ABSTRACT

Joubert Syndrome (JS) is part of a group of predominantly autosomal recessive disorders called “Joubert Syndrome Related Disorders” (JSRD). Genetically this comes under an even broader group of diseases called “ciliopathies” which share an abnormality of genes encoding for proteins of the primary cilium or the centrosome. The “Joubert Syndrome Related Disorders” are characterised by the presence of “Molar tooth midbrain” sign on Axial imaging of the brainstem. The Incidence of these disorders is estimated to be between 1/80,000 and 1/100,000. Classical clinical presentation is with hypotonia, developmental delay with ocular movement abnormalities. They are usually associated with a myriad of associated congenital and developmental anomalies, which need to be evaluated systematically, to determine the prognosis. Herein, we are reporting a case of Joubert syndrome in a one and half year-old girl presenting with hypotonia, developmental delay and abnormal eye movements. A comprehensive review of literature is also portrayed with the emphasis on neuroimaging features.

KEYWORDS  joubert syndrome, ciliopathies, molar tooth sign, hypotonia, MRI, bat-wing fourth ventricle

INTRODUCTION

The case was first clinically described by Marie Joubert in 1969 and over the course of many years various other associated anomalies have been described and classified into numerous syndromes, like Coach Syndrome, Varadi-Papp syndrome, Senior Lenken Syndrome and so on. Recently the term Joubert Syndrome Related Disorders is being used to group all these under one category. All these share common clinical presentation that of hypotonia, developmental delay, and oculomotor apraxia along with respiratory abnormality. Here we are describing a case report of an 18-months-old girl child who was referred to our department of Radiodiagnosis for imaging evaluation.

CASE REPORT

An 18-months-old girl was referred from the paediatric outpatient department for evaluation of developmental delay, hypotonia and abnormal eye movements. She was born at term to a second-degree consanguineous marriage and was first in birth order. She had no history of birth asphyxia. she had no history of breathing, feeding problems or convulsions. Abnormal eye movements were noticed shortly after birth with episodic deviation to lateral extremes of gaze lasting for a few seconds. She had social smile at 4 months, head control at 6 months of age. She was not able to say monosyllables and sit without support. On examination, she had mild facial dysmorphism in the form of forehead prominence, low frontal hairline, open mouth, protruded tongue. Neurological examinations revealed normal cranial nerve function, normal fundus and head circumference. No organomegaly noted on abdominal examination. She had no neurocutaneous markers. Cardiovascular system, respiratory system examination was essentially normal. On motor examination, she had hypotonia of all limbs with normal tendon reflexes. She was referred to our department for MRI of the brain. The MRI was done in a 1.5 Tesla GE Signa HDX MR machine with multiplanar T1, T2 and FLAIR sequences. Diffusion weighted images were also done.

MRI demonstrated Molar Tooth Sign (MTS) on axial section due to the deep interpeduncular fossa, thick superior cerebellar peduncles, bat-wing shaped fourth ventricle, vermianclefting (Fig. 1). Superior cerebellar peduncles are thick, elongated and horizontally oriented on sagittal sections with rostrally deviated fourth ventricle, rounded enlarged fastigium (Fig. 2). MRI brain at the level of midbrain showed foreshortened midbrain with narrow ponto mesencephalic junction and the deep interpeduncular fossa (Fig. 3). Cerebral hemisphere and the rest of the ventricular system appears normal without any evidence of neuronal migrational anomalies. Diffusion weighted image was normal (Fig. 4). Based on clinical and imaging findings, the diagnosis of the pure Joubert syndrome was made.
DISCUSSION

Introduction

Joubert syndrome-related disorders (JSRD) are a group of disorders sharing the common imaging feature of Molar tooth midbrain and similar clinical features of hypotonia, ataxia, neonatal breathing dysregulation, developmental delay and intellectual subnormality1–4.

