

A Missed Cause of Mental Retardation! Joubert Syndrome a Case Report

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Abstract

Case Report

Joubert syndrome (JS) is an uncommon autosomal recessive neurodevelopmental disorder involving cerebellar vermis and brain stem. We report a case of an 8-year-old male boy presented with global developmental delay, abnormal eye movements and ataxia. Magnetic resonance imaging (MRI) revealed characteristic Molar tooth sign (MTS) and bat wing appearance of fourth ventricle.

Keywords: Joubert syndrome, molar tooth sign, mental retardation, ataxia, nystagmus, polydactyly.

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INTRODUCTION

In 1969, Dr. Marie Joubert and colleagues first described four siblings with cognitive impairment, ataxia, episodic tachypnea, eye movement abnormalities, and cerebellar vermis agenesis in a large French-Canadian family with consanguinity traced 11 generations to a common ancestor [1]. This clinical entity is underreported with a prevalence of less than 1 in 1,00,000 [2]. Joubert syndrome (JS) is characterized by episodes of abnormal respiratory pattern, oculomotor findings, hypotonia, ataxia, developmental delay with evidence of neuropathologic abnormalities of cerebellum and brainstem [1].

CASE REPORT

An 8-year-old male child presented to us with complaints of developmental delay, swaying while walking and eye ball jerking movements. He is a preterm baby with birth weight of 1.8 kg. Baby not cried soon after birth. Had respiratory distress during newborn period with NICU stay for few days.

Child has delay in attaining developmental milestones. He started sitting by 2 years and walking by 4 years. He attained pincer grasp by 2 years. He started speaking two word sentences by 3 years and had language delay. There is eye ball jerking movements

noticed from 6 months of age, however no difficulty in moving eyeballs nor any visual impairment. He had tightness of limbs (LL>UL) which has decreased over years with physiotherapy. There was no history of seizure, abnormal breathing pattern, feeding or swallowing difficulty. There is no history of consanguinity. No history of family members affected with similar condition.

The child was conscious, awake at the time of examination, and anthropometric evaluation was within the normal limits for age. On examination there is hypertelorism and polydactyly in both hands. He had no neurocutaneous markers. He is hyperactive, responding slow to questions with poor interaction. His IQ is low for his age. There is jerk nystagmus in both eyes and convergent squint in left eye. Fundoscopic examination was normal. Child had normal tone and deep tendon reflexes. He had ataxia, which is well pronounced in tandem walking. Other systemic examination was normal.

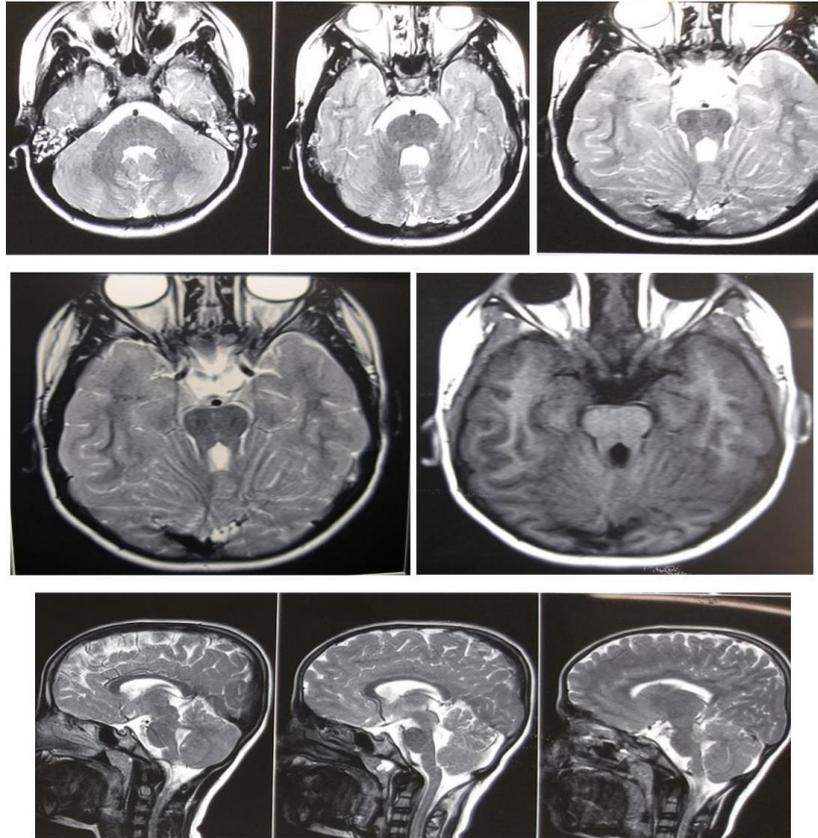
Laboratory investigations, including hemogram, blood sugar, electrolytes, C reactive protein, liver enzymes, urea and creatinine were all normal. There is no acanthocytes in smear. AFP (alpha feto protein) and thyroid profile were within normal limits.



