Juvenile Alexander Disease: a Case Report

Juvenil Alexander Hastalığı: Vaka sunumu

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Abstract

Alexander disease is a rare autosomal recessive disorder that is characterized by degeneration of the white matter in the central nervous system. Alexander disease is a leukodystrophy that is usually observed in early childhood but rarely in adults. It is characterized by megalencephaly, demyelination and multiple Rosenthal fibers. Specific magnetic resonance imaging (MRI) findings and genetic investigations are necessary to diagnose the disorder. Signs of leukodystrophy were found in the bilateral white matter on a brain MRI of our four-year-old patient. He had megalencephaly since birth. We use this case to discuss Alexander disease.

Key Words: Alexander disease, Megalencephaly, Leukodystrophy, Pediatric neurology

Introduction

Alexander disease is a rare, sporadic leukoencephalopathy that is characterized by white matter abnormalities with a frontal predominance; it is associated with megalencephaly, seizures, spasticity and psychomotor deterioration [1]. Four types can be distinguished based on the age at clinical presentation: neonatal, infantile, juvenile, and adult [2].

The clinical features of typical infantile-onset Alexander disease, with onset before the age of two, include megalencephaly, seizures, spastic paresis and psychomotor deterioration with leukoencephalopathy that is characterized by white matter abnormalities particularly in the frontal lobes. The juvenile type, with an onset in childhood, shows a variable clinical course: slowly progressive paresis, bulbar signs, and brisk reflexes, but often with an intact mental state [2, 3]. Adult-onset Alexander disease, with onset after the age of 12, is characterized by more slowly progressive bulbar or pseudobulbar palsy, spastic paresis, ataxia, palatal myoclonus, and essentially normal psychic and intellectual functions.

The pathological hallmark of the disease is the accumulation of ubiquitinated intracytoplasmic inclusions in astrocytes, called Rosenthal fibers, which are composed of glial fibrillary acidic protein (GFAP), the main intermediate filament of astrocytes, in association with the small heat shock proteins, HSP27 and αB-crystallin [3].

We report a male, four-year-old patient with leukodystrophic findings in the frontal white matter bilaterally on magnetic resonance imaging. The patient had megalencephaly since the infantile period. We use this case to discuss Alexander disease.

Case Report

A four-years-old boy was admitted to our outpatient clinic with a history of two seizures and a large head size. His height was 102 cm (25-50 percentile), his weight was 16 kg (25-50 percentile), and his head circumference was 55 cm (>95 percentile The patient is the first child of unrelated parents without any family history of neurological disorders and was born after a full-term pregnancy with no complications. The prenatal and natal history was also unremarkable. Postnatally, the boy was able to sit with support when he was 9 months old and sat unsupported when he was 11 months. He first
walked when he was 18 months old. He spoke single words when he was 2 years old, and he currently still cannot form sentences. When he was 2 years old, he had two generalized tonic clonic seizures. After the second seizure, treatment with valproic acid was initiated, and the seizures were controlled. The patient has a large head and mental retardation. Both gross and fine motor skills were affected, but there was no orolingual involvement or bulbar dysfunction. There was no diurnal variation in the child’s symptoms. Extensive neuro-metabolic investigations involving serum, urine, and cerebrospinal fluid were non-diagnostic. Cranial MRI was consistent with Alexander disease, and leukodystrophic frontal white matter degenerations were observed (Figure 1). Genetic testing was consistent with Alexander disease.

**Discussion**

Alexander disease is a slowly progressing, fatal neurodegenerative disease. It is a very rare disorder that results from a genetic mutation. It mainly affects infants and children, causing developmental delays and changes in physical characteristics. The following are some of the observed features of Alexander disease: delays in the development of physical, psychological and behavioral skills; progressive enlargement of the head (macrocephaly); seizures; spasticity; dementia; and in some cases, hydrocephalus.

