J. Transl. Med. Res 2015;20(3):168-171

Neonatal Graves-Basedow disease due to long-standing TRAb persistence following total thyroidectomy

Emiliana Teodora Dragomir-Ananie[1], Camelia Procopiuc[2], Florea Caliopsia[3], Maricica Gusa[3], Carmen Cristina Diaconu[4*]

Corresponding author:
Carmen C. Diaconu, MD
Cellular and Molecular Pathology Department, Stefan S. Nicolau Institute of Virology
285 Mihai Bravu, Bucharest 030304, Romania
E-mail: ccdiaconu@yahoo.com
carmen.diaconu@virology.ro

[1]Endocrinology and Metabolic Disorders, Dunarea de Jos University of Galati, Romania
[2"]C.I. Parhon" National Institute of Endocrinology, Bucharest, Romania
[3"]Sf. Ioan" Children Emergency Hospital, Galati, Romania
[4]Cellular and Molecular Pathology Department, "Stefan S. Nicolau" Institute of Virology, Bucharest, Romania

ABSTRACT

Background: Neonatal Graves-Basedow disease is a rare and transient complication due to mother's Basedow disease, occurring extremely rare due to Hashimoto thyroiditis or as a persistent hyperthyroidism due to activating mutations of the Thyroid-Stimulating Hormone (TSH) receptor. It may cause goiter and hyperthyroidism in the neonate, prematurity or fetal death, in some cases needing therapy and pre-conception counseling.
Case presentation: We report the case of a premature newborn from a mother who underwent total thyroidectomy for Basedow disease 7 years before conception, euthyroid before and during pregnancy on levothyroxine therapy. The mother was not checked for antibodies against thyroid stimulating hormone (TSH) receptor (TRAb) persistence before pregnancy. Despite response to anti-thyroid therapy, hyperthyroidism, cardiac congenital disease and prematurity complicated the evolutionof the newborn, leading to death in the 27th day of life.
Conclusion: The case is interesting due to long-standing persistence of TRAb after total thyroidectomy and the severe impact of hyperthyroidism in the fetus and neonate, despite low circulating levels of TRAb in mother which point out that other microenvironmental and/or genetic factors might be involved in the dramatic demise of the neonate. Fertile-aged women should be counseled.
Key words: Neonatal Graves-Basedow disease, neonatal hyperthyroidism, TSH receptor mutations/polymorphisms, pre-conception counseling

INTRODUCTION

Hyperthyroidism in the neonate is usually a transient and rare form of hyperthyroidism which occurs mostly in babies born from mothers with Graves-Basedow disease, only seldom in Hashimoto thyroiditis as a result of the cytotoxic effect of anti-thyroidperoxidase (AAT-TPO) and extremely rare as a permanent form, in cases of activating mutations of the TSH receptor. Classically described in 1-2% of pregnancies in mothers with Basedow disease, prevalence

rising up to 22% (1) in mothers who need antithyroid therapy until the third trimester or even 30% in a recent series of casesof mothers, positive for anti-thyrotropin receptor or anti-TSH receptor antibodies (TRAb)during pregnancy (2).

Subtotal thyroidectomy is usually followed by progressive decline in TRAb levels, while total thyroidectomy is usually followed by prompt decline and negativation of TRAb levels (3). However, an elevated TRAb level before thyroidectomy seems to correlate with longer persistence of TRAb after surgery (4). Radioiodine therapy is followed by rising levels in the first 12 months, and then slow progressive decline, while antithyroid drug therapy also gradually decreases TRAb levels (5). Yet some women have positive TRAb many years after total thyroidectomy, one case series of 7 years monitoring detecting such women even 7 years after total surgical ablation (6).

Neonatal Graves-Basedow disease can have different degree of severity from mild to moderate or severe even for the offspring of the same mother (7). Complications of untreated fetal hyperthyroidism are potentiallylife threatening: from fetal death or stillbirth, to prematurity, intrauterine growth retardation and neonatal hyperthyroidism with goiter, ocular signs and signs and symptoms of adrenergic stimulation or cardiac failure. Other clinical manifestations in the hyperthyroid neonate are hepato-splenomegaly, persisting acrocyanosis, lymphadenopathy, thymic enlargement, microcephaly due to cranyosinostosis, advanced bone age and thrombocytopenia. Death occurs in some severe cases of neonatal thyrotoxicosis. Hyperthyroidism may become obvious from birth or in the following weeks, with remission to euthyroid status until 48 weeks. The infants having only mild hyperthyroidism do not require any specific treatment, while in the moderate forms symptomatics are used.

