# JOUBERT SYNDROME IN A CHILD WITH CLASSICAL RADIOLOGICAL SIGNS

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**Abstract**
Joubert syndrome (JS) is an uncommon genetically heterogeneous autosomal recessive developmental disease which manifests as hypotonia, delay in gross motor developmental milestones, hypoplastic vermis of cerebellum and malformation of brainstem, episodic tachypnea or apnea, atypical eye movements, truncal ataxia and cognitive or intellectual impairment. MRI being the gold standard revealed the classic Molar Tooth Sign and Bat wing appearance of fourth ventricle. So high suspicion with early detection and genetic counselling play a vital role in this syndrome.
**Keywords**: Joubert syndrome, hypoplastic cerebellar vermis, Molar Tooth Sign, Bat wing sign.

**Introduction**
Joubert syndrome is one of the rarest genetic disorder with the estimated incidence of 1 in 100,000 among which more than 30 genes are heterogeneous autosomal recessive whereas X-linked are thin on the ground.[1] It is named after Dr. Marie Joubert (pediatric neurologist) at Montreal Neurological institute who identified it for the first time in 1969. She was encountered with 4 affected French-Canadian siblings as a result of consanguineous marriage.[2]
Classical type presents with three primary signs which includes hypotonia, delay in gross motor developmental milestones and a distinct cerebellar vermis and brainstem malformation. It is often accompanied by other phenotype findings which are produced due to defects in the structure of primary cilium involving different systems of the body resulting in episodes of tachypnea or apnea, atypical eye movements, **r**etinal dystrophy, truncal ataxia, cognitive/ intellectual impairment, renal disease, occipital encephalocele and hepatic fibrosis.[3] Some of these patients exhibit dysmorphic features of the face which can be broad forehead, arched shaped eyebrows, drooping of the eyelids, hypertelorism, triangular mouth appearance and decreased tone of facial muscles. We present a case report who presented with the following features.

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**Case Report**
A 15-months male child presented to Department of pediatrics complaining of difficulty in holding his head, unable to sit and delay in achieving global developmental milestones of his age. His mother had history of regular normal antenatal checkups and the delivery was made through an uneventful elective caesarian section. His parents had non-consanguineous marriage and had two normal siblings.
On examination, he had globally decreased tone, decreased power and diminished deep tendon reflexes. Rest of the systemic examination were unremarkable including general physical appearance.
Routine baseline investigations including hematology, urine analysis, echocardiography and thyroid function tests were within normal range.
Nerve conduction study showed no evidence of peripheral neuropathy, myopathy or spinal muscular atrophy.
MR imaging of the brain was advised which revealed deepened interpeduncular cleft (red arrow) thickened, elongated superior cerebellar peduncles with a narrow ponto-mesencephalic isthmus looking like a typical Molar tooth on axial images (Figure:1a, b, c & d). Vermian hypoplasia/dysplasia (blue arrow) with distortion and enlargement of the fourth ventricle (yellow arrow) in Figure:2 with 4th ventricle displaying Batwing appearance (Figure-3). Addition findings included FLAIR (fluid attenuated inversion recovery) high signals in centrum semiovale and periventricular locations (Figure-4a & 4b respectively), however diffusion restriction were not seen in these areas on DWI images or corresponding ADC maps (Figure-5). These centrum semiovale and peri-ventricular high signal were given follow up as these could be delayed myelination or pathological findings if

persistent even after 2 years. T1WIIR (T1 weighted inversion recovery) sequence (Figure 5) did not reveal any radiological signs of mesial temporal lobe sclerosis.

Prominent, thickened and elongated superior peduncles of cerebellum with a narrow ponto-mesencephalic isthmus and vermian hypoplasia/dysplasia, distorted and enlarged fourth ventricle giving classical molar tooth and Batwing appearance respectively were consistent with Joubert's syndrome.

The genetic analysis was advised for further workup.

