International Journal of Contemporary Pediatrics
Mehta RS et al. Int J Contemp Pediatr. 2025 Jun;12(6):993-996
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20251482

Case Report

Joubert syndrome: a rare disorder case report

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Received: 02 May 2025
Revised: 16 May 2025
Accepted: 17 May 2025

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ABSTRACT

Joubert syndrome (JS) is a rare neurodevelopmental disorder characterized by hypotonia, ataxia, and delayed developmental milestones. In some cases, disorders related to JS may involve other organ systems beyond the central nervous system, potentially resulting in multi-organ dysfunction. We describe a patient with pure JS who had ataxia, reduced muscular tone, and developmental delay. A provisional diagnosis was established based on the detection of the characteristic molar tooth sign on magnetic resonance imaging. Genetic testing subsequently confirmed the diagnosis. The patient was managed conservatively with supportive symptomatic treatment. Although rare, JS can present with systemic involvement affecting multiple organs, necessitating comprehensive evaluation and management. Therefore, whenever an infant exhibits the previously stated neurodevelopmental symptoms, doctors should always keep this medical condition in mind.

Keywords: Joubert syndrome, Neurodevelopmental disorder, Genetic testing

INTRODUCTION

Joubert syndrome (JS) is a rare autosomal recessive neurodevelopmental disorder, clinically characterized by abnormal respiratory patterns, global developmental delay, ataxia, ocular motor apraxia, and hypotonia. Neuropathologically, it presents with cerebellar vermian aplasia or hypoplasia and brainstem malformations.[1,2] The condition was first described by Marie Joubert in 1969.[2] The estimated prevalence is fewer than 1 in 100,000 live births.[1,2] A diagnostic triad comprising developmental delay, hypotonia, and the molar tooth sign (MTS) on magnetic resonance imaging (MRI) serves as the hallmark of JS.[2,3] The term 'Joubert syndrome related disorders' (JSRD) encompasses a broader group of phenotypes that share the MTS along with involvement of other organ systems.[2,4] Six major clinical subtypes have been proposed based on the pattern of organ involvement.[4] Due to variable expressivity and late recognition of specific features, diagnosis during infancy remains a challenge.[5] Although the disorder predominantly follows an autosomal recessive inheritance pattern, sporadic cases have also been reported.[6] Here, we report a case of an 8-month-old male infant exhibiting classical features of JS, with neuroimaging and further genetic analysis confirming the diagnosis. Early identification through multidisciplinary evaluation is essential for optimal management and prevention of long-term complications.[2]

CASE REPORT

An 8-month-old male child (Figure 1) from a non-consanguineous marriage was brought in complaining of a low-grade fever, a history of recurrent respiratory tract infections, a persistent cough that had been present for two months, and missed developmental milestones. Due to prenatal hypoxia, he needed ventilatory assistance at birth and was admitted to the NICU as a second order male child born via normal vaginal delivery (home delivered). Due to birth asphyxia, the first pregnancy ended in death within 24 hours of delivery. 2D ECHO was done at 6 months of age suggestive of a small ASD (0.5 cm) following which child was started on

symptomatic treatment. The child had been receiving anti-tubercular therapy (AKT) for the past two months based on a clinical suspicion of pulmonary tuberculosis.

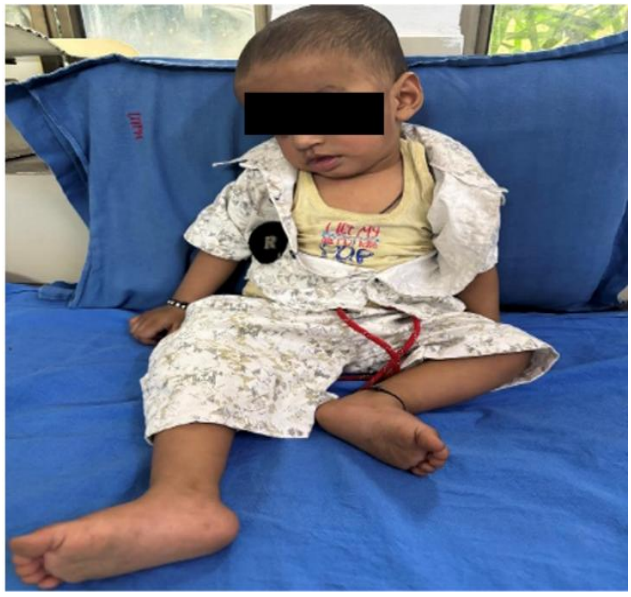

Figure 1: Case study patient-8-month-old male child.

