researchers to identify the genetic basis of Rett syndrome. Understanding the role of the MECP2 gene has provided significant insights into the molecular mechanisms and pathogenesis of the disorder.

Since the discovery of the genetic basis, research in Rett syndrome has focused on understanding the function of the MECP2 gene, investigating potential therapeutic approaches, and improving diagnostic techniques. Ongoing efforts continue to expand our knowledge of Rett syndrome and explore potential treatments to improve the lives of individuals affected by this condition.

Classification of Rett syndrome

Rett syndrome is classified into several stages based on the specific clinical features and developmental progression. The classification system helps to describe the different stages of the disorder as it progresses over time. Here is a commonly used classification of Rett syndrome based on stages:

Stage I: Early Onset Stage or Early Regression Stage:

This stage typically begins between 6 and 18 months of age.

Symptoms may include a slowing of development, loss of purposeful hand skills, and a decrease in social engagement.

Hand-wringing or hand movements may start to emerge during this stage.

Stage II: Rapid Destructive Stage or Regression Stage:

This stage usually occurs between ages 1 and 4.

Regression becomes more apparent, with a loss of acquired skills such as purposeful hand movements, spoken language, and social engagement.

Repetitive hand movements, such as hand-wringing, tapping, or clapping, become more pronounced.

Stage III: Plateau or Pseudo-Stationary Stage:

This stage typically occurs between ages 2 and 10.

The regression stabilizes, and some individuals may show limited improvements or plateau in their symptoms.

There may be increased motor difficulties, abnormal movements, breathing abnormalities, and the emergence of motor stereotypes.

Stage IV: Late Motor Deterioration Stage or Late Motor Stage:

This stage usually occurs after age 10 and can last for several decades.

Individuals may experience further loss of motor skills, mobility challenges, increased muscle weakness, and rigidity.

Communication may be severely impaired, and breathing irregularities can be more pronounced.

It is important to note that the progression through these stages can vary among individuals with Rett syndrome. Some individuals may not experience a clear progression through all stages, and the rate of regression and symptom severity can differ.

This classification system helps healthcare professionals and researchers understand the typical course of Rett syndrome and provides a framework for evaluating and monitoring the progression of symptoms over time. However, it is important to consider that each person with Rett syndrome is unique, and the classification may not perfectly align with every individual's experience.

Symptom and sign in Rett syndrome

Rett syndrome is a neurodevelopmental disorder that primarily affects females. It is characterized by a range of symptoms and signs that typically emerge in early childhood. Here are some common symptoms and signs seen in individuals with Rett syndrome:

Loss of Purposeful Hand Skills:

One of the hallmark features of Rett syndrome is the loss of previously acquired purposeful hand skills. This includes a regression in abilities such as reaching, grasping, and manipulating objects.

Communication Impairment:

Individuals with Rett syndrome often experience significant communication difficulties. They may lose the ability to speak and develop limited or absent speech skills. Nonverbal communication, such as eye gaze, facial expressions, and body language, may also be impaired.

Motor Abnormalities:

Rett syndrome is associated with a range of motor abnormalities. This includes stereotypical hand movements, such as hand-wringing, tapping, clapping, or squeezing. Individuals may also exhibit repetitive body movements, such as rocking or swaying.

Breathing Irregularities:

Many individuals with Rett syndrome develop breathing abnormalities, including episodes of hyperventilation, breath-holding, or irregular patterns of breathing. These breathing irregularities can occur during wakefulness and sleep.

Gait and Movement Difficulties:

Rett syndrome can cause problems with coordination and mobility. Individuals may have an unsteady gait, difficulty with balance, and problems with purposeful movements. Some individuals may require assistive devices, such as walkers or wheelchairs, to aid in mobility.

Intellectual and Developmental Disability:

Individuals with Rett syndrome typically have intellectual and developmental disabilities of varying degrees. This can include cognitive impairment, difficulty with learning and problem-solving, and delays in achieving developmental milestones.

Social and Behavioral Changes:

Individuals with Rett syndrome often exhibit changes in social interaction and behavior. This can include social withdrawal, decreased interest in surroundings, and increased anxiety or agitation. They may also develop stereotyped behaviors, such as hand-wringing or repetitive movements.

It's important to note that the symptoms and severity of Rett syndrome can vary widely among individuals. The loss of purposeful hand skills and regression in development are characteristic features, but other symptoms may manifest differently in each person. Early identification, proper diagnosis, and individualized interventions and support are crucial in managing the symptoms and optimizing the quality of life for individuals with Rett syndrome.

Image study in Rett syndrome

In the diagnosis and evaluation of Rett syndrome, various imaging studies may be used to assess brain structure and function. These imaging techniques help provide additional information about the neurological aspects of the condition. Here are some commonly used imaging studies in Rett syndrome:

Magnetic Resonance Imaging (MRI):

MRI uses powerful magnets and radio waves to create detailed images of the brain's structure.

In Rett syndrome, MRI scans can help identify any structural abnormalities or changes in brain volume.

It can also be useful in ruling out other conditions that may have similar symptoms.

Computed Tomography (CT) Scan:

CT scans use X-rays to create cross-sectional images of the brain.

CT scans may be used to assess brain structure and detect any abnormalities, such as brain atrophy or calcifications.

However, MRI is generally preferred over CT due to its superior ability to visualize soft tissues.

Electroencephalogram (EEG):

EEG is a test that measures electrical activity in the brain using electrodes placed on the scalp.

In Rett syndrome, EEG can help detect abnormal brain wave patterns, such as epileptic activity or characteristic patterns associated with the condition.

EEG findings can assist in the diagnosis and management of seizures and other neurological symptoms.

Positron Emission Tomography (PET) Scan:

PET scans involve the injection of a radioactive substance into the bloodstream, which allows visualization of brain activity.

PET scans can be used to assess brain metabolism and identify any areas of abnormal activity or dysfunction.

This imaging technique may help in understanding the underlying neurological changes in Rett syndrome.

It's important to note that while these imaging studies can provide valuable information, they are typically used in conjunction with clinical assessments, genetic testing, and other diagnostic criteria to diagnose Rett syndrome. The primary diagnostic tool for Rett syndrome remains the clinical evaluation and observation of characteristic symptoms and signs. The imaging studies help support the diagnosis and provide additional insights into the neurological aspects of the condition.

Genetic mutation in Rett syndrome

Rett syndrome is primarily caused by mutations in the MECP2 gene, which stands for Methyl-CpG-binding protein 2. The MECP2 gene provides instructions for producing the MeCP2 protein, which plays a crucial role in the development and function of the nervous system. The majority of individuals with Rett syndrome (around 95%) have mutations in the MECP2 gene. Here are some key points about the genetic mutations in Rett syndrome:

MECP2 Mutations: The mutations in the MECP2 gene can occur in different regions of the gene and can involve various types of genetic changes, including deletions, insertions, duplications, and point mutations. These mutations typically occur randomly and are not inherited from parents in the majority of cases.

X-Linked Dominant Inheritance: The MECP2 gene is located on the X chromosome, and Rett syndrome follows an X-linked dominant pattern of inheritance. This means that a single copy of the mutated gene is sufficient to cause the disorder in females. In males, a mutation in the MECP2 gene is usually lethal, leading to severe developmental problems.

Mosaic Mutations: In some cases, individuals with Rett syndrome may have a mosaic pattern of MECP2 mutations. This means that the mutation is present in some cells but not all, leading to a variable expression and milder symptoms.

Genetic Testing: Genetic testing, such as DNA sequencing, can be performed to identify MECP2 mutations in individuals suspected of having Rett syndrome. Testing can help confirm the diagnosis and provide genetic counseling to families.

Atypical Mutations: In a small percentage of individuals with atypical Rett syndrome or Rett-like presentations, mutations in genes other than MECP2 may be identified. Some of these genes include CDKL5, FOXP1, and others. These mutations result in similar clinical features but may have distinct genetic causes.

It's important to note that while MECP2 mutations are the most common genetic cause of Rett syndrome, not all individuals with Rett-like symptoms have identifiable mutations in these genes. Ongoing research continues to uncover new genetic causes and further our understanding of the underlying genetic mechanisms of Rett syndrome.

Mitochondrial dysfunction in Rett syndrome

Rett syndrome is a rare genetic disorder that primarily affects girls and is characterized by severe cognitive and developmental impairments. While the primary cause of Rett syndrome is known to be mutations in the MECP2 gene, mitochondrial dysfunction has been proposed as a contributing factor in the pathogenesis of the disorder.

Mitochondrial dysfunction in Rett syndrome is thought to result from the dysfunction of the MECP2 gene, which plays a critical role in regulating gene expression and protein production in cells, including those in the mitochondria. Studies have shown that MECP2 mutations can lead to altered mitochondrial function, including impaired mitochondrial respiration, reduced ATP production, and increased production of reactive oxygen species (ROS).

The precise mechanisms through which mitochondrial dysfunction contributes to the symptoms of Rett syndrome are not fully understood. However, it is believed that the energy deficits and oxidative stress resulting from mitochondrial dysfunction may contribute to the neurodevelopmental and neurological symptoms observed in Rett syndrome, such as loss of purposeful hand skills, cognitive impairment, motor dysfunction, and autonomic dysregulation.

Additionally, impaired mitochondrial function and the associated energy deficits can impact various cellular processes, including synaptic plasticity, neuronal survival, and neurotransmitter signaling, which are crucial for normal brain function. These disruptions in cellular processes may further contribute to the cognitive and behavioral impairments observed in individuals with Rett syndrome.

While mitochondrial dysfunction appears to be a secondary consequence of MECP2 mutations in Rett syndrome, it is an area of ongoing research and investigation.

Understanding the interplay between MECP2 mutations and mitochondrial dysfunction may provide insights into potential therapeutic strategies aimed at restoring mitochondrial function and ameliorating the symptoms of Rett syndrome.

It is important to note that the management of Rett syndrome is currently focused on providing supportive care and interventions to address specific symptoms and complications associated with the disorder. This may include physical therapy, occupational therapy, speech therapy, and medications to manage specific symptoms such as seizures and motor abnormalities. Genetic counseling and regular medical follow-up are essential for individuals with Rett syndrome to ensure comprehensive care and support.