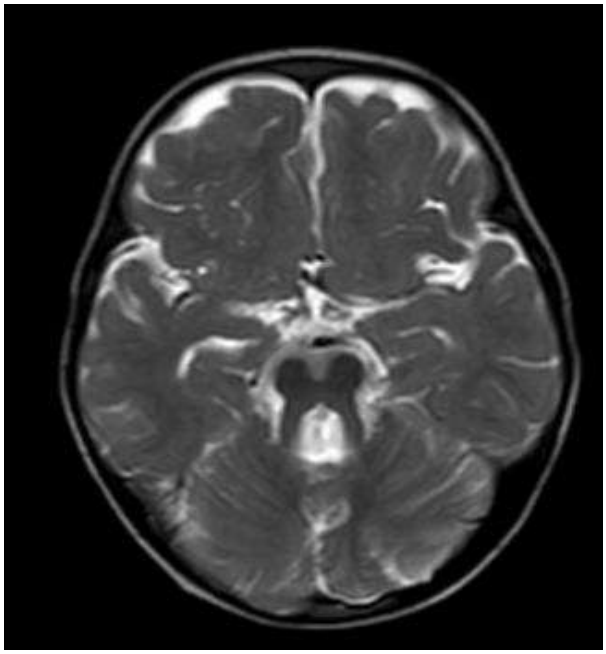


*Figure 1a: MRI brain axial section T2 weighted. Image at the level of posterior fossa*

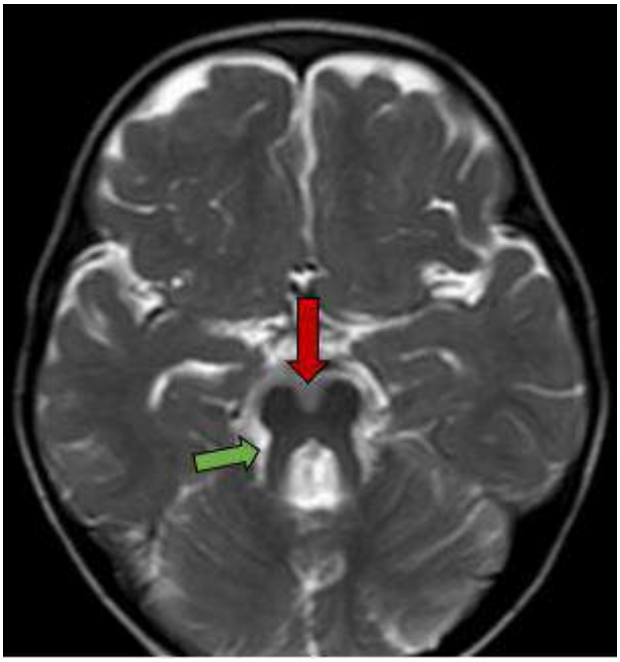
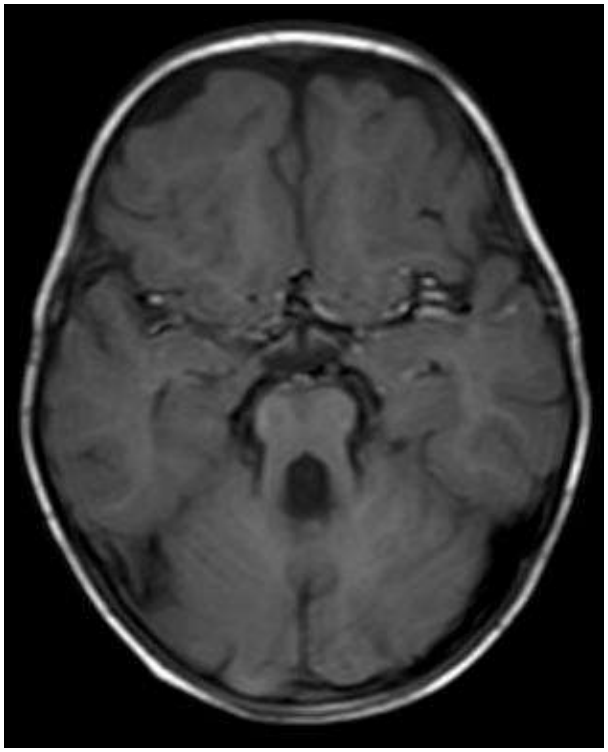


*Figure 1b (annotated image): MRI brain T2WI, axial view at the level of posterior fossa showing deepened interpeduncular fossa (red arrow) narrowing of pontomesencephalic junction with elongated, thickened superior cerebellar peduncles (green arrow) giving typical molar tooth appearance.*



