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The Role of Genetic Mutations on Gene GFAP in Alexander Syndrome

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Abstract

Alexander disease is one of a group of neurological conditions known as the leukodystrophies. Leukodystrophies are disorders that result from abnormalities in myelin, the "white matter" that protects nerve fibers in the brain. In Alexander disease, the destruction of white matter is accompanied by the formation of Rosenthal fibers--abnormal clumps of protein that accumulate in non-nerve cells (astrocytes) in the brain. The most common type of Alexander disease is the infantile form that usually begins during the first two years of life. Symptoms include mental and physical developmental delays, followed by the loss of developmental milestones, an abnormal increase in head size, and seizures. The juvenile form of Alexander disease has an onset between the ages of two and thirteen years. These children may have excessive vomiting, difficulty swallowing and speaking, poor coordination, and loss of motor control. Adult-onset forms of Alexander disease are less common. The symptoms sometimes mimic those of Parkinson's disease or multiple sclerosis, or may present primarily as a psychiatric disorder. The disease occurs in both males and females, and there are no ethnic, racial, geographic, or cultural / economic differences in its distribution. Alexander disease is a progressive and often fatal disease.

Keywords

Alexander Syndrome; Genetic Disorder; GFAP gene; Nervous System

Overview of Alexander Syndrome

Alexander's syndrome is a rare genetic disorder that affects the nervous system. This syndrome is a group of disorders called leukodystrophy that involves the destruction of myelin. Myelin is a coating of fat that insulates nerve fibers and causes the nerve to transmit rapidly. If the myelin is not properly maintained, the transmission of nerve waves may be impaired. Myelin dysfunction also weakens the function of the nervous system [1] (Figure 1).

Figure 1: Image of children with Alexander syndrome with related disorders

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Clinical Signs and Symptoms of Alexander Syndrome

Most cases of Alexander's syndrome begin before the age of 2 and are described in infancy form. Signs and symptoms of neonatal form of Alexander's syndrome usually include abnormal brain and head enlargement (megaloencephalus), seizures, stiffness in the arms or legs (spastic), mental disorder and developmental delay. In rare cases, the onset of the disease occurs after childhood (young form) or in adulthood. Common problems in adolescence and adulthood include: speech disorders, dysphagia, seizures, and poor motor coordination (ataxia). In rare cases, symptoms of neonatal form of Alexander's syndrome occur in the first month of life and are associated with severe mental disability, developmental delay, fluid buildup in the brain (hydrocephalus) and seizures [2] (Figure 2).

Alexander's syndrome is also characterized by abnormal deposits of a protein known as rosental fibers. These deposits are found in specific astroglial cells that support and nourish other cells in the brain and spinal cord (central nervous system) [3].

Etiology of Alexander Syndrome

Alexander syndrome is caused by a GFAP gene mutation located on the long arm of chromosome 17 as 17q21.31. This gene provides instructions for the synthesis of a protein called glial fibrillary acidic protein. Several molecules of this protein combine to form intermediate filaments that support cellular strength and function [4] (Figure 3).

Mutation in the GFAP gene results in the production of altered glial fibrillary acidic protein. The altered protein appears to disrupt the formation of normal mediated filaments. As a result, glial fibrillary acidic protein accumulates abnormally in astroglial cells, leading to excessive degradation of the rostral fibers, which disrupts cell function. It is not yet well understood how disruption of astroglial cells disrupts myelin production, leading to symptoms of Alexander's syndrome [5] (Figure 4).

Figure 2: Image of a child with Alexander syndrome with hydrocephalus and megalensphalysis

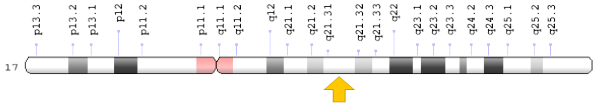

Figure 3: Schematic overview of chromosome 17 where the GFAP gene is located on the long arm of chromosome 17q21.31

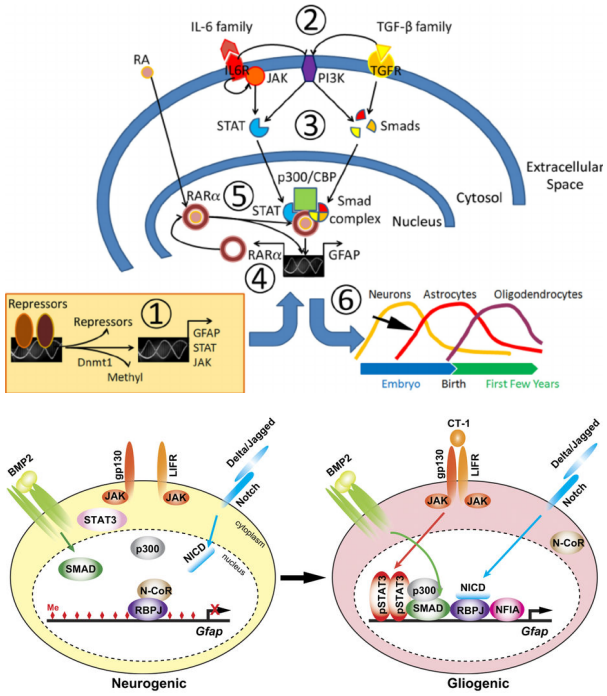

Figure 4: Schematic of the molecular pathway of the GFAP gene in neurogenic and gliogenic cells

