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MRI in Children with familial developmental delay: Joubert syndrome in Siblings

KEYWORDS

Joubert, MRI, molar tooth, autosomal recessive.

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ABSTRACT In this report, we describe the occurrence of familial developmental delay in two siblings with emphasis on the role of MRI in making the diagnosis. MRI is seldom a very useful diagnostic test in the evaluation of children with developmental delay. "Molar tooth sign", seen on brain magnetic resonance imaging illustrates the typical neuro-radiological appearance of Joubert syndrome where all other investigations will be normal.

In this syndrome children with delayed development associated with hypotonia,abnormal respiratory pattern, ocular abnormalities, ataxia and developmental retardation will show malformations of brain stem and cerebellum in MRI

Introduction

A group of clinically and genetically heterogeneous conditions that share mid- and hindbrain malformations (Quisling RG et al 1999, Joubert M, Eisenring JJ et al1969,Saraiva JM et al 1992) comes under the group Joubert syndrome-related disorders. Their clinical features include hypotonia, ataxia, developmental delay tachypnoea, and abnormal eye movements(Joubert M,Eisenring et al 1969,Maria BL et al , 1999) .The pathognomonic sign of JSRD is the molar tooth sign seen on brain magnetic resonance imaging (Joubert M,Eisenring et al 1969).

In this paper we report two siblings with Joubert syndrome and discuss their clinical and imaging features with emphasis of brain MRI findings.

2. Case report

One and two years old normal birth weight male siblings born out of a second-degree consanguineous marriage were brought to pediatric department for evaluation of developmental delay; their antenatal and immediate postnatal periods were normal.

2.1. Sibling 1

The elder of the two siblings had history of episodic tachypnoea and global developmental delay, involving the motor, social, verbal and cognitive milestones. The child achieved partial head control at one and half years of age. At the time of presentation, the gross motor and cognitive milestones corresponded to 6 and 4 months of age, respectively, while there was no speech development.

On physical examination, there was frontal bossing, plagiocephaly and partial cleft palate Opthalmological evaluation revealed alternating exotropia and horizontal gaze nystagmus. On motor examination, there was generalized hypotonia with loss of deep tendon reflexes. Cerebellar sign like past pointing and extra pyramidal signs like choreoathetoid movements were also demonstrated. Sensory examination was normal. Brain stem auditory evoked potentials showed bilateral moderate hearing loss, and absent speech. Electroencephalography showed normal waves. Routine laboratory investigations, and work-up for metabolic disorders showed no abnormalities.

2.2. Sibling 2

The one year old male infant's gross motor, language and personal social development corresponded to 7 months, 4 months, and 3months, respectively. Physical, ocular, Ear, nose, throat, and central nervous system (CNS) examination revealed findings similar to that seen in the elder sibling except normal palate. Laboratory investigations for metabolic disorders and electroencephalography were unremarkable.

The parents of the children also failed to show any phenotypical abnormalities.

A diagnosis of neurodevelopmental delay based on the clinical features was made in both siblings. MRI examination of the brain was performed on both siblings, to rule out morphological CNS abnormalities. T1-weighted, T2-weighted, fluid attenuated inversion recovery (FLAIR), and spoiled gradient recalled (SPGR) sequences were obtained. Similar findings were obtained in both siblings. The cerebellar vermis was dysplastic. There was elongation and nearly horizontal stretching of the superior cerebellar peduncles with resultant widening of the foramen of Magendie and deep interpeduncular fossa forming the typical ' Molar tooth' configuration on axial images. The fourth ventricle was wider than normal, demonstrating the "bat's wing" appearance on axial images. The cerebellar hemispheres apposed one another in the midline. Mid-sagittal image showed thickened and maloriented superior cerebellar peduncles, vermian dysplasia and a large fourth ventricle. Supratentorial structures were normal. A diagnosis of JS was suggested based on the characteristic MRI findings.

3. Discussion

JSRD are a group of recessively inherited conditions, showing CNS malformation involving the midbrain-hindbrain junction (1,5). Joubert et al. (2) first described this syndrome in 1969, in a family of four siblings, who presented with episodic hyperpnea, abnormal eye movements, ataxia and mental retardation with cerebellar vermis agenesis. Since its first description, more than 200 cases have been reported (1,6).

All the loci implicated in JSRD, JR-1 (mapped on chromosome 9q34.3), JR-2 (mapped on chromosome 11p12-q13), JR-3 caused by mutations in the AHI1 gene (mapped on chromosome 6q23.3), JR-4 caused by mutation in the NPHP1 gene (mapped on chromosome 2q13), JR-5 caused by mutation in the CEP290 gene also called NPHP6 (mapped on chromosome 12q21.3), JR-6 caused by mutation in the MKS3 gene also called TMEM67 (mapped on chromosome 8q24), JR-7 caused by mutation in the RPGRIP1L gene (mapped on

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chromosome 16q12.2) and JR-8 caused by mutation in the ARL13B gene (mapped on chromosome 3p12.3-q12.3), which functions in the primary cilium/basal body organelle, and hence included in the group of disorders called ciliopathies, (3,5,7) Using homozygosity mapping in consanguineous families, loss-of-function mutations in CC2D2A (JR-9 mapped on chromosome 4p15.33-p15.2) in JSRD patients has been described recently (7).