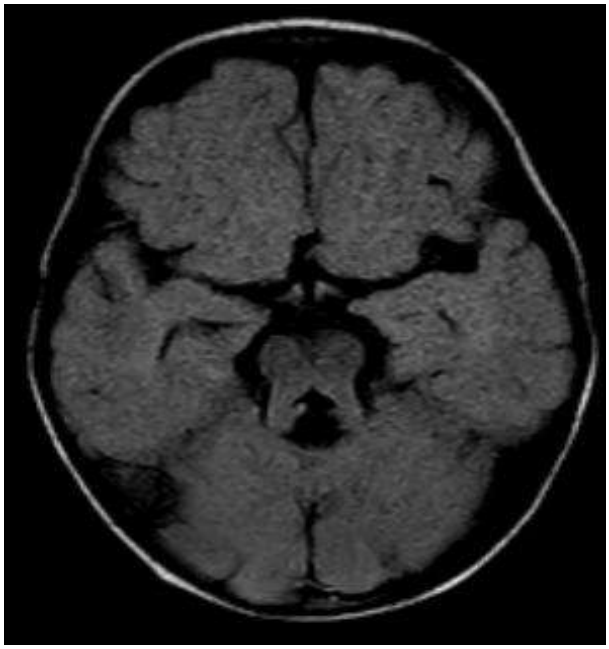


*Figure 1c and 1d: MRI brain axial section T1 weighted (image 2a) and MRI brain axial section FLAIR (Fluid attenuation inversion recovery) sequence at the level of posterior fossa also reveals similar findings*

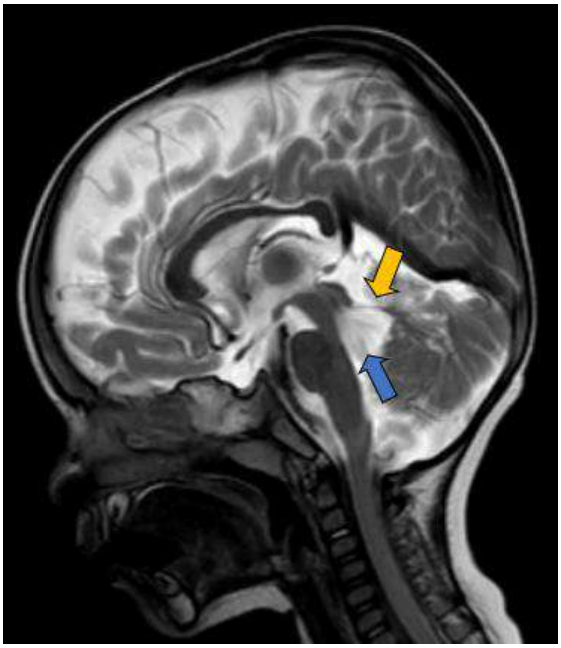


*Figure 2: MRI brain T2W midline sagittal image showing hypoplastic cerebellar vermis, elongated stretched out superior cerebellar peduncle (yellow arrow) and hypoplastic superior cerebellar hemisphere (blue arrow).*

