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Case Report

Neonatal Hyperthyroidism in a Premature Infant Born to a Thyroidectomized Mother with Graves' Disease and High Levels of TSH Receptor Autoantibodies

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Abstract

Graves' disease is the most frequent cause of hyperthyroidism in pregnant women; however, only 1% of children born to these women are described as having hypertyroidism. We report neonatal hyperthyroidism developed in a premature infant born at 32 weeks of gestation to a thyroidectomized mother with Graves' disease and high levels of TSH receptor autoantibodies (TRAb). We conclude that, as placental transfer of maternal autoantibodies may cause hyperthyroidism in the fetal and early neonatal periods, early diagnosis and treatment of hyperthyroidism are important in infants born to mothers with Graves' disease.

Keywords: *Neonatal Hyperthyroidism; Transplacental Passage; TSH Receptor Autoantibodies; Graves' Disease*

Introduction

Graves' disease is the most frequent cause of hyperthyroidism in pregnant women; however, only 1% of children born to these women are described as having hypertyroidism.

Case Report

A male infant was born at 32 weeks of gestational age to a 36-year-old mother diagnosed at age 28 years with thyrotoxicosis attributable to Graves' disease. The mother was noncompliant with medication. Thus she performed radioiodine ablation twice, with no benefit. At the age of 33 she underwent surgical subtotal thyroidectomy, with subsequent hypothyroidism, and began substitutive therapy with L-thyroxine. Maternal TRAb levels were elevated (> 40 UI/L at 22 weeks; normal values 0 - 1) with high thyroid stimulating activity during pregnancy (> 400% at 18 weeks; normal values < 15); no antithyroid drugs were administered. Her thyroid function was: free thyroxine (fT4) 0.88 ng/dL (normal values 0.9 - 1.7), thyroid-stimulating hormone (TSH) 0.25 mU/mL (normal values 0.27 - 4.2) at the time of delivery. She underwent emergency cesarean section because of hypertension.

The infant had a 1-minute Apgar score of 8, a 5-minute Apgar score of 9 and weighed 1940g (50° percentile). He required respiratory support by nCPAP for the first 3 days of life for respiratory distress.

During the first week of life he developed tachycardia (200 beats per minute); moreover he had exophthalmos and became more and more irritable and hungry. He did not show goiter and his thyroid on ultrasound had normal structure and dimensions.

We diagnosed thyrotoxicosis (fT4 7.77 ng/dL, fT3 1.64 ng/dL, TSH < 0.01 mU/mL) at 9 days of life according to the reference fT4 level (1.3 - 4.7 ng/dL) for 30 to 36 weeks of gestation [1] and tachycardia and began oral administration of methimazole (0.5 mg/kg per day) and propanolol (1 mg/kg per day). TRAb were > 40 UI/L.

Apart from tachycardia, ECG was normal and there were no signs of heart failure on ultrasound examination. Antithyroid peroxidase antibodies and antithyroglobulin antibodies were normal.

Twenty-four hours after the beginning of therapy, the heart rate decreased to 145 beats per minute. At 13 days of life thyroid function was decreased while TSH remained low (for fT4, TSH and TRAb values see graph 1).

Withdrawal of methimazole by day 16 led to rebound of fT4 levels and a recrudescence of thyrotoxic symptoms, so that it was cautiously recommenced.

At 33 days of life the thyroid function was decreased and therapy with methimazole was halfened. Therapy with propanolol was gradually decreased and discontinued at 38 days of life.

After a 5% birth weight decrease during the first week of life, growth rate raised to 11 g/kg/day weekly, with caloric intake of 120 kcl/kg/day. The baby was dismissed from hospital at 40 days of life; he weighed 3 kilos.

At 46 days of life for the first time TSH levels began to raise while TRAb levels were very low: therapy with methimazole was successfully discontinued.

TSH levels normalized by the third month of life, TRAb levels were completely normal by 100 days of life.

Ultrasound cerebral examinations resulted normal at birth and in the first weeks of life. Neurobehavioural development was normal at 18 months of corrected age.

At the age of 3 the infant had asymptomatic transient elevation of TRAb, reaching a higher level of 7.7 UI/L (normal value < 0.9). Thyroid function was normal and the level of TRAb decreased spontaneously in 6 months.

Discussion

Neonatal hyperthyroidism is rare, concerning one neonate out of 50,000. The most common cause of fetal and neonatal hyperthyroidism is maternal Graves' disease.

About 0.2% of pregnant women have Graves' disease, however only 1% of children born to these women develop hyperthyroidism [2], due to transplacental transfer of TSH receptor autoantibodies which stimulate fetal thyroid hormone secretion by activating the TSH receptor. This effect lasts until the maternal antibodies have disappeared from the infant's circulation, which occurs at the latest by 4 months of life [3].

