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Beyond Childhood: Joubert Syndrome in a 34-Year-Old Female – A Case Report

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Abstract
A 34 years old female presented with developmental delay, hypotonia, ataxia, oculomotor apraxia, and intellectual disability. Cranial magnetic resonance imaging (MRI) revealed molar tooth sign (MTS) which is pathognomonic for Joubert Syndrome (JS). Joubert syndrome is a congenital autosomal recessive disorder that affects the area of the brain responsible for balance and coordination. Most cases are diagnosed in the neonatal period and most do not survive into adulthood. We report a case of Classic JS diagnosed in an adult, a first in our institution.

Keywords: Joubert Syndrome, Molar Tooth Sign

1. Introduction

Joubert syndrome (JS) is a rare autosomal recessive disorder. It is estimated to affect between 0.5 per 100,000 to 1.8 per 100,000 in children.(Al-Smair et al., 2022) It is characterized by hypotonia, ataxia, abnormal breathing patterns, sleep apnea and abnormal eye movements including nystagmus and oculomotor apraxia, developmental retardation with evidence of neuropathologic abnormalities of the cerebellum and brainstem.(Bainade et al., 2020) It is radiographically characterized by hypoplasia of the cerebellar vermis and a molar tooth sign (MTS) that can be seen on magnetic resonance imaging (MRI).(Al-Smair et al., 2022) More than thirty genes have been identified that cause Joubert syndrome. Mutations in the genes associated with Joubert syndrome lead to problems with the structure and function of primary cilia, which can disrupt important chemical signaling pathways during development but is not yet completely understood how it leads to specific developmental abnormalities. The signs and symptoms of this condition vary among affected individuals. Although some survive into adulthood with variable cognitive and motor impairments, depending on whether the cerebellar vermis is entirely absent or partially developed, many others do not survive.(Al-Smair et al., 2022) JS is mostly presented as sporadic cases. However, there are some familial incidents which appear to be inherited via recessive genes.

Here, we present a rare case of an adult female with Joubert Syndrome. We report typical features and characteristics in correlation to its radiologic findings and management. This is the first reported case of Joubert Syndrome in this institution.

2. Case Report

A 34-year-old female presented to our out-patient department with parental complaints of generalized chorea of the head, neck, arms and legs with difficulty in ambulation and speech. Her developmental history could not be followed up entirely in detail. But here are some of the developmental history of the patient that we were able to extract from the parent: she was born at home, delivered by a traditional birth attendant via vaginal delivery in breech presentation. She was exclusively breastfed up to 2 months old then formula milk-fed up to age 5. She was able to roll over from back to stomach at 8 months old and was able to stand and walk at 6 years old, when she was also noted to have abnormal movements. At 7 years old, her language included one-syllable words such as "nay". She had no history of problems in respiration or breathing.

Pertinent physical examination findings showed her eyes looking into different directions, atrophic changes in both arms and feet, and hypotonia. Neurological examination showed ptosis of the left eye, truncal ataxia, severe dysarthria, and global hyperreflexia (Fig.1). There was absence of retinal anomalies or degeneration on ophthalmologic examination. In her psychiatric evaluation, she was deemed to have lack of appropriate awareness to surrounding environmental changes. She is able to follow simple commands such as "raise your hands" and to identify body parts by pointing to it, and was able to communicate by answering yes or no. She can identify the numbers 1 to 4 by answering through fingers. During the entire consultation her communication was done with the assistance of her mother. She was notably stuttering and severely dysarthric with one syllable only. The patient showed abnormal gait, had major difficulty in walking that of the appearance of a staggering-like gait disorder. She could not perform her own personal care activities, such as independent bathing and dressing.

Figure 1: Images of patient showing truncal ataxia.

A cranial MRI was done which revealed thickened and elongated superior cerebellar peduncle giving the midbrain a molar tooth appearance; the 4th ventricle showed a "bat wing" appearance, cerebellar vermis appeared mildly deformed (Fig. 2,3,4). The diagnosis of Joubert syndrome was made based on the patient's history, physical examination, and pathognomonic neuroimaging features. No genetic testing was done due to its unavailability in our institution.

