

NEONATAL HYPERTHYROIDISM

Maria Segni, M.D. Associated Professor of Pediatrics. Sapienza University. Department of Pediatrics, Rome, Italy. Pediatric Endocrinology Unit, Policlinico Umberto I, Viale Regina Elena 364 -00161- Rome Italy. Email maria.segni@uniroma1.it.

Updated April 14, 2019

INTRODUCTION

Neonatal hyperthyroidism in most cases is transient and results from the transplacental passage of maternal stimulating TSH receptor antibodies (TRAb) known as neonatal Graves' disease (GD). Permanent non autoimmune neonatal hyperthyroidism is rare and is due to activating mutations of TSH receptor or due to somatic activating mutations in the stimulatory alpha subunit of the guanine nucleotide-binding protein (GNAS gene) in McCune-Albright syndrome. Exposure to topical iodine has also been reported as a rare cause of hyperthyroidism in newborns.

TRANSIENT NEONATAL HYPERTHYROIDISM

Neonatal Graves' disease (GD) is usually a self-limited disease, but it can be life threatening and permanently damage the brain. Neonatal GD is caused by transplacental passage of TSH receptor antibodies (TRAb) with stimulatory activity.

TRAb are Immunoglobulin of G class and freely cross the placenta. Different types of TRAb can be found: TRAb that bind to the TSH receptor and stimulates the production of thyroid hormones, (TSH receptor stimulating antibodies, TSI), TRAb that bind to the TSH receptor, do not stimulate the production of thyroid hormones and can block the binding of TSH (TSH receptor blocking antibodies TBI).

Hyperthyroidism develops only in babies born to mothers with the most potent stimulatory activity in serum. This corresponds to 1-2% of mothers with Graves' disease, or 1 in 50,000 newborns, an incidence that is approximately four times higher than is that for transient neonatal hypothyroidism due to maternal TSH receptor blocking antibodies. Some mothers have mixtures of stimulating and blocking antibodies in their circulation, the relative proportion of which may change over time. Not surprisingly, the clinical picture in the fetus and neonate of these mothers is more complex and depends not only on the relative proportion of each activity in the maternal circulation at any one time but on the rate of their clearance from the neonatal circulation postpartum.

Occasionally, neonatal hyperthyroidism may even occur in infants born to hypothyroid mothers. A prospective study showed that 40% of patients treated for Graves' disease with radioactive iodine had TRAb detectable after 5 years (13). In these situations, the maternal thyroid has been destroyed either by prior radioablation, surgery, or by coincident destructive autoimmune processes so that potent thyroid stimulating antibodies, present in the maternal circulation, are silent in contrast to the neonate whose thyroid gland is normal. Persistence of TRAb after thyroidectomy is higher in females with Graves' ophthalmopathy or smokers. Fetal/neonatal thyrotoxicosis can occur also in newborn from hypothyroid mothers with chronic lymphocytic thyroiditis.

CLINICAL MANIFESTATIONS

TABLE 1. Situations That Should Prompt Consideration of Neonatal Hyperthyroidism
Unexplained tachycardia, goiter or stare
Unexplained petechiae, hyperbilirubinemia, or hepatosplenomegaly
History of persistently high TSH receptor antibody titer in mother during pregnancy
History of persistently high requirement for antithyroid medication in mother during pregnancy
History of thyroid ablation for hyperthyroidism in mother
History of previously affected sibling

Maternal TSH receptor antibody-mediated hyperthyroidism may present in utero. Fetal hyperthyroidism is suspected in the presence of fetal tachycardia (pulse greater than 160/min) especially if there is evidence of failure to thrive. Obstetric complications are common. Fetal goiter (fetal neck circumference >95%) can by monitored by ultrasound using nomograms for fetal thyroid growth. Fetal goiter can cause esophageal and/or tracheal obstructions and polyhydramnios. Fetal goiter can also be due to transplacental passage of antithyroid drugs that cause hypothyroidism in the fetus.

TABLE 2. Clinical Manifestations in the Fetus
Unexplained tachycardia,
Failure to thrive
Intrauterine growth retardation
Goiter
Advanced bone age
Prematurity
Craniosynostosis, microcephaly
Fetal death

In the neonate infant typically, the onset is during the first one two weeks of life but can occur by 45 days. This is due both to the clearance of maternally administered antithyroid drug (propylthiouracil- PTU, methimazole- MMI, or carbimazole) from the infant 's circulation and to the increased conversion of T4 to the more metabolically active T3 after birth. Rarely, as noted earlier, the onset of neonatal hyperthyroidism may be delayed until later if higher affinity blocking antibodies are also present.

In the newborn infant, characteristic signs and symptoms include tachycardia, irritability, poor weight gain, and prominent eyes. Goiter, when present, may be related to maternal antithyroid drug treatment as well as to the neonatal Graves' disease itself.