In the severe form of hyperthyroidism, treatment consists of tionamides, either methimazole or carbimazole, or propylthiouracil-to suppress thyroid hormones synthesis, which may be associated with stable iodine-additionally inhibiting the release of thyroid hormones from the colloid. Beta-blockers are used to control symptoms of adrenergic stimulation and inhibit deiodination of T4 to the more potent T3. Glucocorticoids may be added also for inhibition of deiodination. Other unspecific therapies could be required for complications, like digoxin, diuretics etc.

In the light of the previously discussed complications, pre-conception counseling of women wishing to become pregnant is required (3). All women should be euthyroid before conception, keeping a TSH value to an upper limit of 2.5 µU/mL (8). Total thyroidectomy followed by substitution may be offered to diminish TRAb, and medical treatment with tionamides is also relatively safe, with few adverse reactions for the fetus (3). Yet patients should be carefully informed of the potential risks of medical treatment and that no procedure guarantees TRAbnegativation at a certain moment. Radioiodine therapy is less adequate because it requires 6 months for clearance and it is followed by the highest TRAb levels (9).

CASE REPORT

We report the case of a 3rd degree premature infant, female sex, transferred from maternity for goiter, periorbitaledema, exophthalmia, tachycardia and systolic murmur II-III/VI, obvious from birth. The infant was born at 32 weeks, with a gestational weight of 1700g and severe hypoxia, first Apgar score 2. The infant was admitted in the Intensive Care Unit in the 6th day of life. Parents were young(30 years of age), it was the couple's first baby, and the mother had suffered a complete thyroidectomy for Basedow disease, 7 years before, at the age of 23. Before and during pregnancy she was on substitution therapy with 150 µg levothyroxine, having normal TSH and FT4 values throughout this entire period (TSH just before pregnancy below 1.5 µUI/mL, during pregnancy TSH values ranging from 1.2 to 2.8 µUI/ml). After thyroidectomy she was never checked again for TRAb or AAT-TPO levels.

At admission the infant had a deteriorated general status with pallor, jaundice, irritability, tachycardia, fever, exophthalmia and large goiter, especially the left lobe. Paraclinical findings showed low hemoglobin values 10.1 g/dl, hematocrit 31.1%, MCV 79fl, low platelets 48000/mmc (normal values range (N) 150-400 x 10^3/mmc), normal WBC 7400/mmc, high VSH, fibrinogen and CRP, slightly elevated liver enzymes, high unconjugatedbilirubin.

Immunological and hormonal values were as it follows: thyrotoxicosis with TSH<0.010 mUI/L (N: 0.4-8.6 mIU/L), elevated thyroid hormones FT4>6 ng/dL (N: 0.65-2.3ng/dL), T4=35.6 µg/dl (N: 3.52-17.4), FT3 = 11.8 pg/mL (N: 1.87-14.8), T3=527ng/dl (N: 0-256), negative anti-thyroperoxidase AAT-TPO<10 UI/mL, AAT-TG <20 UI/mLand positive TRAb=2.1UI/l (N<1). Thyroid ultrasound showed global enalargement 2.7 ml with hypoechoic pattern and extremely increased vascularity. Transfonatanelar ultrasound and neurological examination found mild ventriculomegaly. Ecocardiography showed intact interventricular septum, interatrial communication type ostiumprimum of 4 mm, right

ventricular hypertrophy, hypertrophic cardiomyopathy. In mother's blood TRAb was slightly elevated 1.8 UIL and AAT-TPO was negative, despite absence of thyroid tissue on neck ultrasound and negative Thyroglobulin values (for TSH in range).

The diagnosis of neonatal Basedow disease was established and the infant was started on metimazole therapy 2.5 mg/day divided in 3 daily doses, in association with propranolol starting with 1mg/kg/day depending on the heart-rate. Hydrocortisone hemisuccinate was started in maternity and then continued at small doses (we did not supplement corticotherapy because it was not required by the hormonal status: thyrotoxicosis with T4). Breast-feeding was interrupted. After the 2nd day of methimazole the infant developed rash and the hepatic function deteriorated. As a premature infant does not develop allergic reactions and she was also found with bronchopneumonia, these effects were supposed to be due to prematurity and infection and treatment with methimazole was continued. Thyroid enlargement became more prominent, thyroid volume reaching 4.5 ml with 2.6mm at the isthmus but without tracheal compression, while thyroid function gradually improved, with normal thyroid hormones and suppressed TSH, allowing reduction ofmethimazole doses.

