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Case Report

Joubert Syndrome *Minor* - A Case Report

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Abstract

Joubert Syndrome (JS) is a rare genetic disorder characterized by developmental abnormalities in the cerebellum, affecting motor coordination and cognitive development.

We describe a case of a child initially observed at 4 months of age with a diagnosis of the Joubert Minor variant. The child presented atypical neuromotor development, mild cerebellar ataxia and oculomotor apraxia, but did not experienced apnea episodes, which are common in the classic form of the disease. Magnetic resonance imaging (MRI) findings were subtle, but resembled a "*molar tooth sign*", which is pathognomonic of JS. In keeping with the suggestive MRI findings, the definitive diagnosis was obtained through genetic testing, which identified a homozygous variant in the gene *CPLANE1*, related to JS. The treatment focused on physiotherapy and adapted pedagogical support.

This case highlights the importance of a comprehensive diagnostic evaluation, especially genetic, even when imaging indicators are evident, demonstrating the clinical and therapeutic heterogeneity of JS.

Keywords: Cerebellar Ataxia; Genetic Diagnosis; Joubert Syndrome; Joubert Minor; Molar Tooth Sign; Pediatric Age

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Introduction

Joubert Syndrome (JS) and Joubert Syndrome *Minor* represent a continuum of rare genetic disorders that showcase a unique interplay between neurodevelopmental anomalies and ciliary dysfunction. The neurological presentation of these conditions is rooted in the underdevelopment of the cerebellar vermis (which may be aplastic or small and dysplastic) and associated brainstem abnormalities (especially the absence of fiber decussation in the superior cerebellar peduncles and pyramidal tracts), which translate into the signature "*molar tooth sign*" (MTS) on MRI [1]. Clinically, JS is manifested through a constellation of symptoms, including hypotonia, ataxia, cognitive impairment, ocular manifestations [2], and in some cases, multi-organ dysfunction [3]. JS *Minor*, on the other hand, is characterized by more subtle manifestations, typically without the respiratory symptoms that are more pronounced in the classic form of JS [4].

Central to the pathogenesis of JS and its variants is the disruption of primary cilia function. Primary cilia are cellular appendages that play a pivotal role in cell signaling pathways and sensory functions, essential for proper development and function of various organ systems [5]. Pathogenic variants affecting over 30 genes related to ciliogenesis and ciliary function contribute to the complexity and heterogeneity of these syndromes [6]. Of these, mutations in the *CPLANE1* gene have been identified, which highlight the syndromes' diverse genetic underpinnings and the necessity for comprehensive genetic testing in the diagnostic process [7].

The therapeutic approach to managing JS and JS *Minor* is multidisciplinary, involving tailored interventions such as physiotherapy, occupational therapy, and specialized educational programs [8]. These strategies aim to address the neurodevelopmental challenges and improve the quality of life for affected individuals. Despite the milder prognosis associated with JS *Minor*, early and appropriate intervention remains paramount for optimizing patient outcomes [9].

While JS *Minor* typically predicts a milder clinical course, the need for early intervention remains critical. Appropriate management can significantly improve the quality of life and functional outcomes for individuals affected by this condition. The ongoing research and clinical observation contribute to a growing body of literature that highlights the clinical and genetic intricacies of JS and the vital importance of a detailed diagnostic approach in informing patient management strategies [10].

Both JS and JS *Minor* exemplify the complex interaction between genetics, clinical presentation, and patient care, which are crucial for advancing the understanding and management of these rare neurodevelopmental disorders [11].

Clinical Case

A 4-month-old infant, referred from an ophthalmology department, exhibited concerning symptoms since birth, including poor eye contact, a tendency for right gaze deviation, and a head turned preferentially to the same side with oculomotor apraxia. Despite

initial breastfeeding efforts, the child faced feeding difficulties, leading to poor weight gain and a transition to exclusive formula feeding from 1.5 months. Described as "*floppier, quieter, and sleepier than her siblings*," in neuropediatric evaluation at 4 month-old the infant presented poor head control and reduced movement in the left upper limb with normal osteotendinous reflexes. The perinatal period was uneventful and the parents are healthy and non-consanguineous.