Alexander disease was first described in 1949, when W. Stewart Alexander reported a 15-month-old child with megalencephaly, hydrocephalus, and psychomotor retardation [1]. The child died eight months later, and the brain pathology revealed “a progressive fibrinoid degeneration of fibrillary astrocytes”. These astrocytic inclusions were later found to be identical to Rosenthal fibers [2]. The presence of GFAP in Rosenthal fibers led to the identification of mutations of the gene encoding GFAP as the cause of Alexander disease [4]. Rosenthal fibers, which are hyaline eosinophilic rods, are present throughout the central nervous system (CNS) in Alexander disease. These intracytoplasmic astrocytic inclusions are the hallmark of Alexander disease [5]. They are commonly observed in subpial, subependymal, and perivascular regions. The inclusions occur in the perikarya, processes, and end-feet of astrocytes and appear round or oblong with extensive glial intermediate filaments observed on electron microscopy. They also contain GFAP. In addition, alpha B-crystallin, heat shock protein 27, and ubiquitin are also present in the Rosenthal fibers [6-10].

In 2001, nonconservative mutations were identified in the regions of chromosome 17q21, which encode the GFAP gene, from patients with different Alexander disease phenotypes [4]. GFAP is an intermediate filament protein that is found in mature astrocytes and is rapidly synthesized during central nervous system (CNS) injury and reactive astrogliosis [11].

Since the initial description of Alexander disease, fewer than 450 cases have been reported [12]. Nevertheless, in a series from Germany, Alexander disease accounted for 1.6 percent of all leukodystrophies [13]. Rosenthal fibers are not found in the astrocytes of healthy people and contain large quantities of the GFAP. Defects in GFAP have been found to be the major cause of Alexander disease.

The neonatal form is associated with increased intracranial pressure, elevated cerebrospinal fluid (CSF) protein, intractable seizures, severe motor retardation (even in the
absence of spasticity), mental retardation, and ataxia. These features reflect involvement of the frontal white matter, basal ganglia, and cerebellum [14, 15]. In the neonatal form, death usually occurs within the first few weeks to years of life, although some affected infants survive until the end of the first decade [12, 14, 15].

The infantile form is the most common, accounting for 63 percent of all cases [12]. The onset occurs before the age of two [15]. 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. Infants and young children have spasticity, feeding difficulties, and psychomotor retardation with loss of developmental milestones. Affected infants may have head enlargement (macrocephaly) secondary to brain enlargement (megalencephaly), frontal bossing, seizures, and hydrocephalus. Most children with the infantile form do not survive past the age of 6. The usual course of the disease is progressive, leading to eventual severe mental retardation and spastic quadripareis. Feeding often becomes a problem, and assisted feeding (with a nasogastric tube) may become necessary. Generally, the earlier the age of onset of Alexander disease, the more severe and rapid the course. The clinical findings include megalencephaly, failure to thrive, seizures, spasticity/spastic quadripareis, progressive psychomotor retardation, difficulties with walking, speech difficulties, and mental regression.

The juvenile phenotype, observed in approximately 24 percent of affected patients, typically presents between ages 4 and 14 [12, 16]. It is associated with pseudobulbar and bulbar signs, including swallowing and speech difficulties. Patients may have vomiting, ataxia, spasticity (principally affecting the lower extremities), and kyphoscoliosis. 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 the infantile form of the disease, mental ability and head size may be normal. Survival can extend several years following the onset of symptoms, with occasional longer survival into middle age. Mental function often slowly declines, although in some cases, the intellectual skills remain intact. 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 in the juvenile form than in the infantile form.

Adult-onset Alexander disease is the rarest of the disease forms and is generally the most mild. Onset can occur anywhere from the late teens to very late in life. In older patients, ataxia 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. Adult-onset forms of Alexander disease are rare but have been reported. The symptoms sometimes mimic those of Parkinson’s disease, multiple sclerosis or brain tumors.

