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Case Report

Hepatic Dysfunction and Growth Failure Resulting from Undiagnosed Neonatal Graves Disease - A Case Report

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Abstract

Hyperthyroidism is a common condition and presents most commonly as Graves disease in adults, but in neonates, congenital hyperthyroidism is a much rarer finding. Congenital hyperthyroidism is shown to be present in about 1:4000 patients and can cause significant disease with serious life-long ramifications if not recognized early. Neonates usually present with tachycardia, arrhythmias, growth retardation and prematurity in the fetal period and subsequently irritability, hypertension, and poor weight gain after birth. The etiology of congenital hyperthyroidism is most commonly due to transplacental transfer of maternal antibodies in mothers with Graves disease. Hyperthyroidism can also have effects on liver enzymes and lead to liver dysfunction as thyroid hormones are processed in the liver and excreted in bile. We present the case of a 14-day old preterm patient who presented with significant hepatic dysfunction and growth failure secondary to congenital hyperthyroidism due to maternal Graves disease. The Infant had been investigated for obstructive, genetic, infectious, and metabolic causes of liver dysfunction prior to transfer which were negative. Further investigation revealed elevated thyroxine levels with significant suppression of thyroid stimulating hormone (TSH) and elevation of TSH receptor antibody (TRAb) levels. We present this case to highlight the importance of recognizing hepatic dysfunction as a clinical feature of congenital hyperthyroidism, as failure to accurately diagnose neonatal hyperthyroidism can result in long term complications such as craniosynostosis, severe developmental delay and mental retardation.

ABBREVIATIONS

TSH: Thyroid Stimulating Hormone; TRAb: TSH receptor antibody; T4: Thyroxine; T3: Triiodothyronine; GD: Graves Disease; TSHR: TSH receptor; VSD: Ventricular septal defect; ASD: Atrial septal defect; DOL: Day of life; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GI: Gastroenterology; ATA: American Thyroid Association; PTU: Propylthiouracil, MMI: Methimazole; TFTs: Thyroid function tests; ATD: Antithyroid drug; FDA: Food and Drug Administration; NASPGHAN: North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

INTRODUCTION

Hyperthyroidism is a common condition in adults and is known to present most commonly as Graves disease. However, in neonates, congenital hyperthyroidism occurs rarely. One of the first published cases of congenital hyperthyroidism was by Ochsner and Thompson in 1910 which described an infant born to a mother with an exophthalmic goiter who presented with prematurity, low birth weight, abnormal head shape and eye protrusion [1].

In utero, thyroid gland development is well delineated. The thyroid gland develops from a midline thickening of the pharyngeal floor and paired caudal extensions of the fourth pharyngobranchial pouches [2]. By the 7th week of life, the thyroid gland has migrated to its final position in the anterior neck. Thyroid hormone secretion begins around the 10th week of gestation and is dependent on availability of iodine and stimulation of thyroid stimulating hormone (TSH) receptors by pituitary thyrotropin to stimulate the proliferation, differentiation, and function of the thyroid follicular cells to produce thyroid hormones; thyroxine (T4) and triiodothyronine (T3). As the fetal thyroid develops, there is also transplacental transfer of maternal thyroxine beginning in the 1st trimester and continuing till birth, which is critical for central nervous system development [3,4].

The causes of neonatal hyperthyroidism can be separated into autoimmune and non-autoimmune causes. Autoimmune neonatal hyperthyroidism is usually transient and due to transplacental passage of thyroid stimulating hormone (TSH) receptor antibodies (TRAb) due more commonly to maternal Graves disease (GD) or less commonly to maternal Hashimoto's thyroiditis. TRAb belongs to the immunoglobulin G class and freely

crosses the placenta. There are 2 types of TRAb: TSH receptor stimulating antibodies which bind to the TSH-receptor on thyroid follicular cells and lead to autonomous thyroid hormone production, and TSH-receptor blocking antibodies, which bind to the TSH-receptor but do not initiate intracellular signaling [5]. Less frequently, permanent neonatal hyperthyroidism is due to non-autoimmune causes resulting from activating mutations in the TSH receptor (TSHR) gene, activating mutations in the stimulatory G protein/cAMP signaling pathway as in McCune Albright syndrome, and thyroid hormone resistance due to a mutation in the thyroid hormone receptor β gene [6]. Other rarer causes of neonatal hyperthyroidism to be considered are congenital hypothyroidism treated with high dose thyroxine, iodine-induced hyperthyroidism, and the use of biotin [6,7].

