Case Report

Hepatopathy in an adult, secondary to congenital untreated panhypopituitarism and ectopic posterior pituitary gland

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ABSTRACT

We report a rare case of an adult with advanced liver failure in the setting of an untreated congenital panhypopituitarism. A 32-years-old man presented with a newly onset seizure episode secondary to hypoglycemia. In the initial exploration, we found eunuchoid habitus, absence of secondary sexual characteristics, ascites, and hepatic encephalopathy. Hormonal evaluation confirmed the absence of anterior hypophyseal hormones and the liver function tests showed derangement of liver function. Magnetic Resonance Imaging (MRI) showed hypoplastic adenohypophysis and ectopic posterior pituitary gland. In the approach to liver disease, no cause was identified, besides the untreated panhypopituitarism.

Key words: Cirrhosis, neurohypophyseal ectopy, untreated panhypopituitarism

Introduction

Congenital panhypopituitarism is a rare cause of cholestatic hepatitis in newborns. The cause seems to be thyroxine, cortisol, and growth hormone (GH) deficiency; however, the precise pathophysiology is poorly understood and only a few cases in adults have been described in the literature. Adults with this disorder develop irreversible chronic liver failure, which is why hormonal replacement must begin in the early childhood. Here, we describe a case of cirrhosis secondary to untreated panhypopituitarism in an adult.

Case Report

A 32-year-old man with no relevant medical background was admitted to our hospital due to a sudden loss of consciousness and a seizure episode. The patient had been well until the day of admission. On examination, he was found to have eunuchoid body proportions, low nasal bridge, high-arched palate, micropenis with testis smaller than 1 cm, and an absence of hair in the face, armpits, and genitalia.

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Laboratory test results showed hypoglycemia (68 mg/dL), hyponatremia (132 mmol/L), potassium in the upper limit (4.82 mmol/L), leukopenia (2.1 × 10^3/ mm^3), and thrombocytopenia (29 × 10^3/ mm^3). Liver chemistry was suggestive of chronic hepatopathy with high aspartate aminotrasferase [(AST) 98 U/L], alkaline phosphatase (160 U/L), hypoalbuminemia (2.7 g/dL), and prothrombin time prolongation >3 seconds above control (Prothrombin time 13.9 seconds/10.8 seconds).

Liver ultrasound findings were compatible with chronic liver disease, portal hypertension, and ascites [Figure 1]. Upper gastrointestinal endoscopy confirmed portal gastropathy. Patient had no history of endocrine, hepatic, or metabolic disorder. Alcohol abuse, drug intake, viral infection (B and C virus), autoimmune liver disease, and iron overload were all ruled out.

Hormonal evaluation was remarkable for a complete deficiency of adenohypophyseal hormones, with luteinizing hormone (LH) <0.1 mU/mL (reference range

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1.7–8.6 mU/mL), follicle-stimulating hormone (FSH) 0.2 mU/mL (reference range 1.5–1.2 mU/mL), testosterone <0.02 ng/dL (reference range 2.8–8 ng/dL), and insulin-like growth factor (IGF-1) <14 ng/mL (below the detectable range). Additionally, the patient had central hypothyroidism with normal thyroid stimulating hormone (TSH) 3.39 mIU/L, and low T3 [0.8 nmol/L (reference range 1.3–3.1 nmol/L)] and T4 [40 nmol/L (reference range 66–181 nmol/L)]. We also noted hypocortisolism 0.4 mcg/dL (reference range 6.2–19 mcg/dL) and inappropriately normal adrenocorticotropic hormone (ACTH) 37 pg/mL (reference range 10–100 pg/mL).

MRI showed very hypoplastic adenohypophysis, attenuated stalk, and poor development of sella turcica, and T1-weighted image revealed an ectopic hyperintense suprasellar bright spot compatible with ectopic posterior pituitary tissue [Figure 2]. Furthermore, the hand-wrist X-ray showed delayed bone age [Figure 3], and bone densitometry revealed osteoporosis [total T-score −4.5 (spine) and −3.3 (hip)]. There were no alterations in the karyotype (46, XY).

During the first days of his hospitalization, the patient had persistently low glucose levels (<80 mg/dL) and hypotension, which improved with hormonal replacement therapy with hydrocortisone, levothyroxine, and testosterone.

