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Case Series

Joubert Syndrome: A Case Report of Three Patients and Review of Literature

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Abstract

Introduction: Joubert syndrome (JS) is a rare autosomal recessive neurodevelopmental disorder characterized by the pathognomonic "Molar Tooth Sign" (MTS) on brain MRI, resulting from cerebellar vermis hypoplasia and abnormal superior cerebellar peduncles. It is now recognized as a multisystem ciliopathy with variable neurological, ocular, renal, and hepatic involvement.

Case Presentation: We report three pediatric Moroccan cases of JS. The first was an 8-year-old girl presenting with psychomotor delay, cerebellar ataxia, nystagmus, and conjunctival telangiectasia, with MRI revealing severe vermian hypoplasia and the MTS. The second case was a 19-month-old girl, born of consanguineous parents, who presented with developmental delay, hypotonia, facial dysmorphism, and retinal abnormalities; brain MRI showed the MTS and thinning of the corpus callosum. The third case was a 2.5-year-old girl with psychomotor delay and dysmorphic features, whose MRI confirmed the MTS. In all cases, management was symptomatic and supportive, consisting of functional rehabilitation, psychomotor and speech therapy, and recommendations for specialized education.

Discussion: These cases illustrate the clinical and radiological variability of JS and emphasize the importance of recognizing the MTS as a diagnostic hallmark. Given its multisystemic nature, early diagnosis, genetic counseling, and multidisciplinary follow-up are essential for optimal outcomes.

Conclusion: Joubert syndrome remains a clinically and genetically heterogeneous ciliopathy. Our case series highlights the diagnostic value of neuroimaging and the need for comprehensive, multidisciplinary management to improve prognosis and quality of life.

Keywords: *Joubert Syndrome; Molar Tooth Sign; Case Report; Ciliopathy; Neurodevelopmental Disorder*

Introduction

Joubert syndrome (JS) is a rare autosomal recessive neurodevelopmental disorder first described in 1968. It is defined by a distinctive midbrain-hindbrain malformation known as the "Molar Tooth Sign" (MTS) on brain MRI, which reflects cerebellar vermis hypoplasia, thickened superior cerebellar peduncles, and a deep interpeduncular fossa. Clinically, affected individuals present with hypotonia, abnormal eye movements, abnormal respiratory control in infancy, and later with ataxia and developmental delay.

Although initially considered a purely neurological disorder, JS is now recognized as a multisystem ciliopathy, with frequent involvement of the retina, kidney, liver, and skeleton. The prevalence is estimated between 1 in 55,000 and 1 in 200,000 live births, though it may be

underdiagnosed. More than 35 genes have been implicated, all encoding proteins of the primary cilium, highlighting the central role of ciliary dysfunction in the pathogenesis of the syndrome.

The clinical spectrum of JS is broad, ranging from isolated neurological impairment to severe, progressive multiorgan disease. Early recognition and multidisciplinary care are therefore essential for prognosis and management.

In this article we report three Moroccan pediatric cases with neurological and occular presentations

Case Reports

Case 1

An 8-year-old girl with a history of psychomotor developmental delay and recurrent respiratory infections with dyspnea was admitted to the pediatric department of the Military Hospital of Rabat for walking disorder. Clinical examination revealed cerebellar ataxia, nystagmus, and bilateral conjunctival telangiectasias. Laboratory investigations were normal, and karyotype analysis was normal (46,XX). Brain MRI demonstrated vermian hypoplasia, enlargement of the fourth ventricle, and elongation with deformation of the cerebellar peduncles. In the absence of a specific treatment, management was symptomatic and included functional rehabilitation, psychomotor therapy, speech therapy and recommendation for education in a specialized center.

