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Case Report

Joubert syndrome related disorder (JSRD): a case report and review of literature

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ABSTRACT

Joubert syndrome and related disorder (JSRD) is a rare disorder of midline structure of brain having characteristic clinical and neuro-radiological findings. The hallmark of diagnosis is molar tooth sign (MTS). Early accurate diagnosis can help in planning early intervention measures to reduce the morbidity. We are hereby presenting a case of eight months old female infant with abnormal eye movements since birth along with developmental delay. Clinical and radiological evidence proved that child is having Joubert syndrome related disorder.

Keywords: Joubert, MTS, Polydactyly

INTRODUCTION

Joubert syndrome (JS) is an autosomal recessive or 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.[1,2] This clinical entity is underreported with a prevalence of less than 1 in 100,000. Only about 200 cases have been reported worldwide.[3] 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]

The average age at diagnosis is 33 months.[4] Recent studies have concluded that it is a genetically heterogenous disorder with one locus mapping to chromosome 9q (3,4).[5] Ten causative genes have been recognized so far, every single one encoding for proteins of the primary cilium or the centrosome, making JSRD part of an expanding group of diseases called "ciliopathies".[6,7] The importance of early detection of the syndrome is stressed so that early intervention can be started as early as possible. Here we present a case of JSRD along with comprehensive review of literature.

CASE REPORT

A 8-month-old female infant born at term, out of non-consanguineous marriage with uneventful perinatal and neonatal period, presented with development delay and abnormal eye movements since birth, followed by nodding of head since 2 months. Abnormal eye movements were noted shortly after birth and involved episodic deviation to lateral extremes of gaze, usually alternating and lasting for a few seconds. The movements were not accompanied by any change in color and activity and were present throughout the day. There was no history of seizures and feeding or swallowing difficulty. There was no history of neurologic or genetic problems in other family members.

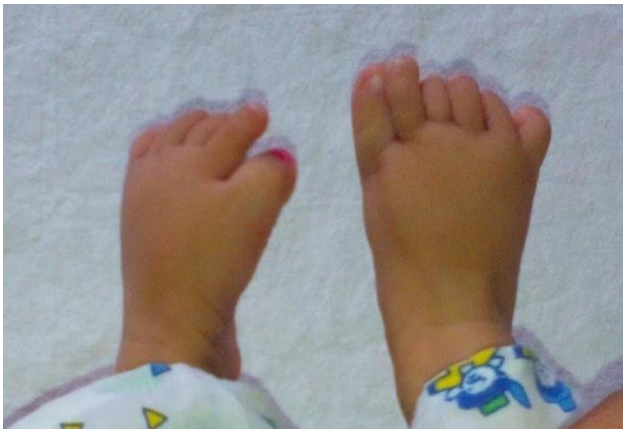

Figure 1: Polydactyly.

On examination infant had facial dysmorphism in the form of prominent forehead, high rounded eyebrows, low set ears, depressed nasal bridge, hypertelorism, polydactyly both feet and hands (Figure 1), horizontal nystagmus with titubation. Neurological examination showed generalized hypotonia with preserved tendon reflexes with developmental age of 4 months. Eye examination revealed pigmentary retinal changes. Examination of the cranial nerves was normal. Rest of the systemic examination was normal.