Treatment in Rett syndrome

Currently, there is no cure for Rett syndrome. However, treatment approaches aim to manage the symptoms, maximize the individual's abilities, and improve their quality of life. The treatment for Rett syndrome is typically multidisciplinary and may involve a combination of the following:

Supportive Care: This includes providing supportive therapies and interventions to address the individual's specific needs. It may involve physical, occupational, and speech therapy to improve motor skills, communication, and daily functioning.

Medications: Medications may be prescribed to manage specific symptoms and comorbidities associated with Rett syndrome. For example, medications may be used to control seizures, manage breathing irregularities, alleviate gastrointestinal issues, or treat behavioral problems such as anxiety or sleep disturbances. Medication choices are tailored to the individual's needs and may require ongoing monitoring and adjustment.

Assistive Devices: Assistive devices and adaptive technologies can help individuals with Rett syndrome enhance their communication, mobility, and independence. These may include augmentative and alternative communication (AAC) devices, mobility aids, and adaptive equipment.

Behavioral Interventions: Behavioral interventions, such as applied behavior analysis (ABA), can help manage challenging behaviors and promote skill development. These interventions focus on reinforcing positive behaviors, teaching adaptive skills, and addressing behavioral challenges.

Educational Support: Educational interventions should be tailored to the individual's specific needs and abilities. Individualized education plans (IEPs) can help create a supportive learning environment, provide accommodations, and facilitate the development of academic and social skills.

Nutritional Management: Nutritional support and management are essential in addressing feeding difficulties and ensuring proper nutrition. A balanced diet, appropriate feeding techniques, and working with healthcare professionals, such as dietitians, can help optimize nutrition and growth.

Family Support and Counseling: Rett syndrome affects not only the individual but also their family members. Providing emotional support, counseling, and connecting families with support groups and resources can be beneficial in managing the challenges associated with the condition.

It's important for individuals with Rett syndrome to receive ongoing medical care and regular evaluations by a team of healthcare professionals experienced in managing the condition. Treatment plans should be tailored to each individual's unique needs and adjusted as they grow and develop. Ongoing research and clinical trials are also exploring potential future therapies aimed at targeting the underlying genetic and molecular mechanisms of Rett syndrome.

27.Spinal muscular atrophy(脊髓性肌肉萎縮症)

History of Spinal muscular atrophy

Spinal muscular atrophy (SMA) is a genetic disorder characterized by the loss of motor neurons in the spinal cord, resulting in progressive muscle weakness and atrophy. Here is a brief overview of the history of spinal muscular atrophy:

1887: French neurologist Louis-Désiré-Jules Géliveau first described a group of patients with a progressive disorder characterized by muscle weakness and atrophy. He referred to the condition as "aranhania" or "amyotrophie spinale progressive."

1891: German neurologist Guido Werdnig provided a detailed clinical description of the disorder, which became known as Werdnig-Hoffmann disease. He recognized the hereditary nature of the condition and identified it as a form of muscular atrophy affecting infants.

1950s: Advances in electromyography (EMG) and muscle biopsy techniques allowed for better understanding and characterization of the disease.

1964: Neurologist Dr. Lina Werdnig and Dr. Burkhard Hoffmann published a comprehensive description of the clinical features and course of the disease, which became widely recognized as Werdnig-Hoffmann disease.

1995: The gene responsible for SMA was identified as the Survival Motor Neuron 1 (SMN1) gene located on chromosome 5. Mutations in the SMN1 gene result in a deficiency of the survival motor neuron protein (SMN), which leads to motor neuron degeneration.

1996: The classification of SMA was revised, and a distinction was made between different types based on the age of onset and clinical features. SMA Type 1 (Werdnig-Hoffmann disease) was identified as the most severe form, while Types 2, 3, and 4 were considered milder forms.

2016: The U.S. Food and Drug Administration (FDA) approved nusinersen (brand name Spinraza) as the first-ever disease-modifying therapy for SMA. Nusinersen is an antisense oligonucleotide that helps increase the production of the SMN protein.

2019: Zolgensma, a gene therapy product, received FDA approval as a one-time treatment for SMA. It is designed to deliver a functional copy of the SMN1 gene to the affected cells, aiming to compensate for the underlying genetic defect.

Ongoing research continues to advance our understanding of SMA and explore new treatment options. As of now, disease-modifying therapies, supportive care, and multidisciplinary management approaches are utilized to improve the quality of life and outcomes for individuals with SMA.

Classification of Spinal muscular atrophy

Spinal muscular atrophy (SMA) is a group of genetic disorders characterized by the degeneration of motor neurons in the spinal cord, leading to muscle weakness and atrophy. The classification of SMA is based on the age of onset, clinical features, and severity of the disease. The current classification system includes the following types:

SMA Type 1 (also known as Werdnig-Hoffmann disease):

Type 1 is the most severe form of SMA, typically manifesting within the first few months of life, often before 6 months of age.

Infants with Type 1 SMA have severe muscle weakness and hypotonia (reduced muscle tone) and may exhibit difficulties with feeding, swallowing, and breathing. The majority of infants with Type 1 SMA do not achieve independent sitting or walking and require significant medical support.

SMA Type 2:

Type 2 SMA usually presents between 6 and 18 months of age.

Children with Type 2 SMA can usually sit independently, but they are unable to walk without assistance.

They may experience progressive muscle weakness, respiratory issues, and orthopedic complications such as scoliosis.

Life expectancy varies, and some individuals with Type 2 SMA may live into adulthood with proper medical management.

SMA Type 3 (also known as Kugelberg-Welander disease):

Type 3 SMA typically manifests after 18 months of age, often in early childhood or adolescence.

Individuals with Type 3 SMA can usually walk independently but may experience a gradual decline in motor function over time.

They may have difficulties with running, climbing stairs, and other motor activities.

The rate of progression can vary, and life expectancy is typically normal.

SMA Type 4:

Type 4 SMA is the mildest form and usually has a later onset, often in adulthood.

Individuals with Type 4 SMA may experience mild muscle weakness and motor difficulties, such as walking and balance issues.

The progression of the disease is generally slow, and life expectancy is normal.

It's important to note that this classification system provides a general framework, but there can be significant variability in the presentation and progression of SMA within each type. Additionally, advances in genetic testing and our understanding of the disease may lead to further refinements in the classification of SMA in the future.

Symptom and sign in Spinal muscular atrophy

Spinal muscular atrophy (SMA) is a genetic disorder that affects the motor neurons in the spinal cord, leading to muscle weakness and atrophy. The severity of symptoms can vary depending on the type of SMA. Here are some common signs and symptoms associated with different types of SMA:

SMA Type 1 (Werdnig-Hoffmann disease):

Severe muscle weakness and hypotonia (reduced muscle tone) from infancy.

Difficulty with feeding and swallowing due to weak muscles involved in sucking and swallowing.

Respiratory difficulties, including weak respiratory muscles and breathing problems.

Delayed motor milestones or inability to achieve them, such as sitting unassisted or crawling.

Tremors or twitching of the tongue and limbs may be present.

Poor weight gain and growth due to feeding difficulties.

Typically, a shortened life expectancy due to respiratory complications.

SMA Type 2:

Progressive muscle weakness and hypotonia that usually becomes apparent between 6 and 18 months of age.

Difficulties with motor skills development, such as sitting independently or standing without support.

Respiratory issues, including breathing difficulties and increased susceptibility to respiratory infections.

Contractures (joint stiffness) and scoliosis (abnormal curvature of the spine) may develop over time.

Some children with Type 2 SMA can achieve independent sitting but are unable to walk without assistance.

SMA Type 3 (Kugelberg-Welander disease):

Muscle weakness and hypotonia that typically become noticeable after 18 months of age, often in early childhood or adolescence.

Difficulties with running, climbing stairs, and other motor activities.

The ability to walk independently but may experience a gradual decline in motor function over time.

Contractures, scoliosis, and respiratory issues can occur but are usually less severe than in Type 2 SMA.

Life expectancy is typically normal.

SMA Type 4:

Milder muscle weakness that usually presents in adulthood.

Walking difficulties, such as weakness and unsteady gait.

Slow progression of symptoms and generally a normal life expectancy.

It's important to note that the symptoms and progression of SMA can vary within each type and among individuals. Early diagnosis, regular monitoring, and appropriate medical care can help manage symptoms, optimize quality of life, and provide necessary support for individuals with SMA.

Image study in Spinal muscular atrophy

In spinal muscular atrophy (SMA), various imaging studies can be helpful in diagnosing the condition, assessing disease severity, and monitoring the progression of the disease. While imaging alone cannot definitively diagnose SMA, it can provide valuable information alongside clinical evaluations and genetic testing. Here are some imaging studies commonly used in SMA:

Electromyography (EMG): EMG measures the electrical activity of muscles and can help identify denervation (loss of nerve supply) and muscle weakness. In SMA, EMG findings typically show abnormal spontaneous activity, reduced recruitment of motor units, and motor unit instability.

Nerve Conduction Studies (NCS): NCS measures the speed and strength of nerve signals as they travel through the peripheral nerves. In SMA, NCS may show reduced or absent compound muscle action potentials (CMAPs), indicating the loss of nerve signals to the muscles.

Magnetic Resonance Imaging (MRI): MRI is a non-invasive imaging technique that uses strong magnetic fields and radio waves to create detailed images of the body. In SMA, MRI of the spinal cord can help assess the extent of motor neuron loss and identify spinal cord abnormalities such as atrophy or signal changes. MRI can also be used to evaluate the brain for any associated abnormalities.

Chest X-ray: A chest X-ray may be performed to assess the respiratory system, as SMA can affect the muscles involved in breathing. X-rays can help identify any signs of respiratory complications, such as lung collapse, scoliosis-related changes, or respiratory infections.

Pulmonary Function Tests (PFTs): PFTs measure lung function, including lung capacity, airflow, and oxygen exchange. These tests can help evaluate respiratory muscle weakness and monitor disease progression. Common PFTs in SMA include spirometry, which assesses lung volumes and airflow, and the measurement of maximal inspiratory and expiratory pressures.

It's important to note that while these imaging studies can provide valuable information, the diagnosis of SMA is primarily based on clinical evaluation and genetic testing, particularly the identification of mutations in the SMN1 gene. Imaging studies are used as adjuncts to support the diagnosis and assess the extent of motor

neuron involvement and associated complications in SMA.

