CASE REPORT

INFANTILE ALEXANDER'S DISEASE: A CASE WITH CHARACTERISTIC MRI FEATURES

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Alexander disease, less commonly known as fibrinoid leukodystrophy is an extremely rare, non-familial, progressive, lethal leukodystrophy which is characterized predominantly by abnormalities of white matter in bilateral frontal regions. It usually presents early within first 2 years of life with clinical features of macrocephaly, recurrent seizures and psychomotor retardation. Diagnosis of this white matter disorder is possible with certain features seen on magnetic resonance imaging (MRI), even without the need for histological confirmation. Our case is a one year old male infant who presented with repeated episodes of focal seizures to the paediatrician. He was referred for an MRI and subsequently based on typical MRI findings the diagnosis of Alexander disease was made.

Keywords: Alexander disease, Magnetic resonance imaging, Frontal lobe white matter abnormalities, Leukodystrophy, Rosenthal fibres

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INDRODUCTION

Leukodystrophies are a group of neurodegenerative disorders predominantly affecting the central nervous system white matter, caused by defects in the synthesis or maintenance of myelin sheath that insulates the nerves, which in turn results in production of abnormal proteinaceous deposits known as Rosenthal fibres. Deposition of this protein aggregates occurs in astrocytes which are supporting cells of brain. Rosenthal fibres usually are found diffusely and in abundance in patients with AD, especially in perivascular, subpial and subependymal astrocytes.[1–4] Currently, three subtypes of AD are recognized, depending upon the age at onset, infantile (under 2 years), juvenile (2–12 years) and adult (after 12 years)[1,5,6], the infantile form being the most common[1,2,7]. Infantile form of AD typically presents before 2 years of life with developmental delay, macrocephaly, seizures, psychomotor retardation, and follows a progressive lethal course.[1,6,7] MRI is considered highly sensitive and specific in the diagnosis, with laboratory investigations usually of no help.[7]

CASE REPORT

Our case is a one year old male infant, first born child from a consanguineous marriage. He progressed normally with normal psychomotor development, until recently, when he started getting repeated attacks of focal seizures, along with lethargy and decreasing response. After visiting multiple outpatient clinics, but with no significant improvement in the symptoms, he was referred to a paediatric consultant in our hospital. According to paediatrician, his cranial nerves were normal on clinical assessment, with normal muscle tone and strength, but with brisk deep tendon reflexes. No abnormality was identified in any other system on physical examination.

Complete laboratory work up, including blood counts, serum electrolytes, blood calcium, magnesium, phosphorous, blood glucose, renal and liver function tests were within normal range.

Multi-sequential, multiplanar MRI of the brain was acquired before and after administration of intravenous Gadolinium contrast. MRI revealed diffuse, symmetrical, bifrontal abnormality of white matter returning low signals on T1-weighted images and appearing hyperintense on T2WI (Figure-1 A,B). Periventricular rim of hyper-intensity was appreciated on T1-weighted images, particularly around frontal horns, which was hypointense on T2-weighted images (Figure-2 A, B). There was bilateral symmetrical, signal abnormality in corpus striatum, especially putamen and caudate nucleus, returning high signals on T2-weighted images (Figure-3). Abnormal signals were appreciated in midbrain and medulla, with cystic areas in periaqueductal brainstem (Figure-4 A, B). Perilesional enhancement of brainstem was noted. There was intense enhancement of periventricular rim especially in frontal region, frontal lobe white matter, anterior commisure, mamillary body, lamina terminalis, periaqueductal midbrain, fornix, optic chiasm and bilateral olfactory nerves (Figure-5 A, B).

Based on characteristic MRI features, the case was concluded as Alexander disease with no relevant differential diagnosis.

Parents of the infant refused brain biopsy. Till the submission of this manuscript, the infant is alive but is following a gradually deteriorating course with progressive worsening of the symptoms.