By 6 months, with various therapies, including physiotherapy and occupational therapy, the parents noted improvements in eye contact and head control. Significant weight improvement was observed, although feeding milestones were delayed. An MRI, scheduled for later in the year, was planned to provide further diagnostic insights.

Throughout this period, the child underwent various assessments, including an electroencephalogram (EEG), metabolic studies, with plasma amino acids and urine organic acids, all without abnormalities. The MRI (Figures 1-4) later revealed a dysplastic appearance of the vermis, with moderate horizontalization and thickening of the superior cerebellar peduncles, resembling a milder form of the MTS suggestive of JS. These findings were crucial in raising suspicion for this hypothesis, and genetic testing subsequently confirmed the diagnosis of JS, specifically the minor variant type 17, with a homozygous likely pathogenic autosomal recessive variant identified in the CPLANE1 gene.

This clinical case underscores the diagnostic challenges of JS *Minor*. From the initial ophthalmological concerns to the neuropediatric evaluation, and finally to the genetic confirmation, the case highlights the necessity for a comprehensive, multi-faceted diagnostic approach.

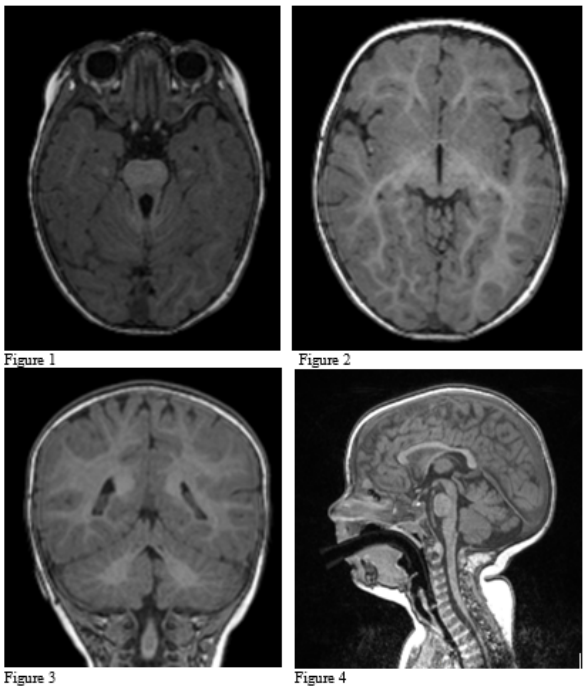

Figure 1 Figure 2

Figure 3 Figure 4

Figures 1-4: In the posterior fossa, particularly in the cerebellum, hypertrophy of the inferior and medial cortex (tonsillar) is observed, with slight right predominance. It causes deviation of the cerebellar vermis, particularly its lower lobes. On axial and coronal planes, the superior vermis seems abnormal, with irregular fissures and slightly hypoplastic the superior cerebellar peduncles are less oblique than normal-slight "*Molar Tooth Sign*".

Conclusion

This case of JS *Minor* in a pediatric patient exemplifies the intricacies and challenges of diagnosing and managing rare neurodevelopmental disorders. The patient's initial presentation with non-specific symptoms, such as poor eye contact, head preference, oculomotor apraxia and feeding difficulties, required careful consideration and a high index of suspicion for underlying neurological conditions when analyzing MRI findings. The pivotal role of MRI, particularly the identification of vermian abnormalities and horizontalization of the superior cerebellar peduncles (suggesting MTS in the context of possible JS), along with the conclusive genetic findings, underscores the importance of combining advanced imaging techniques and genetic testing in the diagnostic process. Additionally, this case emphasizes the value of early intervention and personalized therapeutic strategies, including physiotherapy and specialized educational support, in improving developmental outcomes for children with rare neurological disorders. The successful diagnosis and management of this case provides insights into the clinical and genetic nuances of JS, serving as a reminder of the ongoing need for heightened awareness, expertise, and a holistic approach in managing such complex conditions.

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Conflicts of Interest

The authors have declared that no competing interests exist.

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