Congenital hepatic fibrosis in a child with Prader-Willi syndrome: a novel association

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Prader–Willi syndrome (PWS) is a rare genetic disorder caused by deletion or unexpression of the chromosome 15 (q 11-13). Symptomatologies include hypotonia, hyperphagia, cognitive impairment, and characteristic dysmorphic profile. Here, we report a 4-year-old boy with PWS who presented with complications of congenital hepatic fibrosis. The uniparental heterodisomy makes it unlikely that the hepatic fibrosis was caused by unmasking of a recessive mutation on the maternal chromosome 15 although we cannot exclude the possibility of a recessively inherited mutation elsewhere given the parental consanguinity. This is the first report of congenital hepatic fibrosis in PWS.

Congenital hepatic fibrosis (CHF) is an autosomal recessive (AR) disorder characterized by variable degrees of periportal fibrosis and irregularly shaped proliferating bile ducts. The hepatic manifestations of CHF were first described in 1856.[1,2] It is characterized clinically by hepatic fibrosis and manifestation of portal hypertension such as splenomegaly and varices, with renal cystic disease. CHF has been described in a variety of conditions or syndromes; however, up to our knowledge, no previous reports are available about its relationship with Prader–Willi syndrome (PWS). PWS is a rare genetic disorder in which there is loss of paternal contribution to chromosome 15 characterized by early neonatal hypotonia and failure to thrive, which is replaced later on by abnormal weight gain secondary to hyperphagia.[3] We describe here a case of CHF in a 4-year-old boy with PWS secondary to uniparental heterodisomy. We speculate on the nature of this apparently novel relationship with PWS.

CASE

A 4-year-old male Saudi child presented with history of recurrent rectal bleeding, delayed motor development, and delayed speech. He was born at full term via a cesarean section to healthy first-cousin parents. A history of feeding difficulty was reported in early infancy, which later resolved. On physical examination, he was pale but not jaundiced. His weight and height corresponded to the 90th and <5th percentile for age, respectively. He had almond-shaped eyes and small hands and feet. Abdominal examination revealed hepatosplenomegaly. Central nervous system examination was positive for generalized hypotonia. A clinical diagnosis of PWS was made, and methylation analysis of small nuclear ribonucleoprotein-associated protein-N (SNRPN) promoter was requested. Hemoglobin and platelet count were low. His liver enzymes were normal with normal prothrombin time and partial thromboplastin time. Abdominal ultrasound showed hepatosplenomegaly, normal anatomy, echogenecity, and size of both kidneys with no evidence of renal cystic changes. Upper gastrointestinal endoscopy showed esophageal varices, fundal varices, and multiple erosions in the fundus. Liver biopsy confirmed the diagnosis of congenital hepatic fibrosis (**Figure 1**). Methylation analysis confirmed lack of paternal band. Multiplex ligation-dependent probe amplification analysis ruled out the possibility of deletion. Microsatellite analysis confirmed that the lack of paternal contribution was secondary to uniparental heterodisomy. The patient was managed with sclerotherapy and supportive therapy.

DISCUSSION

CHF is an AR disease that is characterized by hepatic fibrosis, portal hypertension, and renal cystic disease.[4] It is a part of fibrocystic disorders in which liver and kid-

neys are commonly affected. Other hepatic fibrocystic disorders include polycystic liver disease, Caroli disease, and Caroli syndrome. Caroli disease is characterized by intrahepatic biliary dilatation without hepatic fibrosis, whereas Caroli syndrome is characterized by both CHF and intrahepatic biliary dilation.

