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Joubert Syndrome: A Rare Entity and the Role of Radiology

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Abstract

Introduction and Importance: Joubert syndrome (JS) is characterized by a distinct constellation of cerebellar and midbrain abnormalities that collectively produce the characteristic "molar tooth sign" on axial MRI scans. This rare genetic disorder affects an estimated 1 in 80,000 to 1 in 100,000 individuals.

Case Presentation

Clinical manifestations typically become evident shortly after birth and include hypotonia, episodic tachypnea, and apnea, often followed by developmental delays and speech apraxia. Associated anomalies may encompass polydactyly, cleft lip or palate, tongue abnormalities, hypotonia, encephalocele, meningocele, hydrocephalus, kidney problems, pituitary abnormalities, and autistic-like behaviors. Seizures are also possible, with varying degrees of motor and cognitive impairment from mild to severe forms.

Discussion: Management of JS primarily involves symptomatic and supportive care. The prognosis depends significantly on the development of the cerebellar vermis.

Conclusion: Joubert syndrome may be overlooked without careful attention to radiological findings, particularly the molar tooth sign observed on MRI scans. Early recognition and diagnosis are critical for appropriate management and intervention strategies.

Keywords: Joubert Syndrome, Muscle Weakness, Abnormality in the Cerebellum

Introduction

Joubert Syndrome (JS) is a rare autosomal recessive disorder first identified by Marie Joubert in 1969 [1]. It is characterized by a distinctive set of clinical features including hypotonia, ataxia, oculomotor apraxia, facial dysmorphism, irregular neonatal breathing, and a specific mid-hindbrain malformation known as the "molar tooth sign" [[2], [3], [4]]. This radiological hallmark manifests as cerebellar vermis hypoplasia or dysplasia, thick and horizontally oriented superior cerebellar peduncles, and an abnormally deep interpeduncular fossa [[5], [6], [7]]. Additional associated disorders include occipital encephalocele, polymicrogyria, polydactyly, ocular coloboma, retinal dystrophy, cystic kidney disease, nephronophthisis, and hepatic fibrosis [8]. JS exhibits a

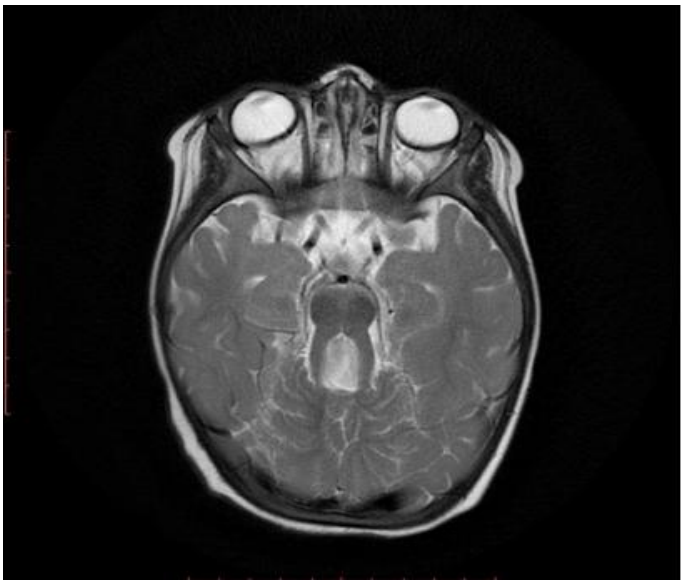
reported incidence ranging between 1:80,000 and 1:100,000 [9,10], and can occur sporadically or be inherited [10]. Here, we present a case of a 17-month-old male baby with typical features of JS.

