

Case Report**Joubert Syndrome: A Rare Cause for Developmental Delay**

Authors

**Dr Sivatha Gopinath<sup>\*1</sup>, Dr C.Santhosh<sup>2</sup>, Dr C Sanjeevi<sup>2</sup>, Dr S.Rajadirajan<sup>2</sup>  
Dr S.Sethurajan<sup>2</sup>, Dr M.Sivakolunthu<sup>3</sup>, Dr M.Adaikappan<sup>3</sup>**

<sup>1</sup>Post Graduate RMMCH, Chidambaram, Annamalai University

<sup>2</sup>Assistant professors, RMMCH, Chidambaram, Annamalai University

<sup>3</sup>Professor, RMMCH, Chidambaram, Annamalai University

**ABSTRACT**

*Joubert syndrome (JS) is a very rare autosomal recessive condition. It is a complex mid and hind brain malformations that resembles a molar tooth on axial MR scans. The importance of recognising JS is related to the outcome and its potential complications. We have diagnosed a case of JS in a female infant with delayed motor milestones, abnormal eye and head movements and a generalised hypotonia.*

**Keywords:** Joubert syndrome, Molar tooth sign, Vermian agenesis.

**INTRODUCTION**

Joubert syndrome first described by a French neurologist in 1969 and named after him. It is characterised by episodes of abnormal respiratory patterns, oculomotor findings, hypotonia, ataxia, developmental retardation with evidence of neuropathologic abnormalities of cerebellum and brainstem. The estimated incidence rate is 1 in 80,000 to 1 in 1,00,000 live births.<sup>(1)</sup>

**CASE REPORT**

A 6 month old female baby with history of delayed developmental milestones, seizures, nystagmus and ataxic movements was referred to our department for cranial magnetic resonance imaging (MRI) study. She was the third child of a second degree consanguineous marriage. She was delivered by normal vaginal delivery with birth weight 3 kg and had birth asphyxia with NICU admission for 7 days. Baby has delayed motor

mile stones, abnormal eye movements with tongue protrusion (Figure1) and seizures. Her mother noticed feeding difficulties and frequent chest infections of her baby. She also noticed abnormal head nodding and peculiar eye movements with paucity of movements of limbs.



**Figure 1:** Joubert syndrome baby showing ataxic limb with protruded tongue.

Physical examination revealed a hypotonic child with abnormal head nodding and eye movements.

Head circumference and other anthropometric measurements were normal. Echocardiogram showed Atrial septal defect (Ostium primum). Ophthalmic examination showed bilateral divergent squint, inability to follow moving object, restricted upward gaze of eye and bilateral horizontal gaze evoked nystagmus. Ophthalmoscopic examination was normal.

### IMAGING FINDINGS

Axial T1 and T2 weighted magnetic resonance imaging (MRI) images showed hypoplastic cerebellar vermis with thickened superior cerebellar peduncles around an elongated batwing shaped fourth ventricle forming the classic “molar tooth sign” in the midbrain (Figure 2).



**Figure 2:** Axial T2 weighted showing molar tooth sign in midbrain.

Sagittal T2 weighted image shows small vermis with flat IV<sup>th</sup> ventricle roof and a rounded fastigium. The supratentorial cerebral hemisphere appear normal (Figure 3). Renal ultrasound showed no abnormality.



**Figure 3:** Sagittal T1 weighted image shows flat fourth ventricle roof with rounded fastigium.

### DISCUSSION

JS is inherited as an autosomal recessive disorder with both parents being 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.

There are six major phenotypes in Joubert syndrome related disorders (JSRD). They typically present in infancy and childhood with developmental delay, ataxia, oculomotor and respiratory abnormalities. In the syndrome, midline structures of the brain stem have both anatomic and functional defects. Neuropathological studies reveal agenesis of cerebellar vermis, malformations of several brainstem nuclei and dysplasia of structures at the ponto mesencephalic junction.