Discussion

Congenital panhypopituitarism has been described as a rare cause of cholestasis and neonatal hepatitis.[1] To date, only a few cases have been reported and the pathogenesis of this association is still unknown. Liver abnormalities are present during the first few weeks of life, and these include jaundice, acholia, hyperbilirubinemia, high alkaline phosphatase, and high serum transaminases.[1,2] Most of these liver chemistry abnormalities can reverse with

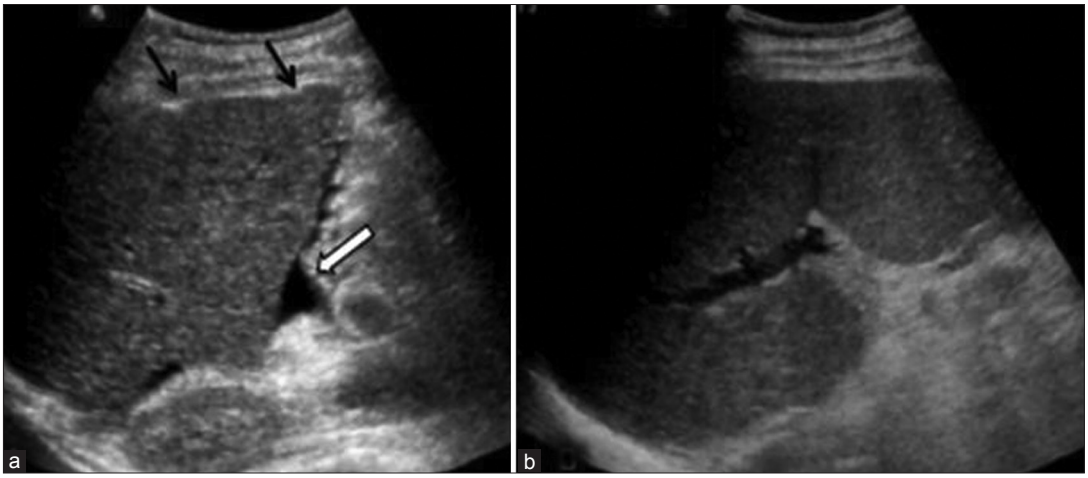

Figure 1: Liver ultrasound using 3.5-MHz transducer. (a) Transverse scan of the right liver lobe shows diffuse surface irregularities (black arrows) and perihepatic free fluid (white arrow). (b) Transverse scan shows enlarged spleen (998 cm^3)

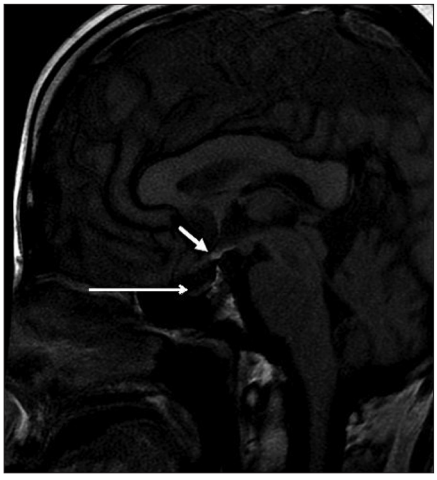

Figure 2: T1-weighted magnetic resonance imaging shows a bright spot in suprasellar location corresponding to ectopic posterior pituitary gland (white arrow). The pituitary gland and sella turcica are small (long arrow)

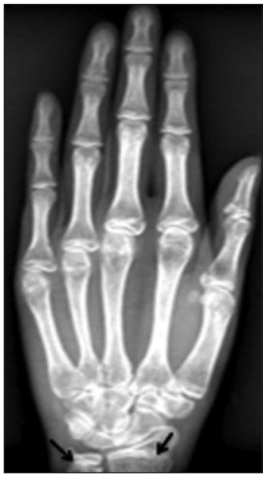

Figure 3: X-ray image showing a delayed bone age (17 years old with lack of obliteration of ossification nuclei in the cubitus and radius (black arrows)

hormonal substitution.[2] Spray *et al.* reported a series of 12 children with neonatal hepatitis and hypopituitarism. They observed in 9 of 12 children that liver disease resolved within 6 weeks after treatment with thyroxine, hydrocortisone, and GH, including a patient for whom diagnosis and treatment were delayed until 3 years old. However, in one patient for whom hormone replacement therapy was started at 5 years old, cirrhosis and portal hypertension developed.[3] Although the association between liver damage and hypophyseal hormone deficit has been known since 1956,[3] the pathogenesis is not well understood. Some reports propose that neonatal hepatitis may be secondary to a deficit in cortisol and/or GH, which participate in the regulation, synthesis, and transport of biliary acids.[1] In fact, it was reported that newborns with isolated deficiency of GH and cortisol have liver disorders comparable to those observed in children with complete panhypopituitarism.[4]

Some evidence supports the possibility that TSH deficiency affects canalicular bile secretion, probably by alterations in the Na^+/K^+ ATPase activity in the plasma membrane of hepatocytes.[4] Moreover, adenohypophyseal hormone deficiency produces abnormalities of bile canalicular structure, essential for bile excretion.[4] In summary, the deficiency of one or more pituitary hormones delays the maturation of the transport mechanisms of bile, causing bile accumulation and finally cholestasis and jaundice.