Images of the child showing hypertelorism, left convergent squint, both right-and left-hand having polydactyly

Magnetic resonance imaging (MRI) T1 and T2 axial showed hypoplasia of the vermis with deepening of interpenduncular fossa, thickened superior cerebellar peduncles resembling molar tooth sign (MTS). The more caudal T2 and T1 weighted axial MRI showed 4th ventricle shaped like a bat wing. The sagittal images also showed cerebellar vermis hypoplasia. Based on this clinical and magnetic resonance imaging (MRI) findings, diagnosis of Joubert Syndrome was made.

This child was treated as psychomotor retardation secondary to prematurity and perinatal asphyxia elsewhere. After admitting to our SAT Hospital, we worked up in line of mental retardation (MR) with ataxia. We found MTS sign in MRI, which clinched the diagnosis. The cause for mental retardation (MR) in this child is found to be Joubert syndrome. Hence, we infer that in children presenting as mental retardation with ataxia, Joubert (JS) needs to be considered.



The MRI Brain of child showing molar tooth sign on axial views comprised of deepened interpeduncular fossa, and thick, elongated superior cerebellar peduncles. There is bat wing appearance of 4th ventricle. The sagittal view show cerebellar vermis hypoplasia (CVH)

DISCUSSION

The features necessary for a diagnosis of classic Joubert syndrome include the following:

- Cranial MRI findings demonstrating the MTS on axial imaging with these three components: midline cerebellar vermis hypoplasia (CVH), deepened interpeduncular fossa, and thick elongated superior cerebellar peduncles (SCP) [3].
- Hypotonia in infancy.
- Developmental delay/mental retardation.
- One or both of the following (not absolutely required but helpful for the diagnosis):
 - Irregular breathing pattern in infancy (intermittent tachypnea and/or apnea).
 - Abnormal eye movements.(including nystagmus, jerky eye movements, and Oculomotor apraxia, difficulty with smooth visual pursuits) [4, 5].

Our patient had all the clinical symptoms with the exception of breathing abnormalities and hypotonia.

Joubert syndrome related disorders are categorized into six phenotypic subgroups [6]:

- Pure JS,
- JS with ocular defect,
- JS with renal defect,
- JS with oculorenal defects,
- JS with hepatic defect,

- JS with orofaciocigital defects.

Our Child Had Orofaciocigital Phenotype

Joubert Syndrome has characteristic neuroradiological findings. The absence of vermis leads to a midline cleft between the cerebellar hemispheres. *The combination of hypoplasia of the cerebellar vermis (CVH), abnormally oriented thickened superior cerebellar peduncles (SCP) and a widened interpeduncular fossa (IF) resulting in molar tooth sign (MTS)* [7]. The 4th ventricle is enlarged and distorted, giving rise to the bat wing appearance. Our child had molar tooth sign and bat wing appearance in MRI characteristic of Joubert syndrome.

While reading MRI, extent of CVH can be graded according to Quisling *et al.*, [8]. On axial images, the shape of the inter hemispheric cleft (linear, like an inverted Y) can be assessed and its width graded ("slit" if <1, 1–2, or >2 mm). The depth of the IF can be graded (minimally or obviously deepened).The SCP can be evaluated on axial images for width (minimally or obviously thickened), length (normal, elongated), and orientation (parallel, A-like, V-like, or curved) [9].

Imaging findings in Joubert syndrome

- Partial or complete absence of the cerebellar vermis
- Hypoplastic cerebellar peduncles

- Fourth ventricular deformity, lateral ventricular enlargement (6%-20%) (batwing deformity)
- Corpus callosum dysgenesis (6%-10%)
- Deepening of the interpeduncular fossa (molar tooth sign)
- Elongation and thinning of the isthmus of Ponto mesencephalic junction[3]
- Wide foramen of Magendie [2]
- Brainstem, predominantly the medulla and upper cervical spinal cord, tends to be small [10, 11].

