BASIC RESEARCH JOURNALS

Basic Research Journal of Medicine and Clinical Sciences ISSN 2315-6864 Vol. 4(10) pp. 237-239 October 2015
Available online http//www.basicresearchjournals.org

Short Communication

Neonatal Cholestasis: Beyond Thyroid Hormones

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Accepted 22 October, 2015

ABSTRACT

The diagnosis of hypopituitarism should be considered in infants with unexplained neonatal hepatitis. Delay in diagnosis and appropriate treatment is associated with persistently abnormal liver function tests and may lead to irreversible liver disease. A 2-week-old female child presented with hyperbilirubinemia and found to have hypopituitarism. The diagnosis was confirmed by demonstrating low levels of cortisol and thyroxine and resolution of symptoms with replacement therapy.

Keywords: Hyperbilirubin, neonate, panhypopituitarism.

INTRODUCTION

Cholestasis is the commonest abnormal finding during the first week of life. Cholestasis is universally present in the newborn period and is recognized as a clinical jaundice in approximately 20-50% of full term neonates and 80% of preterm neonates (Hinkes and Cloherty, 1998; Anand and Mayotra, 1978; Mac Mahan et al., 1994). Congenital hypothyroidism (CHT) is a well-known cause of prolonged unconjugated hyperbilirubinemia and appears to be associated with the delayed maturation of hepatic uridine diphosphate glucuronyltransferase (UDPG-T) enzyme activity (Van Stenberg et al 1988; Virtanen 1998, Singh et al 2003).

Prolonged unconjugated hyperbilirubinemia occurs in approximately 10% of all neonate with hypothyroidism. Virtanen et al. (1998) studied the clinical manifestation of congenital hypothyroidism (CHT) in the first week of life and found that 57.3% of infants developed visible jaundice as compared to 27.8% in euthyroid infants. Congenital hypopituitarism is a recognized cause of neonatal hepatitis, but the diagnosis may be difficult to establish even if clinically suspected.

In this article, we report on an infant who presented with hyperbilirubinemia and panhypopituitarism.

Case summary

A 2-week-old female child was referred for evaluation of prolonged neonatal jaundice. No clinical evidence of ABO incompatibility, nor Rh isoimmunization and child was not septic. There was no cephalhematoma, nor extravasation of blood. The patient was not glucose-6-phosphate deficient. Liver function revealed a total bilirubin of 267 µmol/L (normal <17), direct bilirubin was 251 µmol/L, total protein 32 g/L, aspartate aminotransferase (AST), 834 U/L (normal; <60), alanine aminotransferase (ALT) 488 U/L (normal; 30-60), alkaline phosphatase (AP) 355 U/L normal < 600), and gamma glutamyltransferase (GGT) 106 U/L (normal 12-60). Infectious causes were excluded based on appropriate screening (TORCH) and 1-α-antitrypsin was normal. Hepatobiliary scintigraphy following a standard procedure (El Deouki et al., 1997) ruled out obstruction and suggested of neonatal hepatitis. Free thyroxine (FT4) was very low at 7.5 pmol/L (normal

