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Case Report

Infantile Alexander's disease

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ABSTRACT

Alexander disease is a rare, progressive debilitating disorder that affects the nervous system and causes significant neurological problems and developmental delays. The symptoms of Alexander disease vary depending on the type and severity of the disorder, but they typically include developmental delay, intellectual disability, seizures and progressive neurological problems such as spasticity, weakness and ataxia. The proband is a case of a 9-month-old boy presenting with macrocephaly and neuroregression. Magnetic resonance imaging (MRI) revealed hyperintense signal in white matter with predominant involvement of frontal white matter, ventriculomegaly and involvement of basal ganglia, brainstem and cerebellum. The diagnosis was confirmed on genetic analysis. Alexander's disease is a rare neurodegenerative condition that characteristically presents with macrocephaly and high T2 signal in frontal white matter in infants.

Keywords: Alexander disease, Nervous system, Developmental delay, Intellectual disability, Neurodegeneration

INTRODUCTION

Alexander's disease is a rare autosomal dominant progressive neurodegenerative condition with incidence of 1 in 2.7 million. It is a primary astrocytic disorder, affecting bilateral frontal white matter predominantly. A mutation of GFAP gene encoding for glial fibrillary acidic protein is responsible for this disease. Most of the reported cases with genetically confirmed Alexander's disease reveal de novo GFAP pathogenic variants.[1]

CASE REPORT

A nine-month old male presented to paediatric department with recurrent respiratory tract infection and progressively enlarging head size (>95th percentile). He was the first born of a non-consanguineous marriage following full term normal vaginal delivery and uneventful antenatal history. As per his mother, the infant was able to sit in a tripod position by the sixth month. Later the child was facing difficulty to sit properly and also had feeding difficulty. The patient was stabilised in the paediatric critical care unit and referred for magnetic resonance imaging (MRI) brain.

MRI was carried out on 3T Siemens 'SOMATOM'. It revealed hyperintense signal intensity on T2WI and FLAIR images in deep and subcortical white matter in bilateral cerebral hemispheres (Figure 1a and b), in bilateral caudate nuclei, internal capsules, dorsal brainstem and bilateral cerebellar hemispheres (Figure 1c and d). Based on imaging and clinical findings, a possibility of leukodystrophy, such as Alexander's disease, was suspected and the patient was advised to undergo a genetic test.

Genetic analysis was carried out using Illumina next generation sequencing (NGS) system by sequencing of protein coding regions of approximately 30 Mb of human exome. A missense variant mutation was identified in the

GFAP gene in chromosome 17q21. Thus, diagnosis of Alexander's disease was confirmed. Supportive treatment and genetic counselling was provided to the patient and the parents.

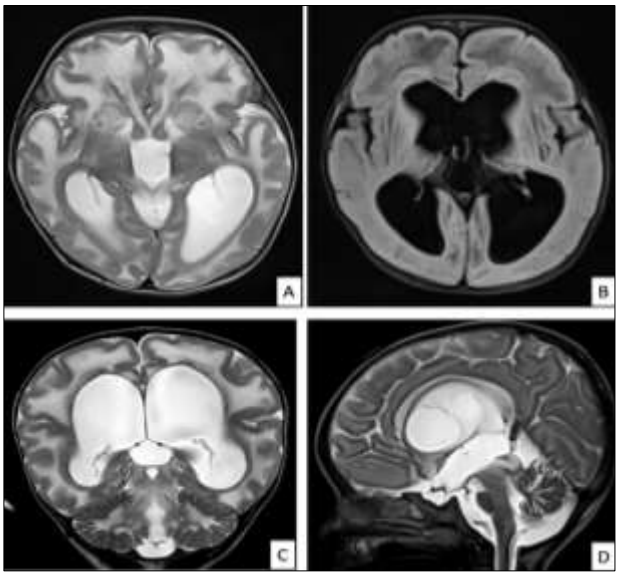

Figure 1: (A) Axial T2WI, (B) axial FLAIR image - showing abnormal high signal intensity in white matter of bilateral frontal and temporal lobes, heads of caudate nuclei and midbrain with dilated bilateral lateral and third ventricle, (C) coronal T2WI - ventriculomegaly is noted along with hyperintense signal in white matter in bilateral cerebral and cerebellar hemispheres, and (D) sagittal T2WI - high signal intensity is noted in the dorsal brainstem.

