Alexander and Canavan Disease

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Alexander disease is a rare genetic disorder that predominantly affects infants and children and is associated with cerebral white matter disease.

Intracytoplasmicastrocytic inclusions known as Rosenthal fibers are the hallmark of Alexander disease.Sporadic mutations in the GFAP gene are the cause of most cases of Alexander disease.

Four subtypes of Alexander disease — neonatal, infantile, juvenile, and adult — are traditionally recognized but a revised classification of Alexander disease proposes two subtypes – types I and II – based upon statistical analyses:

type I is characterized by early onset, seizures, macrocephaly, motor delay, encephalopathy, sudden deterioration, and typical neuroimaging features

Type II onset may occur across the lifespan, and is characterized by autonomic dysfunction, eye movement abnormalities, bulbar symptoms, and atypical neuroimaging features

Typical MRI features of Alexander disease are:Extensive cerebral white matter changes with frontal predominance, Periventricular rim of high T1 signal and low T2 signal, Basal ganglia and thalamic abnormalities, Brainstem abnormalities, Contrast enhancement of selected gray and white matter structures

Less common MRI features of Alexander disease include: Multifocal brainstem lesions resembling multiple tumors, Medullary and cervical spinal cord signal abnormalities or atrophy and Ventricular garlands

The diagnosis of Alexander disease can be established based upon clinical and radiographic (MRI) features. The diagnosis is usually confirmed by demonstrating a GFAP gene mutation. Although genetic testing is not necessarily required for the diagnosis, genetic confirmation should always be attempted due to the heterogeneity of the disease and its presentation.

The differential diagnosis of Alexander disease involves consideration of other disorders that present with macrocephaly and/or cerebral white matter changes.

Treatment of Alexander disease remains supportive.

Canavan disease or aspartoacylase deficiency is an autosomal recessive spongiform leukodystrophy that is prevalent in the Ashkenazi Jewish population. The disease typically begins in infancy and is marked by relentless progression.

Aspartoacylase deficiency is caused by mutations in the ASPA gene that encodes the enzyme aspartoacylase. The resulting deficiency of aspartoacylase leads to accumulation of N-acetylaspartic acid (NAA) in brain and to oligodendrocyte dysfunction, spongiform changes, and absence of myelin. However, the precise mechanisms causing to spongiform degeneration are uncertain.

Aspartoacylase deficiency typically presents at about age three months with

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lethargy and listlessness, weak cry and suck, poor head control, and hypotonia with a paucity of extremity movement. Macrocephaly becomes prominent by three to six months. Thereafter hypotonia progresses to spasticity and tonic extensor spasms. By age six months, neurologic abnormalities are invariant. Little subsequent development is noted. Blindness from optic atrophy occurs between 6 and 18 months. Seizures are noted in about 50 percent of patients. Pseudobulbar signs and decerebrate posturing dominate the end stage.

The presence of variant forms of aspartoacylase deficiency is controversial.

Brain imaging by CT and MRI reveals diffuse and symmetrical white matter involvement.

The gross pathologic findings are dominated by spongy degeneration of deep cortex, subcortical white matter, and cerebellum. The spongiform changes reflect vacuolated astrocytes in deeper cortical layers and in adjacent subcortical white matter.

In symptomatic infants with compatible clinical features (eg, hypotonia, poor head control, macrocephaly) and neuroimaging findings, the diagnosis of aspartoacylase deficiency is supported by elevated levels of urine N-acetylaspartic acid (NAA) and deficient aspartoacylase activity in cultured skin fibroblasts. Genetic testing may be obtained for purposes of genetic counseling.

The differential diagnosis of aspartoacylase deficiency includes other progressive white matter diseases of infancy, particularly Krabbe disease, metachromatic leukodystrophy, early-onset adrenoleukodystrophy, Alexander disease, and demyelinating disorders.

No effective treatment is available for aspartoacylase deficiency. Management is supportive and aimed at maintaining nutrition and hydration, protecting the airway, preventing seizures, minimizing contractures, and treating infections.

Keywords: Alexander, Canavan, Leukodystrophy