Genetic mutation in Spinal muscular atrophy

Spinal muscular atrophy (SMA) is primarily caused by mutations in the Survival Motor Neuron 1 (SMN1) gene, located on chromosome 5. The SMN1 gene provides instructions for producing the survival motor neuron (SMN) protein, which is essential for the survival and function of motor neurons. Mutations in the SMN1 gene lead to a deficiency or reduced production of the SMN protein, resulting in the degeneration and loss of motor neurons in the spinal cord.

There are two main types of genetic mutations associated with SMA:

Deletion of the SMN1 gene: The most common mutation in SMA is the deletion of the entire SMN1 gene. Individuals with SMA typically have a homozygous deletion, meaning both copies of the SMN1 gene are deleted. This deletion results in a severe deficiency of the SMN protein, leading to the progressive degeneration of motor neurons and the characteristic symptoms of SMA.

SMN1 gene point mutations: In rare cases, SMA can also be caused by point mutations or small changes in the SMN1 gene rather than a complete deletion. These point mutations can affect the function or production of the SMN protein, leading to varying degrees of motor neuron degeneration and SMA symptoms. Point mutations can result in milder forms of SMA, such as SMA Type 3 or Type 4.

It's important to note that while the majority of SMA cases are caused by mutations in the SMN1 gene, there are also other rare genetic variants and modifiers that can influence the severity and presentation of the disease. One example is the presence of a backup gene called SMN2, which produces a less stable and lower amount of the SMN protein compared to SMN1. The number of copies of the SMN2 gene and the production of functional SMN protein from SMN2 can influence the clinical phenotype and disease severity in SMA.

Genetic testing, such as DNA analysis or genetic sequencing, is used to identify the specific genetic mutations associated with SMA and confirm the diagnosis.

Understanding the genetic mutations involved in SMA is crucial for accurate diagnosis, genetic counseling, and the development of targeted therapies for the management of the disease.

Mitochondrial dysfunction in Spinal muscular atrophy

Spinal muscular atrophy (SMA) is a genetic disorder characterized by the loss of motor neurons in the spinal cord, resulting in progressive muscle weakness and atrophy. While SMA is primarily caused by mutations in the Survival Motor Neuron 1 (SMN1) gene, mitochondrial dysfunction has also been implicated in the pathogenesis

of the disease.

Mitochondria are essential organelles responsible for generating energy in cells through oxidative phosphorylation. In SMA, mitochondrial dysfunction has been observed in affected tissues, including muscle cells and motor neurons. Several mechanisms have been proposed to explain mitochondrial dysfunction in SMA:
Impaired mitochondrial respiration: Studies have shown that SMN protein deficiency, resulting from SMN1 gene mutations, can lead to impaired mitochondrial respiration and reduced ATP production. This energy deficit can contribute to the muscle weakness and fatigue observed in SMA.

Increased oxidative stress: Mitochondrial dysfunction in SMA can result in increased production of reactive oxygen species (ROS), leading to oxidative stress. The excessive ROS can damage cellular components, including DNA, proteins, and lipids, and contribute to the degeneration of motor neurons and muscle tissue.

Altered mitochondrial dynamics: SMN protein plays a role in regulating mitochondrial dynamics, including mitochondrial fusion, fission, and transport. SMN deficiency can disrupt these processes, leading to abnormal mitochondrial morphology and impaired distribution within cells.

The exact interplay between SMN protein function, mitochondrial dysfunction, and the pathogenesis of SMA is still under investigation. However, it is believed that mitochondrial dysfunction contributes to the progressive loss of motor neurons and muscle weakness in SMA.

While there is currently no cure for SMA, recent advancements in treatment options have emerged, particularly with the development of disease-modifying therapies such as gene replacement therapy and small molecule drugs. These treatments aim to increase SMN protein levels and improve motor neuron survival. Additionally, supportive care and management strategies, including physical therapy, respiratory support, and nutritional interventions, are essential for optimizing the quality of life and functional abilities of individuals with SMA.

Mitochondrial dysfunction in SMA highlights the complexity of the disease and the potential involvement of multiple cellular processes in its pathogenesis. Further research into the underlying mechanisms of mitochondrial dysfunction in SMA may provide additional insights into the disease and potential therapeutic targets.

Treatment in Spinal muscular atrophy

Spinal muscular atrophy (SMA) is a genetic disorder that currently has several treatment options available. The primary goal of treatment is to manage symptoms, slow down disease progression, and improve the quality of life for individuals with SMA. Here are some of the treatment approaches used in SMA:

Disease-Modifying Therapy:

Nusinersen (brand name Spinraza): Nusinersen is an antisense oligonucleotide administered via intrathecal injection (injection into the spinal fluid). It works by increasing the production of the survival motor neuron (SMN) protein, compensating for the deficiency caused by the underlying genetic mutation. Nusinersen is approved for use in various types of SMA and has shown to improve motor function and survival.

Gene Replacement Therapy:

Onasemnogene abeparvovec (brand name Zolgensma): Zolgensma is a gene therapy that involves a one-time intravenous infusion of a functional copy of the survival motor neuron 1 (SMN1) gene. It aims to replace the missing or defective SMN1 gene and increase the production of the SMN protein. Zolgensma is approved for the treatment of SMA in infants and young children and has demonstrated significant improvements in motor function.

Supportive Care:

Physical Therapy and Occupational Therapy: These therapies aim to maintain and improve motor function, strength, range of motion, and mobility. They also focus on activities of daily living and adaptive strategies to enhance independence.

Respiratory Care: Regular assessment of respiratory function, including pulmonary function tests, may be necessary. Breathing exercises, coughing techniques, and the use of assistive devices like non-invasive ventilation or mechanical ventilation can help manage respiratory complications.

Nutritional Support: Ensuring adequate nutrition and monitoring growth and weight gain are important. Dietary modifications and interventions, such as tube feeding, may be required for individuals with feeding difficulties.

Orthopedic Management: Orthopedic interventions, such as bracing or surgical correction, may be needed to address scoliosis, contractures, or other musculoskeletal complications.

Symptom Management:

Medications: Some medications, such as muscle relaxants, pain relievers, or respiratory medications, may be prescribed to manage specific symptoms associated with SMA.

Assistive Devices: The use of mobility aids, orthoses, wheelchairs, and other assistive devices can help optimize independence and mobility.

It's important to note that the specific treatment plan for an individual with SMA may vary depending on the type and severity of the disease, as well as the age and individual needs. Early intervention and a multidisciplinary approach involving neurologists, pulmonologists, physical therapists, occupational therapists,

nutritionists, and other healthcare professionals are crucial for the comprehensive management of SMA.

28.Spinocerebellar ataxia (脊髓小腦退化性動作協調障礙)

History of Spinocerebellar ataxia

Spinocerebellar ataxia (SCA) is a group of progressive genetic disorders characterized by degeneration and dysfunction of the cerebellum and its associated pathways. The history of SCA begins with the recognition of ataxia as a clinical symptom and the subsequent identification and classification of the different types of spinocerebellar ataxia. Here is an overview of the history of SCA:

Early Observations:

The term "ataxia" was first coined by Louis Friedrich in the early 19th century to describe a lack of coordination and unsteadiness in movement.

Throughout the 19th and early 20th centuries, several clinicians and researchers described cases of ataxia and recognized it as a distinct clinical entity.

Discovery of Genetic Basis:

In the 1980s, advancements in genetic techniques allowed for the identification of specific genetic mutations associated with ataxia.

In 1993, the first gene mutation associated with SCA, called SCA1, was identified by La Spada and colleagues.

Subsequently, several other genes associated with different types of SCA were discovered, leading to the recognition of SCA as a genetically heterogeneous disorder.

Classification of Spinocerebellar Ataxia:

With the identification of multiple genetic mutations, the classification of SCAs became more refined.

The classification of SCAs is based on the specific gene mutation involved and has expanded over time as new genes and subtypes have been discovered.

As of now, more than 40 different subtypes of SCA have been identified, each associated with a specific genetic mutation.

Advances in Understanding and Research:

As research into SCAs has progressed, scientists have gained a better understanding of the underlying molecular and cellular mechanisms involved in the disease.

Animal models, such as mice carrying SCA gene mutations, have been developed to study the pathogenesis and explore potential therapeutic interventions.

Research efforts have focused on identifying potential targets for treatment and developing novel therapeutic approaches, including gene therapy and small molecule interventions.

Current Status:

Currently, there is no cure for SCAs, and treatment primarily focuses on managing symptoms, providing supportive care, and improving quality of life.

Genetic counseling and testing are essential for individuals and families affected by SCA to determine the specific subtype and provide appropriate guidance. Ongoing research aims to develop targeted therapies to slow disease progression, alleviate symptoms, and improve the prognosis for individuals with SCAs. The history of spinocerebellar ataxia is marked by significant advancements in the understanding of the genetic basis and classification of the disease. Continued research and clinical efforts hold promise for the development of effective treatments and interventions for individuals with SCAs.

Classification of Spinocerebellar ataxia

Spinocerebellar ataxia (SCA) refers to a group of inherited neurodegenerative disorders characterized by progressive ataxia, which is the loss of coordination and control of voluntary movements. SCAs are classified based on the specific genetic mutation involved. Here is a classification of the most common types of spinocerebellar ataxia:

Autosomal Dominant Spinocerebellar Ataxias (AD-SCAs):

SCA1: Caused by a mutation in the ATXN1 gene.

SCA2: Caused by a mutation in the ATXN2 gene.

SCA3, also known as Machado-Joseph disease: Caused by a mutation in the ATXN3 gene.

SCA6: Caused by a mutation in the CACNA1A gene.

SCA7: Caused by a mutation in the ATXN7 gene.

SCA8: Caused by a mutation in the ATXN8OS gene.

SCA10: Caused by a mutation in the ATXN10 gene.

SCA12: Caused by a mutation in the PPP2R2B gene.

SCA13: Caused by a mutation in the KCNC3 gene.

SCA14: Caused by a mutation in the PRKCG gene.

SCA17: Caused by a mutation in the TBP gene.

SCA27: Caused by a mutation in the FGF14 gene.

SCA28: Caused by a mutation in the AFG3L2 gene.

SCA31: Caused by a mutation in the BEAN1 gene.

SCA35: Caused by a mutation in the TGM6 gene.

SCA36: Caused by a mutation in the NOP56 gene.

SCA37: Caused by a mutation in the PPP2R5D gene.

SCA38: Caused by a mutation in the ELOVL5 gene.

Autosomal Recessive Spinocerebellar Ataxias (AR-SCAs):

Friedreich's Ataxia (FRDA): Associated with mutations in the FXN gene.

