

FACT SHEET: ALEXANDER DISEASE

Basic Facts About Alexander Disease

Alexander Disease has been divided into three forms based on age of onset and type of symptoms: infantile, juvenile, and adult forms. All of the forms are rare, although adult onset Alexander disease is the most rare of the group. Although the three forms of the disease are generally thought to have the same genetic basis, the symptoms vary between the three groups.

What causes Alexander Disease?

Generally, Alexander Disease does not appear to be genetically inherited. This means that although a genetic defect is present in the patient, neither of the parents of the patient have that genetic defect. This type of genetic basis of disease is sometimes called sporadic, meaning that the defect in the gene occurred spontaneously. Practically, this means that if parents have one child with Alexander Disease, any other children they might have will be very unlikely to have the disease. However, it should be noted that some cases of familial (genetically inherited) Alexander disease have been reported; these familial cases may be more prevalent in the juvenile form of Alexander Disease than in the infantile form (see descriptions of these under *Symptoms of Alexander Disease*).

The majority of infantile and juvenile Alexander Disease are caused by a defect in a specific gene called GFAP, which stands for Glial Fibrillary Acidic Protein. GFAP is an intermediate filament protein, which means that it is involved in the structural development of the cells. Studies of the role of this protein in both health and disease are ongoing.

Infantile Alexander Disease occurs in different ethnic groups and areas of the world, and does not appear to be prevalent in any particular group. There does

not appear to be a difference in frequency between the sexes.

What pathological changes does Alexander Disease cause?

Alexander Disease was first described on the basis of pathological findings of the brain during autopsy. First, a brief expansion on the general discussion of nervous system cells, which can be found in the *Leukodystrophy* fact sheet from the ULF. We described one type of brain cell called a neuron, which is a cell responsible for transmitting electrical signals throughout the body. There is a second type of brain cell called a glial cell. Glial cells support the neurons; that is, they give them nutrients they need to stay healthy, they digest dead neurons, and they provide physical support for the neurons.

In Alexander Disease, a specific type of glial cell known as an astrocyte has abnormal structures known as Rosenthal fibers. Rosenthal fibers are not in the astrocytes of healthy people (as far as we know), and contain large quantities of the protein GFAP. Defects in GFAP have been found to be the major cause of Alexander Disease (see What causes Alexander Disease, above). Rosenthal fibers are found in conditions other than Alexander disease, including some cancers, although the significance of this is not clear. Properly functioning glial cells are necessary for myelin formation, and so the disruption of the glial cells caused by the Rosenthal fibers may be the reason that GFAP mutations result in an adrenoleukodystrophy.

How is Alexander Disease diagnosed?

Because the genetic defect in Alexander disease is known, genetic testing on a blood sample can be used to diagnose most cases of Alexander Disease. A

suggestive diagnosis can also be made from the clinical symptoms, including enlarged head size, combined with radiological studies and negative tests for other leukodystrophies. MRIs often reveal a characteristic pattern.

What are the symptoms of Alexander Disease?

Symptoms vary between the three forms of the disease (infantile, juvenile, and adult-onset), so we have separated them into categories below. However, it should be noted that there is no sharp line that can be drawn between the different forms of these disorders, and within each form the symptoms and severity can vary dramatically.

Infantile Alexander Disease

Infantile Alexander Disease leads to symptoms in the first two years of life; while some children die in the first year of life, a larger number live to be 5-10 years old. The usual course of the disease is progressive, leading to eventual severe mental retardation and spastic quadriplegia (spasms that may involve all four limbs). However, in some children the degree of disability develops slowly over several years, and some children retain responsiveness and emotional contact until near the end of their lives. Feeding often becomes a problem, and assisted feeding (as with a nasogastric tube) may become necessary. Their head circumference is often enlarged. Children with hydrocephalus caused by Alexander disease usually have increased intracranial pressure and a more rapid progression of the disease. Generally, the earlier the age of onset of Alexander disease, the more severe and rapid the course.

Below is a list of the clinical terms of some of the symptoms and pathologies of Infantile Alexander Disease, along with definitions of each term. Please keep in mind that severity and symptoms will vary, and so all children will not have all symptoms.

Megalencephaly: Megalencephaly means that the brain is abnormally large; this can be associated with delayed development, convulsive disorders, corticospinal (brain cortex and spinal cord) dysfunction, and seizures.

