Joubert Syndrome: Imaging Findings and Report of a Case

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ABSTRACT

Background: Joubert syndrome (JS) is a very rare autosomal recessive disorder characterized by agenesis of cerebellar vermis, abnormal eye movements, respiratory irregularities, and delayed generalized motor development. Retinal dystrophy and cystic kidneys may also be associated with this clinical syndrome. The importance of recognizing JS is related to the outcome and its potential complications. This syndrome is difficult to diagnose clinically because of its variable phenotype. Its neuroimaging hallmarks include the characteristic molar tooth sign and bat wing-shaped fourth ventricle.

Keywords: Joubert syndrome; Magnetic resonance imaging; Molar tooth sign; Vermian agenesis; Case report.

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Joubert syndrome (JS) is a very rare, autosomal-recessive condition, first described by Joubert in 1969 and characterized by episodes of abnormal respiratory pattern, abnormal eye movements, hypotonia, ataxia, developmental retardation with evidence of neuropathologic abnormalities of cerebellum and brainstem [1]. This syndrome has been rarely reported elsewhere in the world with a prevalence of less than 1 in 100,000 [2]. It is a syndrome with a variable phenotype making it difficult to establish the exact clinical diagnostic boundaries of the syndrome. Even though the clinical features of the disorder are present in the newborn period, the correct diagnosis is often not made for several months or years after birth [3]. As early as possible this syndrome is detected, the suitable preventive measures can be started. Because of the rarity of this syndrome, we are reporting this case in order to increase awareness on it. A comprehensive review of the clinical and imaging findings and the differential diagnosis are also presented.

Case Report:

A 19-months-old boy presented to our institution with history of delayed developmental milestone, mild mental retardation, abnormal limb movement, generalized hypotonia and abnormal head movements with nystagmus. There was also history of abnormal breathing pattern with episodes of alternate rapid breathing and normal breathing. There was history of feeding difficulties and frequent chest infection from the early months of life. There was no history of seizure. He was born by normal vaginal delivery in a hospital at term with history suggestive of significant birth asphyxia. His parents had a consanguineous marriage. Prenatal history was uneventful. No similar illness in any siblings in the family was reported. Immunization was incomplete. There was gross delay in development of mental and motor milestones.

Physical examination revealed a hypotonic child, abnormal head movement sideways and limb movements, and intermittent movements of eyes to extremes of gaze. Head circumference and other anthropometric examinations were normal for age. No morphological abnormality was detected and he had no neurocutaneous markers. Heart and lungs were normal on auscultation. No organomegaly was present. Ocular examinations revealed bilateral divergent squint, inability to follow moving object, restricted upward gaze of eye and bilateral horizontal gaze-evoked nystagmus. Ophthalmoscopy revealed no retinal defect. Neurological examination revealed normal cranial nerves and fundus. Complete blood count, renal function test and liver function test were normal.

The axial T2-weighted [Figure 1] Magnetic resonance (MR) image showed abnormally oriented and thickened superior cerebellar peduncles that resulted in a molar tooth configuration. The more caudal T2-weighted axial MR image [Figure 2] showed vermian agenesis, bat wing shaped like fourth ventricle communicating through a thin CSF fissure with foramen of Magendie. MRI sagital T1-weighted image revealed vermian agenesis [Figure 3]. The size of the posterior fossa and corpus callosum was normal. There was no ventriculomegaly or any evidence of neuronal migration anomalies. Renal ultrasound showed no abnormality. Based on clinical and magnetic resonance imaging (MRI) findings, diagnosis of JS was made and parents were counseled. The patient was kept on supportive treatment which consisted of neuropsychological support and rehabilitation.

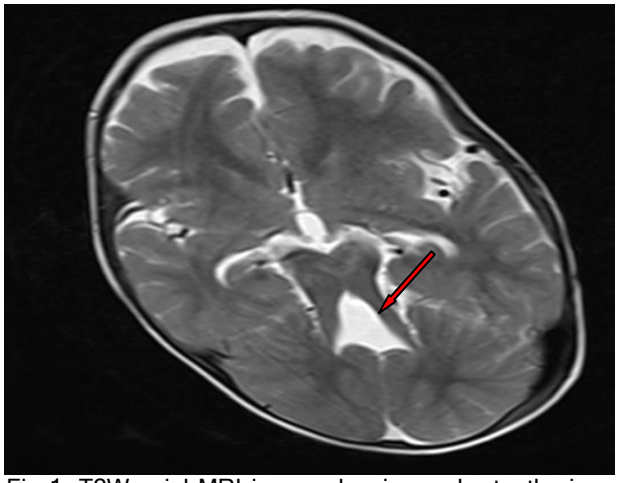

Fig 1. T2W axial MRI image showing molar tooth sign (arrow).

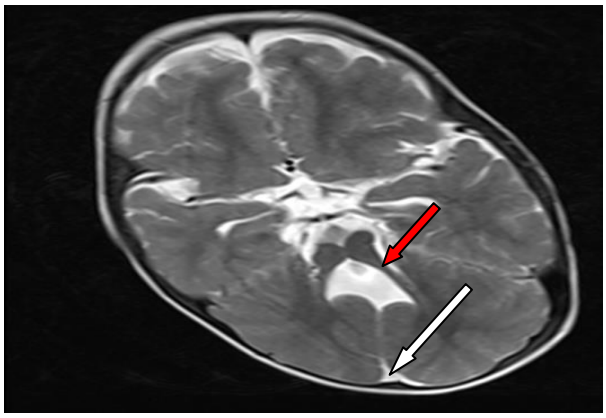

Fig 2. T2W axial MRI image showing bat wing appearance of the fourth ventricle (red arrow), vermian agenesis and extension of the cerebrospinal fluid cleft (white arrow) through it.