Ataxia with vitamin E deficiency (AVED): Associated with mutations in the TTPA

gene.

Ataxia-telangiectasia (AT): Associated with mutations in the ATM gene.

Ataxia with oculomotor apraxia type 1 (AOA1): Associated with mutations in the APTX gene.

Ataxia with oculomotor apraxia type 2 (AOA2): Associated with mutations in the SETX gene.

Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS): Associated with mutations in the SACS gene.

X-Linked Spinocerebellar Ataxias:

Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS): Associated with an expanded CGG repeat in the FMR1 gene.

It's important to note that the classification of SCAs is continually evolving as new gene mutations are discovered and additional subtypes are identified. Each subtype of SCA has distinct clinical features, age of onset, and disease progression patterns.

Genetic testing is essential for an accurate diagnosis and classification of spinocerebellar ataxia, as it guides appropriate management and genetic counseling for affected individuals and their families.

Symptom and sign in Spinocerebellar ataxia

Spinocerebellar ataxia (SCA) is a group of disorders characterized by progressive ataxia, which refers to the loss of coordination and control of voluntary movements.

While the specific symptoms and signs can vary depending on the subtype of SCA and the individual, here are some common features seen in individuals with SCA:

Ataxia: The hallmark symptom of SCA is ataxia, which can affect both the upper and lower limbs. It typically presents as unsteadiness, clumsiness, and difficulty with precise movements. Individuals may experience problems with balance, coordination, gait abnormalities, and fine motor skills.

Dysarthria: Many individuals with SCA develop dysarthria, a speech disorder characterized by slurred or slow speech, changes in voice quality, and difficulty articulating words. Speech can become progressively more difficult to understand as the disease progresses.

Tremors: Some forms of SCA may involve tremors, which are involuntary rhythmic movements. Tremors may affect the hands, arms, or other parts of the body and can worsen with intentional movements.

Eye Movement Abnormalities: Oculomotor abnormalities are common in SCA and can include gaze-evoked nystagmus (involuntary eye movements), impaired smooth pursuit (tracking objects with the eyes), and difficulty controlling eye movements.

Muscle Weakness and Atrophy: As SCA progresses, individuals may experience

muscle weakness and atrophy (shrinking) due to the degeneration of nerve cells that control muscle movement. This can result in difficulty with tasks requiring strength and endurance.

Sensory Dysfunction: Some individuals with SCA may experience sensory abnormalities such as numbness, tingling, or loss of sensation in the limbs. These sensory disturbances can contribute to difficulties with coordination and balance.

Cognitive and Psychological Changes: In certain subtypes of SCA, cognitive impairments and psychiatric symptoms may be present. These can include memory problems, executive dysfunction, mood changes, depression, anxiety, and behavioral changes.

Other Manifestations: Depending on the specific subtype, additional features may be present, such as peripheral neuropathy (damage to the peripheral nerves), epilepsy, cardiac abnormalities, or ophthalmologic issues like retinal degeneration.

It's important to note that the severity and progression of symptoms can vary widely among individuals with SCA, even within the same subtype. The age of onset and rate of disease progression can also differ, ranging from childhood-onset forms with rapid progression to adult-onset forms with slower progression. A comprehensive evaluation by a neurologist specializing in movement disorders is crucial for diagnosing SCA and managing its associated symptoms.

Image study in Spinocerebellar ataxia

Imaging studies play an important role in the evaluation of individuals with spinocerebellar ataxia (SCA). They help assess the structural and functional changes in the brain and spinal cord, aiding in the diagnosis and management of the condition. Here are some common imaging modalities used in the evaluation of SCA:

Magnetic Resonance Imaging (MRI): MRI is the most commonly used imaging technique for evaluating SCA. It provides detailed images of the brain, spinal cord, and cerebellum. MRI can help identify atrophy (shrinkage) of the cerebellum and other affected brain regions, as well as detect abnormalities in white matter tracts. It can also help rule out other conditions that may present with similar symptoms.

Diffusion Tensor Imaging (DTI): DTI is a specialized MRI technique that provides information about the integrity and connectivity of white matter tracts in the brain. It can help assess the disruption or degeneration of these tracts, which are often affected in SCA. DTI can provide insights into the underlying microstructural changes in the brain, such as axonal loss or demyelination.

Positron Emission Tomography (PET): PET scans can be used to assess the metabolic activity and blood flow in the brain. It can help identify regions of decreased metabolism or hypoperfusion, indicating areas of dysfunction in the brain affected by

SCA. PET scans can be particularly useful in distinguishing SCA from other conditions and in monitoring disease progression.

Single-Photon Emission Computed Tomography (SPECT): SPECT imaging is another technique that measures cerebral blood flow. It can help identify regional abnormalities in blood perfusion in the brain and detect areas of reduced or altered blood flow associated with SCA.

Functional MRI (fMRI): fMRI measures changes in blood oxygenation and can provide insights into brain activity during specific tasks or at rest. It can help identify alterations in functional connectivity networks and assess how the brain compensates for areas affected by SCA.

These imaging studies, in conjunction with clinical evaluations and genetic testing, can help in the diagnosis and monitoring of SCA. They provide valuable information about the structural and functional changes in the brain and aid in understanding the underlying pathology and progression of the disease. The specific choice of imaging modality depends on factors such as availability, clinical presentation, and individual patient characteristics. Genetic mutation in Spinocerebellar ataxia

Genetic mutation in Spinocerebellar ataxia

Spinocerebellar ataxia (SCA) refers to a group of genetic disorders characterized by progressive degeneration of the cerebellum and other regions of the central nervous system. There are several types of spinocerebellar ataxia, each associated with a specific genetic mutation. The genetic mutations in spinocerebellar ataxia can vary, but they typically involve an abnormal expansion of repetitive DNA sequences within certain genes. This expansion leads to the production of toxic proteins or RNA molecules that interfere with normal cellular function and cause the degeneration of neurons.

The specific gene mutations and corresponding types of spinocerebellar ataxia include:

SCA1: Caused by a mutation in the ATXN1 gene, which leads to the production of an abnormal form of the ataxin-1 protein.

SCA2: Caused by a mutation in the ATXN2 gene, resulting in the production of an abnormal form of the ataxin-2 protein.

SCA3 (also known as Machado-Joseph disease): Caused by a mutation in the ATXN3 gene, leading to the production of an abnormal form of the ataxin-3 protein.

SCA6: Caused by a mutation in the CACNA1A gene, which encodes a calcium channel protein.

SCA7: Caused by a mutation in the ATXN7 gene, resulting in the production of an abnormal form of the ataxin-7 protein.

SCA8: Caused by a CTG trinucleotide repeat expansion in the ATXN8OS gene.

SCA10: Caused by an ATTCT pentanucleotide repeat expansion in the ATXN10 gene.

SCA12: Caused by a CAG trinucleotide repeat expansion in the PPP2R2B gene.

SCA17: Caused by a mutation in the TBP gene, which leads to the production of an abnormal form of the TATA-binding protein.

SCA23: Caused by mutations in the PDYN gene.

SCA25: Caused by mutations in the ELOVL4 gene.

SCA27: Caused by mutations in the FGF14 gene.

SCA28: Caused by mutations in the AFG3L2 gene.

SCA31: Caused by repeat expansions in the BEAN1 gene.

SCA36: Caused by repeat expansions in the NOP56 gene.

These are just a few examples of the many types of spinocerebellar ataxia, and each type is associated with a specific genetic mutation. The genetic mutations can be inherited in an autosomal dominant manner, meaning that an affected individual has a 50% chance of passing the mutation on to their children.

It's worth noting that not all cases of spinocerebellar ataxia are linked to a known genetic mutation. In some individuals, the genetic cause may not yet be identified, and further research is ongoing to better understand the underlying genetic factors involved in these cases.

Mitochondrial dysfunction in Spinocerebellar ataxia

Spinocerebellar ataxias (SCAs) are a group of genetic disorders characterized by progressive degeneration of the cerebellum and spinal cord, leading to movement problems and coordination difficulties. While the primary cause of SCAs is genetic mutations in specific genes, mitochondrial dysfunction has been implicated in the pathogenesis of some forms of spinocerebellar ataxia.

Mitochondria are responsible for generating energy in cells through oxidative phosphorylation, and they play a crucial role in maintaining cellular homeostasis. In the context of spinocerebellar ataxia, mitochondrial dysfunction can occur through various mechanisms, including:

Impaired energy metabolism: Mitochondrial dysfunction in SCAs can lead to a decrease in ATP production, which is essential for normal cellular functions. This energy deficit can affect the high-energy demands of neurons, particularly those in the cerebellum and spinal cord, leading to neuronal dysfunction and degeneration.

Oxidative stress: Mitochondrial dysfunction can result in the excessive production of reactive oxygen species (ROS) within cells. ROS are highly reactive molecules that can damage cellular components, including proteins, lipids, and DNA. The

accumulation of oxidative damage can contribute to the degeneration of neurons in the cerebellum and spinal cord, exacerbating the symptoms of ataxia.

Impaired calcium handling: Mitochondria are involved in regulating intracellular calcium levels, which is crucial for various cellular processes. In some forms of spinocerebellar ataxia, mitochondrial dysfunction can disrupt calcium homeostasis, leading to abnormal neuronal signaling and neuronal death.

The specific mechanisms of mitochondrial dysfunction can vary among different types of spinocerebellar ataxia, as each subtype is associated with distinct genetic mutations. For example, in spinocerebellar ataxia type 3 (SCA3), also known as Machado-Joseph disease, there is evidence of mitochondrial dysfunction and impaired energy metabolism.

Understanding the role of mitochondrial dysfunction in spinocerebellar ataxia is still an active area of research. Targeting mitochondrial dysfunction and associated pathways may hold therapeutic potential for treating or managing the disease. However, further studies are needed to elucidate the precise mechanisms and develop effective interventions specifically targeting mitochondrial dysfunction in spinocerebellar ataxia.

Treatment in Spinocerebellar ataxia

Currently, there is no cure for spinocerebellar ataxia (SCA) and treatment primarily focuses on managing symptoms, improving quality of life, and providing supportive care. The treatment approach may vary depending on the specific subtype of SCA and the individual's symptoms. Here are some common strategies employed in the management of SCA:

Symptom Management:

Physical and occupational therapy: These therapies aim to improve coordination, balance, and motor skills, and to help individuals adapt to functional limitations caused by ataxia.