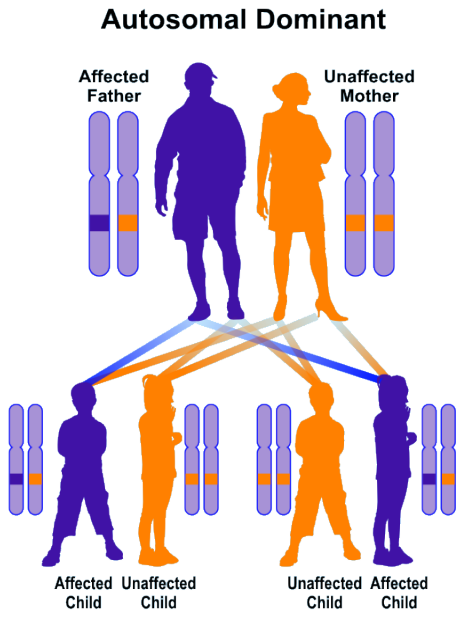

Figure 5: Schematic overview of the dominant autosomal inherited pattern that follows Alexander's syndrome.

Alexander's syndrome follows the dominant autosomal inherited pattern. Therefore, a version of the GFAP mutant (parent or mother) is required to develop this syndrome and the chance of having a child with this syndrome in autosomal dominant state is 50% for each possible pregnancy. Most cases of Alexander's syndrome are caused by new gene mutations with no family history [6] (Figure 5).

Frequency of Alexander Syndrome

Alexander's syndrome is a very rare genetic disorder with an estimated prevalence of about 1 in 1 million live births worldwide.

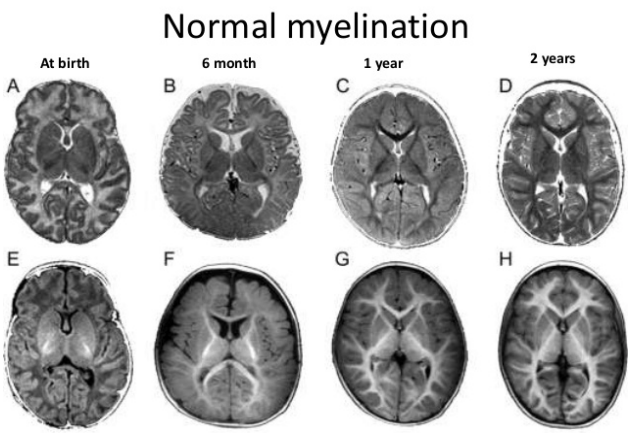

Figure 6: Image of normal brain myelination at different ages

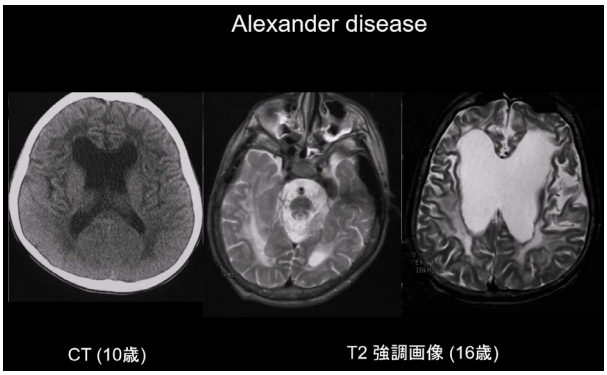

Figure 7: Radiological image of brain with Alexander syndrome.

About 500 cases of this syndrome have been reported in the medical literature worldwide [7].

Diagnosis of Alexander syndrome

Alexander's syndrome is diagnosed based on clinical and clinical findings of patients and some pathological and neurological tests. The most accurate method for detecting this syndrome is molecular genetic testing for the GFAP gene to detect possible mutations [8] (Figure 6).

Alexander syndrome treatment pathways

The treatment and management strategy for Alexander's syndrome is symptomatic and supportive. Treatment may be coordinated with a team of professionals including a pediatrician, a neurologist, an orthopedist, a pharmacist, a physiotherapist, surgeons, and other health care professionals. There is no cure for this syndrome and all clinical measures are to reduce the suffering of patients. Genetic counseling is also needed for all parents who want a healthy child [8].

History of Alexander Syndrome

Alexander's syndrome was first reported in 1949 by Dr. WS Alexander, a neurologist [8] (Figure 7).

Discussion and Conclusion

Alexander disease is a type of leukodystrophy characterized by the destruction of the myelin sheath (the fatty covering that acts as an insulator around nerve fiber) and abnormal protein deposits known as Rosenthal fibers. Most cases of Alexander disease begin before age 2 years (the infantile form). Symptoms of the infantile form include an enlarged brain and head, seizures, stiffness in the arms and/or legs, mental retardation, and delayed physical development. Less frequently, onset occurs later in childhood (the juvenile form) or adulthood. Common problems in juvenile and adult forms of Alexander disease include speech abnormalities, swallowing difficulties, and poor coordination. Alexander disease is caused by mutations in the GFAP gene. While this condition is inherited in an autosomal dominant fashion, most cases result from new mutations in the gene. No specific therapy is currently available for Alexander disease. Management is supportive and includes attention to general care, physical and occupational therapy, nutritional requirements, antibiotic treatment for any infection, and Antiepileptic Drugs (AED) for seizure control [1-8].

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