Ninety-four percent of the Alexander disease cases are associated with mutations in the coding region of the GFAP gene [3, 12, 17]. Approximately 50 GFAP mutations have been reported in the literature, and a genetic diagnosis of Alexander disease has been confirmed in 137 patients [11]. An updated list of GFAP mutations associated with Alexander disease is available online from the Waisman Center [17].

GFAP mutations usually arise de novo. At present, there is no precise animal model for Alexander disease; however, mice have been engineered to produce the same mutant forms of GFAP found in individuals with the disease. These mice form Rosenthal fibers and have a predisposition for seizures, but they do not yet mimic all features of human disease (such as the leukodystrophies).

Most affected individuals with infantile and juvenile onset do not live until child-bearing age and do not reproduce, indicating that the majority of cases are sporadic [18]. Molecular genetic testing in those cases was consistent with Alexander disease.

The diagnosis of Alexander disease can be established based on clinical and radiographic (MRI) features. Van der Knaap et al. [19] suggested that the presence of four of the five following criteria establish an MRI-based diagnosis of Alexander disease:

1. Extensive cerebral white matter abnormalities with a frontal predominance;
2. A periventricular rim of decreased signal intensity on T2-weighted images;
3. Elevated signal intensity on T1-weighted images;
4. Abnormalities of the basal ganglia and thalami that may include any of the following: elevated signal intensity and swelling; atrophy; elevated or decreased signal intensity on T2-weighted images; and brain stem abnormalities particularly involving the medulla and midbrain;
5. Contrast enhancement of one or more of the following: ventricular lining, periventricular rim, frontal white matter, optic chiasm, fornix, basal ganglia, thalamus, dentate nucleus, and brain stem.

The availability of molecular genetic testing practically eliminates the need for immunohistochemical staining of brain biopsy material as a diagnostic tool even in very young infants. In addition, the diagnosis is confirmed by demonstrating a GFAP gene mutation. Although genetic testing is not necessarily required for the diagnosis, genetic confirma-
tion should always be attempted due to the heterogeneity of the disease and its presentation [20]. Prenatal testing for pregnancies that are at increased risk is possible if the disease-causing mutation has been identified in an affected family member. Increased levels of αβ-crystallin and heat shock protein 27 have been observed in cerebrospinal fluid (CSF) of individuals with Alexander disease. Increased levels of glial fibrillary acidic protein were documented in the CSF of individuals with Alexander disease. These studies have transformed our view of this disorder and opened new directions for investigation and clinical practice, particularly with respect to diagnosis [22, 23].

The differential diagnosis of Alexander disease involves consideration of other disorders that present with macrocephaly and/or cerebral white matter changes; adrenoleukodystrophy, Canavan disease, megalencephalic leukoencephalopathy with subcortical cysts, metachromatic leukodystrophy, and multiple sclerosis.

Treatment is supportive and includes attention to general care and nutritional requirements, antibiotic treatment for intercurrent infection, antiepileptic drugs (AEDs) for seizure control, assessment of learning disabilities and cognitive impairment, and physical and occupational therapy as needed. In the neonatal and infantile forms associated with hydrocephalus, a ventriculoperitoneal shunt may be required.

Recent genetic studies identified heterozygous missense mutations in -GFAP, the major intermediate filament protein in astrocytes, as the cause of almost all cases of Alexander disease. These studies have transformed our view of this disorder and opened new directions for investigation and clinical practice, particularly with respect to diagnosis [22, 23].

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. 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. The symptoms sometimes mimic those of Parkinson’s disease or multiple sclerosis.

There is no cure for Alexander disease, and there is no standard course of treatment, which is symptomatic and supportive. The prognosis is generally poor; most children with the infantile form do not survive past the age of 6. Juvenile and adult onset forms of the disorder have a slower, lengthier course. Families with megalencephaly, seizures, spastic paresis and psychomotor deterioration with leukoencephalopathy characterized by white matter abnormalities predominating in the frontal lobes.

Conflict of interest statement: The authors declare that they have no conflict of interest to the publication of this article.

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