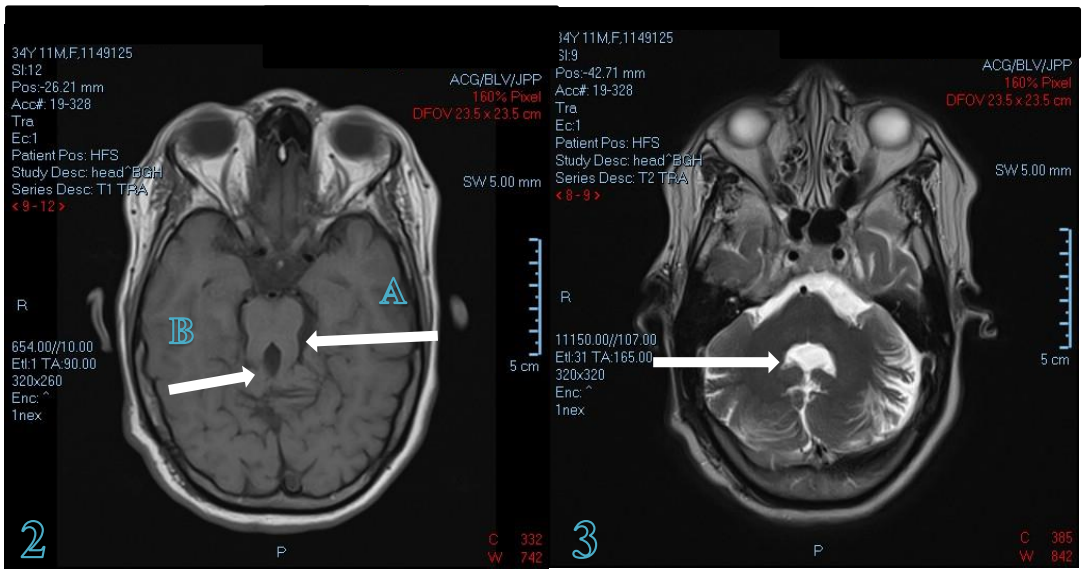

Figure 2: Axial T1 image showing (A) elongated superior cerebellar peduncles, (B) a hypoplastic cerebellar vermis (A, B) showing characteristic molar tooth sign; Figure 3: Axial T2 image showing the batwing shape of the fourth ventricle

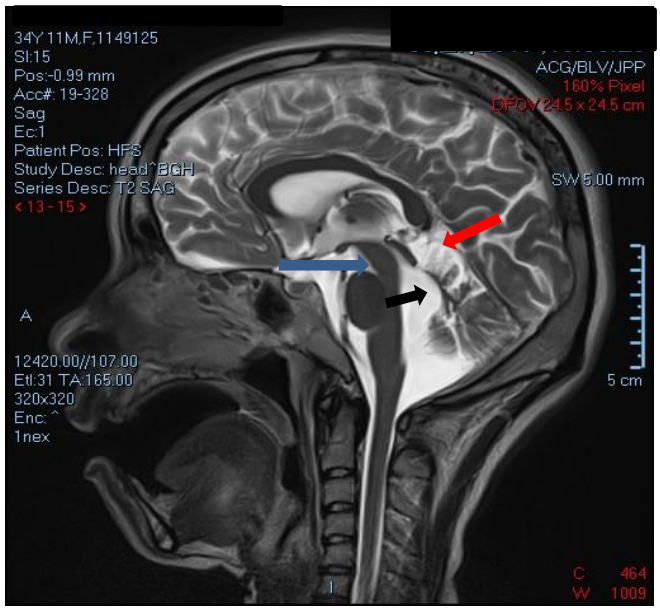

Figure 4: Midsagittal T2 -weighted MR image shows severe vermian hypoplasia-dysplasia (red arrow) and enlargement of the fourth ventricle with rostral shifting of fastigium (black arrow), deepened interpenduncular fossa (blue arrow)

3. Discussion

Joubert syndrome (JS) is a rare autosomal recessive neurodevelopmental disorder first identified in 1969 by Marie Joubert in siblings with agenesis of the cerebellar vermis, episodic hyperpnea, abnormal eye movements, ataxia and intellectual disability.(Elhassanien et al., 2013, Brancati et al., 2010) It is estimated to affect between 0.5 per 100,000 to 1.8 per 100,000 in children.(Al-Smair et al., 2022) However, this estimate may be too low because Joubert syndrome has such a large range of possible features, hence, is likely underdiagnosed. The mean age of diagnosis in JS is typically 33 months.(Al-Smair et al., 2022, Bainade et al., 2020) Many of the clinical symptoms of Joubert syndrome are evident in infancy and most affected children have delays in gross motor milestones. Our patient was diagnosed at 34 years old, but could have been diagnosed earlier if the parents sought consult at the first sign of delay in her development. The most common features are lack of muscle control (ataxia), abnormal breathing patterns (hyperpnea), sleep apnea, abnormal eye and tongue movements and low muscle

tone.(Brancati et al., 2010, Bachmann-Gagescu et al., 2019) Intellect ranges from normal to severe intellectual disability.