Speech therapy: Speech therapy can assist in improving speech and communication difficulties associated with dysarthria.

Assistive devices: The use of mobility aids, such as canes or walkers, and adaptive devices for activities of daily living can enhance independence and safety.

Medications: While there is no specific medication to treat the underlying cause of SCA, certain medications may be prescribed to manage specific symptoms. For example, medications to control tremors, manage muscle stiffness or spasticity, and alleviate mood disturbances or sleep problems may be considered.

Rehabilitation and Supportive Care:

Genetic counseling: Genetic counseling is recommended for individuals with SCA

and their families to understand the inheritance pattern, provide information about the disease, and discuss family planning options.

Psychological support: Counseling or therapy can help individuals and their families cope with the emotional and psychological challenges associated with SCA.

Support groups: Joining support groups or connecting with others affected by SCA can provide valuable emotional support, practical tips, and shared experiences.

Regular monitoring: Routine follow-up visits with a neurologist specializing in movement disorders are important to monitor disease progression, manage symptoms, and address any complications that may arise.

Research and Clinical Trials:

As SCA is a genetic disorder, ongoing research is focused on developing targeted therapies to slow or halt disease progression. Clinical trials are being conducted to test potential treatments, including gene-based therapies and pharmacological interventions.

It's important for individuals with SCA to work closely with a healthcare team, including neurologists, physical therapists, occupational therapists, and other specialists, to develop an individualized treatment plan. Since the specific management strategies can vary depending on the subtype and individual needs, it's essential to consult with healthcare professionals for tailored guidance and support.

29.Stiffperson syndrome(僵體症候群)

History of Stiffperson syndrome

Stiffperson syndrome (SPS), also known as stiff-man syndrome, is a rare neurological disorder characterized by stiffness and muscle spasms. It was first described in the medical literature in the 1950s by Dr. Fred Plum and Dr. Jerome Posner.

The history of Stiffperson syndrome can be traced back to the mid-20th century. In 1956, Plum and Posner published a landmark paper describing the clinical features of three patients with a peculiar stiffness of the axial muscles, leading to the term "stiff-man syndrome." They noted that the patients experienced muscle stiffness and spasms that were triggered by emotional stress, sudden movements, or unexpected stimuli.

Over the years, further research and clinical observations have expanded our understanding of Stiffperson syndrome. It was recognized that the disorder can affect both men and women of any age, although it appears to be more common in women. The prevalence of SPS is estimated to be around 1 in 1 million individuals.

In the 1980s, the discovery of autoantibodies against the enzyme glutamic acid decarboxylase (GAD) provided important insights into the underlying pathophysiology of Stiffperson syndrome. GAD is involved in the synthesis of gamma-aminobutyric acid (GABA), a neurotransmitter that plays a key role in inhibiting the activity of nerve cells. The presence of GAD antibodies suggested an autoimmune component in the development of the disorder.

With the recognition of the autoimmune nature of Stiffperson syndrome, treatment approaches shifted towards immunomodulatory therapies. Medications such as intravenous immunoglobulins (IVIG), corticosteroids, and plasma exchange have been used to manage the symptoms and modulate the immune response.

In recent years, advancements in understanding the pathogenesis of Stiffperson syndrome have led to the identification of other autoantibodies associated with the disorder, including antibodies against amphiphysin, gephyrin, and glycine receptors. These discoveries have helped refine the classification and diagnosis of Stiffperson syndrome and have opened up new avenues for targeted therapies.

Despite ongoing research, Stiffperson syndrome remains a challenging condition to manage, and there is no definitive cure. Treatment aims to reduce muscle stiffness, control spasms, and improve quality of life for affected individuals. Multidisciplinary approaches, including physical therapy, pharmacological interventions, and psychological support, are often employed to address the complex needs of individuals with Stiffperson syndrome.

Classification of Stiffperson syndrome

Stiffperson syndrome (SPS) is a rare neurological disorder that is classified into different subtypes based on certain clinical characteristics and associated features. While the classification system for Stiffperson syndrome is not universally agreed upon, the following classification scheme is commonly used:

Classic Stiffperson syndrome (cSPS):

This is the most common form of Stiffperson syndrome.

It is characterized by muscle stiffness and spasms, predominantly affecting the axial muscles, particularly the trunk and lower limbs.

The muscle stiffness may be continuous or intermittent and is often triggered by emotional stress or sudden movements.

Individuals with cSPS typically have elevated levels of autoantibodies against glutamic acid decarboxylase (GAD), an enzyme involved in the production of the neurotransmitter gamma-aminobutyric acid (GABA).

Jerking Stiffperson syndrome (jSPS):

This subtype of Stiffperson syndrome is characterized by muscle stiffness, spasms, and prominent jerking movements.

In addition to the classic symptoms of SPS, individuals with jSPS experience sudden, involuntary muscle contractions or jerks, known as myoclonus.

The myoclonus can affect various muscle groups and can be spontaneous or triggered by sensory stimuli.

Autoantibodies against GAD are often present in individuals with jSPS as well.

Progressive encephalomyelitis with rigidity and myoclonus (PERM):

PERM is a severe and progressive form of Stiffperson syndrome.

In addition to the characteristic muscle stiffness and spasms, individuals with PERM experience other neurological symptoms, including encephalopathy (brain dysfunction) and myoclonus.

The encephalopathy can manifest as cognitive impairment, behavioral changes, and autonomic dysfunction.

Autoantibodies against GAD or other neuronal proteins may be present in PERM.

It is important to note that the classification of Stiffperson syndrome can be complex, and some individuals may not fit neatly into one specific subtype. Additionally, there may be other rare variants or overlapping syndromes associated with Stiffperson syndrome that have not been widely characterized.

The classification of Stiffperson syndrome helps in understanding the different clinical presentations and guiding treatment approaches. However, it is always important to consult with a healthcare professional specializing in neurological disorders for an accurate diagnosis and individualized management plan.

Symptom and sign in Stiffperson syndrome

Stiffperson syndrome (SPS) is characterized by a unique set of symptoms and signs that primarily affect the muscles, leading to stiffness, spasms, and impaired movement. The following are the key symptoms and signs associated with Stiffperson syndrome:

Muscle Stiffness:

Persistent and generalized muscle stiffness is the hallmark symptom of Stiffperson syndrome.

The stiffness typically affects the axial muscles, including the trunk, abdomen, and lower back.

The stiffness may also involve the muscles of the limbs, such as the legs and arms.

Muscle Spasms:

Muscle spasms, also referred to as muscle cramps or involuntary contractions, are common in Stiffperson syndrome.

These spasms are usually brief but can be intense and painful.

Spasms can occur spontaneously or may be triggered by specific factors, such as sudden movements, emotional stress, or sensory stimuli.

Gait Disturbance:

Stiffperson syndrome can lead to difficulties with walking and impaired coordination.

Individuals may have a stiff and awkward gait, often described as "walking on tiptoes" or "walking like a robot."

Balance may be affected, and individuals may be prone to falls.

Hyperreflexia:

Hyperreflexia refers to an exaggerated reflex response.

In Stiffperson syndrome, hyperreflexia may be observed, meaning that reflexes such as the knee-jerk reflex are overly sensitive and produce a stronger response than normal.

Sensory Symptoms:

Some individuals with Stiffperson syndrome may experience abnormal sensations, such as tingling, numbness, or heightened sensitivity to touch or sound.

Sensory symptoms may be intermittent or persistent.

Autonomic Dysfunction:

Stiffperson syndrome can affect the autonomic nervous system, leading to symptoms such as excessive sweating (hyperhidrosis) or lack of sweating (anhidrosis), fluctuating blood pressure, and irregular heart rate.

It is important to note that the severity and specific combination of symptoms can vary among individuals with Stiffperson syndrome. The symptoms can also fluctuate over time, with periods of exacerbation and relative stability.

If you suspect you or someone you know may have Stiffperson syndrome, it is

essential to consult with a healthcare professional experienced in neurological disorders for a comprehensive evaluation and diagnosis.

Image study in Stiffperson syndrome

Image studies, such as neuroimaging techniques, are commonly used in the evaluation of individuals with Stiffperson syndrome (SPS) to help understand the underlying structural and functional changes in the nervous system. While there are no specific imaging findings that are diagnostic of SPS, certain studies may be helpful in the diagnostic process and to rule out other conditions. The following image studies may be performed in individuals with suspected Stiffperson syndrome:

Magnetic Resonance Imaging (MRI):

MRI uses a strong magnetic field and radio waves to generate detailed images of the brain and spinal cord.

MRI scans can help detect any structural abnormalities in the central nervous system (CNS) that may contribute to the symptoms observed in SPS.

In individuals with Stiffperson syndrome, MRI findings are typically normal or may show nonspecific findings.

Positron Emission Tomography (PET) Scan:

PET scans provide functional information about the brain and can help assess metabolic activity and blood flow.

In Stiffperson syndrome, PET scans may reveal abnormal patterns of brain activity, particularly in regions involved in movement and motor control.

Single-Photon Emission Computed Tomography (SPECT) Scan:

SPECT scans are another type of nuclear imaging that can assess blood flow and brain function.

SPECT imaging may show changes in cerebral blood flow patterns that correlate with the clinical symptoms observed in Stiffperson syndrome.

Electromyography (EMG) and Nerve Conduction Studies (NCS):

While not image studies in the traditional sense, EMG and NCS are often performed to evaluate the electrical activity and nerve conduction in the muscles.

These tests can help differentiate Stiffperson syndrome from other neuromuscular disorders and assess the degree of muscle hyperexcitability.

It is important to note that the imaging findings in Stiffperson syndrome are often nonspecific and do not provide a definitive diagnosis. The diagnosis of SPS is primarily based on clinical symptoms, characteristic electromyographic findings, and the exclusion of other conditions that may mimic SPS.

Ultimately, the decision to perform image studies in Stiffperson syndrome is based on the individual's specific clinical presentation and the need to rule out other potential

causes of their symptoms. The healthcare provider will determine the most appropriate imaging modality based on the individual's clinical history and examination findings.

Genetic mutation in Stiffperson syndrome

Stiffperson syndrome (SPS) is associated with specific genetic mutations that are believed to contribute to the development of the disorder. The primary genetic mutation associated with SPS involves the production of autoantibodies against glutamic acid decarboxylase (GAD), an enzyme responsible for synthesizing the neurotransmitter gamma-aminobutyric acid (GABA). These autoantibodies target GAD and disrupt GABA signaling, leading to abnormal muscle activity and the characteristic symptoms of SPS.