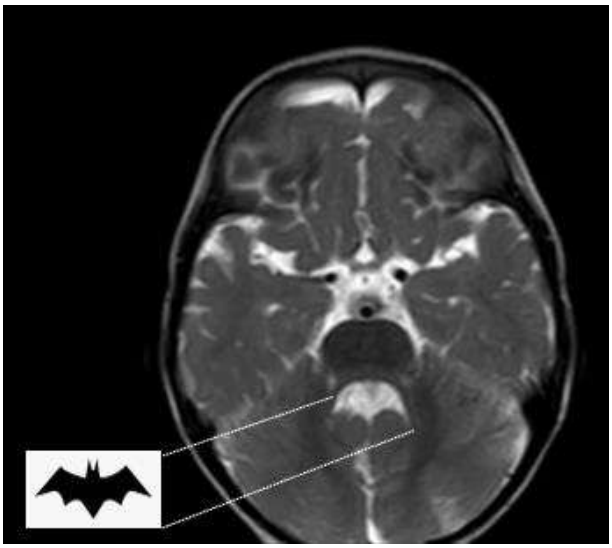
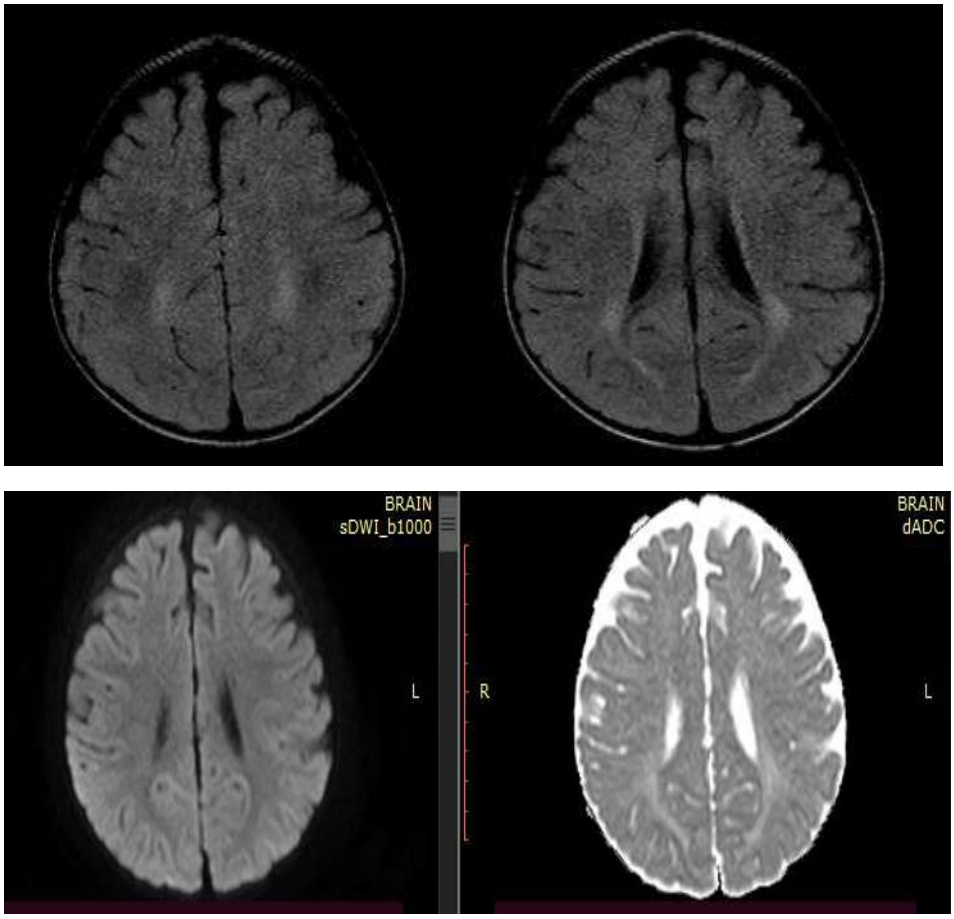


*Figure 3: MRI brain T2W axial image at the level of 4$^{th}$ ventricle showing 'Bat wing' configuration of the 4th ventricle.*




*Figures 4a, 4b & 4c: MRI brain FLAIR images axial sections at the level of centrum semiovale (5a) and lateral ventricles (5b) reveal subtle high signals in centrum semiovale and periventricular location, however evidence of restricted diffusion noted on DWI images or corresponding ADC map (5c).*

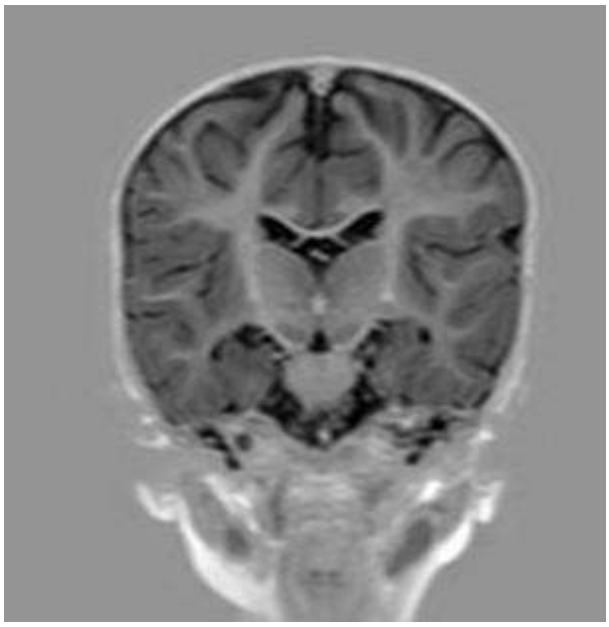


*Figure 5: MRI Brain Inversion recovery images coronal section at the level of mesial temporal lobe showing no evidence of any mesial temporal lobe sclerosis.*

**Discussion**

Joubert syndrome is one of the rarest autosomal-recessive developmental disorders due to defect in primary cilium. It has been attributed to genetic mutations involved in up to 90% of cases. Few cases have been reported of unknown cause as well. Mutations in more than thirty genes has been identified in children of JS. It has been noted that mutated primary cilium plays role in disrupting signaling pathway during fetal development. On the basis of mutation JS has been classified into its subtypes.[5,6] Although clinically it varies widely from individual to individual. It manifests in early infancy in majority of the cases as delay in achieving gross motor milestones. Other common presentations include ataxia , abnormal patterns of breathing, sleep apnea, hypotonia and abnormal movements of tongue and eye. Other abnormalities such as polydactyly, cleft lip, cleft palate, abnormalities of tongue may also be seen. Delay in developmental milestones, including intellectual/cognitive disorders are also present to some extent.[7] In severe cases, hypoplasia of the corpus callosum has also been noted.[8,9]