MR imaging is the cornerstone in establishing the diagnosis. Midline sagittal scans shows a small dysmorphic vermis. The fourth ventricle appears deformed with a thin upwardly convex roof and loss of normal pointed fastigium. Axial scans demonstrate foreshortened midbrain, narrow isthmus, deep interpeduncular fossa, thickened superior cerebellar peduncles (SCP), surrounding an batwing shaped IV ventricle. The superior vermis is clefted and cistern magna appear enlarged.

DTI imaging shows fibres of SCP do not decussate in the mesencephalon and that the corticospinal tracts fail to cross in the caudal medulla. Extensive brain stem malformation could explain the oculomotor apraxia and hyperpnea. Anomalies of the gracile nuclei and solitary tract are thought to contribute to the abnormal respiratory pattern. Hypotonia and mental retardation are nonvariable features of JS.

Kidney involvement may occur in the form of cystic dysplasia, juvenile nephronophthiasis and tubulointerstitial nephritis. Other important features are congenital hepatic fibrosis, polydactyly and thyroid hormone dysfunction.<sup>(2)</sup> Eye involvement may range from congenital

blindness to retinal dystrophy and unilateral or bilateral coloboma of retinal pigment epithelium. This multiorgan involvement and pleomorphic character is probably due to its genetic foci. At least 10 genes have been identified to be causative of JS related disorder like 1NPPSW, NPHPS, AH1, CEP290 and 1CC2D2A.<sup>(3,4)</sup> All these genes code for protein of primary cilium.

Defective cilia are malfunctioning in the retina, renal tubule and neural cell migration thus producing heterogenous syndrome complex known as “ciliopathies”. Other ciliopathies like senior Lokes syndrome, Bardet Biedl syndrome and isolated nephronophthisis must be considered as the differential diagnosis of JS.

Molar tooth sign is not specific for JS. This may be seen in varadi popp syndrome, Malta syndrome, senior loken syndrome and COACH syndrome.<sup>(5)</sup> Developmental delay and hypotonia should be present with either abnormal breathing movements or eye movements plus molar tooth midbrain leads to a diagnosis of JS.

The importance of recognising JS is related to its outcome. Retinal dysplasia is highly correlated with renal cystic disease and seems to carry a worse prognosis in terms of survival. Therefore regular ocular screening should be performed. In patients with retinal anomalies, it is also advisable to monitor renal function and perform ultrasound of the kidneys to detect cystic renal disease.

Patients with JS are extremely sensitive to the respiratory depressant effects of anesthetic agents such as opioids and NO and susceptible to post op respiratory infection.<sup>(6)</sup> Therefore these agents should be avoided and close perioperative respiratory monitoring and care are essential. Genetic counselling is important in a family history of JS. Mutation screening of known gene mutation can pick up less than 50% of the cases. Further, antenatal US of fetal brain should be done in subsequent pregnancy.

## REFERENCES

1. Parisi MA, Doherty D, Chance PF, Glass IA. Joubert syndrome (and related disorders) (OMIM 213300) Eur J Hum Genet. 2007;15:511–21.
2. Parisi MA. Clinical and molecular features of Joubert syndrome and related disorders. Am J Med Genet C Semin Med Genet. 2009;151C:326–40.
3. Parisi MA. Clinical and molecular features of Joubert syndrome and related disorders. Am J Med Genet C Semin Med Genet. 2009;151C:326–40.
4. Castori M, Valente EM, Donati MA, Salvi S, Fazzi E, Procopio E, et al. NPHP1 gene deletion is a rare cause of Joubert syndrome related disorders. J Med Genet. 2005; 42:e9.
5. Brancati F, Dallapiccola B, Valente EM. Joubert Syndrome and related disorders. Orphanet J Rare Dis. 2010; 5:20.
6. Christina J, Steven MN. Anesthesia for a Patient with Joubert Syndrome Presenting for MRI of a Transplanted Kidney. The Internet Journal of Anesthesiology. 2007; 14 Number 1. DOI: 10.5580/22bd.