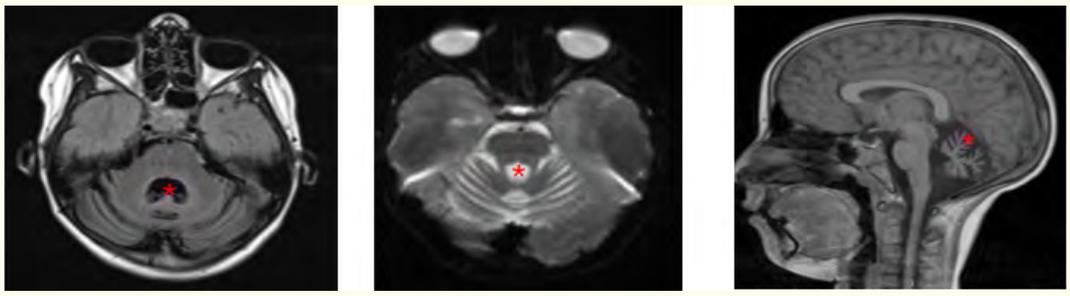

Figure 1: *Brain MRI showing severe cerebellar vermis hypoplasia, enlarged cisterna magna, dilated fourth ventricle (bat wing sign), and elongated parallel cerebellar peduncles (Y-shaped appearance).*

Case 2

A 19-month-old female infant, born from a first-degree consanguineous marriage, was admitted for psychomotor delay associated with hypotony and nystagmus. On examination, she presented with facial dysmorphism, axial hypotonia, and growth and language retardation. Ophthalmologic evaluation revealed retinal dysmorphism. Laboratory tests were normal, and the karyotype was 46,XX. Brain MRI showed the characteristic "molar tooth sign," vermian hypoplasia, deformation of the fourth ventricle (umbrella-shaped appearance), and thinning of the corpus callosum. Management was based on functional rehabilitation, psychomotor therapy.

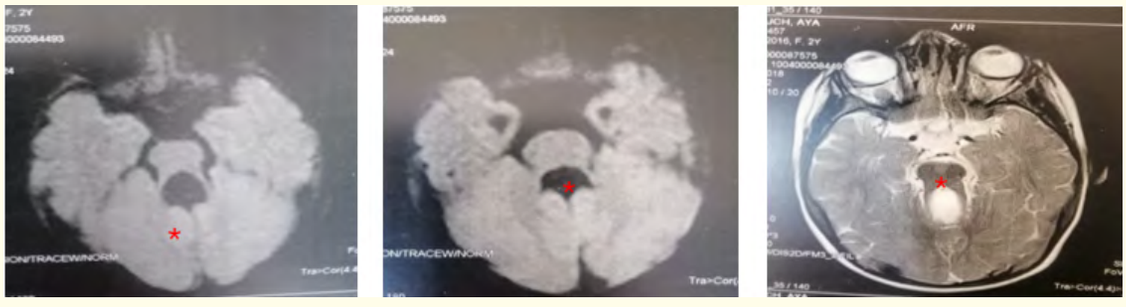

Figure 2: *Brain MRI showing thickened, elongated, and parallel superior cerebellar peduncles with an enlarged fourth ventricle ('bat wing' or 'umbrella' sign) and agenesis of the cerebellar vermis.*

Case 3

A 2.5-year-old girl, born from a first-degree consanguineous marriage, was admitted for psychomotor developmental delay. Clinical examination revealed facial dysmorphism. Laboratory investigations were normal, and the karyotype was normal (46,XX). Brain MRI demonstrated vermian hypoplasia associated with the "molar tooth sign". Since there is no specific cure, treatment focused on symptom relief and supportive care, including: Functional rehabilitation, Psychomotor training, Speech and language therapy.

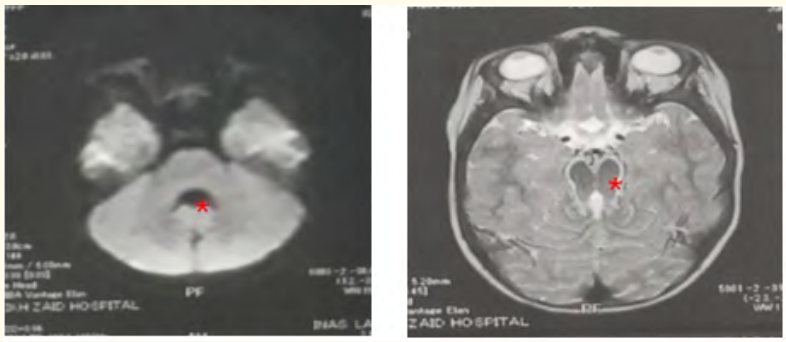

Figure 3: *Brain MRI showing thickened, elongated, and parallel superior cerebellar peduncles with an enlarged fourth ventricle ('umbrella' sign).*