Case Presentation

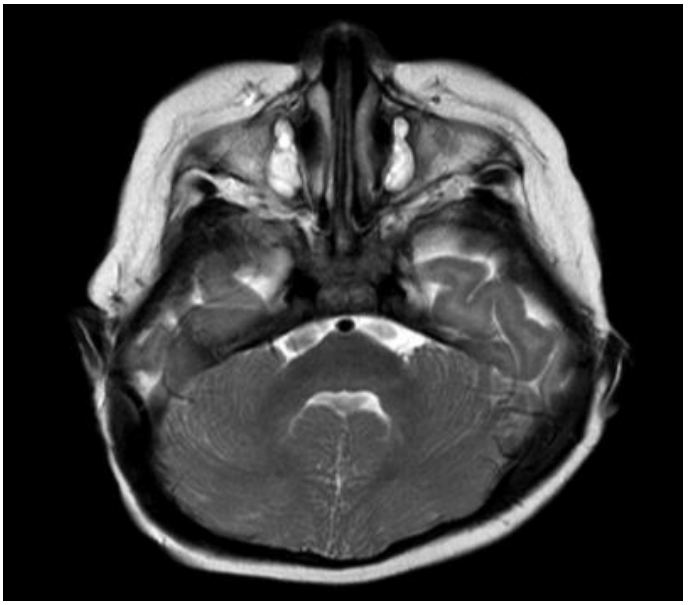
The 17-month-old male baby, born to non consanguineous parents via C-section without perinatal complications, presented with delayed motor and speech milestones (Fig. 1). His birth history was uneventful, with full-term delivery and normal findings in two older siblings (both sisters). On examination, the baby displayed a head circumference of 46 cm and weighed 8 kg. Physical examination revealed hypotonia, decreased reflexes, reduced muscle strength, tongue fasciculations, and down going plantar reflexes, consistent with the characteristic clinical findings of Joubert syndrome.

The laboratory results indicated a hemoglobin level of 9.7 g/L, total leukocyte count (TLC) of 7.4 x 10^9/L, platelet count of 203 x 10^9/L, thyroid stimulating hormone (TSH) level of 3.37 µIU/mL, triiodothyronine (T3) level of 2.10 pg/ml, thyroxine (T4) level of 125.11 nmol/L, and creatine phosphokinase (CPK) level of 33 U/L. Previously diagnosed with cerebral palsy, the patient underwent a normal abdominal ultrasound. Nerve conduction studies and electromyography showed no signs of peripheral neuropathy, spinal muscle atrophy, or myopathy. Brain magnetic resonance imaging (MRI) revealed hypoplasia of the cerebellar vermis and superior cerebellar peduncle, presenting with a bat wing sign in the fourth ventricle (Fig. 2A), and a prominent thickened elongated cerebellar peduncle resembling a molar tooth (Fig. 2B). Additionally, prepontine mesencephaly with an enlarged quadrigeminal system indicated midbrain atrophy (Fig. 2C), while an enlarged cerebrospinal fluid (CSF) space around the vermis suggested vermis atrophy (Fig. 2D).

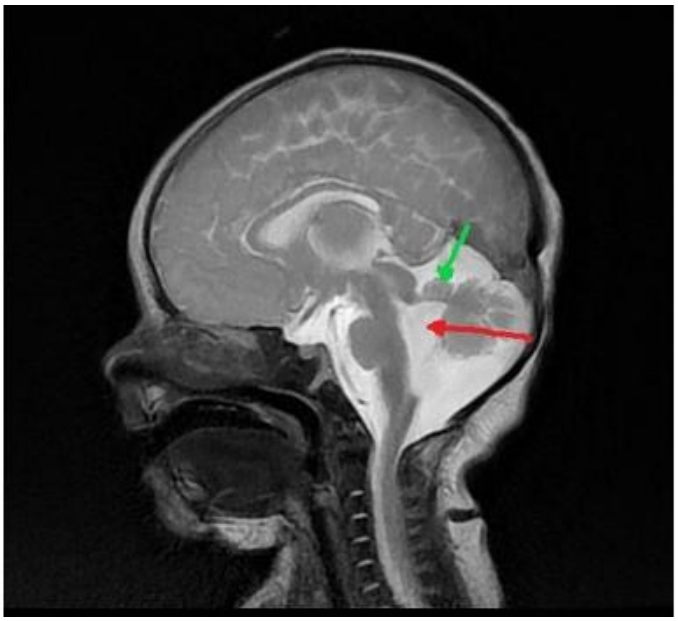
Based on these clinical and MRI findings, the patient was diagnosed with Joubert Syndrome and prescribed multivitamins. Detailed counseling was provided to the parents, and informed consent was obtained from the patient's guardian for this case report, adhering to the SCARE Criteria [11]



Anomalous shape of the midbrain characterized by the distinctive "molar tooth" appearance



Absence of the cerebellar vermis, with the cerebellar hemispheres positioned close together but not fused. The fourth ventricle exhibits a bat-wing configuration.