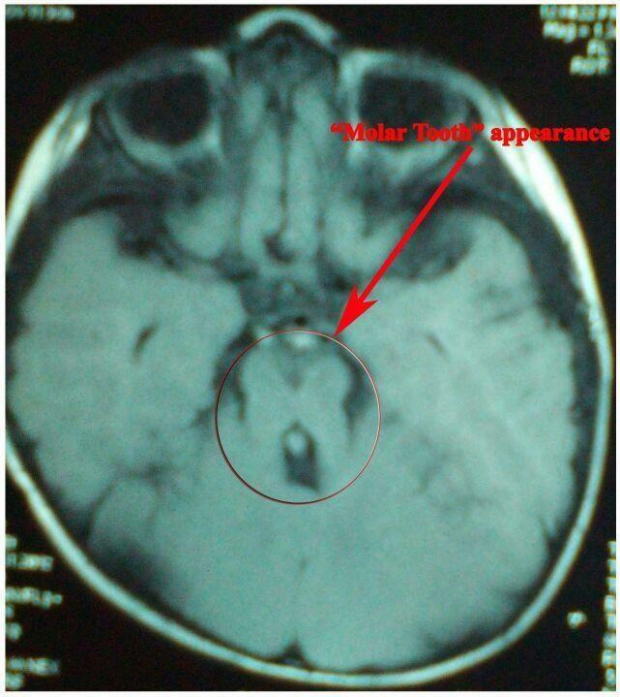

Figure 2. MRI brain showing deepening of the interpeduncular fossa, thickening of superior cerebellar peduncles and aplasia of vermis: "molar tooth appearance."

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 2) The more caudal T1- and T2-weighted axial MR images showed the fourth ventricle shaped like a bat wing (Figure 3). A Chromosomal study showed a normal karyotype (46, XY). Based on clinical and magnetic resonance imaging (MRI) findings, diagnosis of JSRD was made and parents were counselled. On Follow-up at 12 months of age patient was able to sit without support.

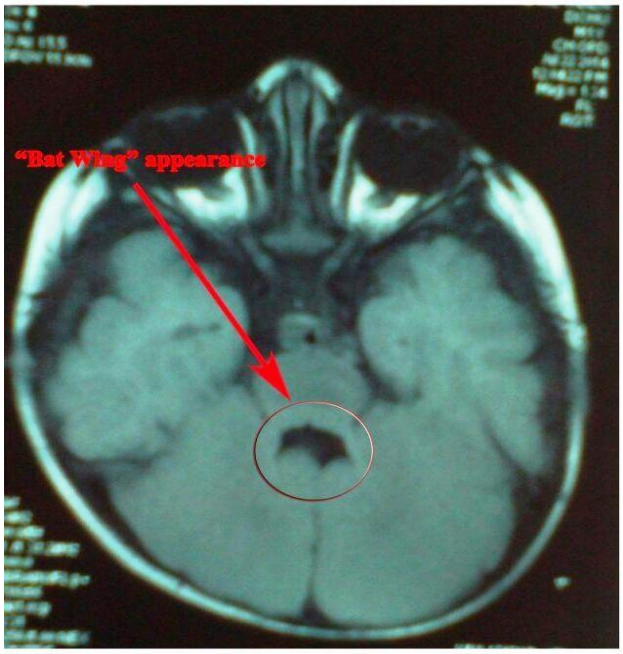

Figure 3: MR Brain showing "bat wing appearance" of 4th ventricle.

DISCUSSION

JS is a rare autosomal recessive disorder of characteristic clinical and neuroradiological findings of midline structures of the brain-stem.[8] Neuropathological studies reveal agenesis of cerebellar vermis, hypo-plasia or fragmentation of several brainstem nuclei and dysplasia of structures at the ponto-mesencephalic junction. Extensive brainstem malformation explains the oculomotor apraxia and hyperpnea; anomalies of the gracile nuclei and solitary tract are thought to contribute to the abnormal respiratory pattern.[9] The breathing pattern in Joubert syndrome is effortless hyperventilation (upto 200 breaths/min) which is more conspicuous in awake state and intensifies when the patient is stimulated, interspersed with central apnea.

The neuroradiological hallmark of Joubert syndrome is the characteristic MTS visible on axial MRI films. The hallmark imaging features of JS are:

- Dysgenesis of the isthmus, thinning of ponto mesencephalic junction, and deep interpeduncular fossa
- Thickening of superior cerebellar peduncles

- Hypo-plasia of vermis characterized by incomplete lobulation and enlarged fourth ventricles
- Incomplete fusion of the halves of the vermis creating a sagittal vermis cleft.

