Alexander disease (ALXD) is a rare demyelinating disease of the white matter of the brain that is caused by a mutation in the glial fibrillary acidic protein (GFAP) gene. The overexpression of GFAP in astrocytes induces a failure in the developmental growth of the myelin sheath. The neurodegenerative destruction of the myelin sheath of the white matter is accompanied by an accumulation of abnormal deposits of Rosenthal fibers in astrocytes, which is the hallmark of ALXD. The disease can be divided into four groups based on the onset age of the patients: neonatal, infantile, juvenile, or adult. Early-onset disease is more severe, progresses rapidly, and results in a shorter life span than late-onset cases. Magnetic resonance imaging and genetic tests are mostly used for diagnostic purposes. Pathological tests of brain tissue for Rosenthal fibers are definitive diagnostic methods. Therapeutic strategies are being investigated. Ceftriaxone, which is an enhancer of glial glutamate transporter (GLT-1) expression, is currently in clinical trials for the treatment of patients with ALXD. To date, there are no clinically available treatments. The cause, pathology, pathophysiology, inheritance, clinical features, diagnosis, and treatment of ALXD will be reviewed comprehensively.

Key words: Alexander disease, Cause, Pathology, Pathophysiology, Inheritance, Clinical features, Diagnosis, Treatment

Introduction

Alexander disease (ALXD, MIM#203450), which is a rare and often fatal demyelinating disease of the white matter of the central nervous system, is caused by a glial fibrillary acidic protein (GFAP) gene mutation. Alexander first described an infantile case of ALXD in 1949. Since Alexander’s initial description, about 450 patients have been reported. The progressive degeneration of the myelin sheath of the white matter is accompanied by the accumulation of abnormal deposits of Rosenthal fibers in astrocytes, which is the hallmark of ALXD. It can be classified as an astrogliopathy, which is a primary disease of astrocytes, because the GFAP gene is expressed principally in astrocytes, and astrocytes are the primary focus of pathophysiology, which is associated with an astrocytic dysfunction in ALXD. The disease can be divided into four groups based on the onset age of the patients: neonatal, infantile, juvenile, or adult. The early-onset subtypes are more severe, rapidly progressive, and have a shorter life span than the late-onset subtypes. Most cases of ALXD occur in infancy and the symptoms are grave and eventually fatal. With the advance of DNA analysis technology, genetic diagnoses for ALXD are available in the clinical field. Magnetic resonance imaging (MRI) and genetic tests are mostly used for diagnostic purposes. Even though therapeutic strategies have been investigated and suggested, there are no specific clinically available treatments. This review will discuss the cause, pathology, pathophysiology, inheritance, clinical manifestations, diagnosis, and treatment of ALXD.
Causes

ALXD is caused by a GFAP gene mutation. GFAP is a type-III intermediate filament protein that is encoded by the GFAP gene that maps to 17q21 in humans. GFAP was named and first isolated by Lawrence F. Eng in 1969. The existence of GFAP in Rosenthal fibers, which are the pathologic hallmark of ALXD, suggested that mutations of the gene encoding GFAP were the cause of ALXD. This protein is expressed in astrocytes and in ependymal cells of the central nervous system. Its function is thought to involve the maintenance of mechanical strength as well as the shape of astrocytes. Because of the gain-of-function mutation, GFAP is overexpressed in astrocytes, and the synthesis or maintenance of the myelin sheath is faulty. Eventually, the myelin sheath degenerates, and various functions of the nervous system are altered.

Pathology

GFAP, which is found in mature astrocytes of the central nervous system, is rapidly synthesized during brain injury and reactive astrogliosis. In 1949, W. Stewart Alexander described a 15-month-old child with megalencephaly, hydrocephalus, and psychomotor retardation. The brain autopsy revealed a progressive fibrinoid degeneration of fibrillary astrocytes. These astrocytic inclusions were called Rosenthal fibers as they were named after Werner Rosenthal. Morphologically, Rosenthal fibers are concentrated in the astrocytic endfeet that surround a blood vessel and that are enclosed by intermediate filaments in an astrocyte cell body. In addition to GFAP, Rosenthal fibers contain a-crystallin, heat shock protein 27, and ubiquitin. Rosenthal fibers are not specific for ALXD. Rosenthal fibers are also focal in astrocytomas, hamartomas, glial scars, and multiple sclerosis, while their characteristic pattern in ALXD is diffuse and abundant. According to the clinical phenotypes of ALXD, the developmental failure of myelin is variable. In the infantile form, the myelin loss is severe, while patients with juvenile or adult-onset ALXD have mild and patchy myelin loss.