Hydrocephaly: Literally means "water on the brain." Characterized by the accumulation of fluid in the brain or between the brain and the skull. Can cause

pressure on the brain, resulting in developmental defects. Also can lead to an abnormally large head size (to greater than 90% of normal).

Failure to thrive: A general term meaning the the child is not growing and gaining weight at the expected rate.

Seizures: The brain controls how the body moves by sending electrical signals. Seizures (also called convulsions) occur when the normal signals from the brain are changed. Severity of a seizure can vary dramatically. Some people may only shake slightly and do not lose consciousness. Other people may become unconscious and have violent shaking of the entire body.

Spasticity/spastic quadriplegia: This means that the child tends to suffer spasms, or involuntary contractions of muscles. Muscles are abnormally stiff and movement is restricted. Quadriplegia means that all four limbs are involved.

Progressive Psychomotor Retardation This can include difficulties with walking, speech difficulties, and mental regression. Eventually this can lead to loss of all meaningful contact with the environment. Progressive means that the condition worsens as time goes on.

Juvenile Alexander Disease

Juvenile Alexander Disease is characterized by difficulty with talking and swallowing and the inability to cough. There can also be weakness and spasticity of the extremities, particularly the legs. Unlike in the infantile form of the disease, mental ability and head size may be normal. Age of onset is usually between the ages of 4 and 10. Survival can extend several years following onset of symptoms, with occasional longer survival into middle age.

The course of the disease may involve signs of swallowing or speech difficulty, vomiting, ataxia, and/or spasticity. Kyphoscoliosis can occur. Mental function often slowly declines, although in some cases the intellectual skills remain intact.

Pathologically, whereas the infantile form of Alexander disease generally affects the brain, the juvenile form generally leads to changes in the brain stem rather than in the brain. There are many Rosenthal fibers (as in infantile Alexander Disease), but the lack of myelin is less prominent than in the infantile form.

Adult-onset Alexander Disease

Adult-onset Alexander Disease is the most rare of the forms, and also is generally the most mild. Onset can be anywhere from the late teens to very late in life. In older patients ataxia (impaired coordination) often occurs and difficulties in speech articulation, swallowing, and sleep disturbances may occur. Symptoms can be similar to those in juvenile disease, although the disease may also be so mild that symptoms are not even noticed until an autopsy reveals the presence of the Rosenthal fibers. Symptoms may resemble multiple sclerosis or a tumor.

What is the treatment for Alexander Disease?

There is no cure for Alexander Disease. The treatment for Alexander disease is symptomatic and supportive. Hydrocephaly (water on the brain) may be partially relieved by surgery, in which a shunt can drain away some of the fluid causing the pressure. Bone marrow transplantation was performed on one child, but did not produce improvement.

How is scientific research on Alexander Disease progressing towards improvement treatment or diagnosis?

The identification of the genetic basis of Alexander Disease in 2001 was a great step forward. The combined use of the often characteristic MRI pattern and DNA analysis has greatly improved the diagnosis of Alexander disease, so that biopsy is no longer required. It is strongly recommended that DNA tests be performed on both parents. If they are normal, the child has a novel mutation (sporadic); other family members are then unlikely to be carriers of the disease, and need not be tested. If one of the parents does carry the abnormality, then at-risk family members should be screened. This will allow other family members who carry the genetic mutation for the disease to make informed decisions about having children.

In addition, animal models of disease (in mice and zebrafish) are being developed in order to better study the role of GFAP in Alexander Disease. The hope is that these studies will eventually lead to potential treatments that can be tested in clinical trials.

Other Clinical Names for Alexander Disease

Although Alexander Disease is the most common term used to describe this leukodystrophy, you may encounter other names for it. Other clinical names of Alexander Disease include:

- Dysmyelogenic Leukodystrophy
- Dysmyelogenic Leukodystrophy-Megalobare
- Dysmyelogenic Leukodystrophy with megalobarencephaly
- Fibrinoid Degeneration of Astrocytes
- Fibrinoid Leukodystrophy
- Hyaline Panneuropathy
- Leukodystrophy with Rosenthal Fibers
- Megalencephaly with Hyaline Inclusion
- Megalencephaly with Hyaline Panneuropathy