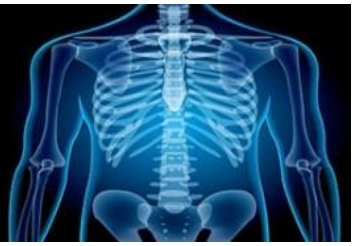
International Journal of Radiology and Diagnostic Imaging



E-ISSN: 2664-4444
P-ISSN: 2664-4436
Impact Factor (RJIF): 5.68
www.radiologypaper.com
IJRDI 2025; 8(3): 136-140
Received: 09-06-2025
Accepted: 11-07-2025

Dr. Nivedita Radder
Department of Radiology, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA

Shrinivas Radder
Department of Radiology, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA

Corresponding Author:
Dr. Nivedita Radder
Department of Radiology, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA

Molar tooth sign and multi-organ involvement: neuroimaging and systemic manifestations of joubert syndrome in a 4-year-old child

Nivedita Radder and Shrinivas Radder

DOI: https://www.doi.org/10.33545/26644436.2025.v8.i3c.485

Abstract
Joubert syndrome (JS) is a rare autosomal recessive disorder associated with a characteristic hindbrain malformation on neuroimaging termed the "molar tooth sign". We report a case of a 4-year-old female who was admitted with hypotonia, ataxia, and intellectual disability. The pathognomonic molar tooth sign was accompanied by cerebellar vermis hypoplasia, superior cerebellar peduncles, elongated and horizontally oriented, and a bat-wing appearance of the fourth ventricle on brain magnetic resonance imaging (MRI). Abdominal ultrasonography revealed hepatic fibrosis with increased liver stiffness (9 kPa on elastography) and chronic kidney disease as evidenced by increased renal cortical echogenicity with loss of corticomedullary differentiation. This case illustrates the multi-organ involvement in JS with the need to assess the systemic involvement beyond the neuroimaging findings. Early identification of neurological and extra-neurological manifestations is important for appropriate multidisciplinary management and genetic counseling. The coexistence of marked hepatorenal involvement in our patient emphasises the need for close monitoring of liver and renal function in children with JS.

Keywords: Pediatric neuroimaging, ciliopathy, nephronophthisis, hepatic fibrosis, Joubert syndrome, cerebellar vermis hypoplasia, molar tooth sign

Introduction
Joubert syndrome (JS) is a rare genetic disorder that belongs to the group of ciliopathies with an estimated incidence of 1 in 80,000 to 1 in 100,000 live births [1, 2]. First described by Marie Joubert *et al*. in 1969, this condition is autosomal recessive and characterized by a distinctive constellation of neurological and systemic manifestations [3]. The characteristic of JS is a "molar tooth sign" on axial neuroimaging caused by cerebellar vermis hypoplasia, enlarged and thickened superior cerebellar peduncles, and a deep interpeduncular fossa [4].
The clinical phenotype of JS usually involves neonatal respiratory distress, hypotonia, ataxia, developmental delay, mental retardation, and ocular dyskinesia [5]. However, since its first description, a considerable phenotypic expansion has occurred [6], with the recognition of the multi-organ involvement leading to the broader term Joubert syndrome and related disorders (JSRD). In addition to the retinal dystrophy, nephronophthisis, hepatic fibrosis, and polydactyly, other clinical signs reflect the central role of primary cilia in the multiple organ systems [7].
To date, mutations in more than 35 genes have been reported in JS and all encode proteins that are important for ciliary structure or function [8]. The underlying clinical variability of this condition is genetically heterogeneous. We describe a case of a 4-year-old girl with classic neuroimaging features of JS combined with important hepatorenal involvement, which emphasizes the need for systemic evaluation in these patients.

Case Presentation
A 4-year-old girl was referred to our pediatric neurology clinic by her parents with concerns that their daughter was lagging behind her peers' developmental milestones and had problems with balance. The mother said her daughter had always been "floppy" as a baby, slower than normal to hold her head up and sit unaided. The child had reached a seated position without support at 14 months of age, and started walking at 24 months of age with a largely unstable gait.

