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Joubert syndrome and related disorders: a rare cause of intrahepatic portal hypertension in childhood

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Abstract. – OBJECTIVE: Joubert syndrome (JS) and related disorders (JSRD) (OMIM #213300) are a group of developmental delay/multiple congenital anomalies syndromes in which the pathognomonic "the molar tooth sign" (MTS) is present, is caused by the defects in the structure or function of the primary cilium. Liver disease is observed in minority of JSRD, usually manifesting as congenital hepatic fibrosis (CHF).

In this paper we report a child with JSRD in whom signs of portal hypertension and chronic liver disease appeared and in the follow-up nephrologic features were added to her clinical signs.

CONCLUSIONS: The physicians must be aware of this disorder in the differential diagnosis of portal hypertension of unknown origin.

Key Words:
Joubert syndrome and related disorders, Child, Liver.

Abbreviations

CHF = Congenital hepatic fibrosis; JS = Joubert Syndrome; JSRD = Joubert syndrome related disorders; MTS = Molar tooth sign; UDKA = ursodeoxycolic acid.

Introduction

Joubert syndrome (JS) and related disorders (JSRD) (OMIM #213300) are a group of developmental delay/multiple congenital anomalies syndromes in which the pathognomonic the molar tooth sign (MTS) is present, a complex midbrain-hindbrain malformation visible on brain imaging, first recognized in JS[1]. It's caused by the defects in the structure or function of the primary cilium[2]. The pathogenic basis of this clinically and genetically heterogeneous disorder relates to the dysfunction of a subcellular organelle, the primary cilium, which makes Joubert syndrome part of an expanding group of disorders collectively called ciliopathies[3].

Hepatic involvement in JSRD is likely underreported, as manifestations of liver disease are usually not apparent at birth[4]. One JSRD is the condition known by the acronym COACH syndrome (Coloboma, Oligophrenia/developmental delay, Ataxia, Cerebellar vermis hypoplasia, Hepatic fibrosis) which has recently been descibed to require MTS with evidence of liver disease; congenital hepatic fibrosis[5].

We describe a 10-year old girl patient, referring elevated liver enzymes before strabismus operation and was determined chronic liver disease and portal hypertension with MTS in the MRI findings which is typical for JS, in this report. Ocular and neurologic symptoms were also accompanied to the disease and nephrologic signs were added to the clinical signs in the follow-up.

Case

A nine-year old girl patient was referred to our pediatric gastroenterology outpatient clinic because of elevated liver enzymes before strabismus operation. Her past medical history was re-

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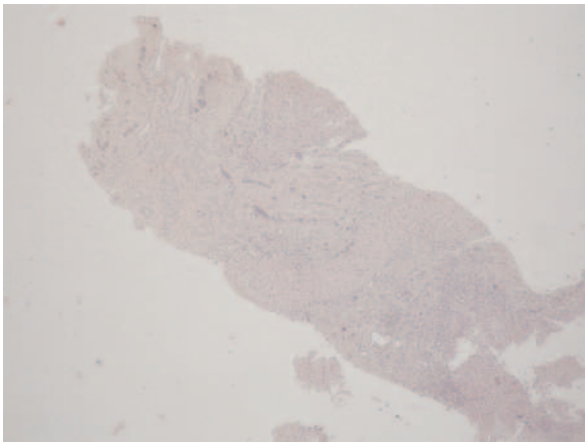

Figure 1. Parenchymal irregularly shaped islands, nodule formation, severe type of biliary fibrosis, ductal proliferation (the findings compatible with ductal plate malformation). Hematoxilin-eosin, x40.

markable for ptosis operation and mild mental retardation. In newborn period the patient was hospitalised in neonatal intensive care unit (NICU) because of respiratory distress and convulsion. She was born to a second degree cousin marriage. On physical examination her height was 116 cm (< 3rd percentile) her weight was 20.5 kg (< 3rd percentile). Hypertelorism, prominent forehead, a high set palate, difficulty in speech, motor and mental retardation, were found in physical examination. Systemic examination of the patient also revealed hepatomegaly with the liver noted to be 0/6 cm, splenomegaly with the spleen noted to be 7 cm.

