INFANTILE ALEXANDER DISEASE- A CASE REPORT
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Abstract: Alexander disease, a rare and fatal disorder of the central nervous system, most commonly affects infants and young children but can also occur in older children and sometimes adults. Megalencephaly, demyelination and multiple Rosenthal fibers (1) characterize it. Specific magnetic resonance imaging (MRI) findings and genetic investigations are necessary to diagnose the disorder (2). Here we report a rare case of Alexander disease in an 8 months old infant, who presented with developmental regression, megalancephaly and seizures with leukodystrophic findings in the frontal white matter bilaterally on magnetic resonance imaging, suggestive of Alexander disease.

Keywords: Alexander, leukodystrophy, Rosenthal fibers

INTRODUCTION: Alexander disease is a rare, sporadic leukoencephalopathy that is characterized by white matter abnormalities with frontal predominance; it is caused by mutation in GFAP gene, which codes for glial fibrillary acidic protein (1). It is associated with megalencephaly, seizures, spasticity and psychomotor deterioration (2). Four types can be distinguished based on the age at clinical presentation: neonatal, infantile, juvenile, and adult (2). 63% of cases described have been the infantile form. About 24% of patients have the juvenile form, and adult cases are rare (2). All three forms of disease are identified by the presence of Rosenthal fibers, microscopic protein aggregates that are found in astrocytes in the brain and spinal cord (1). Alexander disease is considered an autosomal dominant disorder, but almost all cases result from new mutations in the gene (1). Diagnosis formerly depended on autopsy, now diagnosis is possible by classical MRI findings (1).

CASE REPORT: 2nd born female child of distantly related parents, who had an uneventful antenatal and perinatal history presented at day 8 of life with neonatal seizures. Metabolic parameters and CSF was normal, EEG was abnormal, hence started on anticonvulsants (phenobarbitone) and discharged. DEVELOPMENT: child attained social smile at 4 months, cooing at 3 months, head control at 5 months, sitting with support by 7 months and reaching for objects at 6 months. At 8 months of age child developed recurrent seizures, not associated with fever in spite of regular anticonvulsants. Child was admitted and managed as status epilepticus. On examination child was drowsy, responding to painful stimuli, had bipyramidal signs, DEM was present, neurocutaneous markers and meningeal signs were not present.

Head circumference was 49cm (macrocephaly). Other system examination was normal. Child was in altered sensorium for 24 hours. Child lost all the previously acquired milestones following the seizures. CT-brain showed bilateral symmetrical white matter hypodensity (?ADEM ?leukodystrophy). CSF analysis was normal. In view of acute clinical presentation and findings in neuroimaging, ADEM was considered and IV methyl prednisolone was given for 3 days under cover of antibiotics. Tandem mass spectrometry and metabolic workup was normal. Ophthalmic examination revealed normal fundi.

FIG-1: CT –brain showing B/L symmetrical white matter hypodensity
MRI Brain was taken, which showed T2 /flair hyperintensity in frontal and temporal white matter, external capsule, basal ganglia, thalamus, brainstem & periventricular whitematter. Garlands were seen in peritrigonal occipital region without diffusion restriction. On contrast there was mild enhancement noted along the ventricular lining in the frontal region, suggestive of Alexander disease. The child was diagnosed as Alexander disease based on classical clinical features and MRI-brain findings fulfilling van der knaap et al criteria (9) among which all 5 criteria was present.

FIG 2: T1 image showing leukodystrophy with predominant white matter involvement & increased signal intensity in periventricular region.

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**CLINICAL FEATURES:**

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 (8). 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 (4,8). The infantile form is the most common, accounting for 63 percent of all cases. The onset is before 2 years of age (4).

Affected children tend to have progressive physical and mental retardation with loss of previously attained milestones. Head size becomes increasingly large and the forehead appears prominent as a result of megalencephaly (3).

**DISCUSSION:**

Alexander disease is a slowly progressing, fatal neurodegenerative disease. Alexander disease is named after Dr. W. Stewart Alexander, an Australian pathologist who first described an infantile case in 1949 (3). It is caused by dominant mutations in glial fibrillary acidic protein (GFAP) gene, on chromosome 17q21 and cases are usually sporadic in their families (7).

Mutations in the GFAP gene alter the structure of glial fibrillary acidic protein. As a result, glial fibrillary acidic protein may accumulate as a component of Rosenthal fibers. A major pathological hallmark is the formation of Rosenthal fibers, which are found throughout the brain and spinal cord, accumulating particularly in astrocyte end-feet in the subpial and perivascular zones.

They are composed of glial fibrillary acidic protein (GFAP), the major intermediate filament of astrocytes, as well as ubiquitin and the small heat-shock proteins HSP27 and aB-crystallin (6).

**REFERENCES:**

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.
6. Other disease manifestations include seizures, spasticity, quadriplegia, feeding problems, and ataxia. Hydrocephalus may also occur, especially in children with early onset of symptoms (4).
7. The juvenile phenotype, observed in approximately 24 percent of affected patients, typically presents between ages 4 and 14 years. The symptomatology differs from that of infantile form and consists mainly of spastic paraparesis and progressive bulbar signs, cognitive functions are usually spared. 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. Most patients have relapsing neurological symptoms suggestive of multiple sclerosis. Diagnosis can be made only after neurohistopathological examination demonstrating Rosenthal fibers.
8. It is justified to presume a diagnosis of Alexander disease without histologic confirmation, and that only in atypical cases of the disease is a brain biopsy still necessary for a definitive diagnosis. Genetic testing is accomplished by looking for known or detectable mutations in the GFAP gene. Prenatal diagnosis is possible by using cells obtained from chorionic villus sampling (CVS) or amniocentesis.
9. The presence of four of the 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 increased 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.

**DIAGNOSIS:**

The diagnosis of Alexander disease can be established based on clinical and radiographic (MRI) features. Van der Knaap et al (9) 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 increased 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.

**TREATMENT:**

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.

**PROGNOSIS:**

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 (2).

**FIG-3:** T2 image showing frontal white matter predominance & decreased signal intensity in periventricular white matter.

**FIG-4:** T1 image showing progressive leukodystrophy with frontal predominance & periventricular increased signal intensity.

**FIG-5:** T2 image showing progressive frontal white matter involvement & periventricular decreased signal intensity.

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