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Case report

Early neonatal presentation of Joubert syndrome: a case report

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Abstract

Introduction: Joubert syndrome (JS) is a rare genetic disorder characterized by a distinctive midbrain-hindbrain malformation identifiable through brain imaging. Clinically, JS manifests as hypotonia, irregular respiratory patterns, oculomotor apraxia, ataxia, and developmental delay, and it is often accompanied by multi-organ involvement. Although no definitive treatment exists, early diagnosis is crucial for timely intervention and improved outcomes. This case report describes a neonatal presentation of JS, emphasizing the importance of early recognition and radiological data.

Case report: We present the case of a female neonate born at 39 weeks and 3 days, initially diagnosed with transient respiratory distress. The infant subsequently exhibited recurrent episodes of desaturation, abnormal eye movements, and hypotonia. Magnetic resonance imaging (MRI) revealed posterior fossa malformations consistent with JS, including vermian dysplasia, the characteristic "molar tooth sign" of the mesencephalon, and a "bat-wing" morphology of the fourth ventricle. Genetic testing confirmed JS. Further evaluations showed no evidence of systemic involvement.

Discussion: JS remains a diagnostic challenge due to its broad phenotypic spectrum. Early symptoms, such as respiratory distress and oculomotor

abnormalities, can be subtle or mistaken for other neonatal conditions. MRI findings play a critical role in confirming the diagnosis, while genetic testing provides valuable information for family counseling. Comprehensive and multidisciplinary management, including neurological, ophthalmological, and developmental monitoring, is key for improving patient outcomes. This case highlights the importance of early diagnosis and multidisciplinary care in rare genetic disorders such as JS.

Keywords

Joubert syndrome, rare genetic disorder, neonatal presentation, magnetic resonance imaging, early recognition, differential diagnoses.

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Introduction

Joubert Syndrome (JS) is a rare genetic disorder characterized by a distinctive midbrain-hindbrain malformation known as the "molar tooth sign," identifiable through brain imaging [1]. First described by Marie Joubert in 1969, the syndrome has an estimated prevalence of 1:80,000 to 1:100,000 live births and is typically inherited in an autosomal recessive pattern, though X-linked cases have also been reported [1, 2].

Clinically, JS manifests as neonatal hypotonia, irregular respiratory patterns, oculomotor apraxia, ataxia, and developmental delay. Additionally, the syndrome often involves multiple organs, with renal, hepatic, and retinal abnormalities contributing to its wide phenotypic variability. Advances in genetic research have identified multiple genes associated with JS, all encoding proteins involved in primary cilia function, thereby classifying the syndrome within the expanding group of ciliopathies [1, 3].

Although no curative therapy exists, early diagnosis of JS is crucial for timely intervention and multidisciplinary management, which can significantly improve patient outcomes [1].

This case report describes a neonatal presentation of JS, highlighting the importance of early recognition and comprehensive evaluation for improved prognostic assessment and genetic counseling.

Case report

A female neonate was delivered via cesarean section at 39 weeks and 3 days of gestation due to non-reassuring cardiotocography. Her birth weight was 3,610 g (50^{th}-90^{th} percentile), length was 50.5 cm (50^{th} percentile), and head circumference was 35 cm (50^{th}-90^{th} percentile). Apgar scores were 5, 7, and 9 at 1, 5, and 10 minutes, respectively. Immediate resuscitation was necessary, with positive pressure ventilation and supplemental oxygen provided up to 100%. By 10 minutes of life, the newborn showed improved oxygen saturation, though mild subcostal retractions and polypnea persisted, gradually resolving within the first 6 hours of life.