DISCUSSION

Alexander disease is a rare genetic disorder that affects the nervous system and is characterised by the accumulation of abnormal protein called glial fibrillary acidic protein (GFAP) in the brain. GFAP is a structural protein that is involved in regulating the morphology and motility of astrocytes. It is also involved in interaction between astrocytes and oligodendrocytes. Mutation in GFAP gene acts as gain of function mutation that disrupts the dimerization of intermediate filaments resulting in abnormal protein aggregation and cytoskeleton collapse.[2,3] Although it is considered a rare disease, it is estimated that Alexander's disease is underdiagnosed, and the true incidence may be higher.[1]

Symptoms of Alexander disease usually appear in infancy or early childhood and can include developmental delays, difficulty with movement and coordination, and problems with speech and language. As the disease progresses, affected individuals may experience seizures, muscle stiffness, and difficulty swallowing.[4]

There are three main types of Alexander disease: infantile, juvenile, and adult. Infantile Alexander disease is the most severe form and is characterised by rapid progression and early death. Patients usually present with macrocephaly, developmental delay, progressive quadriparesis and seizures. Juvenile and adult forms are less severe and may not be diagnosed until later in life. Clinical presentation varies based on the site of involvement in adult patients. Early onset is associated with a severe and rapid course of disease.[1,4]

MRI is a non-invasive imaging technique that is commonly used to diagnose and monitor the progression of Alexander disease. MRI can be used to detect the presence of brain abnormalities, such as white matter changes and histopathology shows the formation of abnormal brain intracytoplasmic inclusions called Rosenthal fibres. These abnormalities are typically visible on MRI as hyperintense signal intensity with predominant involvement of frontal lobes of bilateral cerebral hemispheres, basal ganglia and cerebellum. In early stages, subcortical U- fibres are spared. Van Der Knaap et al described MRI criteria for diagnosis of Alexander's disease. Four of five criteria are required to make a diagnosis including white matter hyperintensity with frontal predominance, periventricular rim of low signal intensity on T2WI and high signal on T1WI, abnormalities in basal ganglia, brainstem abnormalities, and contrast enhancement in any of the regions including ventricular lining, periventricular rim, frontal white matter, optic chiasma, and fornix/ basal ganglia.[5] Periventricular rim showing high signal on T1WI and low signal on T2WI is hypothesised to be due to accumulation of Rosenthal fibres. Alexander's disease is one of the few leukodystrophies showing contrast enhancement after gadolinium administration which indicates a break in blood-brain barrier.[6] Other leukodystrophies showing contrast enhancement include Adrenoleukodystrophy and Krabbe's disease. Cystic changes are also reported in a few cases in later stages.[6] MR spectroscopy can be useful as a problem-solving tool in selected cases and shows increased choline in basal ganglia, elevated lactate and reduced NAA in frontal white matter.[7]

The differential diagnosis includes other leukodystrophies presenting with macrocephaly namely Canavan's disease, and megalencephalic leukoencephalopathy with subcortical cysts (Van der Knaap disease).[1,5]

Currently, there is no cure for Alexander disease and treatment is primarily supportive, focused on managing symptoms and providing comfort. Treatment options may include medication for seizures, physical therapy to help with movement and coordination, and speech therapy to improve communication.

CONCLUSION

It is important to note that the diagnosis of Alexander disease is made based on a combination of clinical features, neuroimaging, and genetic testing.

Research into Alexander disease is ongoing, with the goal of developing effective treatments and therapies for the disorder. Studies are currently focusing on identifying the underlying causes of the disorder, developing animal models to study the disease, and testing potential therapies in the lab.

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