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Joubert syndrome -The molar tooth abnormality of midbrain

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ABSTRACT

Joubert Syndrome (JS) is a very rare autosomal recessive genetic condition associated with agenesis/ dysgenesis of parts of brainstem and cerebellar vermis. We report a rare case of Joubert Syndrome in an eighteen month old male child. He presented with delayed neuro-developmental milestones, hypotonia, progressive abnormal lateral gaze deviation and abnormal head movements. MRI of brain stem showed the Molar Tooth sign in brainstem caused by absence of isthmic portion and deformity of fourth ventricle. On follow up, the patient improved slightly. This could be the first report of this rare developmental disorder from Eastern India.

INTRODUCTION

Joubert syndrome (JS) is a very rare, autosomal recessive condition, first described by Joubert in 1969[1]. It is characterized by agenesis of cerebellar vermis, generalized hypotonia, abnormal respiratory pattern and abnormal eye movements. Associated features may include sleep apnea, supernumerary digits and seizures. It is a genetic disorder, but multiple genes have been implicated in causation. It is sometimes associated with other syndromes like retinitis pigmentosa. This syndrome has been rarely reported elsewhere in the world including India. It is difficult to diagnose clinically due to variable presentation [2]. We report a case of Joubert Syndrome, diagnosed by clinical features and radiology, in an 18 month old male child. This is probably the first report of this syndrome from Eastern India.

CASE REPORT

A one year six month old male infant presented with history of delayed mental and motor development, abnormal limb movement, generalized hypotonia, abnormal head and eye movements and nystagmus. There was also history of abnormal breathing pattern with episodes of rapid breathing in between normal breathing. There was history of feeding difficulty and frequent chest infections from first few months after birth.

On reviewing past history, it was found that the child was born out of a non consanguinous marriage and was delivered institutionally at term with no history suggestive of birth asphyxia. The birth weight of the baby was 5.2 kg. Postnatally, mother noticed feeding difficulties. She also noticed abnormal head and eye movements with lateral gaze deviation of the eyes but decreased movement in the limbs. The gaze deviation occurred many times per day and the child did not follow objects visually. The symptoms were progressive.

Prenatal history was uneventful. No similar illness was present in any siblings. Immunization was incomplete. There was gross delay in development of mental and motor milestones. At the time of presentation, the child had not developed any speech. He could only sit with support. No congenital malformations were present. Heart and lungs were normal on auscultation. Head circumference was normal for age. Neurological examination revealed generalized hypotonia but no other focal neurological signs. Routine blood tests were all normal.

IMAGING FINDINGS: MRI of brain showed hypoplastic cerebellar vermis with hypoplasia of the superior cerebellar peduncle resembling the ``Molar Tooth Sign`` in mid-brain. (Figures 1 and 2). This finding, along with the clinical features, led to the diagnosis of Joubert Syndrome. After 1 year of follow up, the child has developed only preliminary speech, but hypotonia and gaze deviation remains.

DISCUSSION

Joubert syndrome is an autosomal recessive disorder with defective development of midline structures in brain stem [3]. Pathological studies have revealed hypoplasia or fragmentation

Table 1: Table showing the different causes of molar tooth sign

Syndrome/condition	Clinical features	Genetic defect
COACH syndrome [7]	Cerebellar vermis hypoplasia/aplasia, Oligophrenia, Ataxia, Coloboma, and Hepatic fibrosis	Not known
Varadi Papp Syndrome [8]	Metacarpal abnormalities with central polydactyly and cerebellar malformations, mainly vermis aplasia/hypoplasia. renal agenesis or dysplasia, highly arched/cleft palate, tongue clefts, tongue nodules, hyperplastic frenula, cleft lip, and broad nasal tip.	EN-1
Senior loken syndrome [9]	Nephronopthisis, retinitis pigmentosa, oculomotor apraxia, cranioectodermal dysplasia	NPHP-1
Dekaban Arima Syndrome [10]	Cerebellar Vermis Hypoplasia with Leber Amaurosis and multicystic kidneys	CEP290