On day 2 of life, the neonate experienced an episode of desaturation accompanied by perioral cyanosis, rhythmic limb movements, abnormal (erratic and disconjugate) eye movements, and axial hypotonia. She was admitted to the Neonatal Intensive Care Unit for further evaluation and monitoring. An amplitude-integrated electroencephalogram revealed paroxysmal activity, prompting administration of 20 mg/kg dose of phenobarbital. No further seizure activity was observed following treatment. Ultrasonography showed periventricular hyperechogenicity, and magnetic resonance imaging (MRI) revealed a malformative alteration of the posterior fossa consistent with a JS. The findings included an almost complete agenesis of the vermis, with only part of the superior lobe identifiable, featuring a characteristic fissure and an inferior approximation of the cerebellar hemispheres. Consequently, this structural abnormality changed the normal morphology of the fourth ventricle in the axial plane, resulting in a characteristic "bat-wing" shape, an anomalous superior position of the fastigium, elongation of the superior cerebellar peduncles, and the "molar tooth" morphology of the mesencephalon. There was also evidence of dysgyria of the cerebellar sulci, with a possible neuronal development anomaly in the region of the cerebellar

nuclei. These imaging features were consistent with JS and confirmed the clinical suspicion (**Fig. 1** and **Fig. 2**).

A genetic evaluation was performed, and whole exome sequencing (WES) identified two variants in the *CC2D2A* gene: a nonsense variant c.1267C>T (p.Arg423Ter) (rs757208121), classified as pathogenic, and a missense variant c.4667A>T (p.Asp1556Val) (rs201502401), classified as likely pathogenic (**Fig. 3**). The variants were found in a trans configuration, consistent with a diagnosis of JS, type 9 (OMIM#612285), with an autosomal recessive inheritance pattern.

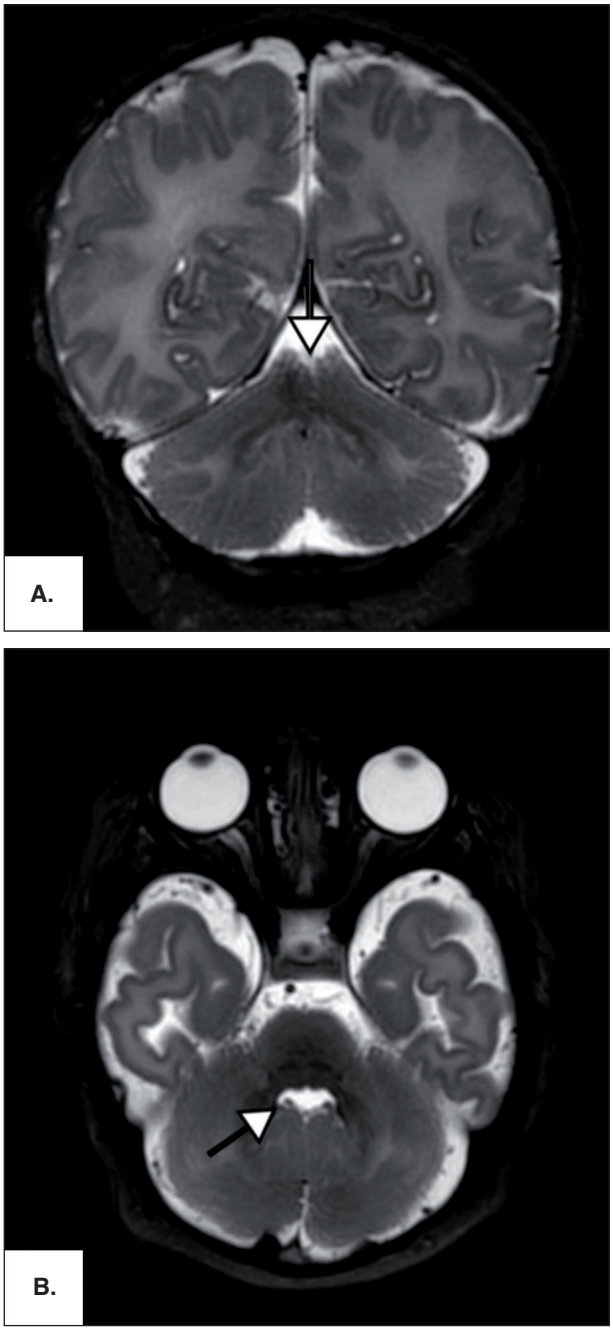

Figure 1. Brain magnetic resonance image (T2 weighted-imaging, coronal and axial planes) showing the vermian fissure (**A**, arrow) and the morphology of the fourth ventricle in the axial plane (**B**, arrow), which exhibits a characteristic "bat-wing" shape.

