Radiological Features of Joubert's Syndrome

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Abstract

Joubert syndrome (JS) is a rare autosomal recessive disorder. All patients affected by this syndrome presented a characteristic picture of cranial fossa malformations, called "molar tooth sign." This sign is defined by the presence in axial section at the level of a deck/midbrain, of hypo/dysplasia of the cerebellar vermis, abnormally deep interpeduncular fossa and horizontalized thickened and elongated superior cerebellar peduncles. Although "molar tooth sign" is peculiar of JS, other radiological findings have been also reported in these patients. Here, the authors briefly assumed the principal magnetic resonance imaging findings of JS.

Keywords
- Joubert syndrome
- radiological findings
- "molar tooth sign"

Introduction

Joubert syndrome (JS) is a rare congenital systemic disease,[1] described for the first time in 1968 by Dr. Marie Joubert in patients with agenesis of the cerebellar vermis, episodic hyperpnea, abnormal eye movements, ataxia, mental retardation, and occipital meningoencephalocele. Similar to other syndromes,[2–5] this condition is sometimes associated with other eye abnormalities (such as retinal dystrophy, which can cause vision loss), kidney disease, liver disease, skeletal abnormalities (such as the presence of extra fingers and toes), and hormone (endocrine) problems.[6–8] Vermian hypoplasia and abnormalities of the pontomesencephalic junction are the distinguishing features that lead to the diagnosis of JS.[9,10]

All patients presented a characteristic picture of cranial fossa malformations, called "molar tooth sign" (MTS), which has been reported in approximately 85% patients with JS (►**Fig. 1**). This sign is defined by the presence in axial section at the level of a deck/midbrain, of hypo/dysplasia of the cerebellar vermis, abnormally deep interpeduncular fossa, and horizontalized thickened and elongated superior cerebellar peduncles. Since the first description, many cases were reported with expansion of the phenotype and nosological and genetic evolution.

Several disorders are more difficult to analyze because their genetic causes are often unclear, and they do not follow the patterns of inheritance. Fortunately, molecular characterization can contribute to valuable information in terms of the patient's diagnosis, prognosis, and the potential for

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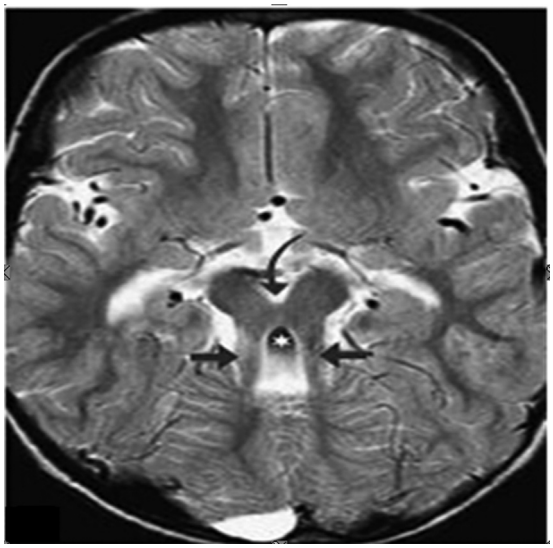

Fig. 1 The roots of this ''tooth'' are represented by thick and perpendicular non-decussated superior cerebellar peduncles, while the crus cerebri (cerebral peduncles) of the brain stem, with the deep interpeduncular fossa in between, represent the body of the ''tooth.''

treatment with targeted therapy.[11] In the last decade, omic-based and experimental investigations yielded an increasing molecular and pathway complexity as causative of several pediatric intellectual disabilities and congenital brain anomalies, including ciliopathies and a wide array of neurodevelopmental disorders.[12–20] This is observed in the context of advances brough by basic sciences in regard to the molecular understanding of many pediatric neurological conditions, both rare and ultra-rare, associated with either genetic and non-genetic etiologies.[21–31] Several pathomechanisms have been identified, allowing a better pediatric-patient care in terms of clinical diagnosis, prognosis, and treatment.[32–39] Pediatric developmental disorders can often result by the combination of environmental and genetic factors and their aberrant interplay may sometimes lead to disease expression and metabolic and neurological abnormalities as part of the clinical phenotype in some cases.[40–48] These molecularly complex disorders may include a variety of monogenic as well as polygenic/genetically complex conditions with increasingly widened molecular heterogeneity and implicating a wide array of disease mechanisms that could potentially affect brain development.[49–56]

Although several genetic mechanisms are involved in the pathogenesis of JS,[57–62] the abovementioned neuroradiological characteristics are exclusively reported in JS. Moreover, other syndromes with posterior-fossa malformations, including Dekaban-Arima, Senior-Löken and cerebellar vermis hypoplasia/aplasia, oligophrenia, ataxia, coloboma and hepatic fibrosis (COACH), frequently lead to diagnostic dilemmas. Here, the authors briefly assumed the principal radiological findings of JS.