The pregnancy was uneventful and the child was born at full term by normal vaginal delivery. However, the parents reported their daughter had suffered episodes of irregular breathing (rapid breathing followed by short pauses) in the neonatal period which had improved gradually by age 6 months. There was no history of a similar disease in the family, although the parents introduced themselves as second cousins.

On physical examination, the child looked alert but there were clear signs of hypotonia with reduced muscle tone in all four limbs. She had a wide-based, ataxic gait and needed an assist to walk. Deep tendon reflexes were reduced on both sides. Ophthalmologic evaluation: Intermittent nystagmus and oculomotor apraxia. She had limited speech no more than two word phrases and greatly delayed for her age. Facial features included a wide forehead, arched eyebrows and an open-mouth appearance with a protruding tongue.

On the basis of the clinical presentation of a cerebellar disorder, a brain MRI was conducted. Radiology revealed gross abnormalities that were typical of Joubert syndrome. The cerebellar vermis was significantly hypoplastic, with abnormal clefts (Figure 1A and 1D). Most prominent were elongated, thickened, horizontally oriented superior cerebellar peduncles that imparted the pathognomonic "molar tooth" appearance to the midbrain on axial images (Figure 1A). The fourth ventricle showed a characteristic bat-wing shape on axial sections (Figure 1B) and there was deepening of the interpeduncular fossa (Figure 1C). The corpus callosum was normal and no signs of hydrocephalus or migration anomalies were found.

