Case Report

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Joubert Syndrome and Related Disorders: Congenital Hepatic Fibrosis, Autosomal Recessive Polycystic Kidney Disease, and Pigmentary Retinopathy

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ABSTRACT

Joubert syndrome and related disorders (JSRDs) are a group of anomalies characterized by hypotonia, ataxia, developmental delay, intellectual disability, abnormal eye movements, and apnea and hyperpnea in infancy with multiorgan involvement in which the pathognomonic "the molar tooth sign" is present on the brain magnetic resonance imaging. In this paper, we reported on a patient with JSRD who presented with congenital hepatic fibrosis, autosomal recessive polycystic kidney disease, and pigmentary retinopathy.

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Introduction

Joubert syndrome (JS), a rare autosomal recessive disorder, is a midbrain-hindbrain malformation, characterized by hypotonia, ataxia, developmental delay, intellectual disability, abnormal eye movements, and irregular breathing pattern in infancy. The molar tooth sign (MTS) is characteristic feature seen on the brain magnetic resonance imaging (MRI). The term "JS and related disorders" (JSRDs) are applied to JS with variable organ involvement other than neurologic system including kidney, liver, retina, and skeleton. Indeed, JSRD belongs to an entity known as ciliopathies in which mutations in ciliary proteins, a subcellular organelle, are responsible for the pathogenesis of these disorders (1-4). Mutations in the eight ciliary/basal body genes *INPP5E*, *AHI1*, nephronophthisis (*NPHP1*), *CEP290*, *TMEM67/MKS3*, *RPGRIP1L*, *ARL13B*, and

CC2D2A have been identified in patients with JSRD (3).

Here, we report an 11-year-old boy with JSRD presented with congenital hepatic fibrosis, autosomal recessive polycystic kidney disease (ARPKD), and pigmentary retinopathy.

Case Report

An 11-year-old male patient referred to our pediatric gastroenterology department for evaluation of abdominal distention and epistaxis. He was born to nonconsanguineous parents. Antenatal and neonatal periods were unremarkable. He had one episode of febrile seizure at 6 months of age. On the physical examination, his height and weight were 121 cm and 17 kg, respectively. He had poor development of speech and motor skills and was mentally retarded. Systemic examination was significant for firm liver on palpation and splenomegaly (8 cm below the costal margin). On ophthalmologic examination with slit-lamp, he had pigmentary retinopathy.

Laboratory data were remarkable for white blood cell count of 2280/mm^3, hemoglobin level of 8.4 g/dl, platelet count of 37,000/mm^3, serum creatinine level of 1.2 mg/dl, aspartate aminotransferase level of 174 IU/l, alanine aminotransferase level of 144 IU/l, and alkaline phosphatase level of 800 IU/l. International normalized ratio, albumin, bilirubin, γ-glutamyl-transferase, ammonia, and lactate levels were within normal range. Ceruloplasmin level, 24-hour urine copper, alpha 1 antitrypsin were within normal range. Auto-antibodies (anti-smooth muscle antibodies, antimitochondrial antibody, antinuclear antibody, and liver kidney microsomal), tumor markers, and viral markers were negative. Thyroid function tests were unremarkable.

Bone marrow aspiration was performed due to pancytopenia. No abnormality was detected and flow cytometry was normal. Thus, pancytopenia was ascribed to splenomegaly. Abdominal ultrasound coarse echogenicity of the liver, splenomegaly, increased echogenicity of both kidneys, and multiple cortical cysts in left kidney suggestive of ARPKD. Color Doppler ultrasound showed normal portal venous flow.

Upper gastrointestinal endoscopy showed Grade II-III esophageal varices that were band ligated. Hepatic fibrosis was diagnosed on the fibro scan. Liver biopsy was not performed.

Congenital hepatic fibrosis was diagnosed, and the patient was evaluated for other organ abnormalities. Brain MRI showed dysplastic change of the posterior fossa with MTS (Figure 1). Echocardiography was not significant except for a small patent foramen oval. Diagnosis of JSRDs was made. The patient was prescribed omeprazole, ursobil, propranolol and vitamin E and is in the follow-up of neurology, gastroenterology, nephrology, and ophthalmology clinics.