The Principal MRI Findings of Joubert Syndrome

The diagnosis is based on characteristic imaging features on computed tomography (CT) or magnetic resonance imaging (MRI). The principal MRI findings of JS are: the MTS (deep interpeduncular fossa with a narrowing of isthmus, fourth ventricle deformity with hypoplasia of the vermis, thickening of the superior cerebellar peduncle, fastigium rostral shift, and sagittal vermian cleft) and the fourth ventricle batwing, resulting in distortion and dilatation of the fourth ventricle. The fastigium is shifted rostrally, and the fourth ventricle assumes a rectangular instead of a normal triangular shape, as seen on midline sagittal images (►**Fig. 2**). Additionally, cerebellar folial disorganization, temporal lobe hypoplasia, ventriculomegaly, occipital encephalocele, atretic encephalocele, callosal dysgenesis, periventricular, subcortical heterotopia, and hypomyelination were also reported. The vermian lobules are generally dysplastic, ranging from hypoplasia to complete dysplasia. Cerebellar hemispheres, occupying most of the posterior fossa, are less involved and are nearly normal and, in axial images, are separated only by a thin cleft. On the coronal images, due to absence of the posterior vermian lobe, the cerebellar hemispheres, being divided only by a midline cleft, can be appreciated as "buttock sign" (►**Fig. 3**). Generally, the superior cerebellar peduncles are thin (approximately 1–2 mm), dysplastic, asymmetric, and are oriented obliquely downward. In JS, the interpeduncular fossa is deep and the isthmus is variably thinner than normal and there is a lack of decussation of the superior cerebellar peduncles. Dilatation of the posterior fossa cisterns (wide prepontine cistern) was noted in almost all

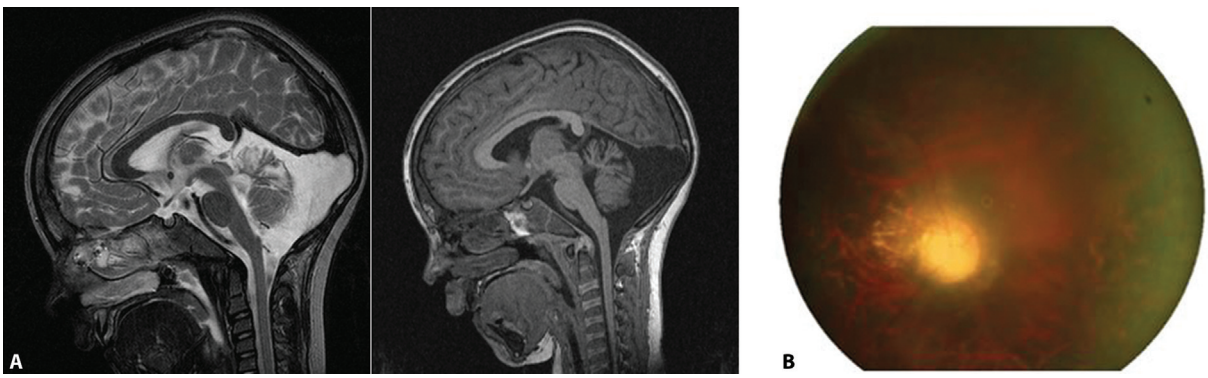

Fig. 2 (**A**, **B**) Dilatation of the fourth ventricle in midline sagittal images.

