

Prakash Kafle

MS, MCh Neurosurgery
Department of Neurosurgery,
Nobel Medical College & Teaching Hospital,
Kathmandu Nepal

Sushil Krishna Shilpakar

MS Neurosurgery
Professor of Neurosurgery,
HOD, Department of Neurosurgery,
Institute of Medicine, TU Teaching Hospital,
Kathmandu Nepal

Mohan Raj Sharma

MS Neurosurgery
Professor of Neurosurgery
Department of Neurosurgery
Institute of Medicine, TU Teaching Hospital,
Kathmandu Nepal

Gopal Sedain

MS, MCh Neurosurgery
Assistant Professor of Neurosurgery
Department of Neurosurgery,
Institute of Medicine, TU Teaching Hospital,
Kathmandu Nepal

Amit K Pradhanang

MS MCh Neurosurgery
Assistant Professor of Neurosurgery
Department of Neurosurgery
Institute of Medicine, TU Teaching Hospital,
Kathmandu Nepal

Binod Raj bhandari

MBBS, MS
MCh Neurosurgery Resident
Department of Neurosurgery, TUTH

Address for correspondence:

Dr. Gopal Sedain
MS MCh Neurosurgery
Assistant Professor of Neurosurgery
IOM, TUTH, Kathmandu Nepal
Email: neuron79@gmail.com

Date received: 16/3/18

Date accepted: 27/4/18

Joubert syndrome is a rare autosomal recessive genetic neurodevelopmental disorder that affects the area of brain that controls balance and coordination.⁶ The common typical clinical manifestations are abnormal respiratory pattern (hyper apnea), oculomotor findings, low muscle tone (hypotonia), lack of muscle control (ataxia), developmental retardation with evidence of neuropathologic abnormalities of cerebellum and

Joubert Syndrome: A Case Report

Joubert syndrome (JS) is a rare autosomal recessive neurodevelopmental disorder involving cerebellar vermis and brainstem, marked by agenesis of cerebellar vermis, ataxia, hypotonia, oculomotor apraxia, neonatal breathing problems and mental retardation. Magnetic Resonance Imaging (MRI) reveals the characteristic *Molar tooth* sign of midbrain and *Batwing* appearance of rostral fourth ventricle.

Key Words: Joubert syndrome, hypotonia, vermian agenesis, molar tooth sign, bat wing appearance

brainstem.⁸ Historically, it was first described by Dr Marie Joubert, French Neurologist in 1969. She described four siblings with cognitive impairment, ataxia, episodic tachypnea, eye movement abnormalities, and cerebellar vermian agenesis in a large French-Canadian family with consanguinity traced 11 generations to a common ancestor. This disorder is characterized by congenital malformation of the hindbrain and a broad spectrum of other phenotypic



Figure 1.A: Baby with Joubert Syndrome

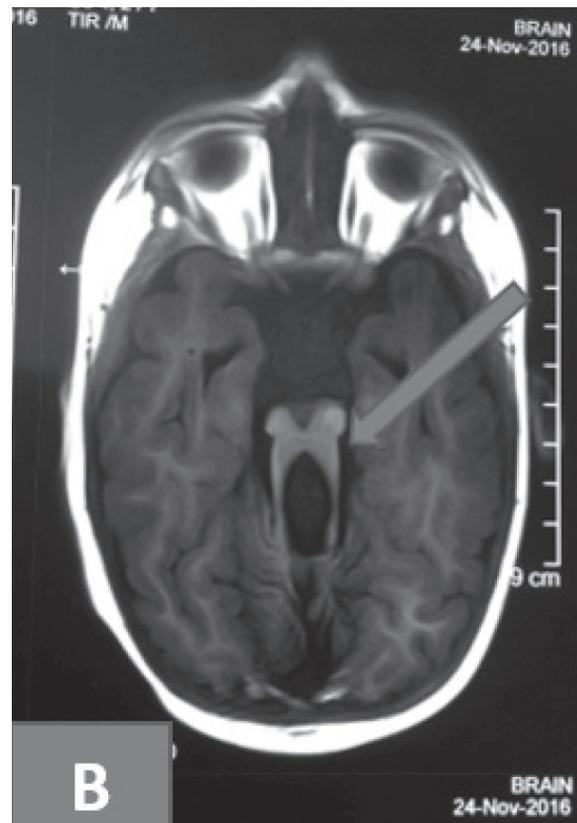


Figure 1.B: The Molar tooth sign appearance of Ponto cephalic junction. Arrow head.

findings which are now known to be caused by defects in the structure and/or function of the primary cilium.¹²