Rarely, infants with neonatal Graves' disease present with thrombocytopenia, jaundice, hepatosplenomegaly, and

hypoprothrombinemia, a picture that may be confused with congenital infections such as toxoplasmosis, rubella, or cytomegalovirus. In addition, arrhythmias and cardiac failure may develop and may cause death, particularly if treatment is delayed or

inadequate. In addition to a significant mortality rate that approximates 20% in some older series, untreated fetal and neonatal hyperthyroidism is associated with deleterious long-term consequences, including premature closure of the cranial sutures (cranial synostosis), failure to

thrive, and developmental delay. The half-life of TSH receptor antibodies is 1 to 2 weeks. The duration of neonatal hyperthyroidism, a function of antibody potency and the rate of their metabolic clearance, is usually 2 to 3 months but may be longer.

TABLE 3. Clinical Manifestations in the Neonate
Irritability, hyperexcitability, sleep disorders
Tachycardia, hypertension, cardiac failure
Flushing, sweating
Respiratory distress, pulmonary hypertension
Goiter, stare
Feeding difficulties, increased appetite but no/poor weight gain
Diarrhea
Unexplained petechiae, hyperbilirubinemia, jaundice, or hepatosplenomegaly
Craniosynostosis, microcephaly,
Death

LABORATORY EVALUATION

The recent guidelines for management of hyperthyroidism and the updated guidelines for the management of thyroid disease during pregnancy released from the American Thyroid Association ATA both suggest determining TRAb levels in pregnant women with Graves' disease at 18-22 weeks instead of 20-24 weeks of gestation because a severe case of fetal Graves' disease has occurred at 18 weeks of pregnancy.

Because of the importance of early diagnosis and treatment, infants at risk for neonatal hyperthyroidism should undergo both clinical and biochemical assessment as soon as possible.

All neonates born from a woman with TRAb positivity in pregnancy should undergo determination of TRAb from cord blood at delivery. If TRAb is negative, the risk to neonatal hyperthyroidism is negligible (Sensitivity is around 100%). FT3, FT4 and TSH determination from cord blood did not predict neonatal hyperthyroidism. Increases in FT4 on day 3 to 5 seems to better indicate the onset of hyperthyroidism. Situations that should prompt consideration of neonatal hyperthyroidism are listed in Table 1. A high index of suspicion is necessary in babies of women who have had thyroid ablation because in them a high titer of TSH receptor antibodies would not be evident clinically. Similarly, women with persistently elevated TSH receptor antibodies and with a high requirement for antithyroid medication are at an increased risk of having an affected child.

The diagnosis of hyperthyroidism is confirmed by the demonstration of an increased concentration of circulating T4 (and free T4, and T3, if possible) accompanied by a suppressed TSH level in neonatal or fetal blood. Results should be compared with normal values during gestation. Fetal ultrasonography may be helpful in detecting the presence of a fetal goiter and in monitoring fetal growth. Demonstration in the baby or mother of a high titer of TSH receptor antibodies will confirm the etiology of the hyperthyroidism and, in babies whose thyroid function testing is normal initially, indicate the degree to which the baby is at risk.

In general, babies likely to become hyperthyroid have the highest TSH receptor antibody titer but levels of maternal TRAb in the serum as low as 4.4 U/L has been associated with neonatal thyrotoxicosis. If TSH receptor antibodies are not detectable, the baby is very unlikely to become hyperthyroid. In the latter case, it can be anticipated that the baby will be euthyroid, have transient hypothalamic-pituitary suppression, or have a transiently elevated TSH, depending on the relative contribution of maternal hyperthyroidism

versus the effects of maternal antithyroid medication, respectively. Close follow up of all babies with abnormal thyroid function tests or detectable TSH receptor antibodies is mandatory.

THERAPY

In the fetus, treatment is accomplished by maternal administration of antithyroid medication. Until recently PTU was the preferred drug for pregnant women in North America, but current recommendations suggest the use of MMI rather than PTU after the first trimester because of concerns about potential PTU-induced hepatotoxicity. The goals of therapy are to utilize the minimal dosage necessary to normalize the fetal heart rate and render the mother euthyroid or slightly hyperthyroid. In the neonate MMI (0.25 to 1.0 mg/kg/day) has been used initially in 3 divided doses. If the hyperthyroidism is severe, a strong iodine solution (Lugol's solution or SSKI, 1 drop every 8 hours) is added to block the release of thyroid hormone immediately. Often the effect of MMI is not as delayed in infants as it is in older children or adults, a consequence of decreased intrathyroidal thyroid hormone storage. Therapy with both antithyroid drug and iodine is adjusted subsequently, depending on the response. Propranolol (2 mg/kg/day in 2 or 3 divided doses) is added if sympathetic overstimulation is severe, particularly in the presence of pronounced tachycardia. If cardiac failure develops, treatment with digoxin should be initiated, and propranolol should be discontinued. Rarely, prednisone (2 mg/kg/day) is added for immediate inhibition of thyroid hormone secretion. Measurement of TSH receptor antibodies in treated babies may be helpful in predicting when antithyroid medication can be safely discontinued. Lactating mothers on antithyroid medication can continue nursing as long as the dosage of PTU or MMI does not exceed 400 mg or 40 mg, respectively. The milk/serum ratio of PTU is 1/10 that of MMI, a consequence of pH differences and increased protein binding, so one might anticipate less transmission to the infant, but concerns about potential PTU toxicity need to be considered. At higher dosages of antithyroid medication, close supervision of the infant is advisable. A review about management of neonates born to mothers with Graves' disease has been recently published.