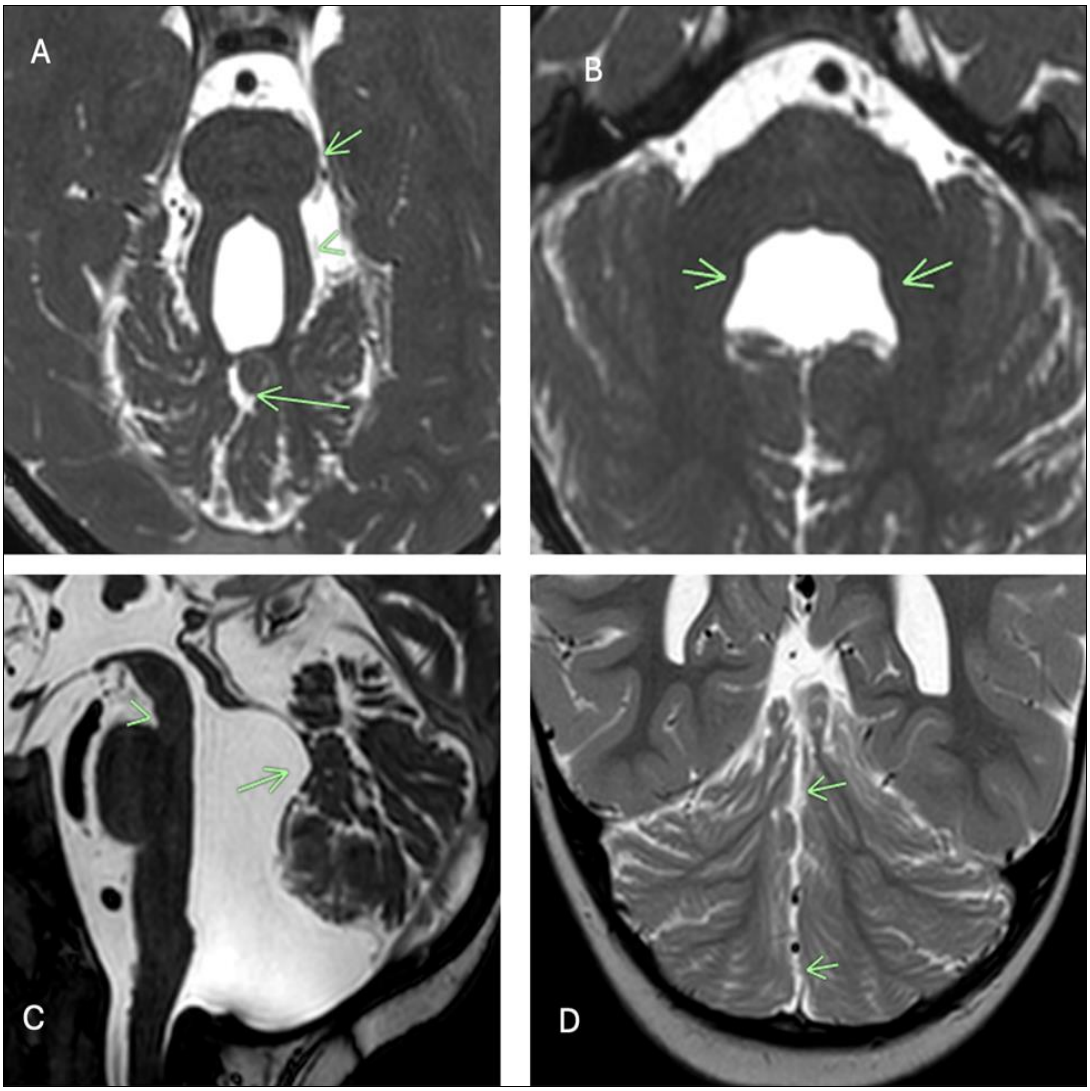


Fig 1: Characteristic MRI findings in Joubert Syndrome. (A) Axial heavily T_2-weighted MRI shows a classic molar tooth sign (*arrowhead*) with a foreshortened midbrain (*short arrow*) and vermis clefting (*long arrow*). (B) Axial heavily T_2-weighted MR shows dysplastic vermis and a "bat-wing "appearance of the 4th ventricle. (C) Sagittal heavily T2-weighted MR shows elongated midbrain and narrow isthmus (*arrowhead*), dysplastic vermis, and high 4th ventricle. (D) Coronal T_2-T_2-weighted MR demonstrates a midline vertical cleft (*arrow*) within the cerebellar vermis. This distinctive cleft is lined with normal-looking cortex. The cerebellar hemispheres are slightly smaller.

After the neuroimaging diagnosis was obtained, an extensive systemic evaluation was undertaken. Abdominal ultrasonography showed alarming features in the liver and the kidneys. Both kidneys had increased cortical echogenicity with loss of normal corticomedullary differentiation, compatible with chronic kidney disease (Figure 2A). No renal cyst, calculi or hydronephrosis were found. The liver parenchyma was coarse and heterogeneous, which is why elastography was performed, and the median liver stiffness of 9 kPa was found, which is indicative of advanced hepatic fibrosis (Figure 2B).

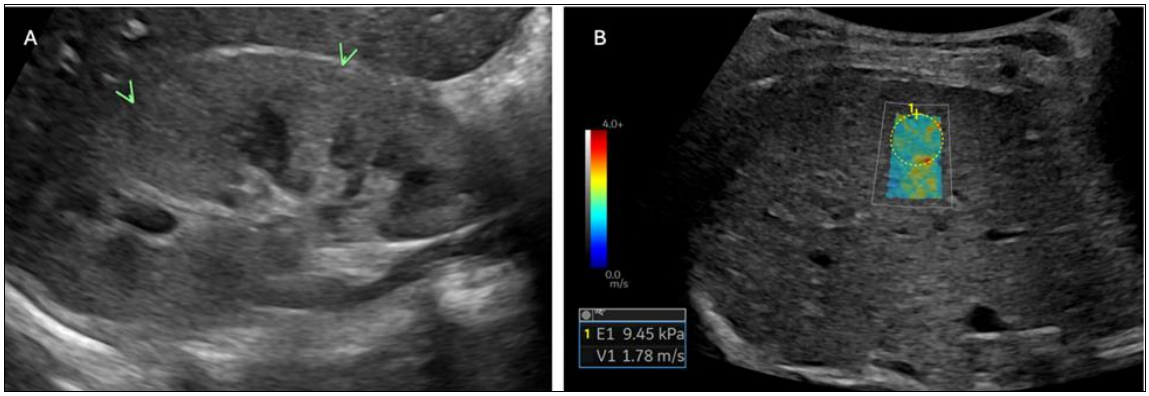


Fig 2: Ultrasound findings in the abdomen. (A) The kidneys showed increased cortical echogenicity with loss of normal corticomedullary differentiation, consistent with chronic kidney disease. (B) The liver parenchyma was coarse and heterogeneous, with elastography showing median liver stiffness of 9 kPa, which is indicative of advanced hepatic fibrosis.