The incidence of JS has been estimated to be between 1/80,000 and 1/100,000 live births.⁷ It is a condition with a variable phenotype making it difficult to establish the full clinical diagnostic spectrum of symptoms 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.¹ The average age at diagnosis is 33 months.¹⁰ The importance of early detection of the syndrome is emphasized; so that suitable measures can be started as early as possible. Many children with JS exhibit dysmorphic facial features that include broad forehead, arched eyebrows, eyelid ptosis, wide-spaced eyes, open-mouth configuration and facial hypotonia.¹¹

The clinical course can be variable; but most children with this disorder survive infancy to reach adulthood. We report a case of Joubert syndrome who presented with delayed developmental milestones, abnormal body posture, hypotonia and typically demonstrating diagnostic *Molar tooth* sign (MTS) and *Batwing* appearance on Magnetic resonance imaging (MRI) in which the

cerebellar vermis of the brain is underdeveloped and the brain stem is abnormal.

Case Detail

A 3-year-old male child was brought to the Neurosurgical Out-Patient Clinic by his parents with chief complaints of delayed developmental milestones and growth retardation, difficulty in holding his head and abnormal movements. The boy was only able to sit, walk and speak at 15, 28 and 48 months respectively which indicated significant delay in developmental milestone. There was no abnormal antenatal history. The child was delivered in a local hospital at term via normal vaginal route. There was no significant perinatal period. He had seizure attacks soon after birth and has been under anticonvulsant medication ever since. His parents had no history of consanguinous marriage.

The boy was restless and abnormally moving his head to and fro. On physical examination, he was hypotonic; but had no dysmorphic facial features. Head circumference was within normal range for age. There were no abnormalities detected on cardiovascular and respiratory system examinations. Similarly, gastrointestinal and genitourinary

system revealed normal findings. His picture is as shown in (Figure 1.A).

Routine hematology, urinalysis, echocardiography and thyroid function tests were all unremarkable.

MRI scan of brain revealed small brainstem with volume loss involving the left half of brainstem and hypoplastic cerebellar vermis. The Molar tooth sign appearance of pontocephalic junction (Figure 1.B) and Batwing appearance of the rostral fourth ventricle were observed on the scan.

The genetic analysis was not performed however, the parents have been advised for further metabolic and chromosomal study on follow up. At present, the child is on regular follow up in Neurosurgical Out-Patient Clinic.

Discussion:

Joubert syndrome is inherited as a rare autosomal recessive disorder, characterized by a specific congenital malformation of the hindbrain and a broad spectrum of other phenotypic findings.¹² Its association with supratentorial anomalies are uncommon; but cerebral cortical dysplasia and gray matter heterotopias have been reported in the literature.³ Moderate lateral ventricular enlargement due to atrophy has been described in 6–20% of cases.⁹ Many authors have reported the prevalence of some of these associated findings, which include extra fingers and toes - polydactyly (8%), abnormality of iris - ocular coloboma (4%), and hamartomas of the tongue (2%), dysmorphic facies, microcephaly, tongue protrusion, polycystic kidney disease, congenital heart disease, unsegmented midbrain tectum, retinal dystrophy and agenesis of the corpus callosum.⁵ In our case, all these aforementioned associated features were absent, suggestive it to be pure JS.

Though diagnosis of JS is generally based on presence of typical clinical features and the "molar tooth sign" as seen on an MRI, the definitive diagnostic criteria for JS is yet to be established. However, the clinical features frequently considered as essential for the diagnosis of classic JS comprise the following:⁸

1. Hypotonia in infancy.
2. Delayed developmental milestone /mental retardation.
3. One or both of the following:
 - a. Irregular breathing pattern in infancy.
 - b. Abnormal eye movements.

In our case, all of the above features were present except for irregular breathing pattern.

Joubert Syndrome and Related Disease (JSRD) are classified into six phenotypic subgroups: pure JS;

JS with ocular defect; JS with renal defect; JS with oculorenal defects; JS with hepatic defect and JS with orofacioidigital defects.² Our case was consistent with the pure JS phenotypic subgroup.