Cough, frequent breathing episodes with tachypnea, and repeated absence seizure episodes with a 10 second apnoea without cyanosis or changes in vital signs were observed in the child upon arrival. Since birth, the infant has only been breastfed, and anthropometry indicates that the infant meets SAM criteria. A general physical examination revealed minor facial dysmorphism shown as a wide-open anterior fontanelle, deep-set eyes, microcephaly, and forehead prominence. A systemic examination revealed bilateral crepitations, brisk lower limb reflexes, poor motor development, and hypotonia.

Laboratory tests showed normal levels of TSH, free T4 and T3, enzymes in liver, C-reactive protein, creatinine and urea, blood sugar, electrolytes, and complete blood count. The blood culture was sterile. Pneumatoceles in the right mid and lower zones were observed on the chest X-ray. The child was initiated on intravenous antibiotics in addition to supportive and symptomatic management.

The results of the EEG were normal. Based on clinical suspicion, the child was later diagnosed with JS, which was subsequently confirmed by MRI of the brain (Figures 2-4). A normal fundus finding was found during the ophthalmology examination. Abdominal ultrasonography and echocardiography were also normal, ruling out multi-organ involvement.

Diagnosis was further confirmed on genetic testing which revealed homozygous pathogenic variant in the CC2D2A gene (NM_001378615.1), located in exon 23, with a nucleotide change c.2999A>T, resulting in an amino acid substitution p.Glu1000Val. It is associated with JS 9, a condition inherited in an autosomal recessive manner.

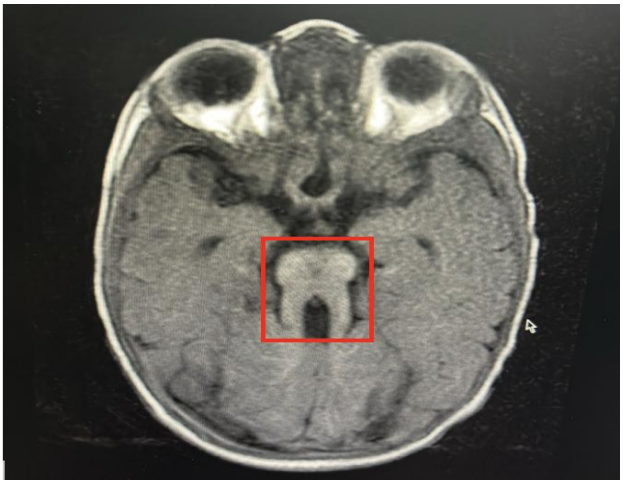

Figure 2: MRI brain shows T1-weighted axial picture at the brainstem level.

Along the ponto-mesencephalic junction, superior cerebellar peduncles are enlarged and lengthened with a midline cleft, creating the appearance of a 'molar tooth' (highlighted in red).

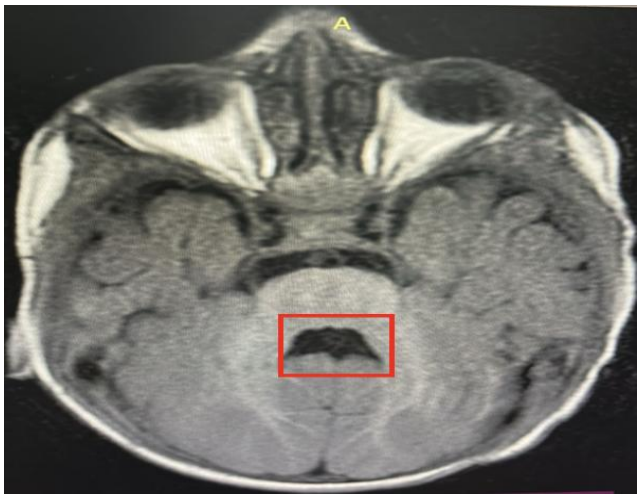

Figure 3: MRI brain of growth and malformation of fourth ventricle.

Giving it a bat wing-like appearance (highlighted in red), as well as its broader contact with the cisterna magna.

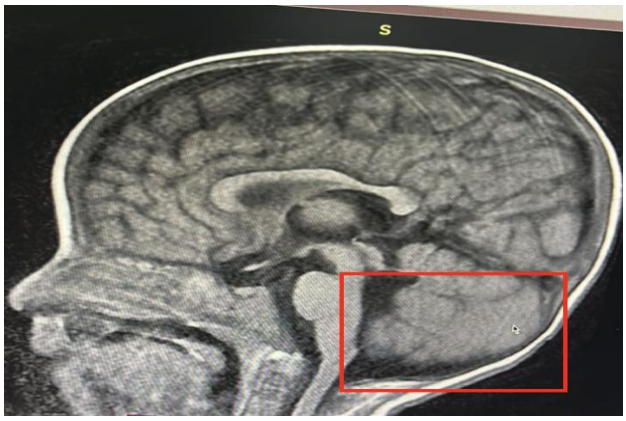

Figure 4: MRI brain shows cerebellar vermis exhibits noticeable hypoplasia in sagittal T1-weighted picture.