Discussion

Joubert syndrome (JS) is a rare autosomal recessive neurodevelopmental disorder characterized by a pathognomonic midbrain-hindbrain malformation, the "Molar Tooth Sign" (MTS), which reflects cerebellar vermis hypoplasia, thickened and elongated superior cerebellar peduncles, and a deepened interpeduncular fossa. Since its initial description by Marie Joubert in 1968, more than 35 genes have been implicated, all encoding proteins involved in the structure or function of the primary cilium. Consequently, JS belongs to the expanding group of human disorders known as ciliopathies.

Clinically, JS is highly heterogeneous. The core neurological features include hypotonia, abnormal ocular movements (especially oculomotor apraxia and nystagmus), abnormal respiratory pattern in infancy, developmental delay, and ataxia. However, the condition frequently extends beyond the central nervous system, affecting multiple organs. Retinal dystrophy, nephronophthisis, congenital hepatic fibrosis, and polydactyly are common systemic associations, leading to the concept of Joubert syndrome and related disorders (JSRD). The clinical spectrum has been subdivided into distinct subgroups, including JS with ocular, renal, hepatic, or orofaciodigital involvement. Such variability underscores the need for a multidisciplinary approach to diagnosis and management.

Radiologically, brain MRI remains the gold standard for diagnosis. The detection of the MTS is crucial, though in some cases it may be subtle and require review by an experienced neuroradiologist. In addition, other malformations such as corpus callosum dysgenesis, occipital encephalocele, or cortical polymicrogyria may coexist. In our reported cases, MRI findings were consistent with the classic neuroradiological hallmarks, supporting the clinical suspicion and establishing the diagnosis.

Genetic testing has become an essential component of JS evaluation. Identifying the causative mutation not only confirms the diagnosis but also provides prognostic information, as specific genotypes are associated with distinct risks for retinal, renal, or hepatic disease. JS is primarily caused by mutations in genes that encode proteins involved in ciliogenesis and primary cilia function. Over 30 genes have been associated with JS, leading to its classification into various subtypes. Notably, mutations in genes such as CEP290, TMEM67, and CC2D2A

have been frequently identified. These genetic mutations disrupt normal ciliary development and function during early embryogenesis, leading to a vast array of symptoms and pathologies. The genetic heterogeneity of JS contributes to its diverse clinical presentations and complicates diagnosis and genetic counseling.

Management of JS remains supportive and multidisciplinary, involving neurologists, geneticists, ophthalmologists, nephrologists, and hepatologists. Regular follow-up is necessary to monitor neurodevelopment, vision, renal function, and hepatic status. Early rehabilitation therapies, including physical, occupational, and speech therapy, can improve functional outcomes. With advances in molecular research, future gene-specific therapies may become feasible, making precise genetic characterization even more relevant.

The prognosis of JS is variable and largely dependent on the extent of multiorgan involvement. Neurologically, many patients achieve independent ambulation, although ataxia and coordination deficits often persist into adulthood. Cognitive outcome ranges from normal intelligence to severe intellectual disability. Visual prognosis depends on the severity of retinal dystrophy, which may lead to progressive vision loss. Similarly, renal disease, often manifesting as nephronophthisis, may progress to end-stage renal failure, while hepatic fibrosis can result in portal hypertension. Early detection of these complications is therefore critical [1-9].

Conclusion

JS represents a clinically and genetically heterogeneous ciliopathy with hallmark neuroimaging findings and multisystem involvement. The cases presented reinforce the importance of recognizing the MTS on MRI and underline the need for comprehensive, multidisciplinary evaluation. Early diagnosis and follow-up not only improve clinical outcomes but also provide families with essential genetic counseling and prognostic guidance.

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