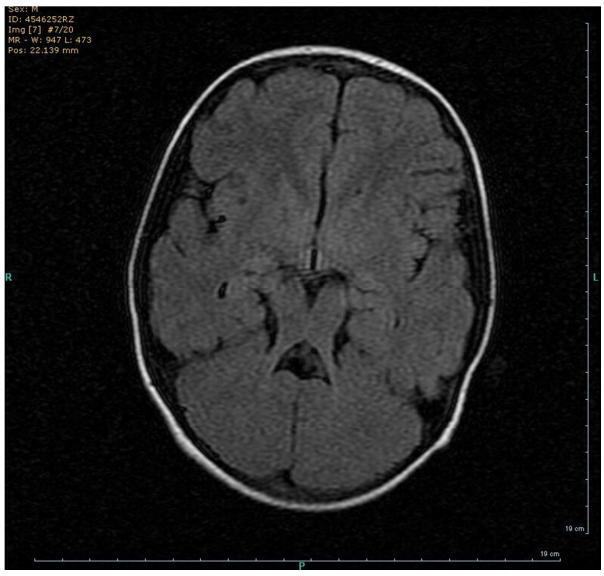

Figure 1. Brain magnetic resonance imaging of the present case showing the molar tooth sign

Discussion

Classic features of the JS include MTS on cranial MRI that is resulted from hypo-dysplasia of the cerebellar vermis, abnormally deep interpeduncular fossa at the level of the isthmus and upper pons, and horizontalized, thickened and elongated superior cerebellar

peduncles; cognitive and motor delay; hypotonia in infancy; irregular breathing pattern in infancy; abnormal eye movement; facial dysmorphologies (5, 6). JSRD is a term that applied to malformations and organ abnormalities mainly of the retina, liver, kidney, and skeleton that share MTS (1, 7). JS was categorized into six subgroups followed as: pure JS, JS plus retinopathy, JS with renal disease, cerebello-oculo-renal syndrome or Senior-Loken syndrome, Cerebellar vermis hypoplasia, Oligophrenia, Ataxia, Coloboma, and Hepatic fibrosis (COACH) oro-facio-digital syndrome (8).

Congenital hepatic fibrosis seen in our patient is the main liver complication reported in previous published reports, resulting from an embryonic malformation of the ductal plate, with cystic dilatation of primitive biliary structures and fibrous enlargement of the portal tracts. Association of JS and congenital hepatic fibrosis has been previously described as COACH syndrome. Other presentations included elevated serum liver enzymes, hepatosplenomegaly, portal hypertension, esophageal varices, and liver cirrhosis (1, 7, 9).

Kidney involvement in JSRD is commonly reported and mainly encompasses cystic dysplasia and juvenile NPHP. The latter characterized by tubulointerstitial nephritis and cysts concentrated at the corticomedullary junction. In addition, there have been some rare cases with features similar to ARPKD (3, 10). Kidney ultrasound of this case also was suggestive of ARPKD.

The present case had pigmentary retinopathy. Retinal involvement has been described in one-third of the patients including severe congenital blindness with a flat electroretinogram recording known as Leber congenital amaurosis, and late-onset pigmentary retinopathy colobomas mainly in poster segment of the eye are also described in JSRD (3, 11).

Our patient had speech and motor skills retardation that is seen in all JSRD patients with variable degrees (1).

Conclusion

We reported a patient with JSRD presented with congenital hepatic fibrosis, pigmentary retinopathy and ARPKD. JSRD is a heterogeneous disease with broad spectrum manifestations and should be suspected in children with neurodevelopmental delay and multiorgan malformations. A careful follow-up should be planed for prompt and proper diagnosis and management of complications. Parents should also be informed about the prenatal diagnosis of JS to prevent it in subsequent pregnancies.

Conflict of Interests

Authors have no conflict of interests.

Acknowledgments

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