The patient was managed conservatively and discharged with a plan for routine follow-up. The parents were provided detailed counselling regarding the diagnosis, prognosis, and long-term care associated with the disease.

DISCUSSION

JS is an uncommon neurodevelopmental disorder presenting with hypotonia, ataxia, developmental delay, and abnormal ocular movements. These clinical features are typically accompanied by characteristic neuroimaging findings, most notably the molar tooth sign and cerebellar vermis hypoplasia. Other malformations such as extra fingers and toes, cleft lip or palate, irregular tongue protrusion, and seizures may also occur.

Diagnostic criteria in pure JS include hypotonia, ataxia, global developmental delay, and the neuroradiological finding of MTS. JSRD was introduced to refer to a group of pleiotropic conditions presenting the pathognomonic features of JS associated with variable involvement of other organs and systems mainly retinal dystrophy, nephronophthisis, hepatic fibrosis and polydactyly, with both inter- and intra-familial variability. JSRD are classified in six phenotypic subgroups: Pure JS; JS with ocular defect; JS with renal defect; JS with oculorenal defects; JS with hepatic defect; JS with orofaciodigital defects.

Patient had a history of recurrent respiratory tract infections, hypotonia, seizures, and delayed developmental milestones. Following an extensive assessment of every organ and system in the body, as well as the discovery of a distinctive MTS on MRI, the patient was diagnosed with pure JS. Due to the possibility of a delayed diagnosis, these cases are exceedingly uncommon worldwide, challenging to identify, and typically result in a wide spectrum of problems.

Extra CNS involvement typically affects the oesophagus, liver, the kidneys, spleen, eyesight, and any section of the gastrointestinal tract, although the central nervous system of the brain (sometimes referred to as the CNS) is the main system affected.[4,14] Since many organs are involved, referrals to subspecialties near place of presentation can result in an early diagnosis and enhanced quality of life.[7]

Studies focussing on genotype-phenotype correlation might assist forecast the presence of disease in subsequent generations and offer valuable hints regarding the probability of recurrence in addition to the clinical diagnosis.[10-13] AHI1, CEP290, NPHP1, and other gene mutations are linked to autosomal recessive diseases.[6] These mutations impact several signalling pathways, which causes aberrant neuronal cell migration and proliferation, which in turn causes a variety of neurological and respiratory disorders.[2]

Brancati et al. provided a comprehensive overview of JSRD, a group of genetically heterogeneous, autosomal recessive ciliopathies defined by the presence of the molar tooth sign (MTS) on MRI.[2] Core clinical features include hypotonia, ataxia, developmental delay, abnormal eye movements, and variable multiorgan involvement. The authors underscored the critical role of timely recognition, coupled with genetic counselling and coordinated multidisciplinary care, in improving clinical outcomes.

Agarwal et al described a neonatal case of JS presenting with respiratory distress and renal anomalies.[16] Neuroimaging revealed hallmark findings including MTS, cerebellar vermian hypoplasia-dysplasia, and corpus callosum thinning. The report highlighted the role of early imaging in timely diagnosis and improved prognosis.

Kumar et al reported a case series involving three siblings with JS from a consanguineous family, all exhibiting renal and neurological involvement.[17] Early diagnosis and intervention led to favourable outcomes in younger siblings, while delayed diagnosis in the eldest resulted in fatal renal failure. The study underscored the necessity of early renal screening in families with a history of chronic kidney disease.

Furthermore, because there is currently no known cure, the majority of patients do not have easy access to specialists (neurologists, psychiatrists, paediatricians, etc.), who must be consulted in order to identify the disease as soon as feasible. Instead, patients are treated conservatively with symptomatic care that combines behavioral, cognitive, occupational, and psychiatric techniques to manage the wide range of disease.

This highlights the ongoing need to educate affected families on the importance of timely referral to relevant subspecialties, as multidisciplinary involvement plays a key role in enhancing the quality and continuity of care in individuals with JS.

CONCLUSION

JS, a rare autosomal recessive disorder, presents with hypotonia, developmental delay, and brainstem-cerebellar malformations. Early subspecialty referral is crucial for detecting multiorgan involvement. Emerging gene-targeted therapies may improve diagnostic accuracy and enhance patient outcomes.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Mehta RS, Saxena A, Sonawane VB, Jatoo ZA, Archana V. Joubert syndrome: a rare disorder case report. Int J Contemp Pediatr 2025;12:993-6.