Laboratory tests showed mildly elevated liver enzymes with ALT of 68 U/L and AST of 72 U/L. Serum creatinine level was elevated for age at 1.2 mg/dL with an estimated glomerular filtration rate of 48 mL/min/1.73m2; confirming moderate chronic kidney disease. Complete blood count and coagulation parameters were normal. Urinalysis was significant for mild proteinuria without hematuria.

Genetic testing was offered to the family and confirmed compound heterozygous mutations in the CEP290 gene and the diagnosis of Joubert syndrome. The parents were offered genetic counselling for the autosomal recessive pattern of inheritance and the 25% recurrence risk for future pregnancies.

She was admitted to a multidisciplinary program including pediatric neurology, nephrology, hepatology, physical therapy and developmental pediatrics. She was started on aggressive physical and occupational therapy for her motor delays and ataxia. Speech therapy was started to assist with language development. Routine monitoring of liver and kidney function was instituted, and more aggressive management was planned if either organ dysfunction developed.

At the end of 6 month follow-up, the child showed minor improvement in motor coordination (with therapy), yet considerable ataxia remained. She had been able to say about 50 words. Laboratory studies were repeated and stable renal function was demonstrated, although liver enzymes remained slightly elevated. The family was advised about the need to avoid nephrotoxic drugs and the need for close monitoring for complications.

In our experience of dealing with similar cases of Joubert syndrome at our institution, we have seen further neuroimaging findings that extend the phenotypic spectrum of the disorder. In one especially instructive case, a 3-year-old boy with confirmed JS presented with a posterior occipital cephalocele with evidence on neuroimaging of meninges herniation through a defect in the dorsal bony margin of the occipital bone (Figure 3A and 3B). There was tectal plate dysplasia with an abnormally elongated and dysplastic tectum (Figure 3B). Although not identified in our patient, this finding has been reported as an important associated malformation in approximately 10% of JS cases. Additionally, there were aberrant loculations in an enlarged prepontine cistern producing a complex multicystic appearance (Figure 3C) on axial T2-weighted sequences. The heterogeneity of imaging presentation, even in patients with the same mutations in the same genes, points to the possibility that modifier genes or environmental factors may also play a role in the phenotypic expression of this ciliopathy.

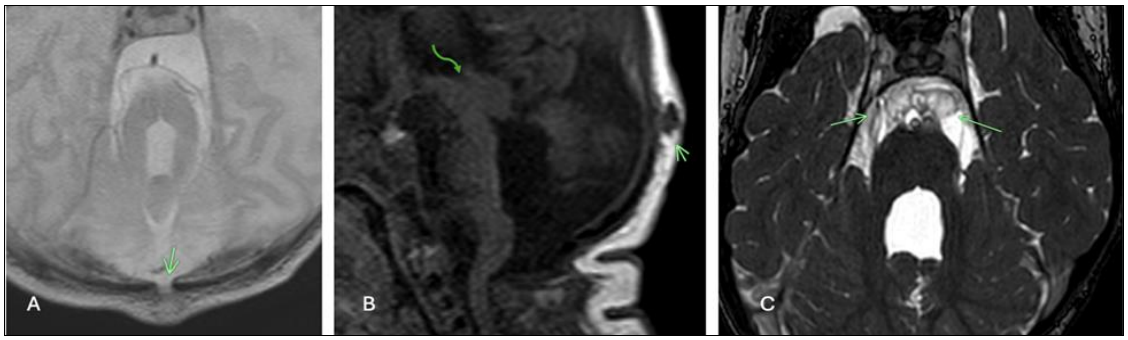


Fig 3: Additional Imaging spectrum of Joubert's syndrome. Axial T_2-weighted (A) and Sagittal T_1-weighted (B) images demonstrate a posterior occipital cephalocele (*arrows)* with evidence of meningeal herniation through a defect in the dorsal bony margin of the occipital bone. (B) Also shows tectal dysplasia (*curved arrow*). (C) Axial heavily T2-weight MR shows aberrant loculations in an enlarged prepontine cistern producing a complex multicystic appearance.

Discussion

Joubert syndrome is a fascinating example of how loss of function of a single cellular organelle, the primary cilium, can result in a wide variety of clinical manifestations in multiple organ systems [9]. Our case presents the classic neuroimaging findings with a considerable hepatorenal involvement and highlights the systemic nature of this ciliopathy.