Important radiological findings of JS include deep interpeduncular fossa, narrow isthmus (the ponto-mesencephalic junction), lack of decussation of superior cerebellar peduncles, dilated, distorted, and rostrally deviated fourth ventricle giving the typical "Batwing" appearance, thick vertical superior cerebellar peduncles, rostral deviation of fastigium of fourth ventricle, wide foramen of Magendie and dysplastic vermis. The brainstem, predominantly the medulla and upper cervical spinal cord, tends to be small. "Molar tooth sign" encompasses deeper than normal posterior interpeduncular fossa, prominent or thickened superior cerebellar peduncles, and vermian hypoplasia or dysplasia.⁹

Genetically, the causative genes have been identified, all encoding for proteins of the primary cilium or the centrosome, making JSRD part of an expanding group of diseases called (Ciliopathies).⁴ Mutations in the AHI1 gene are the cause in 10–15% of the cases. Mutation in the CEP 290 (NPHP6) gene is in 10%. Homozygous deletion of NPHP1 gene is in 1–2%. Fetal ultrasonography may be useful. Fetal MRI is the diagnostic method of choice.² Developmental outcome in JS is variable. Steinlin, *et al*,¹³ suggested that outcomes in JS can be categorized 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 (70–80). Taking into consideration of the neurological deficits, our case belongs to the third subgroup with mildly delayed milestone.

In children with JSRD, managing respiratory and feeding problems related to breathing difficulties and hypotonia must be given utmost priority. Prolonged apnea can be life-threatening. Sometimes, the respiratory abnormalities may resolve spontaneously. Prognosis depends basically on the severity of breathing dysfunction, renal and hepatic complications. After the first months of life, overall prognosis varies considerably among JSRD subgroups, depending on the extent and severity of organ involvement.⁴

Generally, the treatment strategy for JS is symptomatic and supportive. Developmental delays and retardation are usually managed with proper physical therapy, occupational therapy, speech therapy and infant stimulation. Children with JS should be evaluated by numerous specialists on multidisciplinary basis, including nephrologists, ophthalmologists, geneticists and neurologists. Routine

screening is recommended for liver, kidney and retinal abnormalities. Genetic counselling should be recommended for those with JS and their families.

Conclusion:

Joubert syndrome is a rare autosomal recessive neurodevelopmental disorder. Consanguineous marriage carries increased risk. MRI of the brain is diagnostic, demonstrating the characteristic molar tooth appearance of midbrain and bat wing configuration of the rostral fourth ventricle. Patients with JS presents with episodes of abnormal respiratory pattern, oculomotor findings, hypotonia, ataxia, developmental retardation with evidence of neuropathologic abnormalities of cerebellum and brainstem. Diagnosis is based on typical clinicoradiological features. Managing respiratory and feeding problems related to breathing abnormalities or hypotonia should be given the utmost priority. Overall treatment is basically symptomatic and supportive.

References:

1. Akcakus M, Gunes T, Kumandas S, Kurtoglu S, Coskun A. Joubert syndrome: Report of a neonatal case. **Paediatr Child Health** 8:499–502, 2003
2. Adamsbaum C, Moutard ML, André C, Merzoug V, Ferey S, Quéré MP, Lewin F, Fallet-Bianco C. MRI of the fetal posterior fossa. **Pediatr Radiol** 35:124-40, 2005
3. Barkovich AJ. **Pediatric neuroimaging** 2nd ed. New York, NY: Raven; pp. 249–57, 1995
4. Brancati F, Dallapiccola B, Valente EM. Joubert Syndrome and related disorders. **Orphanet J Rare Dis** 5:20, 2010
5. 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** 14:660–6, 1999
6. Edwin JR, van Beek, Charles BLM. Majoie. Case 25: Joubert Syndrome. **Radiology** 216:379–82, 2000
7. Harjinder Gill, Brinda Muthusamy, Denize Atan, Cathy Williams and Matthew Ellis. Joubert Syndrome Presenting with Motor Delay and Oculomotor Apraxia. **Case Reports in Pediatrics** 2011
8. 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. **Neurology** 19:813–25, 1969
9. Kendall B, Kingsley D, Lambert SR, Taylor D, Finn P. Joubert syndrome: A clinico-radiological study. **Neuroradiology** 31:502–6, 1990
10. Maria BL, Quisling RG, Rosainz LC, Yachnis AT, Gitten J, Dede D, et al. Molar tooth sign in Joubert syndrome: Clinical, radiologic, and pathologic significance. **J Child Neurol** 14:368–76, 1999
11. Melissa A. Parisi. Clinical and molecular features of Joubert syndrome and related disorders. **Am J Med Genet C Semin Med Genet** 151: 326–340, 2009
12. Parisi MA. Clinical and molecular features of Joubert syndrome and related disorders. **Am J Med Genet C Semin Med Genet** 151:326-40, 2009
13. Steinlin M, Schmid M, Landau K, Boltshauser E. Follow-up in children with Joubert syndrome. **Neuropediatrics** 28:204–11, 1997