Hyperthyroidism due to Graves disease occurs in 0.5-1.0% of women in the reproductive age range [8]. The incidence of maternal hyperthyroidism due to Graves disease in pregnancy varies from 0.1 -2.7% [5,9]. It is thought that 1-2% of infants born to mothers with Graves disease will develop neonatal hyperthyroidism [10], while others have reported rates as high as 1.5-12% [4,9] resulting in an estimated incidence of fetal and/or neonatal hyperthyroidism ranging from 1:4000 up to 40,000 to 50,000 [3,4,7].

Neonatal Graves disease results from the stimulatory effects of transplacentally acquired maternal TRAb on the TSH receptor of the fetal and newborn thyroid gland resulting in increased thyroid hormone production and release. In maternal Graves disease, the TRAb level in fetal circulation begins to rise around 15 weeks gestation and reaches maternal levels around 30 weeks gestation. Onset of symptoms may occur in the fetus while neonatal hyperthyroidism usually presents within the 1st month of life, usually by 2 weeks of age but has been described as late as day 45 [5]. Onset of presentation can be affected by presence of maternally administered antithyroid medications, increased conversion of T4 to T3 after birth and the presence of TSH receptor blocking antibodies which have an inhibitory effect on the TSH receptor [10]. Neonatal Graves tends to resolve spontaneously usually within 3 -12 weeks, and the duration of illness is a function of antibody potency and rate of metabolic clearance of stimulating or blocking antibodies from the neonatal circulation [9].

Clinical manifestations of neonatal hyperthyroidism can affect various organ systems [3,4,7,10,11]. It may result in poor fetal growth, premature birth, poor postnatal weight gain, advanced bone age and goiter. Gastrointestinal findings are hepatosplenomegaly, prolonged jaundice, and increased stool frequency. Cardiovascular manifestations include tachycardia, arrhythmias, systemic hypertension, pulmonary hypertension, and cardiac failure which may result in death. Ophthalmologic findings can include exophthalmos, lid lag, stare and periorbital edema. Central nervous system manifestations include restlessness, irritability, speech delay, psychomotor retardation, microcephaly, and craniosynostosis. Mortality rates for neonatal hyperthyroidism have been reported as high as 20% [4]. Symptoms of hyperthyroidism in neonates may resemble congenital viral infections, neonatal sepsis, congenital heart disease, tachyarrhythmia, and narcotic withdrawal [7]. Thus, to prevent serious and long term sequelae, neonatal hyperthyroidism needs to be diagnosed and treated early.

CASE PRESENTATION

We present the case of a 14-day old, preterm male infant patient who was transferred to our institution for evaluation of liver dysfunction and growth failure. The patient was delivered vaginally following spontaneous preterm labor at 33 weeks gestation. Apgar scores of 7 at 1 minute and 8 at 5 minutes. Maternal prenatal labs were negative. Maternal history was positive for drug use, namely tobacco and marijuana. The patient's birth weight was 1.750 kg (20th percentile).

At the referring hospital within the 1st week of life, the infant was noted to have a systolic murmur with episodes of tachycardia (HR >200), tachypnea and irritability. Echocardiogram revealed large unrestricted membranous ventricular septal defect (VSD) with a small atrial septal defect (ASD). 24-hour Holter monitoring revealed sinus tachycardia. Propranolol therapy was started per Cardiology recommendations with improvement in clinical symptoms. He was also noted to have poor growth velocity despite enteral feeds of 24 cal/oz at 170 ml/kg and weight declined to the 6th percentile by day of life (DOL) [14]. Additionally, laboratory evaluation revealed elevated direct bilirubin with associated elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) enzymes. Stools were noted to be pale, green in color. Gastroenterology (GI) service was consulted remotely, and the infant was started on Phenobarbital therapy for the cholestasis. Investigations for congenital infections, hepatic disorders, biliary obstruction, genetic or metabolic causes of liver dysfunction were negative (Table 1). Infant was transferred to our facility for direct GI evaluation and further testing.

On admission, examination was positive for mild tachypnea with mild subcostal retractions, grade 2/6 systolic murmur, hepatomegaly (2 cm below costal margin), irritability and mild jaundice with hypopigmented stools. Phenobarbital was discontinued on transfer to facilitate a HIDA scan which was negative. Spinal imaging for evaluation for butterfly vertebrae was negative. Re-evaluation by Cardiology showed sinus rhythm and Propranolol therapy was discontinued on DOL 17 (10 days of therapy). Ursodiol was started for cholestasis on DOL 22.