These children also show some specific features of the face such as widening of forehead, low-set ears, arch shape eyebrows, drooping of eyelids, hypertelorism, and triangle shaped mouth. Besides, abnormalities of other systems of the body include retinal dystrophy, coloboma, kidney diseases (polycystic kidney and nephronophthisis), liver, and endocrine disorders and skeletal deformities.[4]

MR Imaging is the proper test to diagnose along with clinical symptoms. The main findings on MRI of the midbrain include absence of vermis of cerebellum (partially or completely), prominent, straight, and thickened superior peduncles of cerebellum, thinning of isthmus of the brainstem with a deep interpeduncular fossa producing molar tooth sign (MTS)

There is decreased antero-posterior diameter of the brainstem at the level of midbrain and deep inter-peduncular fossa due to absence of crossing fibers. Besides, hypoplastic cerebellar vermis leads to formation of cleft between two hemispheres of cerebellum. This results in batwing appearance of the 4th ventricle on neuroimaging.[10,11]

In a follow up study by Steinlin, et al in cases of JS, they suggested that the outcome in these children can be divided into 03 categories: first category includes those children who die at a young age; second category include those children who survive but develop delayed mile stones of development and also have a different visual and motor deficiencies; and third category includes those who fall in mildly delayed range of developmental milestones and 70–80% are of 3rd category.[12] Considering the sign & symptoms, our case refers to the second category with delayed milestones.

Patients with JS should have multi-specialty consultations, including neurologists, pulmonologists, nephrologists, and ophthalmologists. Assessment about genetics of all cases should also be carried out. All these cases should be routinely screened for eye, liver and kidney abnormalities. Genetic follow up and counseling should also be recommended for their families.

## Conclusion

Joubert syndrome (JS) is one of the rarest genetically heterogeneous autosomal-recessive neurodevelopmental pathology of primary cilium. Consanguinity plays an important role. Diagnosed by clinical features and imaging where MRI remains the Gold standard. Management mainly includes symptomatic and supportive treatment, involvement of multidisciplinary team and genetic counseling.

## References


1. Kroes HY, Fransen van de Putte DE, Ravesloot CJ, Lindhout D. The birth prevalence of Joubert syndrome: a population based study in the Netherlands. Eur J Hum Genet 2007;15:68.
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. Neurology 1969; 19:813–25.
3. arisi MA, The molecular genetics of Joubert syndrome and related ciliopathies: The challenges of genetic and phenotypic heterogeneity. Transl Sci Rare Dis. 2019;4(1-2):25-49.
4. Parisi MA. Clinical and molecular features of Joubert syndrome and related disorders. Am J Med Genet C Semin Med Genet 2009 Nov;151: 326–340.
5. Waters AM, Beales PL. "Ciliopathies: an expanding disease spectrum". Pediatric Nephrology July 2011; 26 (7): 1039–56.
6. Joubert Syndrome - NORD (National Organization for Rare Disorders)".Retrieved 2016-12-19.
7. Parisi MA, Doherty D, Chance PF, Glass IA (May 2007). European Journal of Human Genetics May,2007;15 (5): 511–21.
8. Zamponi N, Rossi B, Messori A, Polonara G, Regnicolo L, CardinaliC .Joubert syndromewith associated corpus callosum agenesis".European Journal of Paediatric Neurology 2002; 6 (1): 63–6.
9. Bader I, Decker E, Mayr JA, Lunzer V, Koch J, Boltshauser E, et al. MKS1 mutations cause Joubert syndrome with agenesis of the corpus callosum". European Journal of Medical Genetics 2016;59 (8): 386–91.
10. Maria BL, Quisling RG, Rosainz LC, *et al.* Molar tooth sign in Joubert syndrome: clinical, radiologic, and pathologic significance. J Child Neurol 1999; 14: 368– 76.
11. Brancati F, Dallapiccola B, Valente EM. "Joubert Syndrome and related disorders". Orphanet Journal of Rare Diseases. July,2010;5:20.
12. Steinlin M, Schmid M, Landau K, Boltshauser E. Follow-up in children with Joubert syndrome. Neuropediatrics 1997; 28:204–11.