

Neonatal hyperbilirubinemia and elevated liver enzymes associated with thyroid hormone deficiency in neonates.

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Abstract

During the period January 2004 and December 2009, 5 infants were seen with congenital hypothyroidism and neonatal hyperbilirubinemia and variable degrees of elevated liver enzymes. Hepato-biliary scintigraphy ruled out biliary atresia and infectious causes were excluded by the appropriate investigation. The neonatal hypothyroidism was due to pituitary (central) hypothyroidism (one), transient hypothyroidism (one), thyroid gland aplasia (one), thyroid gland dysmorphogenesis (two). The treatment with L-thyroxine led to complete resolution in the liver functions within 2 months.

Keywords: Neonate, Hypothyroidism, Hyperbilirubinemia

Accepted July 17 2011

Introduction

Neonatal jaundice is the commonest abnormal physical finding during the first week of life. Hyperbilirubinemia is universally present in the newborn period and is recognized as clinical jaundice in approximately 20-50% of full term neonates and 80% of pre-term neonates [1]. Rh isoimmunization, ABO incompatibility,

Glucose-6-phosphate dehydrogenase (G6PD) deficiency, bacterial infection and extravascular blood collection are the common causes of pathological hyperbilirubinemia in the newborn. However, no cause is identifiable in a significant proportion (8.8%-58%) of population having neonatal jaundice [2-6]. 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 glucosyl transferase (UDPG-T) enzyme activity [7-8].

Prolonged unconjugated hyperbilirubinemia occurs in approximately 10% of all neonates with hypothyroidism [9]. Virtanen et al [10] studied the clinical manifestations of congenital hypothyroidism (CHT) in the first week of life and found that 57.3% of babies developed visible jaundice as compared to 27.8% in euthyroid infants. The exact cause of higher incidence of jaundice in neonatal.

CHT is not known, however, several authors have observed severe non-haemolytic jaundice in neonates with CHT [7,8].

In this article, we report five infants who presented with hyperbilirubinemia and congenital hypothyroidism due to variable causes and variable degrees of elevated liver enzymes who responded to L-thyroxine therapy. The issue of hyperbilirubinemia and congenital hypothyroidism is highlighted.

Material and Methods

Patients who were seen between the period January 2004 and December 2009 with neonatal hyperbilirubinemia and hypothyroidism were reviewed. Septicemia, Rh isoimmunization, ABO incompatibility, G6PD deficiency, cephalhaematoma, and extravasation of blood were excluded. The total serum bilirubin (TSB) levels were estimated by the direct spectrophotometry and the conjugated fraction method. Serial liver function tests were done. 1- α -antitrypsin, hepatitis screen and TORCH screening were done to all infants. Serum TSH (Thyroid stimulating hormone) and FT4 (Free thyroxine) were measured using the Delfia Immunofluorescent method (Pharmacia Diagnostic, Wallacory, Finland) and antithyroid antibodies were measured by haemagglutination method.

Hepatobiliary scintigraphy after administration of 5mg/kg/ day of phenobarbitol for 5 days. 1-2 mCi of ^{99m}Tc-Di-Isopropyl (Disofenin) were administered intravenously to infants after 3-4 hours of fasting. Imaging of abdomen started immediately after injection with flow (16 frame / 2 sec each) on 64 matrix followed by sequential static images of 3-5 min each for 60 min in anterior projection until visualization of gall-bladder (GB) and /or bile ducts was observed, then other views in right anterior oblique, right lateral and posterior projections were taken. If activity in the bowel was not identified, delayed images of the abdomen were obtained at 2, 3, 4-8 and 20-24 hours post injection. The degree and pattern of radioactive tracer uptake (RATU) by the liver. Gall bladder visualization, and time of appearance of activity in the bowel, if occurred, were recorded. Non visualization of the GB and bowel was considered a positive indicator of BA. Poor RATU and/or in homogenous uptake pattern by the liver was considered suggestive of neonatal hepatitis [11].

Technetium-99m pertechnetate was performed in children using a gamma camera equipped with a low-energy general-purpose collimator. ^{99m}Tc pertechnetate was used in a dose of 500 µCi given intravenously. An initial zoomed image of the thyroid gland was obtained 15 min post injection and the uptake was measured between 20 and 30 min post injection. An additional unzoomed image including the salivary gland and stomach was obtained.