PERMANENT NEONATAL HYPERTHYROIDISM

Rarely, neonatal hyperthyroidism is permanent and is due to a germline mutation in the TSH receptor (TSH-R) resulting in its constitutive activation. A gain of function mutation of the TSH-R should be suspected if persistent neonatal hyperthyroidism occurs in the absence of detectable TSH-R antibodies in the maternal circulation. Prematurity, low birth weight, and advanced bone age are common. Most cases result from a mutation in exon 10 which encodes the transmembrane domain and intracytoplasmic tail of the TSH-R, a member of the G protein coupled receptor superfamily. Less frequently, a mutation encoding the extracellular domain has been described. An autosomal dominant inheritance has been noted in many of these infants; other cases have been sporadic, arising from a de novo mutation.

Early recognition is important because the thyroid function of affected infants is frequently difficult to manage medically and, when diagnosis and therapy is delayed, irreversible sequelae, such as cranial synostosis and developmental delay may result. For this reason, early, aggressive therapy with either thyroidectomy or even radioablation has been recommended.

Two clinical forms were described; the first one is the "familial non-autoimmune autosomal dominant hyperthyroidism" (FNAH). High variable age of manifestation from neonatal period to 60 years, with variability also within the same family is reported. Goiter is present in children, with nodules in older age. The second one is "Persistent sporadic congenital non autoimmune hyperthyroidism" (PSNAH) includes forms with sporadic (de novo) germline mutations in the TSH-R. PSNAH is

GUIDELINES

Ross DS, Burch HB, Cooper DS, Greenlee MC, Launberg P, Maia AL, Rivkees S, Samuels M, Sosa JA, Stan MN, Walter MA. 2016 American Thyroid Association Guidelines for Diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid. 2016; 2:1343-1421.

REFERENCES

Samuels SL, Namoc SM, Bauer AJ. Neonatal thyrotoxicosis Clin Perinatol 45:31-40 2018.

Barbesino G, Tomer Y. Clinical utility of TSH receptor antibodies. J Clin Endocrinol Metab. 2013; 98:2247-2255.

van Dijk MM, Smits IH, Fliers E, Bisschop PH. Maternal thyrotropin receptor antibody concentration and the risk of fetal and neonatal thyrotoxicosis: a systematic review. Thyroid 2018: 28:257-

Rivkees S, Pediatric Graves' disease: management in the post - propylthiouracil Era. Int J Pediatr Endocrinol. 2014 10

Van der Kaay D, Wasserman JD, Palmert MR. Management of neonates born to mothers with Graves' disease. Pediatrics. 2016;137:e20151878

characterized by fetal-neonatal onset or within 11 months and more severe hyperthyroidism requiring early aggressive therapy.

Thyroid function in babies with a gain of function mutation of the TSH receptor may be difficult to manage medically and, when diagnosis and therapy is delayed, irreversible sequelae, such as cranial synostosis and developmental delay may result. Thyroid ablation may be required. Thyroid surgery is the preferred approach if an experienced pediatric surgeon is available. The timing at which thyroidectomy can be performed will depend on institutional preference. If this is not feasible, then radioablation may be necessary. Guidelines about this rare condition have recently been published.

MCCUNE ALBRIGHT SYNDROME

McCune Albright is a syndrome due to somatic activating mutations in $Gs\alpha$ gene and can rarely present with neonatal hyperthyroidism.

ACKNOWLEDGEMENTS

This chapter is, in part, based on the previous version written by Professor Rosalind Brown.

Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, Grobman WA, Launberg P, Lazarus JH, Mandel SJ, Peeters RP, Sullivan S. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid: 27:315.

Paschke R, Niedzela M, Vaidya B, Persani L, Rapaport B, Leclere J. The management of

familial and persistent sporadic non-autoimmune hyperthyroidism caused by thyroid stimulating

hormone receptor germline mutations. Eur Thyroid J. 2012; 1:142-147.

Segni M. Disorders of the Thyroid Gland in Infancy, Childhood and Adolescence. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, Dungan K, Grossman A, Hershman JM, Kaltsas G, Koch C, Kopp P, Korbonits M, McLachlan R, Morley JE, New M, Perreault L, Purnell J, Rebar R, Singer F, Trence DL, Vinik A, Wilson DP, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2017 Mar 18.

Kleinau G, Vassart G. TSH Receptor Mutations and Diseases. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, Dungan K, Grossman A, Hershman JM, Kaltsas G, Koch C, Kopp P, Korbonits M, McLachlan R, Morley JE, New M, Perreault L, Purnell J, Rebar R, Singer F, Trence DL, Vinik A, Wilson DP, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2017 Jul 24.