The primary defect in this spectrum of disorders is suggested to be related to ductal plate malformation secondary to defective ciliary proteins (ciliopathies).[1] Primary cilia host critical signal transduction pathways that sense chemical, osmotic, and mechanical stimuli such as luminal fluid flow, and regulate important cellular functions including proliferation and maintenance of planar cell polarity and mitotic spindle orientation to ensure normal epithelial function and normal diameter of tubular structures such as renal and biliary ducts.[5]

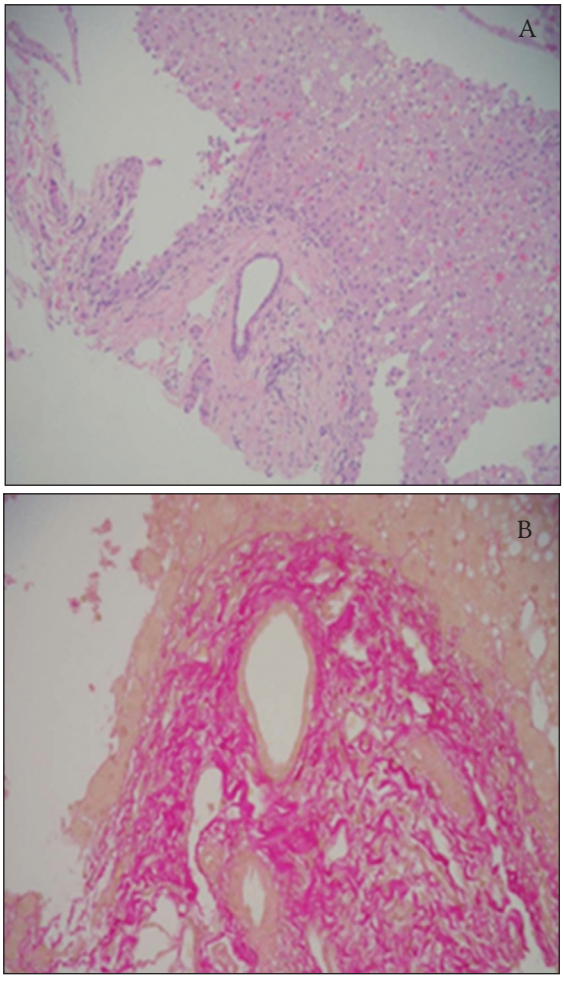

Figure 1. A) Liver biopsy showing typical findings of congenital hepatic fibrosis: widened portal tract with abnormally formed bile ducts and periportal fibrosis (hematoxylin and eosin stain 100×). B) Trichrome stain highlighting the periportal fibrosis (200×).

In the case of CHF, ductal plate malformation causes progressive periportal fibrosis and subsequently results in the development of portal hypertension. Typically, hepatocellular functions are preserved in these patients. However, high liver enzymes are seen if cholangitis occurs, which is typically seen in Calori syndrome.

Normally, CHF is associated with autosomal-recessive polycystic kidney disease (ARPKD), though it can be seen as an isolated finding as seen in our patient who had no evidence of renal cystic changes in the ultrasound. Some investigators consider CHF and ARPKD as a single disorder with a wide spectrum of manifestations, whereas others describe them as two distinct entities that share phenotypically similar biliary lesions.[6] However, recent identification of the gene for ARPKD, PKHD1, provided proof that at least some cases of CHF are indeed caused by PKHD1 mutations, which are seen in 32.1% of adults with CHF or Caroli disease.[7]

CHF has also been observed in relationship with other disorders (many of which are ciliopathies) such as autosomal-dominant polycystic kidney disease, nephronophthisis, congenital disorder of glycosylation Type 1b, Meckel–Gruber syndrome, Joubert syndrome, Jeune syndrome, Bardet–Biedl syndrome, COACH syndrome, Ivemark syndrome type 2, Intestinal lymphangiectasia, enterocolitis cystica, osteochondrodysplasia, von Recklinghausen disease, and Leber amaurosis.[5,8] However, an extensive search in English published studies failed to identify CHF in relationship with PWS. This apparent lack of association despite the relatively high frequency of PWS strongly argues against the causal relationship between the two syndromes in this patient. In other words, it is possible that the coexistence of the 2 disorders is a chance occurrence. We note here that AR inheritance secondary to uniparental disomy was unlikely because it was heterodisomy, i.e., two different maternal chromosome 15 were inherited due to meiosis I defect, which was consistent with the advanced maternal age.[9] Of course, the AR cause of CHF was still a possibility at other loci because the parents were first cousins.

In conclusion, we report the first case of PWS with CHF, and although this relationship may be coincidental in nature, the possibility of CHF being a rare complication of PWS can only be established through additional reports.

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