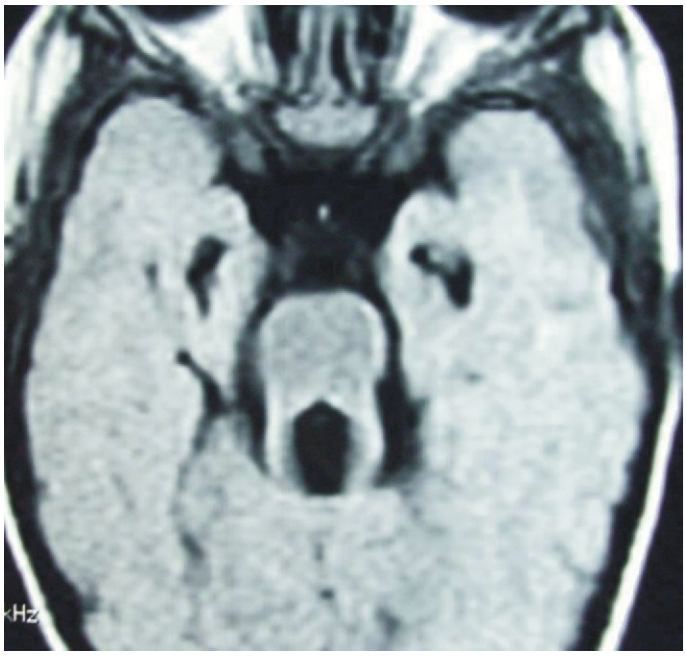

Figure 1: AXIAL T1 MRI image showing vermis hypoplasia and slimming of isthmus in brain stem

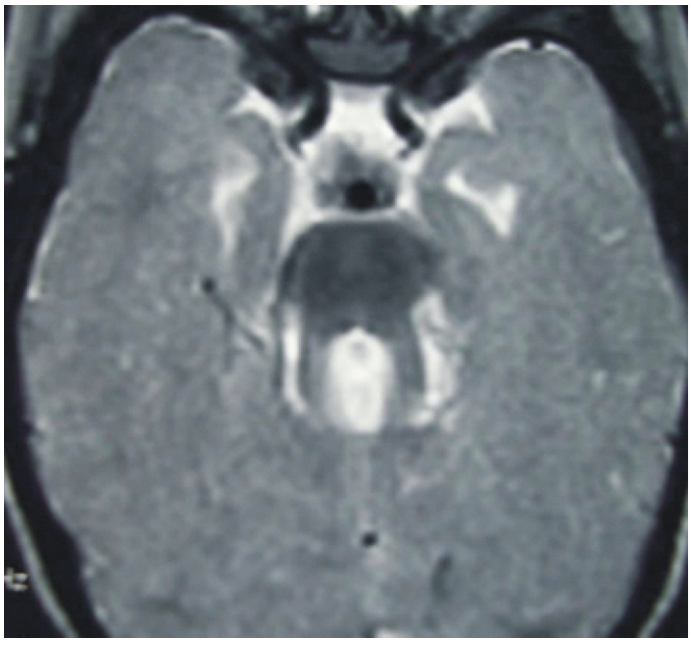

Figure 2: AXIAL T2 MRI image showing molar tooth sign in brain stem with deformity of 4th ventricle

of several brainstem nuclei and dysplasia of structures at the ponto-mesencephalic junction [3]. This gives rise to the various clinical features like oculomotor apraxia, hypotonia, hyperventilation and developmental delay. In our patient, we found progressive feeding difficulties, abnormal eye movements and gaze deviation. However, the behavioral manifestations are not diagnostic and a wide range of manifestation has been described. Associated structural defects include renal cysts, soft tissue tumors and polydactyly [4]. However our patient did not show any of these extra cerebral structural anomalies. In 1992, a set of diagnostic criteria was proposed for the syndrome including vermis hypoplasia, hypotonia, developmental delay and abnormal eye movements or abnormal breathing [5].

Imaging, more specifically MRI brain, is needed for definitive diagnosis. It shows elongation and slimming of the isthmic portion of the brain stem at the ponto-mesencephalic junction, deep interpeduncular fossa, thick and nearly perpendicular cerebellar peduncles, and deformity of the 4th ventricle resulting from complete or partial absence of the vermis [6]. The combination of these findings give rise to the classical 'Molar Tooth sign' which was present in our case in T1 and T2 weighted images.However, although molar tooth sign in typical of Joubert syndrome, there are a few other causes of this radiological appearance too. The following table shows the other causes of this radiological sign.

Sometimes these disorders are called Joubert syndrome related disorders (JSRD) [7].

Besides the classical molar tooth sign, Joubert syndrome may have other radiological features like corpus callosal dysgenesis or partial absence of splenium [6]. These were absent in our case.

There is no known treatment to cure the condition. Infant stimulation and physical, occupational, and speech therapy may benefit some patients [11]. Due to heterogeneous nature of the disorder, some patients may improve subsequently and develop sufficient skills to be independent in daily activities [12]. However, there is no way to predict the subsequent course and early supportive management is instituted.

CONCLUSION

When a child presents with mental retardation or abnormal signs like nystagmus or hyperpnea, developmental disorders like Joubert Syndrome need to be excluded. Subtle clinical features like gaze deviation, must be looked for. This will help to narrow down the possibilities and proper imaging of the central neuraxis may help in quick diagnosis of the disorders. When such a genetic disorder is diagnosed, associated conditions like renal pathology or retinal degeneration should also be ruled out. Thus early rehabilitation therapies can be instituted. Parents and other family members need to be educated about the conditions.

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