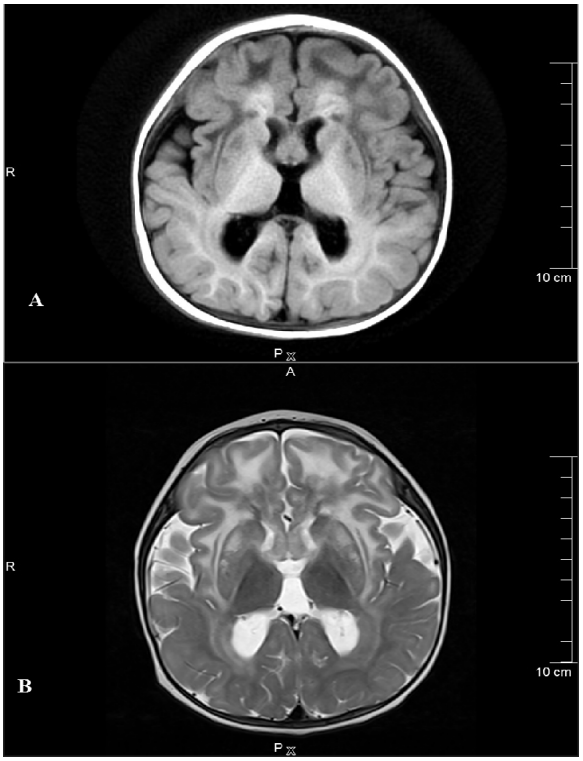

Figure-1: Abnormal symmetrical low signals in bifrontal white matter on axial T1WI (A) and high signals on axial T2WI (B) than rest of the normal white matter in parieto-occipital regions.

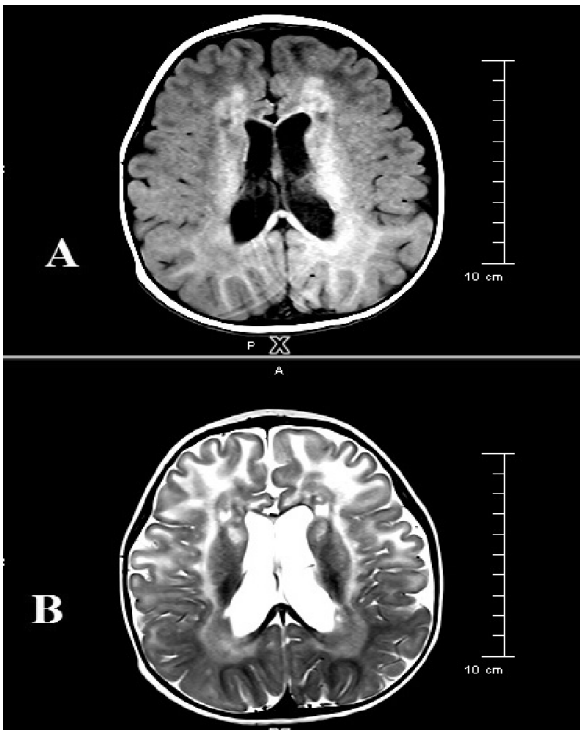

Figure-2: Periventricular rim of hyperintensity on axial T1WI (A) images with corresponding low signal intensity on axial T2WI (B).

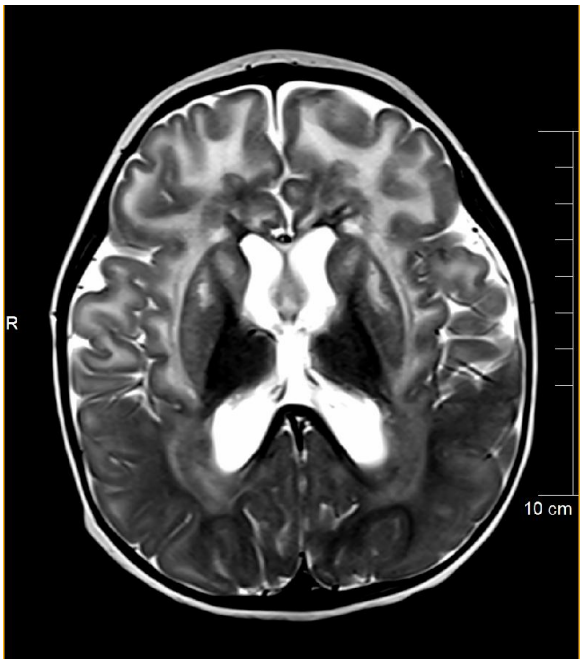

Figure-3: Head of caudate and putamen are swollen and also showing high signals on T2WI.