GAD is encoded by two genes: GAD1 and GAD2. The majority of individuals with SPS have autoantibodies targeting GAD65, which is the isoform encoded by the GAD2 gene. However, autoantibodies targeting GAD67 (encoded by GAD1) have also been detected in some individuals with SPS.

It is important to note that while the presence of GAD autoantibodies is strongly associated with SPS, not all individuals with SPS have detectable autoantibodies. Additionally, GAD autoantibodies can also be found in other neurological disorders, albeit less commonly.

The underlying mechanisms by which these GAD autoantibodies contribute to the development of SPS are still not fully understood. It is believed that the binding of these autoantibodies to GAD interferes with GABA synthesis, leading to reduced GABA levels and impaired inhibition of nerve signaling in the affected muscles. While GAD autoantibodies are the primary genetic markers associated with SPS, it is important to note that SPS is not considered a hereditary disorder in the traditional sense. The presence of GAD autoantibodies is thought to result from a combination of genetic susceptibility and environmental triggers. The exact factors that trigger the production of these autoantibodies in susceptible individuals are not yet fully understood.

Genetic testing for SPS typically focuses on detecting the presence of GAD autoantibodies rather than identifying specific genetic mutations. The detection of these autoantibodies in blood serum or cerebrospinal fluid can help support the diagnosis of SPS.

It is worth noting that research in this field is ongoing, and additional genetic and immunological factors may contribute to the development of SPS.

Mitochondrial dysfunction in Stiffperson syndrome

Stiffperson syndrome (SPS) is a rare neurological disorder characterized by muscle stiffness and spasms, typically involving the axial muscles of the trunk and limbs. While the exact cause of SPS is not fully understood, there is emerging evidence suggesting a potential role of mitochondrial dysfunction in the pathogenesis of the disease.

Mitochondria are responsible for generating energy in cells through oxidative phosphorylation, and they play a crucial role in maintaining cellular homeostasis. In the context of Stiffperson syndrome, mitochondrial dysfunction can occur through several mechanisms:

Impaired energy metabolism: Mitochondrial dysfunction can lead to a decrease in ATP production, which is essential for normal muscle function. Energy deficits in the affected muscles may contribute to the muscle stiffness and spasms observed in SPS.

Dysregulated calcium homeostasis: Mitochondria are involved in maintaining intracellular calcium levels and regulating calcium signaling. Dysfunction in calcium handling by mitochondria can disrupt normal muscle contraction and relaxation processes, leading to the characteristic muscle stiffness and spasms seen in SPS.

Increased oxidative stress: Mitochondrial dysfunction can result in the production of excessive reactive oxygen species (ROS), which are highly reactive molecules that can damage cellular components. The accumulation of oxidative stress in muscle cells may contribute to the pathogenesis of SPS.

It's important to note that the relationship between mitochondrial dysfunction and SPS is still an area of ongoing research, and the exact mechanisms linking the two are not fully understood. Mitochondrial dysfunction may represent one aspect of the complex pathophysiology of SPS, and further studies are needed to elucidate the precise role and significance of mitochondrial dysfunction in the development and progression of the disease.

Currently, the treatment of Stiffperson syndrome primarily focuses on symptom management and includes medications such as benzodiazepines, muscle relaxants, and immunomodulatory therapies. Targeting mitochondrial dysfunction as a therapeutic approach in SPS is an area of potential future investigation, but more research is needed to determine the effectiveness of such interventions.

Treatment in Stiffperson syndrome

The treatment of Stiffperson syndrome (SPS) aims to alleviate symptoms, improve function, and enhance the individual's quality of life. Since SPS is a rare and complex neurological disorder, treatment approaches may vary depending on the specific needs and responses of each patient. Here are some common treatment options for SPS:

Medications:

Benzodiazepines: Medications such as diazepam and clonazepam can help reduce muscle stiffness and spasms by enhancing the inhibitory effects of GABA.

Baclofen: Baclofen is a muscle relaxant that can also be beneficial in reducing muscle stiffness and improving mobility.

Anti-seizure medications: Drugs like gabapentin and pregabalin may be prescribed to help control muscle spasms and neuropathic pain in some individuals.

Intravenous Immunoglobulin (IVIg):

IVIg therapy involves the administration of high-dose immunoglobulin intravenously.

IVIg can modulate the immune system and reduce the production of autoantibodies, potentially improving symptoms in some individuals with SPS.

Plasma Exchange (Plasmapheresis):

Plasmapheresis involves removing the patient's blood plasma, separating it from blood cells, and then replacing it with donor plasma or a plasma substitute.

Plasma exchange may help remove circulating autoantibodies and other immune factors, providing temporary relief from symptoms.

Physical Therapy:

Physical therapy is essential for managing stiffness, improving mobility, and preventing muscle atrophy.

Stretching exercises, range-of-motion exercises, and balance training can be beneficial.

Assistive devices such as braces, canes, or walkers may be recommended to support mobility.

Psychological Support:

Living with a chronic neurological condition like SPS can have a significant impact on mental health and well-being.

Psychological support, counseling, and support groups can help individuals cope with the emotional and psychological challenges associated with SPS.

It is important to note that treatment approaches may be tailored to the individual's specific symptoms and needs. Since SPS is a chronic condition, long-term management and regular follow-up with healthcare professionals are necessary to assess treatment effectiveness and adjust therapies as needed.

It is advisable for individuals with Stiffperson syndrome to work closely with a multidisciplinary healthcare team, including neurologists, physiatrists, physical therapists, and occupational therapists, to develop a comprehensive treatment plan that addresses their unique needs and goals.

30.Tuberous sclerosis(結節性硬化症)

History of Tuberous sclerosis

Tuberous sclerosis, also known as tuberous sclerosis complex (TSC), is a rare genetic disorder characterized by the growth of benign tumors in various organs of the body. Here is a brief history of tuberous sclerosis:

Discovery and Early Observations:

In 1862, French dermatologist Désiré-Magloire Bourneville first described tuberous sclerosis as a distinct clinical entity. He observed skin lesions and epilepsy in several patients and recognized the connection between these features.

In 1908, Gustav Riehl expanded on Bourneville's work and proposed the term "tuberous sclerosis" due to the presence of tuber-like growths in the brain.

Advances in Understanding and Genetics:

In the 1960s, advances in histology and electron microscopy led to a better understanding of the pathology of tuberous sclerosis. Researchers identified the characteristic tumors, called cortical tubers, in the brains of affected individuals.

In the 1990s, significant progress was made in identifying the genetic basis of tuberous sclerosis. In 1993, the TSC1 gene on chromosome 9 was discovered, followed by the identification of the TSC2 gene on chromosome 16 in 1997.

Mutations in these genes are responsible for most cases of tuberous sclerosis.

Clinical Features and Diagnostic Criteria:

Over time, the clinical features of tuberous sclerosis were better defined. The diagnostic criteria for tuberous sclerosis were established by an international consensus conference in 1998 and revised in 2012. These criteria include major and minor clinical features, such as skin abnormalities, brain tumors, kidney tumors, and cardiac rhabdomyomas.

Treatment and Management:

With increased understanding of the molecular mechanisms involved in tuberous sclerosis, targeted therapies have been developed. In 2010, the U.S. Food and Drug Administration (FDA) approved everolimus, an mTOR inhibitor, for the treatment of certain manifestations of tuberous sclerosis, including renal angiomyolipomas and subependymal giant cell astrocytomas.

Ongoing research continues to explore new treatment approaches and improve the management of tuberous sclerosis. Clinical trials are underway to investigate the potential of other targeted therapies and genetic interventions.

The history of tuberous sclerosis has seen significant advancements in our understanding of the disorder, from its clinical features to the identification of genetic mutations responsible for the condition. These developments have paved the way for

improved diagnosis, management, and potential treatments for individuals with tuberous sclerosis.

Classification of Tuberous sclerosis

Tuberous sclerosis (TSC) is classified into two subtypes based on the genetic mutation involved:

TSC1: TSC1 is caused by mutations in the TSC1 gene, located on chromosome 9q34. TSC1 mutations account for approximately 25-30% of all cases of tuberous sclerosis. TSC1-related tuberous sclerosis tends to have a milder clinical course compared to TSC2-related tuberous sclerosis.

TSC2: TSC2 is caused by mutations in the TSC2 gene, located on chromosome 16p13.3. The majority of tuberous sclerosis cases, approximately 70-75%, are caused by mutations in the TSC2 gene. TSC2-related tuberous sclerosis is associated with a more severe clinical phenotype and an increased risk of intellectual disability.

It's important to note that tuberous sclerosis can present with a wide range of clinical manifestations, even within the same subtype. The severity and specific features can vary significantly among affected individuals, making the classification based on genetic subtype just one aspect of understanding the disease. Diagnosis is typically made based on clinical criteria, including the presence of major and minor features as defined by international consensus guidelines. These features encompass various organ systems, such as the skin, brain, kidneys, heart, and lungs.

Additionally, tuberous sclerosis can be classified into sporadic or familial forms based on the presence or absence of a family history of the disorder. Sporadic cases occur in individuals with no family history of tuberous sclerosis, while familial cases are inherited from an affected parent.

It's worth noting that the classification of tuberous sclerosis continues to evolve as research uncovers new genetic variants and their clinical implications. Genetic testing plays a crucial role in confirming the diagnosis and identifying the specific mutation involved, which can have implications for prognosis and management. A comprehensive evaluation by a healthcare professional with expertise in tuberous sclerosis is necessary for accurate classification and appropriate management of the condition.

Symptom and sign in Tuberous sclerosis

Tuberous sclerosis (TSC) is a multisystem disorder that can affect various organs in the body. The symptoms and signs of tuberous sclerosis can vary widely among individuals, and not everyone with TSC will experience all of the following features. Here are some common symptoms and signs associated with tuberous sclerosis:

Skin Manifestations:

Hypomelanotic macules: These are light-colored patches on the skin, often appearing as pale, ash-colored spots.

Facial angiofibromas: Small red or pink raised bumps on the face, typically on the cheeks and nose.

Shagreen patches: Thickened, leathery skin patches, usually found on the lower back or nape of the neck.

Ungual fibromas: Benign tumors occurring around the nails, appearing as fleshy or wart-like growths.