Classic or Pure JS is characterized by the triad of hypotonia in infancy with later development to ataxia, developmental delays, and pathognomonic brainstem and cerebellar malformation known as the molar tooth sign (MTS) on MRI.(Al-Smair et al., 2022, Akhtar et al., 2019) This syndrome is classified into two groups on the basis of presence or absence of retinal dystrophy. Those who have retinal dystrophy have decreased survival rates and have a higher prevalence of multicystic renal disease.(Bainade et al., 2020) Our patient has no retinal dystrophy thus decreasing the morbidity associated with it.

A group of disorders known as Joubert syndrome and other related disorders (JSRD) share the MTS and some clinical features of JS but also have other manifestations that may represent a distinct syndrome.(Bainade et al., 2020, Elhassanien et al., 2013) JSRD are categorized according to a newly adopted classification system based on genotype-phenotype correlation: Pure JS, JS with ocular defect, JS with renal defect, JS with oculo-renal defects, JS with hepatic defect, and JS with orofaciodigital defects.(Bainade et al., 2020, Brancati et al, 2010, Akhtar et al., 2019)

Another feature of JS is its neuroradiologic characteristics, specifically in magnetic resonance imaging. MRI studies of patients with JS show a constellation of abnormalities of the central nervous system. The primary MR imaging features of JS are thinning of the isthmus with widened interpeduncular fossa, thickened superior cerebellar peduncles, hypoplasia of the cerebellar vermis with fourth ventricular deformity, rostral shift of fastigium, and sagittal vermian cleft due to incomplete fusion of the two halves of vermis.(Bainade et al., 2020, Choh et al., 2009) “Molar tooth sign” encompasses deeper than normal posterior interpeduncular fossa, prominent or thickened superior cerebellar peduncles, and vermian hypoplasia or dysplasia.(Bainade et al., 2020, Choh et al., 2009, Kendall et al., 1990) The characteristic neurologic finding of JS was shown in our patient’s MRI.

When a diagnosis of JS is suspected, a detailed cranial MRI to evaluate for the “molar tooth sign” is essential, as well as other evaluations that have been previously discussed. Because of the marked heterogeneity in this group of disorders and the relatively high frequency of associated medical conditions, it is difficult to make generalizations about outcomes.

Our patient presented with typical findings of hypotonia in infancy manifested as the delayed rolling over from back to tummy, which was also notably delayed for age. She presented with ataxia, nystagmus and oculomotor dysfunction, developmental delays and intellectual disability. No respiratory dysregulation was noted in our patient but the patient’s late diagnosis may account for improvement in breathing dysregulation with age. The patient’s MRI findings of a deeper than normal posterior interpeduncular fossa, thickened superior cerebellar peduncles, and vermian hypoplasia or dysplasia were consistent with the MTS. A fourth ventricle “bat wing” appearance was also seen.

Although the clinical presentation of JS is heterogenous, the diagnosis of classic or pure JS is based on the presence of the following three: molar tooth sign on MRI, hypotonia in infancy with later development of ataxia, and developmental delay or intellectual disabilities.(Al-Smair et al., 2022) Also, any instance that involve the molar tooth sign with the additional signs and symptoms, a diagnosis of JS is usually considered. Our patient satisfies all the above criteria and is diagnosed with classical JS.

4. Conclusion

Joubert Syndrome is a rare autosomal recessive disease which affects approximately 1/80,000 to 1/100,000 people worldwide. The first reported case in this institution was a 34 years old female who consulted in our out-patient clinic. She presented with hypotonia, abnormalities in gait and balance, developmental delay, and the pathognomonic “molar tooth sign” in her MRI. These are the diagnostic criteria suggested by Maria et al for the diagnosis of Joubert Syndrome. A suspicion of JS in a patient should warrant further investigation by neuroimaging study, i.e. MRI, to show the pathognomonic “molar tooth sign”. Genetic studies may also be done if available.

Early recognition and diagnosis of JS is important for early initiation of interventions, monitoring, and supportive therapy.

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