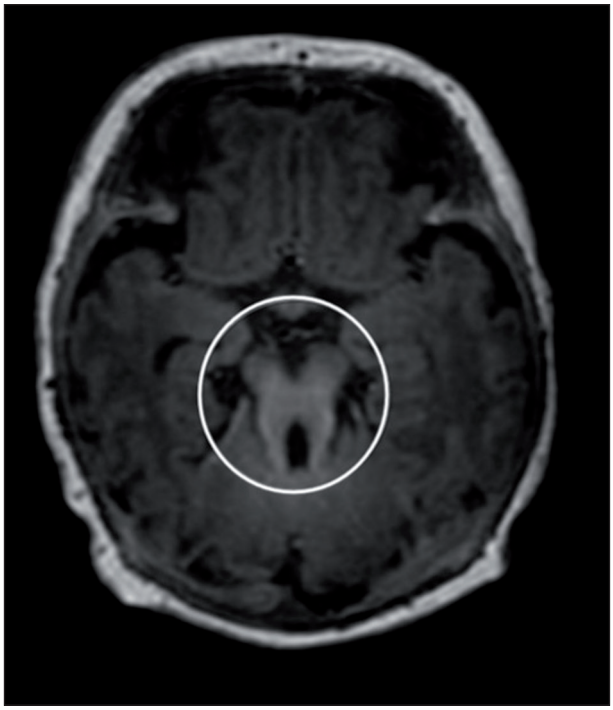

Figure 2. Brain magnetic resonance image (T1- weighted imaging, axial plane) showing the characteristic "molar tooth" sign of the mesencephalon in Joubert syndrome (JS) (circled).

Ophthalmologic evaluation suggested possible bilateral optic nerve hypoplasia, which required further clarification during follow-up. Audiological testing yielded normal results.

The neonate was administered high-flow oxygen therapy (up to 7 L/min, FiO_2 40%) from day 4 to day 10. Hemodynamically, the infant remained stable throughout this period. Infection markers consistently returned negative results.

Enteral feeding began on day 1, initially with a feeding pump before transitioning to full oral feeding by day 11. By day 12, the infant's weight reached a weight of 3,565 g (50^{th} percentile), with breast milk and formula as the sources of nutrition. She also received vitamin D supplementation.

At discharge, the neonate was stable, feeding well, and no longer requiring respiratory support. A multidisciplinary follow-up plan was established, including consultations with neuropediatrics, neonatology, ophthalmology, genetics, and developmental specialists. Detailed ophthalmological and neurodevelopmental assessments were scheduled for 6 months of age.

Figure 3. Integrative Genomics Viewer (IGV) visualization of whole exome sequencing (WES) data showing two heterozygous variants in the *CC2D2A* gene. **Panel A** displays a C>T substitution at position c.1267C>T (p.Arg423Ter), classified as pathogenic. **Panel B** shows an A>T substitution at position c.4667A>T (p.Asp1556Val), classified as likely pathogenic. In both panels, sequencing reads (grey) with colored bases at the variant position confirm the presence of the variants, which are inferred to be in heterozygous state since approximately half of the reads harbor the variant.