Neurological Manifestations:

Seizures: Epileptic seizures are a common feature of TSC, which can vary in type and severity.

Cognitive and behavioral difficulties: Many individuals with TSC may experience intellectual disability, learning disabilities, developmental delays, and behavioral problems.

Autism spectrum disorder: A significant number of individuals with TSC also have features of autism spectrum disorder, including impaired social interaction, communication difficulties, and repetitive behaviors.

Brain and Nervous System Manifestations:

Cortical tubers: Abnormal nodular growths in the brain that can disrupt normal brain function and contribute to neurological symptoms.

Subependymal nodules (SENs): Small growths that develop along the walls of the brain's ventricles.

Subependymal giant cell astrocytomas (SEGAs): Benign brain tumors that can cause obstructive hydrocephalus and other neurological complications.

White matter abnormalities: Disruptions or changes in the white matter of the brain, which can be observed on brain imaging studies.

Other Manifestations:

Cardiac rhabdomyomas: Noncancerous tumors that can develop in the heart, usually detected during infancy or childhood.

Renal angiomyolipomas: Benign tumors consisting of blood vessels, smooth muscle, and fat cells in the kidneys.

Pulmonary manifestations: Lung cysts and pneumothorax (collapsed lung) can occur in some individuals with TSC.

It's important to note that the severity and combination of symptoms can vary widely among individuals with tuberous sclerosis. Regular medical evaluations and screenings are necessary to monitor and manage the different manifestations of the condition. A multidisciplinary approach involving various medical specialists is often

employed to provide comprehensive care and support for individuals with TSC.

Image study in Tuberous sclerosis

Various imaging studies can be useful in the evaluation and diagnosis of tuberous sclerosis (TSC). These imaging modalities help visualize the structural abnormalities and lesions associated with the condition. Here are some common imaging studies used in TSC:

Magnetic Resonance Imaging (MRI): MRI is the primary imaging modality used in TSC. It provides detailed images of the brain, spinal cord, and other affected organs. MRI can reveal the presence of cortical tubers, subependymal nodules (SENs), subependymal giant cell astrocytomas (SEGAs), and other brain abnormalities associated with TSC.

Computed Tomography (CT) Scan: CT scans may be used to evaluate certain aspects of TSC, particularly in cases where MRI is contraindicated or unavailable. CT scans can provide detailed images of the brain and can help identify cortical tubers, calcifications, and other abnormalities.

Ultrasound: Ultrasound imaging may be used to evaluate cardiac rhabdomyomas, which are commonly seen in infants with TSC. Cardiac ultrasound (echocardiography) can detect and monitor the presence, size, and location of these tumors in the heart.

Renal Imaging: Imaging studies such as ultrasound, CT, or MRI may be used to evaluate the kidneys for the presence of angiomyolipomas, which are benign tumors commonly found in individuals with TSC.

Chest X-ray: A chest X-ray may be performed to assess for the presence of lung cysts, which can occur in TSC. It can also help identify complications such as pneumothorax (collapsed lung).

Positron Emission Tomography (PET) Scan: PET scans may be used in certain cases to evaluate the metabolic activity of SEGAs or to assess other aspects of TSC, such as epilepsy and brain function.

These imaging studies can aid in the diagnosis, assessment of disease progression, and monitoring of complications associated with tuberous sclerosis. It's important to consult with a healthcare professional experienced in TSC to determine the appropriate imaging modalities and interpretation for an individual case.

Genetic mutation in Tuberous sclerosis

Tuberous sclerosis (TSC) is caused by mutations in either the TSC1 gene or the TSC2 gene. These genes provide instructions for producing proteins involved in regulating cell growth and division. The specific genetic mutation in either of these genes

disrupts the normal function of the proteins, leading to the development of tuberous sclerosis.

TSC1 Gene Mutation: The TSC1 gene, also known as tuberin, is located on chromosome 9q34. It encodes the tuberin protein, which interacts with the protein product of the TSC2 gene (hamartin) to form a complex that regulates cell growth and proliferation. Mutations in the TSC1 gene account for approximately 15-25% of TSC cases. These mutations can be inherited from an affected parent or occur spontaneously (de novo) without a family history.

TSC2 Gene Mutation: The TSC2 gene, also known as hamartin, is located on chromosome 16p13.3. It encodes the hamartin protein, which, as mentioned earlier, forms a complex with tuberin to regulate cell growth and division. Mutations in the TSC2 gene are responsible for approximately 70-80% of TSC cases. Like TSC1 mutations, TSC2 mutations can be inherited or occur spontaneously.

Both TSC1 and TSC2 mutations lead to the dysregulation of a signaling pathway called the mammalian target of rapamycin (mTOR) pathway. The mTOR pathway plays a crucial role in controlling cell growth, proliferation, and differentiation. When the TSC1 or TSC2 gene is mutated, the mTOR pathway becomes overactive, resulting in the formation of benign tumors in various organs of the body, including the brain, skin, kidneys, heart, and lungs.

It's important to note that the severity and clinical manifestations of TSC can vary even among individuals with the same genetic mutation. Other genetic and environmental factors may also influence the disease's presentation and progression. Genetic testing can be performed to identify the specific mutation in the TSC1 or TSC2 gene, which can aid in confirming the diagnosis and providing valuable information for family planning, genetic counseling, and potential targeted therapies.

Mitochondrial dysfunction in Tuberous sclerosis

Tuberous sclerosis complex (TSC) is a genetic disorder characterized by the development of noncancerous tumors in various organs, including the brain, skin, kidneys, heart, and lungs. While the primary genetic mutations associated with TSC affect the mTOR signaling pathway, recent research has also suggested a potential role of mitochondrial dysfunction in the pathogenesis of the disease.

Mitochondria are involved in various cellular processes, including energy production, metabolism, and calcium homeostasis. In the context of TSC, mitochondrial dysfunction can occur through several mechanisms:

Energy metabolism disruption: Mitochondrial dysfunction in TSC may lead to impaired energy production in affected cells. The mutations in TSC1 or TSC2 genes that cause the disease can disrupt mTOR signaling, which is involved in the regulation

of mitochondrial biogenesis and function. Altered mTOR signaling can result in mitochondrial abnormalities and reduced ATP production, leading to cellular energy deficits.

Oxidative stress and reactive oxygen species (ROS) production: Mitochondrial dysfunction can lead to increased production of ROS, which are highly reactive molecules that can cause oxidative damage to cells. TSC-associated mitochondrial dysfunction may contribute to elevated ROS levels, leading to oxidative stress and potential damage to cellular components.

Calcium dysregulation: Mitochondria play a crucial role in calcium homeostasis, and disrupted mitochondrial function in TSC can lead to abnormal calcium signaling. Dysregulated calcium levels can impact cellular processes, including cell growth, proliferation, and apoptosis, which are already altered in TSC due to mTOR dysregulation.

While the exact mechanisms linking mitochondrial dysfunction to the development and progression of TSC are still being investigated, it is believed that the interplay between mTOR signaling and mitochondrial function plays a role in the pathogenesis of the disease.

Currently, the treatment of TSC focuses on managing symptoms and complications associated with the disease. This may include antiepileptic medications for seizures, medications to manage tumors or their associated symptoms, and supportive therapies tailored to individual needs. Targeting mitochondrial dysfunction as a therapeutic approach in TSC is an area of ongoing research, and future studies may explore potential interventions aimed at restoring mitochondrial function or mitigating its detrimental effects in the context of the disease.

Treatment in Tuberous sclerosis

The management of tuberous sclerosis (TSC) involves a multidisciplinary approach aimed at addressing the various manifestations and complications associated with the condition. Although there is no cure for TSC, treatment focuses on symptom management, early intervention, and supportive care. Here are some key aspects of treatment in TSC:

Seizure Management: Seizures are a common feature of TSC. Antiepileptic medications are often prescribed to help control seizures and improve overall seizure management. The choice of medication depends on the type and frequency of seizures and may require periodic adjustments.

Behavioral and Developmental Interventions: Children with TSC may benefit from early intervention programs, such as speech therapy, occupational therapy, and physical therapy, to address developmental delays, learning disabilities, and

behavioral difficulties. These interventions can help optimize the child's potential and improve their quality of life.

Management of Specific Organ Manifestations:

Brain Manifestations: Treatment options for brain manifestations, such as cortical tubers and subependymal giant cell astrocytomas (SEGAs), may include surgical resection, targeted drug therapy (e.g., mTOR inhibitors like everolimus), or other interventions to manage associated complications.

Skin Manifestations: Dermatological interventions, such as laser therapy or topical treatments, can help manage skin abnormalities like facial angiofibromas and hypomelanotic macules.

Renal Manifestations: Regular monitoring of kidney function and imaging studies to assess the size and growth of angiomyolipomas may be necessary. In some cases, intervention through embolization, surgery, or mTOR inhibitors may be considered.

Cardiac Manifestations: Cardiac rhabdomyomas may require monitoring, and treatment may be necessary if they cause functional impairments or other complications.

Genetic Counseling: Genetic counseling is essential for individuals with TSC and their families to understand the inheritance pattern, the risk of passing the condition to offspring, and the availability of prenatal testing options.

Supportive Care: Psychological support and counseling services can be beneficial for individuals and families affected by TSC. Support groups and community resources can provide emotional support, education, and a platform for sharing experiences and knowledge.

It's important for individuals with TSC to receive ongoing medical care from a team of healthcare professionals, including neurologists, geneticists, dermatologists, nephrologists, cardiologists, and other specialists as needed. Treatment plans should be tailored to the specific needs of each individual, considering the severity and combination of manifestations. Regular follow-up visits and surveillance for potential complications are crucial in the long-term management of TSC.

31. Vanishing White Matter Disease(腦白質消失症)

History of Vanishing White Matter Disease

Vanishing White Matter Disease (VWM) is a rare neurological disorder that was first described in medical literature in the late 1990s. Here is a brief history of VWM:

1993: Dr. Marjo van der Knaap, a Dutch neurologist, first encountered a child with a previously unidentified leukodystrophy, characterized by the progressive destruction of white matter in the brain.

1998: Dr. van der Knaap and her team published a landmark study describing the clinical and radiological features of this new disorder, which they named "vanishing white matter disease" due to the characteristic disappearance of white matter on brain imaging.

2001: A study led by Dr. Susan Schiffmann identified mutations in the EIF2B gene as the underlying cause of VWM. EIF2B is involved in the regulation of protein synthesis, and mutations in this gene disrupt the normal function of myelin-producing cells in the brain.