Laboratory workup is significant for white blood cell (WBC) count of 4760/mm³, hemoglobin 10.6 gr/dL, platelet count of 128000/mm³. Alanine aminotransferase (ALT) was 156 IU/L (N = 0-40 IU/L), aspartate aminotransferase was 277 U/L (N = 0-41 IU/L) and γ-glutamyl-transferase (GGT) was 107 U/L(N = 0-18 IU/L). International Normalised Ratio (INR), albumin, urea and creatinine levels were within normal limits. Abdominal ultrasound with Doppler revealed mildly abnormal hepatic echostructure, splenomegaly, normal portal venous flow. Serologic studies were negative for the infectious cause. Ceruloplasmin level was 39 mg/dL and 24-hour urine copper collection was 38 μg/dL. Alpha-1 antitrypsine level was 167 mg/dL. Autoimmune markers were negative. Liver biopsy of the patient was compatible with characteristic features of ductal plate malformation (Figures 1, 2). Upper gastrointestinal system endoscopy of the patient was remarkable for grade 2 esophageal varices. Cranial MRI of the patient was spesific for the molar tooth sign and small dysplastic cerebellar vermis (Figure 3). Cranial MRI findings, ductal plate malformation in liver biopsy, ophtalmologic findings and syndromic appereance of the patient made us think about Joubert syndrome and related diseases. Abdominal ultrasound of the patient was normal for the kidneys. The patient was prescribed propranolol and ursodeoxycholic acid (UDKA) therapy. At the follow-up the patient was brought to the emergency room because of hemathemesis two years later. On physical examination the patient was pale, and tachycardic. Abdominal examination was remarkable a firm and non tender spleen tip palpated in the midline at 8 cm below left costal margin. The liver span was 3 cm at right costal margin and 4 cm below sternum. Laboratory workup was significant for WBC 3210/mm³, hemoglobin of 7.7 g/dL, platelet count of 108,000/mm³, INR 1.3. Her liver enzymes were elevated. Once the patient was stabilized and upper endoscopy was performed. Esophageal varice bleeding was controlled and band ligation therapy was done. The patient was discharged from NICU. Abdominal Doppler ultrasound was specific for portal hypertension and also kidneys were found enlarged and echogenity of them were increased which were normal in the early follow-up. Creatinine levels were increased (1.7 mg/dL). She was referred to the pediatric nephrology department.

The patient was in the follow-up of pediatric gastroenterology, pediatric nephrology, and pedi-

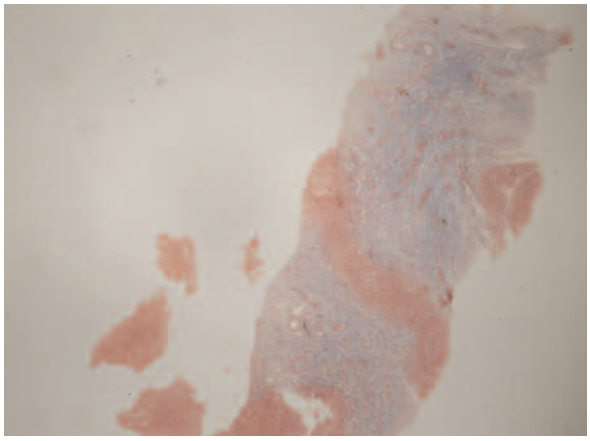

Figure 2. Severe biliary fibrosis in the portal area, ductal proliferation (findings compatible with ductal plate malformation). Masson trichrome, x100.

