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CASE STUDY

FAMILIAL JOUBERT SYNDROME-A CASE REPORT OF TWO SIBLINGS

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ABSTRACT

Joubert syndrome (JS) is a rare autosomal recessive disorder characterized by hypotonia, ataxia, abnormal eye movement, and intellectual disability with a distinctive mid-hindbrain malformation (the "molar tooth sign"). Variable features include retinal dystrophy, cystic kidney disease and polydactyl. Recently, substantial progress has been made in our understanding of the genetic basis of JS, including identification of seven casual genes (NPHP1, AHI1, CEP290, RPGRIP1L, TMEM67/MKS3, ARL13B and CC2D2A.) Despite this progress, the known gene accounts for <50% of cases and few strong genotype-phenotype correlations exist in JS; however, genetic testing can be prioritized based on clinical features. We present to you two sibling with JS, diagnosed on the basis of clinical feature and neuroimaging

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INTRODUCTION

Joubert syndrome (JS) is first described by Canadian neurologist Marie Joubert in 1969. It is a rare autosomal recessive disorder presenting with congenital hypotonia evolving into ataxia, developmental delay, and occulomotor apraxia or abnormalities of respiratory pattern or both. Molar tooth sign is a characteristic Magnetic Resonance appearance of brainstem which results from cerebellar vermis hypoplasia and thick, elongated superior cerebellar peduncles and abnormally deep interpeduncular fossa. The presence of molar tooth sign and appropriate clinical features is almost diagnostic of JS. Joubert syndrome is a ciliopathy, characterised by defective primary ciliary function.

CASE REPORT

A 17 months female child, 3rd living issue of a non-consanguineous marriage, presented with complaints of not achieving milestones as per her age since early infancy. She had global developmental delay with failure to thrive and subtle dysmorphic features- flat forehead, protruding tongue, hypertelorism, epicanthal fold, absent dentition. She had axial hypotonia, right eye ptosis and abnormal eye movement. She had partial neck holding and had no bidextrous reach. There was no organomegaly. Cardiac and respiratory systems were normal on auscultation. The axial T1-weighted and T2-weighted Magnetic resonance (MR) images showed abnormally oriented and thickened superior cerebellar peduncles that resulted in a "Molar Tooth" configuration. The more caudal T2- and T1-weighted axial MR images showed the fourth ventricle shaped like a "Bat Wing". Furthermore, T2-weighted axial MR images showed hypoplasia of the vermis which resulted in median approach of the two cerebellar hemispheres but without evidence of a posterior fossa cyst. Based on clinical and magnetic resonance imaging (MRI) findings, diagnosis of JS was made and parents were counseled. Elder sibling, who was 6 years old, had similar clinical features and her MRI done was suggestive of Joubert syndrome. Ophthalmological and BERA done for both siblings were normal. Genetic counselling of parents was done.

DISCUSSION

JS is a rare autosomal recessive disorder characterized by clinical and characteristic neuroradiological findings. Key neuroimaging features of JS include deep interpeduncular fossa, narrow isthmus (the ponto-mesencephalic junction), lack of decussation of superior cerebellar peduncles, dilated, distorted, and rostrally deviated fourth ventricle giving "Bat Wing" appearance, thick vertical superior cerebellar peduncles, rostral deviation of fastigium of fourth ventricle, wide foramen of Magendie and dysplastic vermis.

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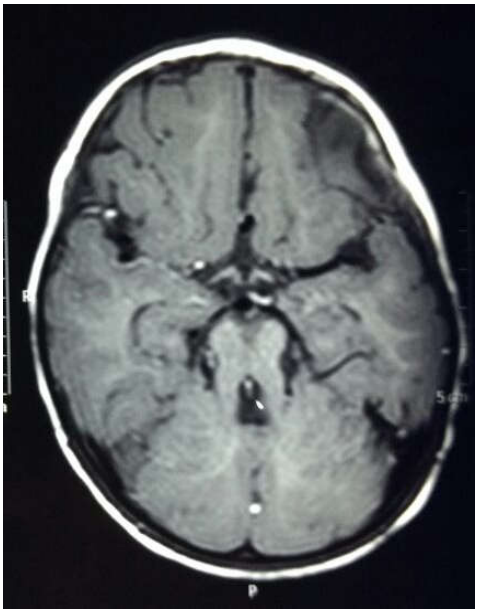