Discussion

JS is a genetically and clinically heterogeneous ciliopathy, caused by dysfunction of the primary cilium, a microtubule-based organelle present in most cell types, essential for cellular signaling, development, and tissue homeostasis [4, 5]. All known causative genes in JS encode proteins that localize to the primary cilium or its associated structures, such as the basal body and centrosome [4, 5]. Disruption of ciliary structure or function leads to the characteristic neurological and multisystem features of JS [1, 4, 5].

Since Marie Joubert and colleagues first described 4 siblings with intellectual disability, ataxia, oculomotor abnormalities, episodic hyperpnea, and cerebellar vermis malformation [2], approximately 200 additional cases have been documented in the literature [1, 6, 7].

In our case, the neonate presented within the first hours after birth with respiratory distress syndrome. While respiratory abnormalities are often considered a key feature of JS, they are not consistently observed in all cases [8, 9, 10]. Studies have reported various frequencies of respiratory distress, with Kendal et al. reporting abnormalities in 44% of cases [11], Pellegrino et al. in 68% [12], and Maria et al. in 71% [13]. These abnormalities are typically seen during the neonatal period and generally improve with age [14]. In our case, the

respiratory distress was initially diagnosed as neonatal respiratory distress syndrome, which did not require special treatment, as the infant was not hypoxemic and respiratory effort improved within the first 6 hours of life. It was only later, following further investigation, that we recognized the potential link between this initial symptom and JS.

After 24 hours of life, the newborn in our case exhibited erratic eye movements, lateral head titubation, and rhythmic upper limb movements unresponsive to restraint. These ocular abnormalities are consistent with oculomotor dysfunctions, such as nystagmus, strabismus, oculomotor ataxia, and vertical gaze palsy, frequently seen in JS [6, 8, 10, 15]. These impairments are key diagnostic features, occurring in approximately 70% to 100% of patients [12, 16, 17].

MRI plays a crucial role in evaluating neonates with seizures, aiding in the differential diagnosis by identifying structural brain abnormalities [6, 18]. In JS, key brain features are predominantly located in the posterior fossa by MRI [10, 15]. A hallmark feature is the absence of fiber decussation in the superior cerebellar peduncles and cerebellar tracts, which can be visualized by tractography [18, 19]. This results in elongated superior cerebellar peduncles [18-20]. This elongation, with a deeper than normal posterior interpeduncular fossa and vermian dysplasia, give the midbrain, in axial images, a distinctive appearance, often described as resembling a molar tooth, known as the "molar tooth sign" [10, 15, 18], which was present in our case (**Fig. 2**). A previous study identified this sign in 85% of patients with the syndrome [13, 15]. Additionally, a small dysplastic or aplastic cerebellar vermis and, consequently, the separation of the cerebellar hemispheres and vermis by a midline cleft resulted in the "buttock sign" [18, 19] on coronal images (**Fig. 1A**). There was dilation or distortion of the fourth ventricle, resulting in the "bat-wing sign" [18, 19] (**Fig. 1B**). Although the cerebrum is typically unaffected, moderate enlargement of the lateral ventricles has been reported in 6% to 20% of cases, and dysgenesis of the corpus callosum occurs in 6% to 10% of cases [6, 10, 18, 21].

Studies have shown that the genetic cause can be identified in approximately 62% of affected individuals [22]. Over 40 genes have been implicated, all affecting primary cilia function, and certain gene-phenotype associations are now well established. The genotype-phenotype correlation is characterized by specific gene mutations being associated with distinct patterns of organ involvement and clinical severity, but with considerable variability even within the same genotype [23-28].

For instance, pathogenic variants in *TMEM67* are closely linked to an increased risk of liver fibrosis and ocular coloboma [23, 28], whereas mutations in *NPHP1*, *RPGRIP1L*, and *TMEM237* are more commonly associated with renal involvement [23, 26-28]. Variants in *CEP290* and *AHI1* confer a higher likelihood of retinal dystrophy, with *CEP290* also implicated in chronic kidney disease [23, 26, 27]. Additionally, the clinical severity of JS may be modulated by the type and position of the mutation within a given gene – as observed in *HYLS1*, where variants located outside the highly conserved domain tend to result in milder, non-lethal JS phenotypes, while mutations within the domain lead to the more severe hydrolethalus syndrome [24].