Pathogenesis

GFAP gene mutations were identified in chromosome 17q21 in various patients representing the ALXD phenotypes. Mutations of the GFAP gene are thought to result in a gain-of-function mutation that induces the overproduction of GFAP. The downstream effects of GFAP toxicity lead to a failure in the dimerization of the GFAP monomer, cytoskeletal breakdown, and abnormal protein aggregation. However, the accumulation of toxic materials could disrupt filament arrangement. Astrocytes in patients with ALXD contain plenty of small heat shock protein and a-B-crystallin. There is activation of stress kinase pathways, such as those for mitogen-activated protein kinase, c-Jun N-terminal kinase, p38 kinases, small heat shock protein genes, and a-B-crystallin, and an increase in autophagy has been found in many animal models. In addition, the accumulation of GFAP results in impairments of proteasomal activity. Proteasome inhibition and the consequent accumulation of short-lived proteins, such as the transcription factor Nrf2, may occur. The most remarkable changes in astrocytes in gray matter are the diminution of the glial glutamate transporter (GLT)-1, which is the major glutamate transporter in astrocytes. A loss of glutamate buffering could also play a role in oligodendrocyte toxicity and the loss of myelin because oligodendrocyte precursors are sensitive to glutamate toxicity. Astrocytes in white matter, which has higher levels of GFAP expression than gray matter, may be affected differently by GFAP mutations than those in gray matter. White matter astrocytes provide critical metabolic support to oligodendrocytes. An additional downstream effect of GFAP toxicity may be the dysfunction of astrocytic potassium buffering, which can lead to a failure in both myelin formation and maintenance. However, the precise interactions between the GFAP mutations and the cellular responses of astrocytes remain unknown.

Inheritance

The gene mutation of GFAP in ALXD has an autosomal dominant inheritance with nearly 100% penetrance. The mutations usually arise de novo. Sporadic mutations are more common than the direct inheritance of the mutant GFAP gene. In addition, the mutations in parents are rarely detected. There are no differences based on ethnic population or gender. In 97 percent of patients GFAP mutations are identified using DNA sequence analysis. Most of mutations are found in exons 1, 4, and 6. More than one-half of ALXD cases exhibit one of four GFAP peptide sequences—R79, R88, R239, or R416. The GFAP mutations in R79 and R239 are the most common and are related to the early-onset type of ALXD. Patients with R79 mutations may
Dysphagia or dysphonia.

Hindbrain dysfunction such as ataxia, palatal myoclonus, and delays, whereas the later-onset cases more often have signs of typically present with seizures, spasticity, or developmental delays, whereas the later-onset cases more often have signs of hindbrain dysfunction such as ataxia, palatal myoclonus, and dysphagia or dysphonia.²⁸ According to previously reported cases,²⁶ early-onset ALXD is more severe, rapidly progressive, and results in a shorter life span than cases with late-onset ALXD. The survival age of patients with neonatal ALXD is between the first few weeks and years of life, although some affected infants survive until the end of the first decade.⁵ The infantile phenotype, which is the most common, is seen in approximately 63% of affected cases and is mostly detected before the age of 2 years, and the patients usually survive until the first years of life, although some children with infantile ALXD survive until the early teenage years.⁵ The juvenile form accounts for 24% of all cases, and it typically presents between ages 4 and 14 years.² The survival range of patients with juvenile ALXD has been shown to be from 15 months to 12 years in an early report,²⁶ and to the third and fourth decades in later reports.² Adult-onset ALXD has variable features. In the largest series of 11 cases, onset occurred up to age 62.²⁰ Each phenotype of ALXD is compared in Table 1. In 2011, Prust et al.²⁰ suggested the revision of the classification of ALXD which was based on the distribution of the lesions and the clinical features using a statistical method of latent class analysis (LCA). As the result of statistical survey, ALXD was divided into two subtypes, type I and II. Type I has an early onset, is generally more severe than type II, and has a reduced median survival. The mortality of type I is increased nearly two-fold than that of type II. Type II manifests across the lifespan, is generally less severe, and has a longer median survival than type I.²¹ Each type is compared in Table 2. Of note, the revised classification is limited in that the LCA models predict trends but are not able to classify absolutely a certain clinical type in individual cases of ALXD.²⁸