Raynes et al. (6) reported JS in three sisters, two of whom were monozygotic twins, showing highly discordant phenotypical abnormalities. The siblings presented in this paper showed episodic apnea, developmental delay, hypotonia, truncal ataxia and ocular abnormalities with similar degree of affection in both of them. The status of affected members in this family, with two affected sibling, and unaffected parents and an eldest brother is in concordance with the recessive inheritance of this condition.

The subtypes of JS are collectively termed as JSRD, and are characterized by additional features such as, polydactyly, retinal anomalies, hepatic fibrosis, cystic kidney disease, occipital encephalocele, and polymicrogyria (5,7). Pigmentary retinopathy, nystagmus, sleep apnea, self-mutilation, and "molar tooth sign" on CNS MRI are variably present. Fluid collection in the posterior fossa, resembling Dandy-Walker malformation may also be present. Facial dysmorphology with a high forehead, flat midface, hypertelorism, open mouth, low-set ears, and other features are often noted (3,5,7).
MRI, given its multiplanar capability, superior gray-white matter differentiation, and unlike computerize tomography, advantage of no radiation exposure is the investigative modality of choice. A wide constellation of CNS abnormalities, described in JS are observed on MRI (1,4). The key imaging features are complete or partial agenesis of cerebellar vermis, thickening and horizontal orientation of the superior cerebellar peduncles with thinning and dysgeneticchanges in the brain stem (1). MRI not only demonstrates the size details of the cerebellum and vermis, but also depicts associated abnormalities in the posterior fossa (1,4)

"Molar tooth sign" (figure1; case1) seen on axial MRI is considered to be pathognomonic for JS (1,8). "Bat-wing" (figure2 ;case2)appearance caused by severe hypoplasia of vermis is also a specific sign (4). Other salient findings include apposition of the cerebellar hemispheres in the midline because of absence of vermis and vermian cleft as a result of lack of peduncular decussation (1). Cerebral hemispheres are generally not involved, however rare association with anomalies, such as mild cerebral atrophy, corpus callosum dysgenesis, cerebral cortical dysplasia, grey matter heterotopia, and encephalomeningocele have been reported (1,4,8). Though MRI is helpful in diagnosis of this syndrome, it does not demonstrate more extensive malformations in the caudal medulla, which probably account for respiratory problems and other features of the disease (2). MRI features in both siblings in our study showed similar features with no demonstrable supratentorial abnormalities.

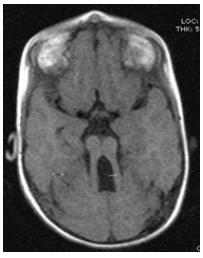

Figure 1

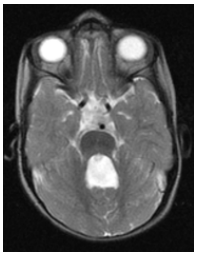

Figure 2

Syndromes like Varadi-Papp (oro-facial-digital type IV), Dekaban-Arima, Senior-Loken, rhombencephalosynapsis, Meckel-Gruber syndrome and COACH syndrome (cerebellar vermis hypoplasia, oligophrenia, ataxia, coloboma, and hepatic fibrosis) occurs as part of a group of genetic conditions that result from an abnormality in the part of the midbrain-hindbrain complex. These disorders are now included in the group of JSRD. They have some characteristics in common, but there is a spectrum of symptoms and abilities in affected individuals (5,7). X-linked cerebellar hypoplasia, ataxia and oculomotor apraxia type 1, tectocerebellar dysplasia, pontocerebellar hypoplasia and Dandy-Walker syndrome are other conditions that might be included in differential diagnosis (1).

Prenatal diagnosis of this condition is gaining importance; the detection of vermian hypoplasia and enlargement of fourth ventricle is possible at about 20th week of gestation. Molar tooth sign has also been documented in fetal brain by MRI, performed in second trimester of pregnancy (9). Isolated localized fetal nuchal lucency (3 mm or greater) in 9- to 14-week fetuses without any additional sonographic abnormalities has been reported in children with JS (10,11). Doherty et al. (11) proposed a protocol for monitoring pregnancies at risk for JS, utilizing serial ultrasounds combined with fetal MRI at 20-22 weeks' gestation to maximize the accuracy of prenatal diagnosis.

The degree of cerebellar vermis dysplasia has prognostic value, since those with severe dysplasia or agenesis have more severe mental and physical disabilities (4,8). Severely affected children die before the age of 3 years due to marked respiratory abnormalities. Those mildly affected need to be followed up, particularly ocular screening and renal function monitoring (4,8). Once a diagnosis of JS is made in 1 neonate, genetic counseling and antenatal ultrasonographic screening should be performed in subsequent pregnancies due to autosomal recessive inheritance of this condition (3,8). The treatment is mainly supportive and symptomatic. Infant stimulation and physical, occupational, and speech therapy have shown to have some benefit (8). Close perioperative monitoring is advocated in patients with JS undergoing anesthesia, as they are extremely sensitive to the respiratory depressant effects of anesthetic agents (8,11).

To conclude, JS is an uncommon inherited disorder, which has distinctive clinical and radiological features. MRI not only helps in confirming the diagnosis, but also has an important role in identifying associated abnormalities, and predicting long-term outcome.

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