Fig. 1. T2W axial image showing molar tooth sign

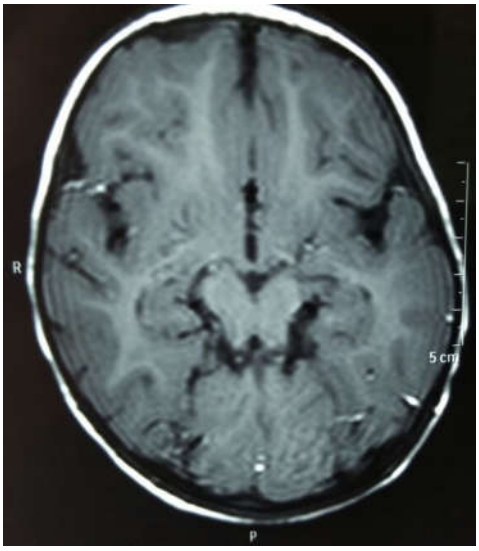

Fig. 2. T1W axial image showing bat wing appearance of the fourth ventricle

The brain stem, predominantly the medulla and upper cervical spinal cord, tends to be small. "Molar tooth sign" encompasses deeper than normal posterior interpeduncular fossa, prominent or thickened superior cerebellar peduncles, and vermian hypoplasia or dysplasia. (Saraiva and Baraitser, 1992; Kendall *et al*., 1990) Although the diagnostic criteria for JS have not been established, the clinical features frequently mentioned as essential for the diagnosis of classic JS comprise: (Joubert *et al*., 1969; Saraiva and Baraitser, 1992; Steinlin *et al*., 1997; Parisi and Glass, 2006).

1. Hypotonia in infancy.
2. Developmental delay/mental retardation.
3. One or both of the following (not absolutely required but helpful for the diagnosis):
   a. Irregular breathing pattern in infancy (intermittent tachypnea and/or apnea).
   b. Abnormal eye movements.

Our patient had all the clinical symptoms with the exception of breathing abnormalities which may have been overlooked. Associated supratentorial anomalies are uncommon, but cerebral cortical dysplasia and gray matter heterotopias have been reported. (Barkovich, 1995) Moderate lateral ventricular enlargement due to atrophy has been described in 6–20% of cases. (Kendall *et al*., 1990) Many authors have reported the prevalence of some of these associated findings, which include polydactyly (8%), ocular coloboma (4%), and hamartomas of the tongue (2%), dysmorphic facies, microcephaly, tongue protrusion, multicystic kidney disease, congenital heart disease, unsegmented midbrain tectum, retinal dystrophy and agenesis of the corpus callosum. (Egger *et al*., 1982; Aslan *et al*., 2002; Chance *et al*., 1999; Maria *et al*., 1997) This syndrome is classified into two groups on the basis of presence or absence of retinal dystrophy. Patients with retinal dystrophy have a higher prevalence of multicystic renal disease and these patients also appear to have decreased survival rates compared with those of patients without retinal dystrophy. (Saraiva and Baraitser, 1992) There was no evidence of retinal disease on ophthalmological examination in our patient. Besides JS, cerebellar vermian anomalies have been reported with other disorders, such as Dandy-Walker syndrome and rhombencephalosynapsis. In Dandy-Walker malformation, the inferior part of the vermis is hypoplastic. However, the fourth ventricle is enlarged and communicates with a cyst in the posterior fossa. In addition, the ponto-mesencephalic junction, interpeduncular fossa and superior cerebellar peduncle are normal. In rhombencephalosynapsis, the cerebellar hemispheres are fused and, unlike in JS, a midline cerebellar cleft is not present. (Van Beek and Majoie, 2000) Molar tooth sign is not specific for JS. Other clinical features define the subtypes of JS termed as Joubert syndrome and related disorders (JSRD). JSRD are categorized 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 orofaciodigital defects. Although the molar tooth sign and other important clinical features of the JS may be seen in these syndromes, they usually have supplementary prominent features. These are syndromes such as the COACH, Varadi-Papp, Dekaban-Arima, Senior-Loken, Joubert with polymicrogyria, and Malta syndromes. Patients with COACH syndrome have bilateral coloboma, hepatic fibrosis and renal calcification, and in the Varadi-Papp syndrome there is mesaxial polydactyly, Y-shaped metacarpal, cleft lip or cleft palate, lingual hamartomas and vermian hypoplasia. The Dekaban-Arima syndrome is allied with Leber's congenital amaurosis and cystic dysplastic kidneys, whereas the Senior-Loken syndrome is related with Leber's congenital amaurosis, retinitis pigmentosa and juvenile nephronophthisis. In the Malta syndrome, these patients have the molar tooth sign, occipital encephalocele, hydrocephalus, cortical renal cysts with or without coloboma, and Leber's congenital amaurosis. Few patients can have features of JS and polymicrogyria. (Gleeson *et al*., 2004; Brancati *et al*., 2010)

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