Clinical features

An incidence is about 1:2.7 million which has been reported on just one survey.²⁶ There are no differences in ethnic population, or gender. The age of onset is ranging from prenatal through the sixth decade. ALXD can be conventionally divided into four clinical subtypes, neonatal, infantile, juvenile, and adult, based on the age of onset. However, the clinical characteristics are variable among cases in the same subtype. The early-onset patients typically present with seizures, spasticity, or developmental delays, whereas the later-onset cases more often have signs of hindbrain dysfunction such as ataxia, palatal myoclonus, and dysphagia or dysphonia.⁵ According to previously reported cases,²⁶ early-onset ALXD is more severe, rapidly progressive, and results in a shorter life span than cases with late-onset ALXD.

Diagnosis

A diagnosis of ALXD is determined by the clinical presentation, electroencephalography, neuroimaging, genetic tests, and pathological examinations. MRI and genetic tests have a reciprocal relationship for the inclusion or exclusion of diagnostic criteria in cases of equivocal genetic testing or atypical imaging features in children and adults.²² The definitive diagnostic method of ALXD is the pathological examination of the brain tissue for Rosenthal fibers, obtained either at biopsy or autopsy. Now, genetic tests for the detection of GFAP gene mutations are generally applicable for the heterogeneity of ALXD. Prenatal genetic studies that use cells obtained from the chorionic villus tissue for Rosenthal fibers, obtained either at biopsy or autopsy. Now, genetic tests for the detection of GFAP gene mutations are generally applicable for the heterogeneity of ALXD. Prenatal genetic studies that use cells obtained from the chorionic villus or amniocentesis are also available for women who have a family history of ALXD. Brain MRI is one of the most useful tools for the diagnosis of ALXD. The MRI characteristics appear to vary with the age of disease onset. Frontal leukodystrophy is common in younger patients, whereas a hindbrain predominance of lesions, which sometimes also exhibit atrophy of the medulla oblongata.

### Table 1. The Clinical Characteristics of the Conventional Subtype of Alexander Disease

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Onset age</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal</td>
<td>neonate</td>
<td>Increased intracranial pressure, intractable seizures, severe motor retardation, ataxia</td>
</tr>
<tr>
<td>Infantile (63%)</td>
<td>&lt;2 years</td>
<td>Psychomotor retardation, spasticity, feeding difficulties, macrocephaly, frontal bossing, seizures, hydrocephalus</td>
</tr>
<tr>
<td>Juvenile (24%)</td>
<td>4-14 years</td>
<td>Pseudobulbar and bulbar sign (swallowing and speech difficulties), vomiting, ataxia, spasticity (principally affecting the lower extremities), kyphoscoliosis</td>
</tr>
<tr>
<td>Adult</td>
<td>adult-up to 62 years</td>
<td>Progressive ataxia, bulbar and pseudobulbar signs (palatal myoclonus, dysphagia, dysphonia, dysarthria), spasticity, quadriparesis, urinary disturbances, dysautonomia, dysmorphic features</td>
</tr>
</tbody>
</table>

### Table 2. The clinical characteristics of the revised classification: type I and II of Alexander disease

<table>
<thead>
<tr>
<th>Type</th>
<th>Median survival from onset</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>14 years</td>
<td>Seizures, Macrocephaly, Motor delay, Encephalopathy, Failure to thrive, Developmental delay, Paroxysmal deterioration, Typical neuroimaging features</td>
</tr>
<tr>
<td>Type II</td>
<td>25 years</td>
<td>Autonomic dysfunction, Eye movement abnormalities, Bulbar symptoms, Palatal myoclonus, Often lacking neurocognitive or developmental deficits, Atypical neuroimaging features</td>
</tr>
</tbody>
</table>
and cervical spinal cord, are common in later-onset patients.\textsuperscript{33} van der Knaap et al.\textsuperscript{33} have defined the following MRI criteria of the disease: extensive cerebral white matter changes with frontal predominance; a periventricular rim of high signal on T1-weighted sequences and low signal on T2-weighted sequences; abnormalities of the basal ganglia and thalamus; abnormalities of the brainstem, which mainly involve the midbrain and medulla; and contrast enhancement involving one or more gray and white matter structures (Fig. 1). Serial follow-up MRI scans have revealed progressive atrophy of the frontoparietal white matter that is accompanied by cystic degeneration, increased size of the lateral ventricles, and atrophic changes of the basal ganglia and thalami (Fig. 2). However, the occipital and temporal lobes are relatively spared.\textsuperscript{33} The differential diagnosis of ALXD should be considered in cases of macrocephaly and/or leukodystrophy such as adrenoleukodystrophy, Canavan disease, megalencephalic leukoencephalopathy with subcortical cysts, and metachromatic leukodystrophy, which have common features of the phenotypical or neuroimaging characteristics.\textsuperscript{33}