Etiopathogenesis and genetics

Most follow an autosomal recessive pattern of inheritance with very few showing X-Linked recessive inheritance5, with a predictable inheritance pattern but with variable severity even amongst affected siblings. More than 10 causative genes have been implicated, with classical pure Joubert syndrome having defects in chromosome 9q34.36.
All these genes code for proteins in the primary cilium, and hence coming under the broad group of diseases called “ciliopathies”. This explains the overlap of features with other ciliopathies like Meckel syndrome and Nephronophthisis.

Clinical features

The classical neurological features of JSRD are hypotonia, evolving ataxia, developmental delay, altered respiratory pattern, usually with subnormal intellect and abnormal ocular movements. The respiratory abnormality is characterised by short periods of hyperpnoea with/without intervening apnoea. Mild to Severe mental retardation ranging from IQ of 30 to 80 is described. The presence of ocular and developmental anomalies makes evaluation of IQ difficult. Various nonspecific facial dysmorphic features have been described varying with the age of the individual in association with JSRD. Other clinical features of JSRD depends on its specific type, described in the classification detailed below.

Classification

JSRD are classified into six phenotypic subgroups: Pure JS; JS with ocular defect; JS with renal defect; JS with oculo-renal defects; JS with hepatic defect; JS with orofaciiodigital defects (Table 1). Pure JS is classified into two types depending on the presence or absence of retinal dystrophy. Type 2 is associated with retinal dystrophy and has a poor prognosis.

Diagnosis and imaging features

Any infant presenting with hypotonia, developmental delay should be examined for ocular movement abnormality, on presence of which JSRD should be clinically suspected and imaging of brain should be done to look for Molar Tooth Sign. On imaging, the absence of the cerebellar vermis, thickening and horizontal reorientation of the superior cerebellar peduncles, and fourth ventricle batwing deformity is noted. The classical imaging finding of Molar Tooth Sign is said to be caused by a lack of normal decussation of superior cerebellar peduncular tracts which can be visualised on Diffusion Tensor Imaging. The abnormal superior cerebellar peduncles along with a deep cisterna interpeduncularis constitute the Molar Tooth Midbrain. The absence of the vermis creates a midline cleft between the two normal-appearing cerebellar hemispheres resulting in a characteristic “batwing” appearance of the fourth ventricle. Even though cerebellar abnormalities are classically not associated with JSRD, yet mild hydrocephalus, corpus callosal dysgenesis and arachnoid cysts have been described in literature.

Evaluation protocol must include a physical examination, Brain MRI, ophthalmology evaluation, kidneys, liver and congenital heart defects.

Prenatal diagnosis

Prenatal diagnosis by chorionic villus sampling at 11 weeks is possible through genetic testing in those few cases where the correct molecular defect is known. As such it is not routinely available. In the rest of the cases, antenatal ultrasound and MRI can help establish the diagnosis albeit usually after a late second trimester.

Management

There is no specific treatment for JSRD. Associated anomalies should be identified by a detailed workup and managed accordingly. Respiratory abnormalities should be managed supportively as they usually regress within about 6 months. Specific rehabilitation programmes must be devised as these patients are usually dependant. Increased sensitivity to fewer general anaesthetic drugs has been reported, hence care is to be taken during any surgical interventions. Antenatal diagnosis and genetic counselling should be done in all families harbouring the trait.

CONCLUSION

A higher awareness of possibility of JSRD should be present in neonates presenting with hypotonia, developmental delay and oculomotor apraxia. Prompt MRI of the

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*COACH synd.: Cerebellar verminar hypoplasia, Oligophrenia, Ataxia, Coloboma and Hepatic fibrosis, **General features which are not specific to any subtype are: postaxial polydactyly, exencephalocele and CNS malformations, polymicrogyria, Hirschsprung disease and congenital heart defects.
brain can help establish the diagnosis. Following which, detailed imaging and clinical workup for associated anomalies can help further classify the subtype, which in turn determine the prognosis and management plan. In all such families, timely antenatal imaging should be done to recognise any affected foetuses.

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REFERENCES