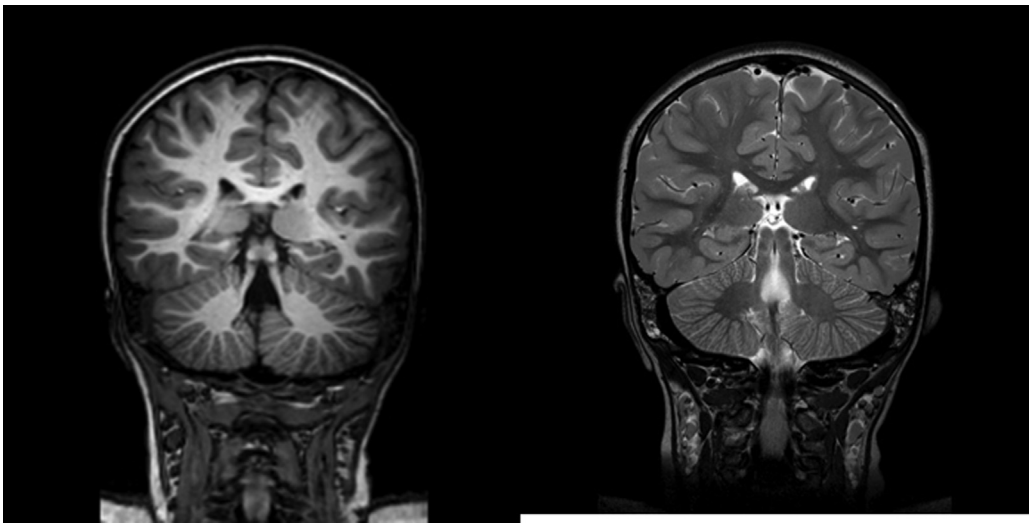

Fig. 3 The ''buttock sign'' on the coronal images.

the patients with a giant cisterna magna.[63] Among other findings, it has also reported dysgenesis of the corpus callosum, mild to moderate cerebral atrophy with prominent ventricles, absent septum pellucidum,[64,65] and misleading presentation of cases as pseudo-tumor cerebri.[66]

The Diffusion Tensor Imaging Technique and Joubert Syndrome

Although all patients reported "MTS," radiologic–genotype correlation in JS is a difficult task because of the low estimated prevalence. Recently, diffusion tensor imaging (DTI) technique has given an insight into the underlying complex radiological findings in JS, especially on fiber tract abnormalities including absence and/or thinning of the dorsal pontocerebellar tract, abnormal thickening of the ventral pontocerebellar tract, abnormal decussation of superior cerebellar peduncles, and finally, the absence of red dot sign.[67]

The Principal Ultrasound Findings of Joubert Syndrome

The shepherd's crook sign must be also considered when evaluating patients for suspected JS. The arc of the crook is made by abnormal superior cerebellar peduncle and cerebellar hemisphere.[68]

There was a shepherd's crook in sagittal views of posterior fossa where the shaft of crook is made by the brainstem and pons. By ultrasound, the shepherd's crook sign was seen through the posterior fontanelle only. CT imaging also showed the shepherd's crook sign.[69]

Radiological Prenatal Findings and Joubert Syndrome

Fetal cerebral MRI can be also useful when evaluating patients for suspected JS, often in families at high risk of recurrence and/or on the ultrasound finding of abnormal posterior fossa anatomy or the presence of associated suggestive features. However, prenatal sonographic findings in fetuses are relatively aspecific and can include increased nuchal translucency, enlarged cisterna magna, cerebellar vermian agenesis, occipital encephalocele, ventriculomegaly, hypoplastic phallus, renal cysts, and polydactyly. Authors have described in-utero visualization of the "MTS" with ultrasound[70] between 22 and 27 weeks of gestation. However, it is not possible to demonstrate vermian hypoplasia before the 18th gestational week.[71] The mature normal fourth ventricle can be assessed from 18 weeks of gestation onward. However, the features of abnormal fourth ventricle are rarely described. The fourth ventricle, an ependymal cavity situated in the bulbopontine area of the brain, appeared enlarged and, in sagittal view, appears rounded, lacking the characteristic posterior "fastigial point" and with a convex roof. Moreover, due to the lack of normal decussation of cerebellar peduncles, floor of fourth ventricle is also abnormal.[71,72]

Authors' Contribution

C.C. did the conceptualization. CC and MDC did the investigation. G.S. and E.C. contributed toward the resources. A.S., G.I., D.I., and E.G. did the data curation. E.D. and F. G. wrote and prepared the original draft. A.S. and A.C. wrote the review and edited it. M.F. and F.B. did the supervision. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

The data presented in this study are available on request from the corresponding author.

Conflict of Interest

None declared.

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