Brain MRI of cases with adrenoleukodystrophy demonstrates various degrees of demyelination that usually predominantly involve the bilateral frontal lobes but affect the occipitoparietal area as well. Canavan disease is characterized by macrocephaly and spongy degeneration of the white matter. Brain MRI of patients with Canavan disease reveals diffuse cerebral white matter degeneration. Patients with megalencephalic leukoencephalopathy with subcortical cysts also demonstrate macrocephaly.\textsuperscript{34} The cysts are located in the deep frontal white matter.\textsuperscript{33} MRI abnormalities include diffuse white matter, especially in the frontoparietal border zone and the anterior-temporal subcortical white matter. Metachromatic leukodystrophy is divided into the following four subtypes: late infantile, early juvenile, late juvenile, and adult forms. MRI reveals diffuse and symmetrical leukodystrophy with a frontal predominance.\textsuperscript{35}

**Treatment**

To date, there have been no specific and clinically available treatments for patients with ALXD. Messing et al.\textsuperscript{36} have reported that several strategies for therapy are being investigated and

![Fig. 1](http://dx.doi.org/10.5734/JGM.2013.10.2.88 • J Genet Med 2013;10:88-93 91)

**Fig. 1.** Typical MRIs for Alexander disease. The three images are from an eight years-old male patient, illustrating the characteristic abnormalities of frontal white matter including decreased signal on T1-weighted image (A), increased signal on T2-weighted image (B), and mild atrophy in the medulla and the cervical spinal cord on T1-weighted midline sagittal section (C).

![Fig. 2](http://dx.doi.org/10.5734/JGM.2013.10.2.88 • J Genet Med 2013;10:88-93 91)

**Fig. 2.** The three follow-up images are from the three years-old male patient (29 months later), illustrating cystic degeneration, increased size of the lateral ventricles on T1(A), T2(B), and markedly atrophic changes of the basal ganglia, thalami, brain stem and spinal cord on T1-weighted midline sagittal section (C).
have been suggested. The most obvious treatment approach is to reduce the expression or accumulation of GFAP. One drug screen has already been completed with wild-type astrocytes in primary culture, and several of these compounds are now being investigated with in vivo models.\(^{27}\) A second approach is to target the downstream effects of GFAP toxicity, with a focus on the deficits in GLT-1 expression. Ceftriaxone, which enhances GLT-1 expression, is already in clinical trials for ALXD.\(^ {38}\)

The manipulation of stress pathways, such as those involving α-B-crystallin or Nrf2, may also prove effective in animal studies.\(^ {39}\)

Conservative treatments, including nutritional support, physiotherapy, seizure control with anticonvulsants, and ventriculoperitoneal shunts for hydrocephalus are available. A prenatal genetic test is required to prevent the gene mutation in future generations. The family members of patients need to have genetic counseling and education.

References

19. Chen YS, Lim SC, Chen MH, Quinlan RA, Perng MD. Alexander disease causing mutations in the C-terminal domain of GFAP are deleterious both to assembly and network formation with the potential to both activate caspase 3 and decrease cell viability. Exp Cell Res 2011;317:2252-66.
25. GFAP mutations associated with Alexander disease. Waisman Center, University of Wisconsin-Madison.[www.waisman.wisc.edu/alexander-


34. van der Knaap MS, Boor I, Estèvez R. Megalencephalic leukoencephalopathy with subcortical cysts: chronic white matter oedema due to a defect in brain ion and water homoeostasis. Lancet Neurol 2012;11:973-85.