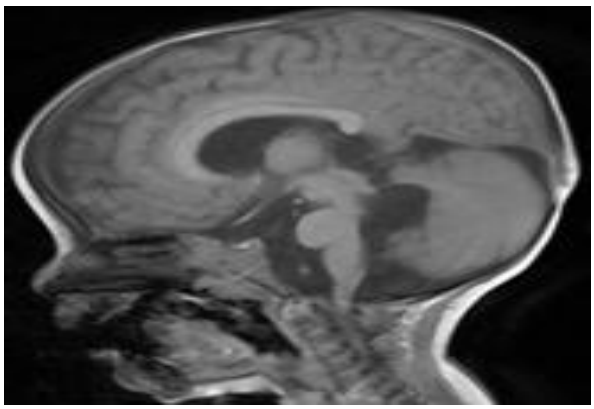

Fig 3. T1W sagittal MRI image showing evidence of vermian agenesis

Discussion: JS is a rare autosomal recessive disorder characterized by clinical and characteristic neuroradiological findings and very few cases have been reported in the world. It is occurring more frequently in the children of consanguineous parents. Both parents are the carriers of the gene. Parents who have a child with JS have a 25% chance of transmission of this disorder in subsequent pregnancy. Prenatal testing with targeted ultrasound may be a mode of investigation to detect prenatally.

This syndrome was originally described by the French neurologist 'Marie Joubert' in 1969 [2]. Later, Joubert syndrome-related disorders (JSRD) were defined based on associated multi-organ involvement (retinal dystrophy, nephronophthisis, hepatic fibrosis and polydactyly). JSRD has six phenotypic subtypes: Pure JS, JS with ocular defect, JS with renal defect, JS with oculorenal defects, JS with hepatic defects and JS with orofaciodigital defects. Pure JS is classified into two groups on the basis of presence or absence of retinal dystrophy. Patients with retinal dystrophy have a higher prevalence of multicystic renal disease and these patients seems to carry a worse prognosis in terms of survival compared with those of patients without retinal dystrophy [1]. Our patient had no retinal defect.

The main clinical features that frequently mentioned as essential for the diagnosis of classic JS include episodic hyperpnoea, abnormal eye movements, hypotonia, ataxia, developmental delay, and mental retardation. Our patient displayed all these main clinical features that are consistent with the diagnosis of JS. Other less common reported clinical features (not presented in our case) include seizures, dysmorphic facies, polydactyly, ocular colobomas, ptosis, renal cysts, hamartomas of tongue and occipital meningocele [2].

MRI is the imaging tool of choice. The main imaging findings that almost uniformly seen are partial or complete absence of the cerebellar vermis, thickened and abnormal orientation of the superior cerebellar peduncles, thinning of the isthmic portion of the brainstem with a deep interpeduncular cistern producing the characteristic molar tooth sign. The molar tooth appearance is also contributed by failure of normal decussation of the superior cerebellar peduncular fibres during embryonic development. Absence of vermis results in a midline cleft between the two cerebellar hemispheres resulting in batwing appearance of the fourth ventricle on axial images. The cerebrum is not affected, although moderate lateral ventricular enlargement, cerebral cortical dysplasia, gray matter heterotopias and corpus callosum dysgenesis were reported in 6-20% of the cases [1, 4]. In our reported case, no supratentorial abnormality was present.

Patients with JS are extremely sensitive to the respiratory depressant effects of anesthetic agents such as opioids and nitrous oxide and susceptible to post-operative respiratory infection [5]. Therefore, these agents should be avoided, and close perioperative respiratory monitoring and care are essential. In addition to JS, partial or complete absence of the cerebellar vermis has been described as a part of Dandy-Walker

syndrome, Down syndrome and rhombencephalosynapsis [6]. In patients with Dandy-Walker syndrome, there is a cyst in the posterior fossa that leads to expansion of the posterior fossa and interpeduncular fossa and superior cerebellar peduncle are normal. In rhombencephalosynapsis, the cerebellar hemispheres are fused and, unlike in JS, a midline cerebellar cleft is not present [7]. Molar tooth sign is not specific for JS. This may be seen in Varadi-Papp syndrome, Malta syndrome, Dekaban-Arima, Senior-Loken syndrome and COACH syndrome [8].

Developmental outcome in JS is variable. Steinlin *et al.*[9] suggested that outcomes in JS can be divided into three courses: first, children who die young; second, patients who survive but are severely developmentally delayed and have a variety of visual and motor handicaps; and third, patients whose developmental quotients fall within the mildly delayed range.

Genetic counseling is important in a family having JS. Furthermore, once a diagnosis of JS is made in one neonate, the diagnosis of JS can be made antenatally by looking for the imaging findings at antenatal US of the fetal brain in a subsequent pregnancy. Antenatal magnetic resonance can also pick up JS carefully [10].

To conclude; with appropriate clinical presentation, elaborate physical evaluation and the typical MR finding of the molar tooth sign and batwing shaped fourth ventricle, diagnosis of Joubert syndrome can be made without much difficulty. As JS is associated with multiorgan involvement, these patients should enter a diagnostic protocol to assess systemic abnormalities. Extreme caution should be taken while administering drugs in these patients as they are prone to respiratory depression.

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