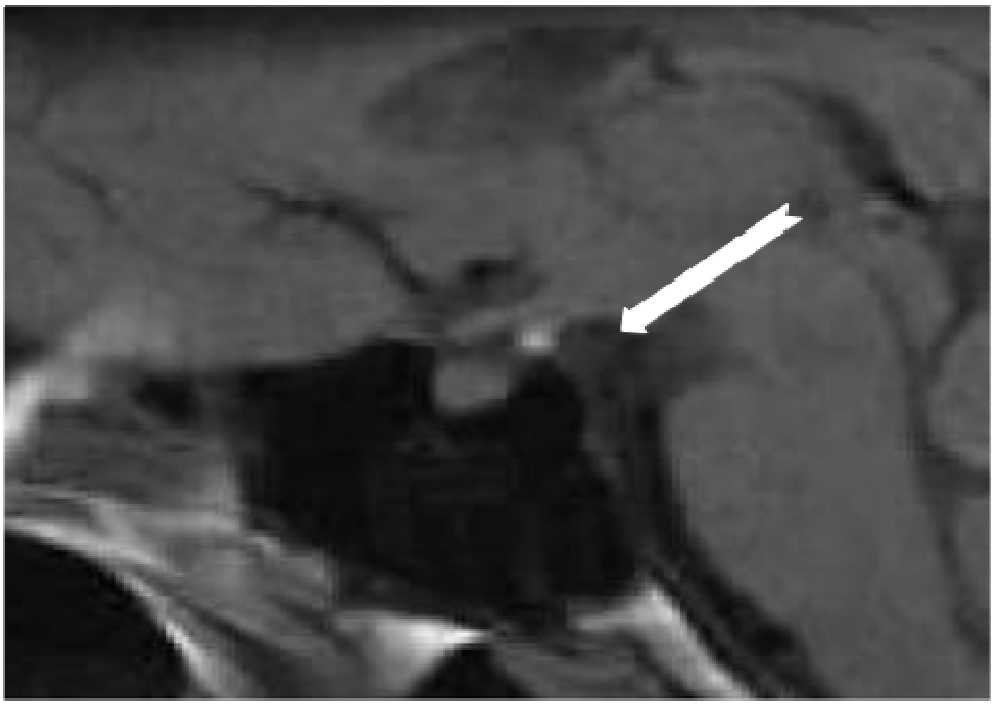

Figure 1. Magnetic Resonance Imaging (MRI), demonstrating hypoplastic anterior pituitary and ectopic posterior pituitary gland. (arrow)

10-25), and thyroid stimulating hormone (TSH) was inappropriately low at 6.4 mU/L (normal, <5) suggesting central hypothyroidism. Magnetic resonance imaging (MRI), figure 1, demonstrated hypoplastic anterior pituitary and an ectopic posterior pituitary gland. Adrenocorticotrophic hormone (ACTH) was low at 2.5 pmol/L (normal; 4.5-13.3), and serum cortisol was 14.5 nmol/L (normal; 83-580). The patient was started on L-thyroxine and cortisol. Liver function returned to normal within 2 weeks.

At 3 years of age, she was also started on growth hormone therapy and continued to grow normally with normal liver function test and there was no evidence of diabetes insipidus (DI).

DISCUSSION

Congenital panhypopituitarism has also been described as a rare cause of cholestasis and neonatal hepatitis. To date, only a few cases have been reported in children as well as adults, (Easley et al., 2008), however, the pathogenesis is still unknown. Spray et al. (2000) reported a series of 12 children with neonatal hepatitis and hypopituitarism. They observed in 9 patients, the liver disorders resolved within 6 weeks of therapy with thyroxine, hydrocortisone and growth hormone. However, in one patient; hormonal replacement therapy was delayed, so cirrhosis and portal hypertension developed. The pathogenesis is not well understood. Some researchers proposed that neonatal hepatitis may be secondary to a deficiency in cortisol and/or growth hormone, which participate in the regulation, synthesis and transport of biliary acids. It was reported that newborns with isolated deficiency of growth hormone and cortisol have disorders, comparable to those observe in children with complete panhypopituitarism (Karnaskul et al., 2007). Some evidence supports the possibility that thyroid stimulating hormone (TSH) deficiency affects canalicular bile secretion, probably by alterations in the Na^+ /K^+ ATPase activity in the plasma membrane of the hepatocytes. Moreover, adenohypophyseal hormones deficiency produce abnormalities of the bile canalicular structure essential for bile excretion. Therefore, a 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 or orchestrated expression of signaling molecules and transcription of factors like HESX1, prop 1, pit x1 and SOX 2. Furthermore, these advances have resulted in better characterization of genetic defects, described previously as idiopathic illness; one patient has adenohypophyseal hypopituitarism and neurohypophyseal ectopy which is a congenital disorder.

Mainly, attributed to a mutation in the Rpx-1 gene that is expressed early in the hypophyseal development. No genetic study was done in our patient. 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 growth hormone deficiency to complete panhypopituitarism including diabetes insipidus (D1) (Kelberman et al., 2009; Mehta and Mehul, 2008; Toogood and stwewart, 2008). Furthermore, such findings in magnetic resonance imaging is another evidence to support the association of an ectopic posterior pituitary gland and hypopituitarism, with one or more hormone deficiencies. The identification of a hyperintense signal out of the sella turcica have been described in children with isolated growth hormone deficiency as well as in children with multiple hormone deficiencies even in the absence of neurohypophyseal disorder (Mitchell et al., 2002; Vitmann et al., 1993; Murray et al., 2008).

Early recognition within the first few days of birth is essential for appropriate diagnosis and treatment. A high index of suspicion and careful investigation of infants who presented with hepatitis and jaundice is imperative to rule out congenital panhypopituitarism.

Al Hussaini et al. (2012) reported an isolated cortisol deficiency and neonatal cholestasis in whom the resolution of cholestasis occurred after hydrocortisone replacement therapy and that suggests a causal relationship between cortisol deficiency and the development of neonatal cholestasis.

ACKNOWLEDGEMENT

The author would like to thank Ms. France Eleanor Solomon for the secretarial assistance and extend his thanks and appreciation to Mr. Abdulrahman N. Al Jurayyan for his help in preparing this manuscript.

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