Combination of the first 3 features produces the characteristic MTS.[10] Pathological evidence shows that there is 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. Moderate lateral ventricular enlargement due to atrophy has been described in 6–20% of cases. Many authors have reported the prevalence of some of these associated findings, which include polydactyly (8%), ocular coloboma (4%), and hamartomas of the tongue (2%), dysmorphic facies, microcephaly, tongue protrusion, multicystic kidney disease, congenital heart disease, unsegmented midbrain tectum, retinal dystrophy and agenesis of the corpus callosum.[11-13] Patients with retinal dystrophy have a higher prevalence of multicystic renal disease and these patients also appear to have decreased survival rates.

Table 1: Classification of JSRD.

Classification of JSRD	
Pure JS	Apart from MTS, patients display the cardinal neurological findings of hypotonia/ataxia and developmental delay, variably associated with irregular breathing, abnormal eye movements and intellectual disability. There is no retinal, renal or liver involvement. No major gene has been associated with this phenotype, but occasional mutations in several genes have been reported.
JS with ocular defect (JS-O)	The neurological features of JS are present in association to retinal dystrophy (including LCA) with variable age at onset, progression and severity. To date, the most frequently mutated gene in this subgroup is AHI1, which accounts for about 20% of cases.
JS with renal defect (JS-R)	Neurological signs of JS are associated with renal disease, which is in most cases juvenile NPH, in the absence of retinal involvement. The two genes most commonly mutated in this rare phenotype are NPHP1 and RPGRIP1L.
JS with oculorenal defects (JS-OR)	This form is characterized by the association of neurological signs of JS with both retinal dystrophy and NPH. About 50% of patients carry mutations in the CEP290gene.
JS with hepatic defect (JS-H)	This subgroup presents the association of JS with CHF. Chorioretinal or optic nerve colobomas and NPH can be part of the phenotype but are not mandatory features. Over 70% of cases are due to mutations in the TMEM67gene.
JS with oro-facio-digital defects (JS-OFD)	In this subgroup, JS features are associated to bifid or lobulated tongue, multiple oral frenulae and polydactyly, that is usually mesaxial, with Y-shaped metacarpals. Hypothalamic hamartoma or congenital absence of the pituitary gland can be part of this spectrum. This phenotype has been recently associated with mutations in the TMEM216 gene

The subtypes of JS termed as Joubert syndrome and related disorders (JSRD). JSRD are categorized into six phenotypic subgroups (Table 1).

Besides JS, cerebellar vermian anomalies have been reported with other disorders, such as Dandy-Walker syndrome and rhombencephalosynapsis. In Dandy-Walker malformation, the inferior part of the vermis is hypoplastic. However, the fourth ventricle is enlarged and communicates with a cyst in the posterior fossa. In addition, the ponto-mesencephalic junction, 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.[14]

There are syndromes such as the COACH, Varadi-Papp, Dekaban-Arima, Senior-Loken, Joubert with polymicrogyria, and Malta syndromes where MTS and other features of JS may be seen. Patients with COACH syndrome have bilateral coloboma, hepatic fibrosis and renal calcification, and in the Varadi-Papp syndrome there is mesaxial polydactyly, Y-shaped metacarpal, cleft lip or cleft palate, lingual hamartomas and vermian hypoplasia. The Dekaban-Arima syndrome is allied with Leber's congenital amaurosis and cystic dysplastic kidneys, whereas the Senior-Loken syndrome is related with Leber's congenital amaurosis, retinitis pigmentosa and juvenile nephronophthisis. In the Malta syndrome, these patients have the molar tooth sign, occipital encephalocele, hydrocephalus, cortical renal cysts with or without coloboma, and Leber's congenital amaurosis. Few patients can have features of JS and polymicrogyria.[15,16] Our patient showed clinical signs of dysmorphism, polydactyly, developmental delay and characteristic radiological evidence of MTS along with bat wing appearance of fourth ventricle hence managed on the line of JSRD with subtype of JS with oro-facio-digital defects (JS-OFD).

Developmental outcome in JSRD is variable. Outcomes in JSRD 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 IQ range of 70-80.