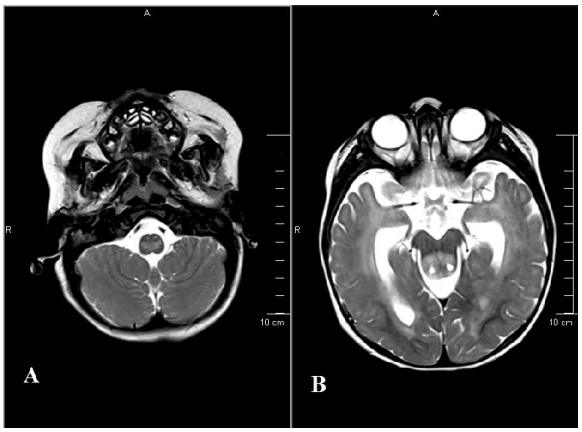

Figure-4: Abnormal high signals in medulla (A) and midbrain (B) except the red nuclei on axial T2WI.

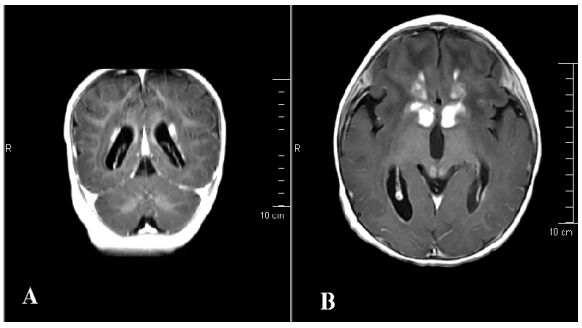

Figure-5: Symmetrical periventricular rim enhancement on coronal post contrastT1WI (A) and bifrontal deep white matter enhancement on post contrast axial T1WI (B).

DISCUSSION

Infantile form of AD, being the most common type of this rare disease, presents before the age of 2 years, usually with macrocephaly, seizures, developmental delay and spasticity.[2,3,5,6] It is characterized by nearly complete absence of myelin sheaths, predominantly affecting the frontal lobe white matter.[1,2,6]

MRI is the non-invasive study of choice for diagnosis of Alexander disease and can detect specific neurodegenerative changes in the white matter of central nervous system. AD may also be revealed by genetic testing.[2,3] A preliminary diagnosis may also be suggested by clinical symptoms.

Van der Knaap established five MR imaging criteria for the diagnosis of Alexander disease in 2001. These consist of: 1) extensive abnormalities of cerebral white matter, predominantly in frontal regions: 2) Abnormal periventricular MR signals which are hyperintense on T1-weighted images and hypointense on T2-weighted images: 3) Atrophy or abnormal signals in basal ganglia and thalami which may be either hyper or hypointense on T2-weighted imaging: 4) brainstem abnormalities, particularly involving medulla and midbrain: and 5) contrast enhancement in one or more of the following structures; periventricular rim of tissue, ventricular lining, white matter of frontal lobes, fornix, optic chiasm, thalamus, basal ganglia, dentate nucleus and brainstem components.[1,7–9] Four out of these five imaging criteria need to be fulfilled for diagnosis of AD, as it is often very difficult to assess white matter abnormalities in infants due to developing white matter and post contrast MR study may not be available in every case.[7]

Our patient fulfilled all five MR imaging diagnostic criteria; therefore the diagnosis was made without any need for further confirmation by biopsy.

MRI features of infantile form of AD differ from juvenile and adult form, as involvement of brainstem is predominant in the later forms.[1]

The clinical picture of AD mimics many other central nervous system disorders like leukodystrophies, mitochondrial myopathy, Canavan disease, encephalopathy, lactic acidosis and stroke (MELAS), glutaric aciduria, Leigh disease, Zellweger syndrome and organic acidurias. However MRI features for all of these are different from Alexander disease and aid in reaching a correct diagnosis.[1]

Currently there is no cure or standard procedure proven for treatment of Alexander disease. The prognosis of Alexander disease is generally poor. In early onset disease, death of the patient usually occurs within 10 years from the onset of symptoms. Juvenile and adult forms have a slower and lengthy course.

In conclusion, if a patient fulfils MR imaging criteria, it is justified to presume a diagnosis of Alexander disease, without the need for histological confirmation, which was considered necessary in the past to make the diagnosis.[7,9]

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