The evolution of TSH and thyroid hormones under specific therapy are presented in *figure 1*.

Despite the good evolution of thyroid disease, in the 11th day after admission the patient's general status aggravated, with fever, lethargia, coughing and cyanosis. Haemocultures were positive for Staphilococcus Hominis. As liver enzymes and bilirubin continued to grow methimazole was replaced with Lugol Solution, which did not influence the evolution. The infant died at 27 days due to bronchopneumonia and the autopsy revealed also a large persistent arterial channel.

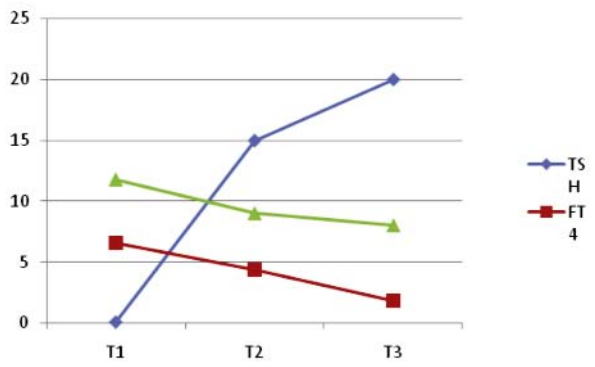

Figure 1 - Levels of TSH (mUI/L), FT4 (ng/dL) and FT3 (pg/mL) in day 1 (T1), 6 (T2) and 13 (T3) after admission.

DISCUSSIONS

This neonate with Basedow disease was particularly fragile due to prematurity. Persistent arterial channel occurs more frequently in premature newborns, and is usually larger in theses patients. In our patient, a very low Apgar score showed fetal distress, with hypoxia generated by tachycardia and congenital cardiac disease. The invasive procedures and prematurity also increased the risk of infection. Starting adequate therapy was promptly followed by improved thyroid function and clearance of the excessive thyroid hormones. Yet the therapy had to be changed, replacing anti-thyroid drugs with stable iodine, due to the suspicion of adverse effects on liver function. Probably this was not the explanation in our case, jaundice and elevated liver enzymes being rather the consequence of the septic status. Switching from one drug to another did not create other complications and thyroid status started to improve.

When the mother was detected TRAb positive we searched for thyroid remnants by neck ultrasound and thyroglobulin determination. Yet we have to mention that the mother was euthyroid under therapy, and thyroglobulin is best detected under elevated TSH values after a period without replacement therapy.

Even long after total thyroidectomy and optimum substitution (euthyroid status, no thyroid remnants and negative thyroglobulin) women of fertile age may have positive TRAb. This can be detected by active monitoring until negativation. Transplacental passage of the antibodies poses the fetus and newborn at risk for hyperthyroidism, no matter the TRAb level. The severity of the disease doesn't depend on circulating TRAb levels. The most dangerous complications remain prematurity, cardiac abnormalities and infections on a premature terrain. In this case fetus hyperthyroidism developed probably just before birth and its deleterious effects were amplified by the congenital cardiac disease. Diagnosis was not suspicioned before birth as at the last visit of the pregnant mother the fetuslooked normally and did not exhibit tachycardia. No fetal morphology was performed, so we have no information regarding potential fetal thyroid enlargement.Cardiac disease was also a risk factor for the premature infant with septicemia.

Increasing amount of data were published regarding TSHR mutations/polimorphisms which are clearly associated with a hyperthyroidism-phenotype, however little is known yet concerning their pathophysiological relevance and the mechanisms by which they trigger or influeces the severity of the disease.

Several Graves-Basedow disease susceptibility loci have been identified, including HLA-DRβ1-Arg74, CD40, CTLA-4, PTPN22, thyroglobulin (Tg), and mutations targeting different cAMP pathway genes, for example, phosphodiesterases or other G protein-coupled receptors (GPCRs) that may also contribute to hyperthyroidism (10, 11).

Recently, it was shown that nongenetic triggers such as viral infections and cytokines, can modulate gene expression through epigenetic mechanisms that may promote loss of immune tolerance (12). IFNα, a crucial cytokine previously shown to trigger autoimmunity, was shown to interact through modulation of chromatin accessibility to transcriptional regulators, with a SNP in intron 1 of the TSHR gene and reduced thymic TSHR expression. These results suggest that epigenetic–genetic interactions leading to decreased thymic self-antigen expression may be a general mechanism in autoimmunity (11).Microenvironmental influences such as cytokine storm triggered by infections may contribute in a major way to reveal the pathogenicity of GD-associated polimorphisms/mutations. However, despite the causative variant and the exact mechanisms by which it predisposes to hyperthyroidism are still unknown, a genetic profiling of the patients at risk to relapse during pregnancy would be beneficial.