Table 1: Investigations

Alpha-1-antitrypsin	Hepatitis A IgM	CMV vial shell culture	Stool fecal fat	Urine drug screen
Toxoplasma IgG	Hepatitis B IgM	CMV IgM	Plasma Amino Acids	Newborn screen
Rubella IgM	Hepatitis B surface Ag	Parvovirus B19 PCR	Urine organic acids	EGL Genetic Cholestasis panel
HSV 1 /2 IgG	Hepatitis C Ab	Blood culture	Abdominal US with Doppler	Microarray

Abbreviations: IgM: Immunoglobulin M; CMV: Cytomegalovirus; IgG: Immunoglobulin G; Ag: Antigen; PCR: Polymerase chain reaction; HSV: Herpes simplex virus; Ab: Antibody; US: Ultrasound

Thyroid function testing on DOL 25 showed suppression of TSH with elevation of free T4. Subsequent questioning of the mother revealed a history of Graves disease with prior radio-iodine ablation (2 years prior to pregnancy), which resulted in a hypothyroid state for which she had received Levothyroxine and Liothyronine therapy during pregnancy. TSH receptor antibody level was also elevated. Endocrinology was consulted and treatment with Methimazole and Lugol's iodine solution was initiated which resulted in improvement in growth, thyroid, and liver function. He was discharged home on DOL 43 on enteral feeds of 27 cal/oz with improved growth velocity, iodine and Ursodiol therapy. Outpatient follow up was continued with Pediatric Endocrinology and Gastroenterology. Iodine therapy was discontinued at 2.5 months of age and Ursodiol therapy was discontinued at 4 months of age with normalization of labs (Table 2).

DISCUSSION

Neonatal GD can lead to significant health complications and as a result, prompt diagnosis and treatment is required. Any infant with a maternal history of previous or current Graves hyperthyroidism is at risk for fetal and neonatal thyroid disease which could include fetal hyperthyroidism, neonatal hyperthyroidism, fetal hypothyroidism, neonatal hypothyroidism, and central hypothyroidism. As a result, the American Thyroid Association (ATA) in its 2017 Guidelines for the Diagnosis and management of Thyroid Disease during Pregnancy and Postpartum [12] states that if a patient has a history of GD or a past history of GD treated with ablation (radioiodine or surgery), a maternal serum determination of TRAb is recommended at initial thyroid function testing during pregnancy as TRAb levels may remain high following ablation therapy even more so after radioiodine treatment than surgical treatment. If the TRAb is elevated (> 3x upper limit of normal or > 5 IU/L) then TRAb levels should be followed at 18-22 weeks of pregnancy and if still elevated repeated at 30-34 weeks of pregnancy. However, if initial maternal TRAb testing is low or undetectable, no further testing is required.

Our patient's mother had been followed by Endocrinology during pregnancy and was on Levothyroxine and Liothyronine replacement therapy for hypothyroidism following radioiodine ablation for GD. A review of maternal records showed no testing for TRAb at any time during pregnancy. In addition, maternal history of Graves disease with radioablative therapy nor current maternal therapy with thyroxine replacement was not documented on neonatal admission notes at the time of delivery by the referring institution. The ATA Guidelines [12] recommends that "A history of maternal thyroid illness, use of antithyroid medications [Propylthiouracil (PTU), methimazole (MMI)] during gestation, or measurements of abnormal maternal thyroid function or TRAb during gestation should be communicated to the newborn's neonatologist or pediatrician". This lack of communication prevented early suspicion of an endocrinologic cause for the patient's clinical features of prematurity, irritability, tachycardia, poor growth, and cholestatic jaundice.

Table 2: Relevant results over time

Test	At diagnosis	~ 1 month on treatment	~2.5 months on treatment	Range
AST	337	132	75	10-40 U/L
ALT	239	140	47	10-44 U/L
Total bilirubin	6.5	2.3	0.5	0.1-1.0 mg/dL
Direct Bilirubin	5	1.6	0.3	0.1 – 0.3 mg/dL
TSH	0.1	<0.010	<0.01	0.4 – 5.0 uIU/mL
Free T4	4.22	1.49	1.17	0.71 – 1.59 ng/dL
TRAb	16	4.96	<1.0	0.0 – 1.75 IU/L

Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TSH: Thyroid Stimulating Hormone; TRAb: TSH receptor antibody; T4: Thyroxine

Van der Kaay [5] suggests a risk-based algorithm for the evaluation of infants born to mothers with GD based on the presence of maternal TRAb. This underlies the importance of obtaining maternal TRAb levels as suggested by the ATA. If maternal TRAb levels are negative (undetectable or within reference range) the infant is not at risk and no further follow up is required. Infants born to mothers with unknown or positive (exceeding the reference range) TRAb levels are regarded at high risk of developing hyperthyroidism.