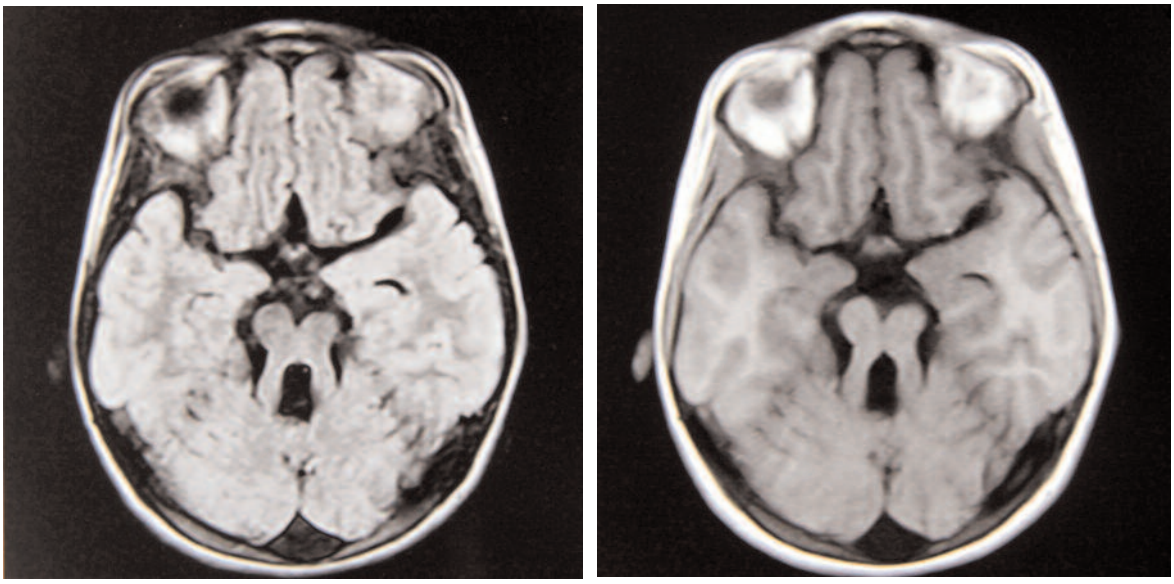

Figure 3. MRI of the patient (molar tooth sign).

atric neurology outpatient clinic. Genetic testing was also performed on the patient. Coding exons of TMEM67 gene was performed with DNA sequence analysis after being amplified by PCR method. It was found that the patient had heterozygous T244A (c.730A > G) nucleotide exchange in the 9th exon of TMEM67 gene with the result of DNA sequence analysis.

Discussion

The features necesssary for the diagnosis classic JS are: (1) the molar tooth sign on axial views from cranial MRI studies (2) intellectual impairment/developmental delay, of variable degree (3) hypotonia in infancy (4) one or both of the following (not required but supportive of the diagnosis): irregular breathing pattern in infancy (episodic apnea and/or tachypnea, sometimes alternating) and abnormal eye movements [(nystagmus and/or oculomotor apraxia (OMA)][4]. The patient's findings supported the criteria.

Liver disease in JSRD may present with raised serum liver enzymes (alanine aminotransferase, aspartate aminotransferase and gamma-glutamyl transpeptidase) at least twice the normal values, early onset hepato(spleno)megaly or more severe manifestations including portal hypertension, esophageal varices and liver cirrhosis[5,6]. The liver biopsy of the patient (Figure 1) was specific for ductal plate malformation (DPM). DPM is the main pathology underlying the liver disease in ciliopathies[7]. Liver dysfunction and portal hypertension-related JSRD is due to congenital hepatic fibrosis (CHF). The diagnosis of the patient is thought to be a ciliopathy with the evidence of (CHF) findings in the liver biopsy and esophageal varices in upper gastrointestinal system endoscopy.

Mutations in the eight ciliary/basal body genes *INPP5E, AHI1, NPHP1, CEP290, TMEM67/MKS3, RPGRIP1L, ARL13B,* and *CC2D2A* have been identified in subjects with JSRD. These eight genes account for an estimated 50% of causative mutations in JSRD[4]. In literature mutations in MKS3/TEMM67 are responsible for the majority of COACH syndrome (JSRD with liver involvement)[8]. Our patient's genetic testing supported this.

There is a varying degree of intellectual impairment that ranges from mild to severe in JSRD. The patient had mild intellectual impairment. Prognosis is largely dependent on the severity of involvement of the organ systems, mostly on renal and hepatic complications that, if not timely diagnosed and managed, represent the major causes of death in JSRD patients. Unfortunately, there are currently no curative therapies for JSRD[1,2]. The patient had upper gastrointestinal bleeding (esophageal varice bleeding) controlled with band ligation theraphy. She is at the follow-up of Pediatric Gastroenterology Department.

Conclusions

We have presented the clinical and pathological features of a girl who suffered from JSRD with liver and at the follow-up with nephrologic involvement. Physicians should be aware of this condition when they examine patients who present with hepatopathy, portal hypertension of unknown origin.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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