Diagnosis of JSRD should be followed by a protocol to assess the possible multiorgan involvement. Ocular investigations include evaluation of visual acuity, ocular motility, fundus oculi, slit lamp examination and electroretinogram. Kidney and liver function should be tested. Standard urine analysis along with urine specific gravity along with a challenge test to assess urinary concentration ability is recommended. Abdominal ultrasound will explore the kidneys for cystic renal disease, and the liver. In patients with retinal anomalies, the renal function should be monitored regularly. The diagnosis is important for future procedures that require anaesthesia. These patients are sensitive to respiratory depressant effects of anaesthetic agents like opiates and nitrous oxide. Hence, the use of these anaesthetic agents should be avoided in these patients. Prognosis of this disease is usually poor with hypotonia and severe developmental delay. Determination of the symptoms, early diagnosis and genetic consultation are the goals for decision-making to begin treatment and rehabilitation programs.

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REFERENCES

1. Singh P, Goraya JS, Saggar K, Ahluwalia A. A report of Joubert syndrome in an infant, with literature review. J Pediatr Neurosci. 2011;6(1):44-7.
2. Joubert M, Eisenring JJ, Robb JP, Andermann F. Familial agenesis of the cerebellar vermis. A syndrome of episodic hyperpnea, abnormal eye movements, ataxia and retardation. Neurol. 1969;19:813-25.
3. Choh SA, Choh NA, Bhat SA, Jehangir M. MRI findings in Joubert syndrome. Indian J Pediatr. 2009;76:231-5.
4. Akcakus M, Gunes T, Kumandas S, Kurtoglu S, Coskun A. Joubert syndrome: Report of a neonatal case. Paediatr Child Health. 2003;8:499-502.
5. Saar K, Al-Gazali L, Sztriha L, Rueschendorf F, Nur-E-Kamal M, Reis A, et al. Homo-zygosity mapping in families with Joubert syndrome identifies a locus on chromosome 9q34.3 and evidence for genetic heterogeneity. Am J Hum Genet. 1999;65:1666-7.
6. Brancati F, Dallapiccola B, Valente EM. Joubert Syndrome and related disorders. Orphanet J Rare Dis. 2010;5:20.
7. Radheshyam P, Rajarshi B, Rituparna D, Uttara C. Association of Joubert syndrome and Hirschsprung disease. Pediatr. 2015;52:61-2.
8. Saraiva JM, Baraitser M. Joubert syndrome: A review. Am J Med Genet. 1992;43:726-31.
9. Kendall B, Kingsley D, Lambert SR, Taylor D, Finn P. Joubert syndrome: a clinico-radiological study. Neuroradiol. 1990;31:502-6.
10. Egger J, Bellman MH, Ross EM, Baraitser M. Joubert-Boltshauser syndrome with polydactyly in siblings. J Neurol Neurosurg Psychiatry. 1982;45:737-9.
11. Aslan H, Ulker V, Gulcan EM, Numanoglu C, Gul A, Agar M, et al. Prenatal diagnosis of Joubert syndrome: a case report. Prenat Diagn. 2002;22:13-6.
12. Chance PF, Cavalier L, Satran D, Pellegrino JE, Koenig M, Dobyns WB. Clinical nosologic and genetic aspects of Joubert and related syndromes. J Child Neurol. 1999;14:660-6.
13. Maria BL, Hoang KB, Tusa RJ, Mancuso AA, Hamed LM, Quisling RG, et al. Joubert syndrome revisited: key ocular motor signs with magnetic resonance imaging correlation. J Child Neurol. 1997;12:423-30.
14. Van Beek EJ, Majoie CB. Case 25: Joubert syndrome. Radiol. 2000;216:379-82.
15. Gleeson JG, Keeler LC, Parisi MA, Marsh SE, Chance PF, Glass IA, et al. Molar tooth sign of the midbrain-hindbrain junction: Occurrence in multiple distinct syndromes. Am J Med Genet A. 2004;125A:125-34.
16. Brancati F, Dallapiccola B, Valente EM. Joubert syndrome and related disorders. Orphanet J Rare Dis. 2010;5:20.

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