The "molar tooth sign" that we observed in our patient is considered to be pathognomonic and is a result of a rare

combination of anatomical abnormalities [10]. The lack of decussation of the superior cerebellar peduncular fibers produces their aberrant horizontal orientation and hypertrophy, and the associated vermian hypoplasia and deep interpeduncular fossa provide the finishing touch to the picture [11]. These structural abnormalities are directly related to the clinical signs of hypotonia and ataxia of our patient.

Other neuroimaging findings seen in our cohort, such as occipital encephalocele and tectal dysplasia, are representative of the wide range of developmental anomalies that may be seen in JS. The occurrence of encephalocele in JS patients might indicate a more complete disruption of dorsal midline development during embryogenesis, being possibly linked to the importance of primary cilia in sonic hedgehog signaling pathway involved in neural tube closure [12]. The abnormalities of the tectal plate dysplasia and the prepontine cistern are probably other manifestations of the same brainstem and posterior fossa maldevelopment which characterizes the syndrome.

Of special interest in our case is the hepatorenal involvement. Around 25% of JS patients develop the progressive tubulo-interstitial kidney disease, nephronophthisis, which is a major cause of morbidity [13]. The ultrasonographic pattern of increased renal echogenicity and loss of corticomedullary differentiation that was observed in our patient is characteristic of this complication. On the other hand, congenital hepatic fibrosis (CHF) has been reported in a small number of patients with JS, especially in those harboring mutations in the genes CEP290 [14], as also in our case.

The CEP290 gene, which is mutated in our patient, produces a centrosomal protein with an important role in ciliary function. Mutations in CEP290 are responsible for around 10% of JS cases and are related to an increased risk of retinal and renal involvement [15]. This genetic-phenotypic correlation re-emphasizes the relevance of genetic testing not only for diagnostic confirmation but also for prognostic counseling and targeted surveillance.

The management of JS involves a multidisciplinary approach that includes the management of both neurologic and systemic manifestations [16]. While there is no cure, supportive treatment can contribute substantially to quality of life. Physical and occupational therapy are necessary to maximize motor function and speech therapy is needed to reduce communication delays. Renal and hepatic function should be closely monitored as early recognition of organ dysfunction will allow for early interventions to slow progression [17].

The respiratory abnormalities experienced by our patient in infancy are typical of JS and most probably represent a manifestation of brainstem dysfunction [18]. This type of abnormal respiratory condition usually improves over time, as in our case, but needs close monitoring during the neonatal period, and might need ventilatory support in severe cases.

An important consideration in the management of JS is the increased sensitivity to anesthetic agents and respiratory depressants in the context of underlying brainstem dysfunction [19]. This means that any surgical procedures, including the routine dental procedures these children need, must be planned and monitored carefully during the perioperative period. The prognosis of JS is very variable and is determined primarily by the degree of neurological deficit and by the existence of extra-neurological complications [20]. While some people may gain independent walking ability and acquire functional communication skills, others have remained severely disabled. As indicated in our patient, the presence of progressive renal or hepatic disease can have a significant influence on long-term outcome and quality of life.

Conclusions

This case underlines the multi-system character of the Joubert syndrome and that the typical neuroimaging findings are only a part of the whole of this complex ciliopathy. The extensive hepatorenal involvement of our young patient highlights the need for detailed systemic assessment and multidisciplinary follow-up over a long period. JS is known to have a pathognomonic imaging presentation and therefore early diagnosis should trigger a careful search for associated extra-neurological features as early management would be likely to maintain organ function and inform a good outcome for the child's development. As our knowledge of the genetic basis and the pathophysiology of JS continues to develop, more specific therapeutic options are expected in the future. Until then, multispecialty coordination of care to support the family and to provide supportive care for these children continues to form the core of management

Conflict of Interest: Not available

Financial Support: Not available

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How to Cite This Article
Radder N, Radder S. Molar tooth sign and multi-organ involvement: neuroimaging and systemic manifestations of joubert syndrome in a 4-year-old child. International Journal of Radiology and Diagnostic Imaging. 2025;8(3):136-140.