In infants at risk, determine TRAb levels in cord blood or as soon as possible after birth. The determination of cord TSH and fT4 levels is not indicated. Thyroid function tests (TFTs): TSH and free T4 should be measured at DOL 3-5 unless warranted earlier by clinical signs and if within reference ranges, TFTs should be repeated at DOL 10-14. If no abnormal levels are identified after 2 weeks of life, routine testing can be discontinued. Infants should be assessed clinically at 4 weeks and 2-3 months of life to identify infants who may have a delayed presentation.

Treatment for hyperthyroidism should only be initiated in infants with both biochemical hyperthyroidism and clinical signs/symptoms to avoid short term and long-term complications.

Methimazole (MMI) is the preferred antithyroid drug (ATD). It inhibits thyroid peroxidase and subsequent synthesis of thyroid hormone. The dose range of MMI is 0.2-1 mg/kg/day in 1-3 divided doses orally [8]. Beta- adrenergic blockers such as propranolol can be used to decrease sympathetic hyperactivity. Propranolol dosing is 2 mg/kg/day in 2 divided doses [8]. Iodine containing solutions such as Lugol's solution or potassium iodide can be added for refractory cases. They act by increasing uptake of iodine, inhibiting thyroid peroxidase, and ultimately blocking the release of thyroid hormones [13]. Lugol's solution dose is 1 drop (0.05 ml) 3 times a day while Potassium iodine is given as 1 drop per day. Finally, critically ill newborns requiring admission to a NICU may require a short course of glucocorticoids which inhibit thyroid hormone secretion and impair peripheral deiodination of T4 to T3 in addition to ATDs. Prednisolone is given as 2 mg/kg/day in 1-2 divided doses. Propylthiouracil, another ATD, inhibits thyroid peroxidase activity however there is a US Food and Drug Administration (FDA) warning regarding the development of liver failure [8] and as such, the ATA guidelines recommend that PTU should be offered only as a short course in case of thyroid storm or severe adverse reactions to MMI treatment, other than agranulocytosis, when treatment options such as radioactive iodine or thyroidectomy are not available [8].

Our patient was initially started on MMI at 0.5 mg/kg/day in 3 divided doses and Lugol's solution at 1 drop daily. MMI and Lugol's solution were discontinued after 5 days of therapy due to significant decrease in fT4 levels. Lugol's solution was resumed 1 week later with increase in fT4 levels and continued till discharge. Iodine therapy was discontinued at 2.5 months of life.

Neonatal thyrotoxicosis can have various cardiac manifestations such as tachycardia, arrhythmia, systemic hypertension, pulmonary hypertension and high cardiac failure. B blockers are effective in treating these symptoms caused by adrenergic stimulation. Our case demonstrated tachycardia, which was controlled with B blocker therapy, Propranolol, prior to diagnosis of hyperthyroidism.

Ventricular septal defects (VSD) and other congenital heart defects have been described in infants of mothers with GD [14,15]. Heart septal defects are also postulated to be a part of the Methimazole/Carbimazole embryopathy which includes, in combination or not, esophageal atresia, omphalocele, choanal atresia, facial dysmorphia and cutis aplasia [16], however there was no prenatal exposure to these medications in our case.

Liver dysfunction including elevation of conjugated bilirubin and transaminases (AST/ALT) has been reported in infants with GD [17-21], thus the Guidelines for the evaluation of Cholestasis in infants from the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) recommend evaluation of TSH, freeT4 and T3 in these infants [22]. The exact mechanism of liver dysfunction in thyrotoxicosis is uncertain. However certain etiologies have been postulated as thyroid hormones are processed in the liver and excreted in bile. Possible thyroid-liver interactions include liver damage secondary to the systemic effects of thyroid excess, direct toxic effects of thyroid hormone on the liver, association of intrinsic liver disease with intrinsic thyroid disease through autoimmune mechanisms, alterations of thyroid hormone metabolism secondary to intrinsic liver disease, and subclinical physiologic effects of thyroid hormone on liver function [23]. In our patient, we hypothesize that elevated thyroid hormone levels caused an increased metabolic rate resulting in hepatic dysfunction and associated growth failure.

SUMMARY

We have presented an infant with liver dysfunction secondary to hyperthyroidism due to maternal Graves disease. The importance of proper screening of infants born to mothers with active or with a history of Graves disease is crucial in avoiding neonatal morbidity and mortality.

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