Despite these established associations, considerable phenotypic variability persists even among individuals with identical genotypes, likely influenced by modifier genes and environmental factors [26, 28].

In this case, genetic evaluation identified two variants in the *CC2D2A* gene, consistent with JS, type 9 (OMIM#612285), which exhibits an autosomal recessive inheritance pattern. The protein encoded by the *CC2D2A* gene is located at the ciliary transition zone and its disruption is associated with the loss of ciliary protein localization [29]. Mutations in *CC2D2A* have been correlated with ventriculomegaly and seizure activity [23, 25, 28].

Genetic testing is critical for diagnosing this syndrome, as it is genetically heterogeneous and manifests differently based on the specific mutation. Identifying the underlying genetic cause helps to predict the disease's progression, facilitates the detection of related health issues, and provides accurate genetic counseling. Moreover, it offers the possibility of prenatal and preimplantation genetic testing.

While the clinical features of JS may be present at birth, a definitive diagnosis is often delayed for several months or even years, with an average age of diagnosis at 33 months [2, 15]. This highlights the importance of early detection to enable timely interventions.

Prenatal diagnosis of JS through ultrasound is challenging, as the characteristic features, such as a widened posterior fossa and cerebellar vermis dysplasia, are non-specific and can overlap with other conditions [10, 15, 19, 30]. However, advances in obstetric ultrasonography and fetal

MRI have improved the ability to diagnose the condition during the third trimester [10, 15, 19, 30]. In our case, despite adequate prenatal care, prenatal diagnosis was not established.

In addition to brain-related abnormalities, patients with JS may experience various comorbidities. As a ciliopathy, JS is often associated with multisystem involvement, including nephronophthisis, retinal dystrophy, hepatic fibrosis, and skeletal anomalies, clinical features that overlap with those of other ciliopathies and reflect the pleiotropic roles of cilia in development and organ function [1, 4, 5, 31].

Kidney disease most commonly presents as nephronophthisis or cystic kidney disease, and renal involvement occurs in approximately 25-30% of affected individuals. The most relevant genes linked to kidney disease in JS are *CEP290*, *TMEM67*, *RPGRIP1L*, and *NPHP1* [23, 26]. Mutations in these genes disrupt ciliary function in renal tubular epithelial cells, leading to progressive renal dysfunction and, in many cases, end-stage renal disease in childhood or adolescence [23, 26]. Genotype-phenotype correlations indicate that patients with mutations in these genes require close renal surveillance, as the risk of kidney involvement is significantly higher in these subgroups [23, 26, 32-35].

Other comorbidities may include ophthalmologic manifestations such as retinal dystrophy; hepatic involvement, such as fibrosis and cystic lesions; and skeletal abnormalities, including polydactyly and scoliosis [5, 31]. Endocrine disruptions, particularly growth impairment, are also common. Furthermore, affected individuals often present with developmental delays, encompassing developmental delays in motor function, cognition, and speech [1].

There is a recognized association between midline palate anomalies and JS, particularly in the orofaciodigital (JS-OFD) subtype. Oral-facial-digital features include cleft palate, midline upper-lip cleft, oral frenulae and tongue hamartomas [31, 36, 37]. The genes most commonly implicated in JS-OFD are *OFD1*, *TMEM216*, *TCTN1*, *TCTN2*, and *C5ORF42* [31, 36, 37]. The presence of midline oral anomalies should prompt consideration of the JS-OFD subtype, which is genetically and clinically distinct within the JS spectrum [31, 36, 37].

