

Joubert Syndrome: Reports of Two Cases

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Abstract:

Joubert syndrome related disorder (JSRD) is an autosomal recessive disorder characterized by hypotonia, abnormal eye movement, ataxia and breathing disturbance. The hall mark of the disease is the presence of molar tooth malformation in magnetic resonance imaging (MRI) of brain. Diagnosis of JSRD is based on clinical and neuro-radiological findings. Early and accurate diagnosis can help in planning the early intervention measures to reduce morbidity. Here, we report two cases. The first case, a 15 month old

female baby, presented with hypotonia, polydactyly and seizure with molar tooth sign (MTS) in the MRI of brain. The second case, a three and a half-year-old child presented with developmental delay, hypotonia, abnormal eye movement, seizure and classical MTS in MRI of brain.

Key words: Joubert syndrome, molar tooth sign, neuro-radiological findings.

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Introduction:

Joubert syndrome (JS) is a rare genetic, heterogeneously inherited disorder, named after Marie Joubert in 1969.¹⁻³ JS is an autosomal recessive or rarely x-linked congenital abnormality of cerebellar vermis and brain stem that is characterized by episodes of abnormal respiratory pattern, oculomotor findings, hypotonia, ataxia, developmental retardation with evidence of neuropathologic abnormalities of cerebellum and brainstem.^{4,5} This clinical entity is underreported with a prevalence of less than 1 in 100,000. Only about 200 cases have been reported worldwide.⁶ Because of its non-specific clinical presentation, its correct diagnosis is usually not made for a long period, up to years after birth, even though the clinical features are present very early in life.^{7,8} Most children with this syndrome survive infancy to reach adulthood. Here, we present two such cases.

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Case Reports:

Case 1

A 15 month-old female baby, 2nd issue of consanguineous marriage, born at term with birth weight 3.5kg, had history of perinatal asphyxia that required hospitalization, presented with development delay and abnormal eye movements since birth, followed by nodding of head from 2 months of age. Abnormal eye movements were noted shortly after birth, characterized by episodic, alternating, lateral extreme gaze which last for few seconds. The movements were not accompanied by any change in body activity and were present throughout the day. There was no history of seizures and feeding or swallowing difficulty and there was no family history of neurologic or genetic problems.

On examination, the baby had facial dysmorphism in the form of prominent forehead, high rounded eyebrows, low set ears, depressed nasal bridge, hypertelorism, polydactyly of both feet and hands (Figure 1A), horizontal nystagmus with titubation and the occipitofrontal circumference (OFC) was normal. Neurological examination showed generalized hypotonia with preserved tendon reflexes, with motor developmental age of 4 months. Other domains of development, including speech and cognitive delay were present. Eye examination revealed pigmentary retinal changes. Examination of the cranial nerves were normal. Rest of the systemic examination was normal.

Complete blood count and routine biochemical tests were within normal ranges. Magnetic resonance imaging (MRI) of brain revealed disorganized cerebellar vermis with thickened superior cerebellar peduncles around the 4th ventricle forming the classical molar tooth sign MTS (Figure 1B). The more caudal T1 and T2-weighted axial images showed the fourth ventricle shaped like a bat wing

(Figure 1C). Chromosomal study showed a normal karyotype (46, XX). Genetic analysis was not done for this child.

Based on clinical and MRI findings, diagnosis of JS related disorders (JSRD) was made and parents were counseled. On follow-up at 12 months of age, patient was able to sit without support.

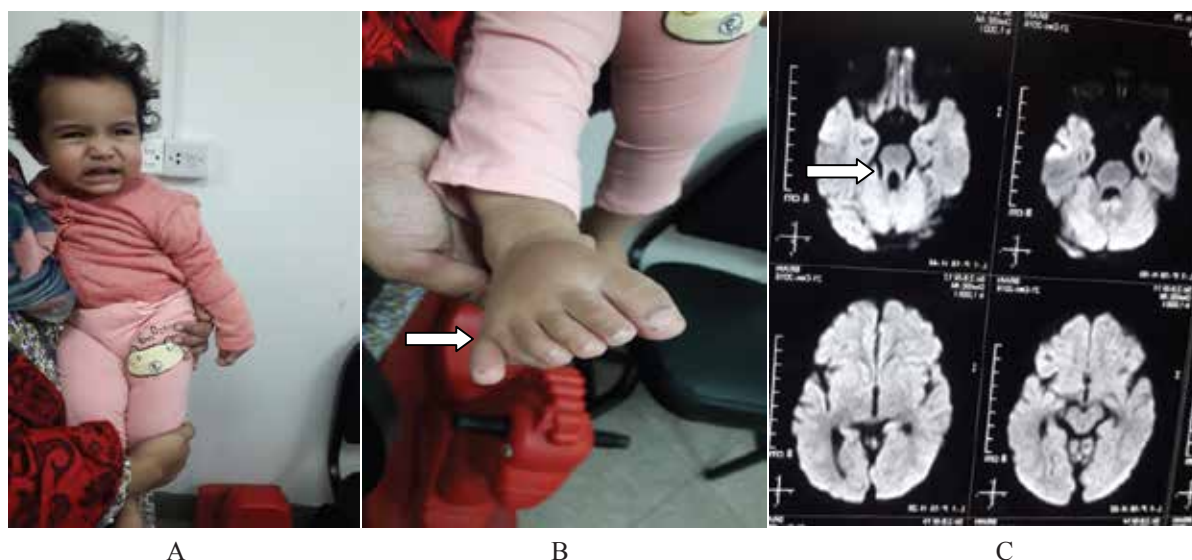


Figure 1. Facial dysmorphism (A) and polydactyly in right foot (B) of a patient with Joubert syndrome. MRI of brain T1 image showing molar tooth malformation in coronal section (C)

Case 2

A three and a half-year-old boy, 3rd issue of consanguineous parents, got admitted with the complaints of inability to stand without support (Figure 2A). He was born at term by Cesarean section with average birth weight. He did not cry immediately after birth and developed neonatal seizure characterized by facial muscle twitching, eye blinking, for which he had been admitted into neonatal intensive care unit (NICU) for 7 days. Subsequently, he developed recurrent episodes of seizures and treated by registered physician but seizures did not subside completely.

