

Joubert Syndrome

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Abstract

Joubert syndrome is a rare genetic disorder characterized by a range of neurological and multisystemic features. It primarily affects the brain, causing a malformation of the cerebellum and brainstem, a distinctive abnormality recognizable as the “molar tooth sign” on brain imaging.

Keywords: Genetic, Brain, Ciliopathy

Case Summary

A toddler was referred to pediatric neurology for evaluation of hypotonia and delay in reaching developmental milestones. An MRI of the brain was performed as part of a comprehensive workup.

Imaging Findings

MRI of the brain showed elongation and thickening of the superior cerebellar peduncles, giving the peduncles a “molar tooth” appearance (Figure 1).

Diagnosis

Joubert syndrome (JS).

Differential diagnoses based on clinical symptoms include Joubert syndrome-related disorders, cerebellar vermis malformations without the molar tooth sign (MTS) (which include Dandy-Walker malformation), X-linked cerebellar

hypoplasia, ataxia with oculomotor apraxia types 1 and 2 (AOA1 and AOA2), congenital disorders of glycosylation (CDG), 3C syndrome, pontocerebellar hypoplasias/atrophies, orofaciocigital syndromes II and III, and Meckel-Gruber syndrome.

Discussion

JS is a rare genetic disorder affecting between 1 in 80,000 to 100,000 individuals.¹ It was initially documented within the French-Canadian, Ashkenazi Jewish, and Arab populations.² Although JS is primarily inherited in an autosomal recessive manner, there are some cases of X-linked inheritance.^{1,3} The condition is caused by mutations in over 35 different genes that result in a range of phenotypic variations.^{1,4}

JS falls under the broader category of ciliopathies, a group of disorders that share genetic characteristics and exhibit overlapping clinical features stemming

from primary cilium dysfunction.³ Many of the proteins affected in these disorders play a crucial role in the cilium-centrosome complex. The cilium-centrosome complex's vital role in the normal functioning of various tissues explains why ciliopathies often affect multiple organ systems.⁵ As such, JS shares common features with other ciliopathies, such as nephronophthisis, Meckel-Gruber syndrome, and Bardet-Biedl syndrome.³

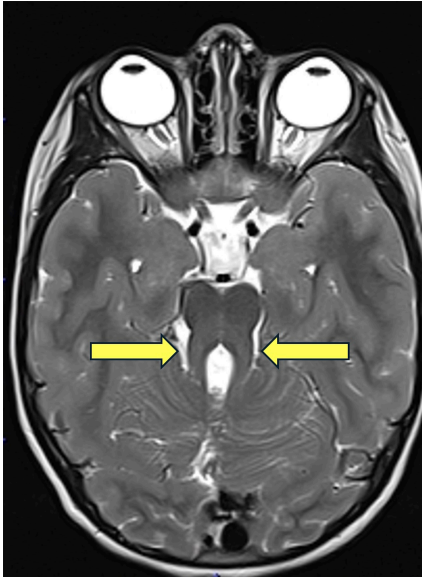
JS is characterized by abnormal brain development, specifically involving the cerebellum and brainstem. Individuals with JS typically display symptoms such as muscle weakness, impaired coordination, intellectual disability, difficulty with eye movement, respiratory issues, and abnormalities in other organ systems. A suspicion of JS is usually evident within the first months of life. JS is diagnosed based on clinical and imaging findings. The three criteria for diagnosis include (1) cerebellar malformation with molar tooth sign (MTS) (2) hypotonia, and (3) developmental delay.²

JS is known for its distinct cerebellar and brainstem malformation, which has a characteristic “MTS” on brain MRI (Figure 1) and CT.^{3,6} This unique radiological appearance is caused by a combination of conditions, including underdevelopment or absence of the cerebellar vermis, thick and horizontally oriented superior cerebellar peduncles,

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Figure 1. MRI T2-weighted sequence of the brain showed elongation and thickening of the superior cerebellar peduncles, giving the peduncles a “molar tooth” appearance.



and occasionally a deep interpeduncular fossa.³ Other imaging findings include an elevated roof of the fourth ventricle on a sagittal view and a cleft vermis on a coronal view, malrotation of the hippocampi, ventriculomegaly, dysgenesis of the

corpus callosum, polymicrogyria, heterotopia, and occipital encephalocele.⁶

Because of the range of mutations seen in JS, the condition can manifest with a variety of symptoms. For instance, JS can be classified into six phenotypic subgroups: pure JS, JS with ocular defect, JS with renal defect, JS with oculorenal defects, JS with hepatic defect, and JS with orofaciocaudal defects such as polydactyly.^{7,8}

There is no cure for JS. However, symptomatic therapy can improve the quality of life. Symptomatic therapies include seizure management, occupational, physical and speech therapy, and treatment of kidney, eye, and liver issues if they occur. With support, patients with JS can live into adulthood.

Conclusion

JS is a rare genetic disorder characterized by a range of neurological and multisystemic features. It primarily affects the brain, causing a malformation of the cerebellum and brainstem, a distinctive abnormality recognizable as the “MTS” on brain imaging.

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