On axial T2-weighted MR image, the characteristic molar tooth sign is evident, featuring thickened, elongated, parallel, and horizontally oriented superior cerebellar peduncles (red arrow).

Discussion

Clinically, Joubert syndrome (JS) is characterized by three primary features: a distinct cerebellar and brain stem malformation known as the molar tooth sign (MTS), hypotonia, and developmental delays [12]. These manifestations are often accompanied by episodic tachypnea or apnea and distinctive eye movements. Respiratory abnormalities typically diminish over time, while truncal ataxia tends to develop progressively [10]. Gross motor milestone delays are commonly observed in JS patients [10]. Hypotonia is consistently highlighted as a significant clinical indicator in various studies [[12], [13], [14]], including a study by Maria et al. which found hypotonia present in all 59 patients examined [15]. Similarly, our patient exhibited decreased reflexes, muscle weakness, reduced muscle tone (hypotonia), tongue fasciculations, and down going plantar reflexes.

Considerations for differential diagnoses may include Dekaban-Arima syndrome, Senior-Loken syndrome, COACH syndrome, and Varadi-Papp syndrome [16]. Radiological diagnosis of JS often involves MRI scans, retinal examinations, renal ultrasonography, electroretinograms, and karyotyping, with most cases diagnosed based on radiographic findings [16].

Patients with JS frequently exhibit a hyperventilatory breathing pattern, particularly noticeable when awake and stimulated, often interspersed with central apnea. This abnormal breathing pattern is more pronounced in the neonatal period and tends to diminish by approximately 11 years of age.

Studies report varying prevalence rates of abnormal breathing patterns among JS patients: Maria et al. found 71%, Pellegrino et al. reported 68%, and Kendall et al. noted 44% [15, 16, 17]. Our patient did not experience respiratory complications.

Abnormal ocular movements, including nystagmus and ocular apraxia, are commonly observed in JS patients [16]. These visual abnormalities may present at birth and improve with age [16].

Additional visual findings associated with JS include strabismus, ocular coloboma, severe visual impairment, ptosis, and pigmentary changes in the fundus [18, 19]. However, our patient did not exhibit nystagmus at birth or later in development.

Although our patient did not present with any cerebral pathology, radiological findings revealed vermian cleft, MTS, and a "bat wing" sign. Multi-organ involvement is well-documented in JS, affecting organs such as the retina, liver, and kidneys, categorizing these conditions as ciliopathic syndromes. Currently, there is no curative therapy available for JS [16], underscoring the importance of early diagnosis and close monitoring for optimal patient outcomes.

To date, 34 pathogenic variants have been reported in JS, predominantly autosomal recessive (33 variants) with

one being X-linked [10]. Biallelic pathogenic variants support the diagnosis in 62-94% of cases [20]. Mutations in 13 ciliary or basal body genes account for approximately 50% of JS-related disorders (JSRD) [21], with studies identifying mutations in genes such as CC2D2A and ARL13B [16, 22]. Notably, CC2D2A mutations are prevalent, accounting for 10% of JSRD cases [22]. Bachmann-Gagescu et al. identified similar mutations in 20 out of 209 families studied [23].

Management of JS focuses on addressing symptoms such as abnormal breathing with stimulatory medications like caffeine or oxygen supplementation, and in rare cases, mechanical ventilation or tracheostomy. Therapy also includes speech, occupational, and physical therapies, as well as educational support tailored for visually impaired individuals. Surgical interventions may be necessary for conditions like polydactyly and strabismus [24]. In our case, the patient received multivitamins, and the parents were educated about supportive therapies. A limitation of our study was the lack of follow-up for the patient. We advocate for robust screening protocols and vigilance in suspected JS cases to enhance early detection and intervention.

Conclusions

Joubert Syndrome (JS) manifests with respiratory dysregulation, infantile hypotonia, developmental delays, nystagmus, oculomotor disturbances, and intellectual impairment. The variability in clinical presentations can lead to delayed diagnosis. Essential diagnostic criteria encompass clinical history, MRI findings, and genetic testing using a multi-gene panel. A hallmark MRI feature is the molar tooth appearance, often accompanied by cerebellar vermis hypoplasia and a batwing-shaped fourth ventricle. Management strategies focus on alleviating respiratory and feeding challenges, alongside rehabilitation addressing cognitive and behavioral issues.

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