Advances in molecular biology have allowed a greater understanding of pituitary development, which demands a carefully orchestrated expression of signaling molecules and transcription of factors, like HESX1, Prop1, Pitx1, and Sox2.[5] Furthermore, these advances have resulted in better characterization of genetic defects, described previously as idiopathic illness.[6] The patient presented in the vignette has adenohypophyseal hypoplasia and neurohypophyseal ectopy, which is a congenital disorder mainly attributed to a mutation in the *Rpx-1 gene (also known as Hesx-1)* that is expressed early in the hypophyseal development.[7] Mutations are usually associated with severe midline defects such as septo-optic dysplasia; however, presentation can be variable, ranging from classic facial malformations to normal phenotype. Hormonal deficiencies also are heterogeneous, varying from isolated GH deficiency to complete panhypopituitarism including diabetes insipidus for antidiuretic hormone deficiency.[7]

The MRI findings are a suprasellar bright (hyperintense) spot on T1-weighted images, corresponding to a functional ectopic tissue of the posterior pituitary, with a hypoplastic anterior pituitary gland over sella poorly developed.[8,9] The evidence supports the association of an ectopic posterior pituitary gland and hypopituitarism, with one or more hormone deficiencies.[8,10] In fact, the identification of a hyperintense signal out of the sella turcica has been described in children with isolated GH deficiency as well as in children with multiple hormone deficiencies even in the absence of neurohypophyseal disorder.[8] In the patient presented here, no data of diabetes insipidus were recognized.

In most of the reported cases, it was observed that if the diagnosis and treatment is delayed beyond 4 years of age, persistent cholestasis and eventually cirrhosis may be caused, while in cases diagnosed in the first 3 months, the evolution is favorable with normalization of the liver function tests.[3] Therefore, early recognition within the first few days after birth is essential for appropriate treatment. A high index of suspicion and careful investigation of infants who present with hepatitis, jaundice, and hypoglycemia is imperative to rule out congenital panhypopituitarism.

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References

1. Leblanc A, Odievre M, Hadchouel M, Gendrel D, Chaussain JL, Rappaport R. Neonatal cholestasis and hypoglycemia: Possible role of cortisol deficiency. J Pediatr 1981;99:577-80.
2. Nakajima K, Hashimoto E, Kaneda H, Tokushige K, Shiratori K, Hizuka N, *et al*. Pediatric nonalcoholic steatohepatitis associated with hypopituitarism. J Gastroenterol 2005;40:312-5.
3. Spray CH, McKiernan P, Waldron KE, Shaw N, Kirk J, Kelly DA. Investigation and outcome of neonatal hepatitis in infants with hypopituitarism. Acta Paediatr 2000;89:951-4.
4. Karnsakul W, Sawathiparnich P, Nimkarn S, Likitmaskul S, Santiprabhob J, Aanpreung P. Anterior pituitary hormone effects on hepatic functions in infants with congenital hypopituitarism. Ann Hepatol 2007;6:97-103.
5. Kelberman D, Rizzoti K, Lovell-Badge R, Robinson IC, Dattani MT. Genetic regulation of pituitary gland development in human and mouse. Endocr Rev 2009;30:790-829.
6. Mehta A., Mehul TD. Developmental disorders of the hypothalamus and pituitary gland associated with congenital hypopituitarism. Best Pract Res Clin Endocrinol Metab 2008;22:191-206.
7. Toogood AA, Stewart PM. Hypopituitarism: clinical features, diagnosis, and management. Endocrinol Metab Clin North Am 2008;37:235-61.
8. Ultmann MC, Siegel SF, Hirsch WL, Finegold DN, Foley TP Jr. Pituitary Stalk and Ectopic Hyperintense T1 Signal on Magnetic Resonance Imaging Implications for Anterior Pituitary Dysfunction. AJDC 1993;147:647-52.
9. Mitchell L, Thomas P, Zacharin M. Ectopic Posterior Pituitary Lobe and Periventricular Heterotopia: Cerebral Malformations with the Same Underlying Mechanism? Am J Neuroradiol 2002;23:1475-81.
10. Murray PG, Hague C, Fafoula O. Associations with multiple pituitary hormone deficiency in patients with an ectopic posterior pituitary gland. Clin Endocrinol 2008;69:597-602.

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