Systemic manifestations in Joubert syndrome

System involved	Manifestations
CNS	Hydrocephalus, cystic enlargement of posterior fossa, hypothalamic hamartoma, absence of pituitary gland cerebral cortical dysplasia and gray matter heterotopias agenesis of the corpus callosum
Ocular	Congenital blindness, congenital ocular fibrosis, refractive errors, astigmatism, retinal dystrophy, unilateral or bilateral coloboma of retinal pigment epithelium, nystagmus, strabismus, ocular motor apraxia, and ptosis
Renal	Cystic dysplasia, juvenile nephronophthisis, and tubulointerstitial nephritis
Others	Congenital hepatic fibrosis, congenital heart disease, polydactyly, hamartomas of the tongue and thyroid hormone dysfunction

Molar tooth sign is not specific for JS. Other clinical features define the subtypes of JS termed as Joubert syndrome and related disorders (JSRD). These

are syndromes such as the COACH, Varadi-Papp, Dekaban-Arima, Senior-Loken, Joubert with polymicrogyria, and Malta syndromes [12, 13].

Differential diagnosis of Joubert syndrome [12, 13]

Differential diagnosis	Findings
Senior-Loken syndrome	Leber’s congenital amaurosis, retinitis pigmentosa, and juvenile nephronophthisis
Malta syndrome	Molar tooth sign, occipital encephalocele, hydrocephalus, cortical renal cysts with or without coloboma, and Leber’s congenital amaurosis
COACH syndrome	Bilateral coloboma, hepatic fibrosis, and renal calcification
Varadi-Papp syndrome	Mesoaxial polydactyly, Y-shaped metacarpal, cleft lip or cleft palate, lingual hamartomas, and vermian hypoplasia
Dekaban-Arima syndrome	Leber’s congenital amaurosis and cystic dysplastic kidneys

Genetics

Joubert syndrome is an autosomal recessive disorder and are genetically heterogeneous with one locus pointing to chromosome 9q. In addition, consanguinity has been documented in a few cases. Nineteen causative genes have been recognized so far, every single one encoding for proteins of the primary cilium or the centrosome, hence falling under “ciliopathies” [13, 14].

The 19 genes in which biallelic mutations are known to cause Joubert syndrome and related disorders are: NPHP1, AHI1, CEP290 (NPHP6), TMEM67 (MKS3), RPGRIP1L, CC2D2A, ARL13B, INPP5E, OFD1, TMEM216, KIF7, TCTN1, TCTN2, TMEM237, CEP41, TMEM138, C5orf42, TMEM231, and TCTN3 [15].

Pathology

Pathological studies in these patients have shown that the cerebellar vermis is hypoplastic and the dentate nucleus is fragmented. The Ponto-

mesencephalic junction is dysplastic, with abnormal decussation of the superior cerebellar peduncle and elongation of rostral fourth ventricle. There is a decrease in neurons of the basis pontis and reticular formation. In the medulla, the inferior olivary nucleus, tractus solitarius, the nucleus and spinal tracts of trigeminal nerves show evidence of hypoplasia. The posterior median sulcus and pyramidal decussation are not present. Besides, there is neuronal enlargement in the nucleus gracilis and cuneatus [16].

Outcome

Developmental outcome in JS can be divided into three courses: first, children who die young; second, patients who survive but have severe developmental delay and have a variety of visual and motor handicaps; and third, patients whose developmental quotients fall within the mildly delayed range [17].

This syndrome 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 also appear to have decreased survival rates compared with those of patients without retinal dystrophy [14]. There is no evidence of retinal disease on ophthalmological examination in our patient.

Monitoring

Once a diagnosis of JS is made in one neonate or an infant, the diagnosis of this syndrome can be made by looking for the specific imaging findings at ultrasound during a subsequent pregnancy [18]. Renal and retinal dysfunction can be progressive. In patients with retinal anomalies, the renal function should be monitored regularly and ultrasonography should be done to detect cystic renal disease [14]. Finally, the diagnosis is important for future procedures that require anesthesia. These patients are sensitive to respiratory depressant effects of anesthetic agents like opiates and nitrous oxide. Hence, the use of these anesthetic agents should be avoided in these patients [19].

CONCLUSION

Joubert syndrome is an uncommon AR inherited condition. Delayed diagnosis is usually related to its variable, nonspecific presentation. Awareness of the characteristic clinical and radiological findings in JS will help in early diagnosis, appropriate counseling and proper rehabilitation. Any child with static developmental delay with ataxia and characteristic MRI features, JS should be suspected. In our case, the child had characteristic oculomotor signs and imaging findings that pointed toward this rare syndrome.

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