Fetal hyperthyroidism due to maternal Graves' disease usually occurs during the third trimester. As a matter of fact, even if the fetal thyroid hormone secretion begins at about 10 weeks of gestation, the TSH receptor becomes responsive to stimulation by TSH or by TRAb only during the second trimester and the fetal concentration of maternal antibodies increases progressively from the 15 - 20th week of amenorrhea to reach the maternal level at around 30 weeks [4].

Infants born to mother's with Graves' disease may have various thyroid disfunctions during fetal and neonatal period: maternal autoantibodies can either stimulate or block the fetal thyroid function [4], resulting in either hypothyroidism or hyperthyroidism. Moreover, T4 transfer from the non compliant mother with thyrotoxicosis may cause hyperthyroidism in fetal and early neonatal life, with later development of pituitary hypothyroidism [5].

In our case the mother had been thyroidectomized and received replacement hormonal therapy; no antithyroid drugs were administered, even if TRAb levels were high during pregnancy, with high thyroid stimulating activity. There is a correlation between level and

activity of TRAb and the appearance of fetal or neonatal thyrotoxicosis [6], with a positive risk when TRAb is higher than 40 U/L [7] or 50% [8]. Antithyroid drugs (ATD) have been suggested to be effective in preventing fetal and neonatal hyperthyroidism even in euthyroid pregnant women with previous Graves' disease and high TRAb levels [9].

In our case pregnancy was complicated by hypertension, which led to premature cesarean section. It is well reported that maternal Graves' disease may be associated to complications such as premature birth, maternal toxemia, hypotrophy, abortion and still birth [10].

As an adequate treatment can significantly reduce fetal and maternal complications, maternal thyroid dysfunction and TRAb levels should be investigated at the 28th week of amenorrhea [11].

Moreover, great attention should be paid to the early detection of fetal signs of hyperthyroidism (goiter, tachycardia, heart failure, growth retardation, craniosynostosis, accelerated bone maturation). Some have suggested that, in the presence of high maternal TRAb levels, fetal thyroid function should also be evaluated by cordocentesis [11,12] at least in selected high risk cases [10].

The treatment is based on the oral administration of synthetic antithyroid agents such as propylthiouracyl, carbimazole and methimazole, monitoring the efficacy through the follow-up of maternal hormonal assays. Therapy should be administered at very low doses to maintain T4 above its normal values in the mother, in order to prevent a iatrogenous fetal hypothyroidism; due to ATD transplacental transfer [3].

In our case no fetal signs of thyrotoxicosis were present, but clinical signs of hyperthyroidism appeared during the first week of life, as it often happens [3], along with high levels of TRAb.

Neonatal hyperthyroidism should be escluded in all infants born to mothers with Graves' disease, at birth and in the first week of life. High levels of TRAb [13] and TRAb activity and low levels of TSH on cord blood are associated to a higher risk for neonatal hyperthyroidism.

As reference intervals for thyroid hormones in premature newborns are not well established, clinical signs may be very useful for the diagnosis of neonatal hyperthyroidism [1]. The most frequent neonatal clinical signs are tachycardia, goiter, hyperexcitability, hepatomegaly, splenomegaly, exophthalmos, diarrhea, increased appetite but failure to thrive, heart failure, sweating and hyperthermia.

The mortality rate in affected infants is 12 - 16% [14]. As the immediate prognosis depends primarily on the cardiac manifestations, with a risk of heart failure, therapy with betablockers should be started if tachicardia is present. Our infant was treated with propanolol (recommended dose of 1 - 2 mg/kg/die per os).

Antithyroid drugs must also be administered as early as possible: methimazole (0.5 - 0.7 mg/kg/day orally twice daily) or propylthiouracyl (5 - 10 mg/kg/day orally thrice daily). A saturated solution of potassium iodide (1 drop/day) or Lugol's solution (1 - 3 drops/day) may be added in severe cases [3].

Thyroid function should be monitored during therapy: TSH levels may persist very low for long, as in our case. If hypothyroidism appears, L-thyroxine administration could be necessary to maintain euthyroid status. Antithyroid drugs must be continued as long as TRAb are present [3]. As a matter of fact our first attempt of discontinuation of methimazole was followed by a further T4 elevation; discontinuation on day 46, when TRAb were very low and TSH levels started to raise, was then successful.

The long-term prognosis of neonates with thyrotoxicosis has not been well documented; fetal and neonatal hyperthyroidism has been associated to early craniosynostosis and neurodevelopmental abnormalities ranging from mild learning disabilities to severe mental retardation [15]. Premature delivery itself may be related to neuropsychological sequelae.

Our baby at 3 months of life (1.5 months of postconceptual age) had a normal neurobehavioural performance. Further follow-up is needed.

Conclusion

In conclusion, even if rare, neonatal hyperthyroidism should be searched in infants born to mothers with Graves' disease, especially when maternal high TRAb levels are present.

It should be remembered that fetal and neonatal hyperthyroidism may occur even if the mother have actually become hypothyroid after thyroid ablation for Graves' disease and is on thyroxine replacement, if she has persistently elevated levels of TRAb.

Early diagnosis and therapy are important in order to prevent cardiac and neurological complications of this disease.

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