There was no history of neonatal sepsis, jaundice, any trauma and abnormal urine or body odor. He developed neck control at 1 year of age and could sit at 2 years of age but could not stand without support and holding anything. He had no startle response to sound, could not fix and follow but could say few

bi-syllable words. Mother gave history of two abortions, another baby is healthy.

On examination, patient was alert but abnormal, intermittent eye movements to extremes of gaze were noted. Vitals were normal. Cranial nerves were intact. The child had global hypotonia, muscle power 3/5, normal tendon reflexes with bilateral flexor plantar response. There was no involuntary movement. Gait could not be elicited.

The child was evaluated by electroencephalogram (EEG), basic metabolic screening, TMS, GCMS and all were found normal but MRI of brain revealed hypoplasia of cerebellar vermis, bird beak appearance (Figure 2B) and abnormally thick horizontal enlarged superior cerebellar peduncles and the characteristic molar tooth appearance of the midbrain on axial views (Figure 2C). So, clinical and radiological diagnosis was JS.



Figure 2. (A) Photograph of patient with Joubert syndrome. (B) MRI of brain T1 image showed bird's beak appearance in mid brain (axial view) and molar tooth malformation (MTM) in coronal section (C).

Then, we searched for associated anomalies and an abdominal ultrasound was negative for kidney and liver involvement, ophthalmological evaluation showed decreased visual acuity, but normal optic disc. There was moderate hearing impairment. Genetic analysis was not done and bone scan showed metaphyseal bony over growth. The patient was managed with genetic counseling, physiotherapy and visual stimulation.

Discussion:

JS is disorder of brain development, characterized by the absence or underdevelopment of the cerebellar vermis and a malformed brain stem. Together, these cause the characteristic appearance of a molar tooth sign in MRI of brain. JS may be caused by mutations in any of many genes.⁹ Ten genes have been identified that cause JS. A mutation in the AHI1 (JBTS3) gene is responsible for this condition in approximately 11% of families. A mutation in the NPHP1 (JBTS4) gene causes approximately 1-2% of JS. A mutation in the CEP290 (JBTS5) gene causes about 4-10% of JS. Mutations in the TMEM67 (JBTS6), JBTS1, JBTS2, JBTS7, JBTS8 and JBTS9 genes are also associated with JS. Other genes responsible for this condition are currently unknown.¹⁰ Maria et al reported 33 months as an average age for its diagnosis.¹¹

This syndrome is characterized by hypotonia, congenital ataxia, developmental delay and at

least one of the following supportive features: neonatal respiratory abnormalities and abnormal oculomotor movements. Abnormal eye movements are characterized by nystagmus and oculomotor apraxia.^{12,13} Both of the cases presented here had abnormal eye movement. Typical dysmorphic features (hypertelorism, small ear lobes, broad forehead, arched eyebrows, broad mouth with intermittent tongue protrusion, ptosis and anteverted nostrils) are present in most of the cases of JS.^{12,14} In our first case, facial dysmorphism was present in the form of prominent forehead, high rounded eyebrows, low set ears, depressed nasal bridge and hypertelorism. Hypotonia is an important associated feature in this syndrome.^{12,14} In our report, both patients presented with hypotonia. Respiratory manifestations are characterized by alternating episodic attacks of hyperpnoea and central apnea or episodic hyperpnoea alone, which intensifies when the patient is stimulated. It starts typically in the neonatal period, gradually diminishes with age and disappears around the 6th month of life.¹³ Ergun et al reported persistence of the respiratory symptoms till the age of 17 years.¹³ The severity of respiratory irregularities can range from mild to severe and prolonged attacks of apnea.¹⁵ The similarity in clinical and radiological aspects between JS and both hypotonic cerebral palsy and

rhombencephalosynapsiscan lead to delayed or erroneous diagnosis.¹⁴ Characteristic radiological findings in computed tomography (CT) and MRI can help to guide and establish the diagnosis of JS. The molar tooth sign is an essential part in the diagnosis of JS and JSRD.¹³ In our both cases, neuro-radiological findings had MTM.

From radiologic point of view, the features necessary for a diagnosis of JS are the MTS on axial views from cranial MRI studies composed of three main findings: cerebellar vermis hypoplasia, deepened interpeduncular fossa and thick, horizontal enlarged superior cerebellar peduncles.⁶ Cerebellar vermis hypoplasia had been reported as a component of other disorders like trisomy 21, occipital encephalocele and Dandy Walker malformation.^{14,16}

JS is classified into two main types, pure JS and JSRD. The term JSRD refers to a group of disorders presenting the pathognomonic features of JS in association with multiple systemic congenital abnormalities. The prevalence of multicystic renal disease and lower survival rate are more observed among patients with retinal dystrophy in patients with JS.¹⁷

Prenatal diagnosis of JS has been documented by others^{14,18} and the ultrasonographic findings showed increased nuchal translucency. The prognosis of JS cases is not bad, if discovered and managed early through implementing an intervention program for patients including special education, occupational, physical and speech therapy. This program has shown significant benefits in advancement of developmental milestones for several patients with JS.¹⁹ The most prevalent causes of death were respiratory failure particularly in individuals younger than 6 years and kidney failure which is more common in older individuals.²⁰

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