Over the following years, further research and case reports expanded our understanding of VWM, including its genetic basis, clinical variability, and disease progression. Subtypes of VWM associated with specific EIF2B gene mutations were identified, contributing to the classification and diagnosis of the disease.

Present: Ongoing research continues to uncover additional genetic factors and pathways involved in VWM, as well as potential therapeutic approaches. The development of animal models and advances in genetic testing have furthered our knowledge of the disease and paved the way for potential treatment options.

It's important to note that VWM remains a rare and complex disorder, and much is still to be learned about its pathogenesis and management. Further research and clinical trials are needed to improve our understanding of VWM and develop effective treatments for affected individuals.

Classification of Vanishing White Matter Disease

Vanishing White Matter Disease (VWM) is classified based on the underlying genetic mutations associated with the disease. Currently, five different genetic subtypes of VWM have been identified:

VWM Type 1 (EIF2B1): This subtype is caused by mutations in the EIF2B1 gene.

VWM Type 2 (EIF2B2): This subtype is caused by mutations in the EIF2B2 gene.

VWM Type 3 (EIF2B3): This subtype is caused by mutations in the EIF2B3 gene.

VWM Type 4 (EIF2B4): This subtype is caused by mutations in the EIF2B4 gene.

VWM Type 5 (EIF2B5): This subtype is caused by mutations in the EIF2B5 gene.

These genetic subtypes of VWM are determined by the specific gene affected by the mutation. Each subtype may have slightly different clinical features, disease progression, and prognosis. Additionally, within each subtype, there can be significant variability in the severity and presentation of symptoms.

It's worth noting that VWM is a progressive disorder, and the clinical spectrum can range from mild cases with late-onset symptoms to more severe forms with early-onset symptoms and rapid disease progression. The classification based on genetic subtypes helps in understanding the underlying molecular mechanisms of the disease and may guide genetic testing and counseling for affected individuals and their families.

Symptom and sign in Vanishing White Matter Disease

Vanishing White Matter Disease (VWM) is a neurological disorder characterized by the progressive degeneration of the brain's white matter. The symptoms and signs of VWM can vary in severity and presentation, but commonly include the following:

Neurological regression: Individuals with VWM often experience a loss of previously acquired motor and cognitive skills. This regression may manifest as a decline in motor coordination, speech and language difficulties, cognitive impairment, and behavioral changes.

Motor abnormalities: Many individuals with VWM develop muscle stiffness (spasticity) and muscle weakness, leading to difficulties with walking and coordination. Some may experience muscle wasting (atrophy) in the limbs.

Ataxia: Ataxia refers to problems with voluntary muscle coordination, resulting in unsteady movements, clumsiness, and difficulties with balance.

Seizures: Seizures are a common feature of VWM and can present in different forms, such as generalized tonic-clonic seizures, focal seizures, or myoclonic seizures.

Optic atrophy: VWM may lead to the degeneration of the optic nerves, resulting in optic atrophy. This can cause vision problems, including blurred or decreased vision.

Cognitive and developmental delays: Many individuals with VWM experience delays in cognitive development, including difficulties with learning, attention, and memory.

Behavioral changes: Some individuals with VWM may exhibit behavioral changes, such as irritability, mood swings, and social withdrawal.

It's important to note that the symptoms of VWM can vary widely between individuals, even within the same family. The age of onset, disease progression, and severity of symptoms can also vary. Early-onset cases tend to have a more severe disease course, while late-onset cases may have milder symptoms and slower progression.

If you suspect that you or someone you know may have VWM or are experiencing

any concerning symptoms, it is important to consult with a healthcare professional for a comprehensive evaluation and diagnosis.

Image study in Vanishing White Matter Disease

Image studies are an important tool in the diagnosis and monitoring of Vanishing White Matter Disease (VWM). Here are some commonly used imaging techniques:

Magnetic Resonance Imaging (MRI): MRI is the primary imaging modality for evaluating the brain in VWM. It can reveal the characteristic white matter abnormalities associated with the disease. The MRI findings in VWM typically show a progressive loss of white matter volume, with a specific pattern of involvement. The white matter may appear abnormally bright (hyperintense) on T2-weighted images, giving rise to the term "vanishing white matter."

Diffusion Tensor Imaging (DTI): DTI is a specialized MRI technique that measures the movement of water molecules in the brain's white matter. It can provide information about the integrity and connectivity of white matter tracts. In VWM, DTI may show reduced fractional anisotropy (a measure of fiber integrity) and increased mean diffusivity (reflecting white matter damage).

Proton Magnetic Resonance Spectroscopy (MRS): MRS is a non-invasive technique that measures the levels of specific metabolites in the brain. In VWM, MRS may show elevated lactate levels, indicating impaired energy metabolism.

Neuroimaging for Seizures: If individuals with VWM experience seizures, additional imaging studies like electroencephalogram (EEG) or video-EEG monitoring may be performed to evaluate the electrical activity in the brain during a seizure episode.

It's important to note that imaging findings alone cannot confirm a diagnosis of VWM. A comprehensive evaluation that includes clinical assessment, genetic testing, and imaging studies is typically necessary for an accurate diagnosis. Additionally, imaging studies may be repeated over time to monitor disease progression and response to treatment.

Genetic mutation in Vanishing White Matter Disease

Vanishing White Matter Disease (VWM), also known as Childhood Ataxia with Central Nervous System Hypomyelination (CACH), is primarily caused by mutations in five genes known as the eIF2B genes. These genes encode the subunits of the eukaryotic initiation factor 2B (eIF2B), a key regulator of protein synthesis in cells. The eIF2B complex is involved in the control of the translation initiation process. Mutations in any of the five eIF2B genes, namely EIF2B1, EIF2B2, EIF2B3, EIF2B4, and EIF2B5, can lead to VWM. These mutations disrupt the normal function of the eIF2B complex, resulting in impaired protein synthesis and abnormal accumulation of

white matter in the brain.

The inheritance pattern of VWM is autosomal recessive, meaning that affected individuals inherit two copies of the mutated gene, one from each parent. However, there can be variations in the severity and age of onset of the disease depending on the specific mutation and other modifying factors.

It's worth noting that not all cases of VWM can be attributed to mutations in the eIF2B genes. In some individuals, mutations in other genes, such as EIF2B5, EIF2AK3, or TATA-binding protein-associated factor 1 (TAF1), have been identified as the cause of VWM-like symptoms.

Genetic testing, including sequencing of the eIF2B genes and other related genes, is typically performed to confirm the diagnosis of VWM and identify the specific genetic mutation present in an affected individual.

Mitochondrial dysfunction in Vanishing White Matter Disease

Vanishing White Matter Disease (VWMD), also known as Childhood Ataxia with Central Nervous System Hypomyelination (CACH), is a rare genetic disorder that affects the white matter of the brain. It is primarily caused by mutations in genes involved in the regulation of the formation and maintenance of myelin, the fatty substance that surrounds and insulates nerve fibers. While the primary pathology of VWMD is related to impaired myelin production and stability, emerging research suggests a potential role of mitochondrial dysfunction in the disease.

Mitochondria are responsible for various cellular processes, including energy production, metabolism, and calcium homeostasis. In VWMD, mitochondrial dysfunction may contribute to disease progression through several mechanisms: Energy deficit: Mitochondrial dysfunction can lead to impaired energy production in affected cells. The mutations in genes associated with VWMD may disrupt mitochondrial function, resulting in decreased ATP production and energy deficits in cells that are critical for myelin formation and maintenance.

Oxidative stress: Mitochondrial dysfunction can lead to increased production of reactive oxygen species (ROS), which can cause oxidative damage to cells. VWMD-associated mitochondrial dysfunction may contribute to elevated ROS levels, leading to oxidative stress and potential damage to cellular components, including myelin.

Impaired mitochondrial dynamics: Mitochondrial dysfunction in VWMD may affect mitochondrial dynamics, including fission and fusion processes. Proper mitochondrial dynamics are essential for maintaining mitochondrial health and function. Disruption of these processes may further contribute to cellular dysfunction and compromise myelin integrity.

While the exact mechanisms linking mitochondrial dysfunction to the pathogenesis of

VWMD are not fully understood, studies have shown evidence of abnormal mitochondrial structure and function in affected individuals.

Currently, there is no cure for VWMD, and treatment mainly focuses on managing symptoms and providing supportive care. This may involve physical and occupational therapy, medications to manage symptoms such as seizures and spasticity, and supportive measures to address complications. Targeting mitochondrial dysfunction as a therapeutic approach in VWMD is an area of ongoing research, and future studies may explore potential interventions aimed at restoring mitochondrial function or mitigating its detrimental effects in the context of the disease.

Treatment in Vanishing White Matter Disease

Currently, there is no cure for Vanishing White Matter Disease (VWM), and treatment primarily focuses on managing symptoms and providing supportive care. The management of VWM typically involves a multidisciplinary approach involving various healthcare professionals, including neurologists, physiotherapists, occupational therapists, and speech therapists.

Treatment options for VWM aim to address specific symptoms and may include:

Medications: Certain medications may be prescribed to manage symptoms such as seizures, spasticity, and pain. Anti-seizure medications (anticonvulsants) can help control seizures, while muscle relaxants or baclofen may be used to reduce muscle stiffness and spasticity.

Physical and Occupational Therapy: Physical and occupational therapy play a crucial role in managing the physical symptoms associated with VWM. These therapies focus on maintaining mobility, improving muscle strength, coordination, and balance, and addressing difficulties with daily living activities.

Speech and Language Therapy: Speech and language therapy can help individuals with VWM improve their communication skills, including speech, language comprehension, and swallowing abilities.

Assistive Devices: Depending on the severity of symptoms, individuals with VWM may benefit from using assistive devices such as braces, walkers, or wheelchairs to enhance mobility and independence.

Symptom Management: Additional measures may be employed to manage specific symptoms such as pain, sleep disturbances, and behavioral issues. This may include the use of pain medications, sleep aids, and behavioral interventions.

It is essential for individuals with VWM to receive regular medical follow-up and monitoring to address any changes in symptoms and to adjust treatment approaches accordingly. Genetic counseling is also recommended for affected individuals and their families to understand the inheritance pattern and the potential risks in future

pregnancies. Researchers are actively working on developing potential disease-modifying treatments for VWM, but currently, these are still in the experimental stages and not widely available.