Radioactivity in the syringe was measured both before and after injection to give the correct administered dose. For thyroid scan, infant were sedated using chloral hydrate at a dose of 50 mg/kg given orally. Imaging patterns were assigned to three categories: (1) no detected thyroid activity, (2) ectopic location, with variable size and uptake, (3) normal location with normal or increased size and uptake, as recommended by the American Academy of Pediatrics, Thyroid Section [12,13]. All patients were treated with L-thyroxine (10-15 µg/kg/day) as recommended [12].

Result

During the period under review, five infants were diagnosed with congenital hypothyroidism and neonatal hyperbilirubinemia associated with variable degrees of raised liver enzymes. There were four males and one female (Table 1) among the study group. In one patient the hypothyroidism was secondary to pituitary abnormality as the magnetic resonance imaging (MRI) demonstrated hypoplastic anterior pituitary and an ectopic posterior pituitary gland associated with other hormonal deficiency such as growth hormone (GH). The liver function test results in five patients is shown in Table.2. Biliary atresia were excluded by hepato-biliary scintigraphy as the dye was demonstrated in the bowel. Infectious causes were excluded based on appropriate screening, and α -1-antitrypsin were normal. Three patients required phototherapy. In all the patients, the liver functions returned to normal within 2 months.

Table 1: Thyroid function tests and thyroid scan results

	Sex	TSH mU/L	Free T ₄ (Pmol/L)	Thyroid scan	Comments
1	F	3	8.4	Normally located / normal uptake	2 ⁰ ry hypothyroidism
2	M	730	10	Normally located with high uptake	Dyshormonogenesis
3	M	348	6.5	No thyroid tissue visualized*	Thyroid gland aplasia
4	M	17	11	Normally located with poor uptake	Transient hypothyroidism+
5	M	998	9	Normally located with high uptake	Dyshormonogenesis

*Magnetic resonance imaging (MRI): showing hypoplastic anterior pituitary with ectopic posterior pituitary, Confirmed at 2 years of age.

Table 2: Liver function tests at the time of initial presentation

	Liver Function Test						
	TB µmol/L	DB µmol/L	Protein /L	AST U/L	ALTU/L	Alk Ph U/L	GTT U/L
1	276	251	32	834	488	335	106
2	198	160	40	200	150	400	80
3	220	180	32	308	220	380	150
4	280	260	38	720	500	420	108
5	160	90	40	98	80	308	98

Discussion

In this study, the evidence of congenital hypothyroidism is based on biochemical findings of low FT₄ associated with high TSH, in primary congenital hypothyroidism supported by thyroid scintigraphy, while a low FT₄ associated with low TSH suggested the secondary hypothyroidism. This is supported by deficiency of other pituitary hormones such as growth hormones and the magnetic resonance imaging (MRI) finding of hypoplastic anterior pituitary with ectopic posterior pituitary.

The serum bilirubin is high associated with elevated liver enzymes. The hepato-biliary scintigraphy findings ruled out biliary atresia [11,14] while infectious cause were unlikely based on screening. The return of the liver enzymes to normal within 2 months of L-thyroxine therapy confirms the relationship of neonatal hyperbilirubinemia and the congenital hypothyroidism.

The origin of jaundice in this situation is still to be determined. Some researchers have suggested that hyperbilirubinemia could be due to a delayed maturation of the hepatic UDPG-T activity [15]. This is supported by Labruno et al [16] who demonstrated absence of detectable enzyme activity. Other mechanisms may be proposed.

The absence of thyroid hormones may result in a decreased hepatic concentration of uridine diphosphate glucuronic acid, which is known to be low in the neonate because of reduced UDP glucose dehydrogenase activity. The absence of thyroid hormones may also be responsible for a delay in bilirubin uptake, due to maturational changes in ligandin.

Few experimental models have already been studied. In adult wistar rats, hypothyroidism results in an increased hepatic UDPG-T activity, a decrease in bile flow and bile salt excretion, and an increased proportion of conjugated bilirubin in serum [17].

An inverse relationship was found between hepatic glucuronidase activity and the ratio of diconjugates to monconjugates in bile. However, hepatic UDPG-T is functionally heterogenous, with two representative substrates for two functional forms of the enzyme (bilirubin and 4-nitrophenol), and opposite effects of thyroid hormones on these two forms have been previously observed [18].

Acknowledgement

The authors would like to thank Ms. Loida M. Sese for the secretarial assistance.

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