CONCLUSIONS

TRAb positive women of fertile age should benefit of pre-conception counseling. Combined replacement and antithyroid therapy in pregnant mother should be considered in the newborn detected with tachycardia. Genetic investigation may be informative for adequate monitoring and follow-up after delivery.

Mothers previously thyroidectomized for Graves-Basedow disease should at least be monitored for TRAb persistence and if detected positive the fetus and then the newborn should be monitored until 48 weeks of age. Until now, there are no guidelines regarding therapy of the hyperthyroid fetus (which can be suspicioned in case of thyroid enlargement and tachycardia onultrasound). Maintaining euthyroidism of the neonate is a challenge for the team composed of obstetrician, neonatologist and endocrinologistand, in the future, a geneticist might help in understanding and adjustingclinical management of neonatal hyperthyroidism.

Acknowledgments

Emiliana TeodoraDragomir-Ananie is supported by the Sectoral Operational Programme Human Resources Development (SOP HRD), financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/159/1.5/S/137390. The authors gratefully acknowledgethe constructive comments of Prof. Simona Fica and also the funding from UEFISCDI Romania: PCCA PNII 133/2014.

REFERENCES

1. Mortimer RH. Thyroid disease and pregnancy.Aust N Z J Med. 1998; Oct;28(5), 647–53.
2. Zuppa AA, Perrone S, Sindico P, Alighieri G, Antichi E, Carducci C, Romagnoli C: Fetal and neonatal outcomes in infants of mothers with TSH receptor antibody positivity in pregnancy. Pediatr Med Chir 2009; 31:72–7.
3. Lazarus JH.Pre-Conception Counselling in Graves' Disease. Eur Thyroid J. 2012; Apr;1(1), 24–29.
4. Mori Y, Matoba N, Miura S, Sakai N, Taira Y. Clinical course and thyroid stimulating hormone (TSH) receptor antibodies during surgical treatment of Grave's disease, World J Surg. 1992; Jul-Aug;16(4):647-52.
5. Laurberg P, Wallin G, Tallstedt L, Abraham-Nordling M, Lundell G, Tψrring O. TSH-receptorautoimmunity in Graves' disease aftertherapy with anti-thyroid drugs, surgery, orradioiodine: a 5-year prospective randomizedstudy. Eur J Endocrinol 2008; 158: 69–75.
6. Takamura Y, Nakano K Uruno T, Ito Y, Miya A, Kobayashi A, et al. Changes in TSH receptor antibody (TRAb) values in patients with Grave's disease after total or subtotal thyroidectomy, Endocrine Journal. 2003; 50(5):595-601.
7. Zuppa AA, Sindico P, Perrone S, Carducci C, Antichi E, Alighieri G, et al. Different fetal-neonatal outcomes in siblings born to a mother with Graves-Basedow disease after total thyroidectomy: a case series. J Med Case Rep 2010; 4(59),1-4. Available from: http://www.jmedicalcasereports.com /content/4/1/59.
8. Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, Nixon A, Pearce EN, Soldin OP, Sullivan S, Wiersinga W: American Thyroid Association Taskforce on Thyroid Disease during Pregnancy and Postpartum: Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid 2011; 21:1081–1125.
9. Amino N, Kubota S: Thyroid disease after pregnancy: postpartum thyroiditis; in Wass JA, Stewart PM (eds): Oxford Textbook of Endocrinology and Diabetes, ed 2. Oxford, Oxford University Press, 2011, pp 552–557.
10. Huth S, Jaeschke H, Schaarschmidt J, Paschke R. Controversial constitutive TSHR activity: patients, physiology, and in vitro characterization. Horm Metab Res. 2014 Jun;46(7):453-61.
11. Stefan M, Wei C, Lombardi A, Wun Li C, Concepcion ES, Inabnet, III WB,et al. Genetic–epigenetic dysregulation of thymic TSH receptor gene expression triggers thyroid autoimmunity. ProcNatlAcadSci U S A, 2014; Aug 26; 111(34): 12562–67.
12. Litherland SA. Immunopathogenic interaction of environmental triggers and genetic susceptibility in diabetes: Is epigenetics the missing link? 2008; Diabetes 57(12): 3184–86.