Differential diagnosis of JS primarily includes other posterior fossa malformations and ciliopathies with overlapping features. Conditions such as Dandy-Walker malformation, pontocerebellar hypoplasia, and rhombencephalosynapsis may mimic the cerebellar vermis abnormalities seen in JS. Additionally, syndromic ciliopathies like Meckel-Gruber, Bardet-Biedl, and Senior-Løken syndromes share overlapping renal, hepatic, retinal, and skeletal manifestations (**Tab. 1**). Distinction relies on identifying the characteristic "molar tooth

Table 1. Key clinical features of Joubert syndrome (JS) and relevant differential diagnoses.

Clinical features		Differential diagnoses
Neurological (Imaging)	"Molar tooth sign" (85%), vermis hypoplasia/aplasia, elongated SCPs, "bat-wing sign", "buttock sign"	Dandy-Walker malformation, Poretti-Boltshauser syndrome, pontocerebellar hypoplasia, other ciliopathies (e.g., Meckel-Gruber)
Neurological (Clinical)	Ataxia, head titubation, hypotonia, seizures, global developmental delay	Cerebral palsy, congenital muscular dystrophies, genetic epileptic syndromes
Respiratory (Neonatal)	Apnea, episodic hyperpnea, tachypnea, improves with age	Neonatal RDS, neonatal sepsis, cerebellar malformations
Oculomotor	Nystagmus, strabismus, oculomotor apraxia, vertical gaze palsy	Moebius syndrome, retinal dystrophies, congenital ataxias
Renal	Nephronophthisis, cystic dysplastic kidneys	Senior-Løken syndrome, ARPKD, Bardet-Biedl syndrome
Ophthalmologic	Retinal dystrophy, coloboma	Leber congenital amaurosis, Senior-Løken syndrome, Alström syndrome
Hepatic	Hepatic fibrosis, liver cysts	Caroli syndrome, fibropolycystic disease, Meckel-Gruber syndrome
Skeletal	Polydactyly, scoliosis	Ellis-van Creveld, Bardet-Biedl, other skeletal ciliopathies
Orofacial	Cleft palate, midline upper-lip cleft, frenulae, tongue hamartomas	OFD1, Pallister-Hall syndrome
Endocrine	Growth retardation, delayed puberty	Congenital hypopituitarism, syndromic ciliopathies

ARPKD: autosomal recessive polycystic kidney disease; OFD1: oral-facial-digital syndrome type I; RDS: respiratory distress syndrome; SCPs: superior cerebellar peduncles.

sign" on brain MRI and confirming the diagnosis through molecular genetic testing targeting cilia-related genes [20, 36, 37].

Following the suspected diagnosis of our patient, a comprehensive evaluation was conducted to screen for associated abnormalities. This included abdominal and renal ultrasonography, which yielded normal results, as well as a full laboratory analysis, which showed normal results. However, an ophthalmological assessment revealed some concerns, which will be monitored and re-evaluated in the future.

The management of JS is primarily symptomatic and requires a multidisciplinary approach. Treatment typically involves physical therapy, as well as educational adaptations tailored to the patient's cognitive and behavioral needs [6, 10, 38]. Additionally, addressing complications or associated symptoms that may arise is an essential component of the care plan.

Prognosis is generally favorable in moderate cases, with outcomes impacted by renal and hepatic complications [6, 9, 36]. In patients with nephronophthisis, end-stage renal disease typically occurs in the second decade of life [9].

Rare genetic diseases can present in the neonatal period with non-specific symptoms that may be mistaken for more common conditions. This case highlights the crucial role of thorough physical examination and clinical judgment in guiding the diagnostic process, ensuring accurate diagnosis and facilitating a tailored treatment plan. Early diagnosis of JS facilitates improved pediatric care, positively influencing long-term outcomes and enhancing the patient's quality of life through comprehensive multidisciplinary management and genetic counseling.

Informed consent

Written informed consent for publication was obtained from the parents of the child.

Declaration of interest

The Authors declare that there are no conflicts of interest. This study was not supported by external funding sources.

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