

## LATE ONSET TRANSIENT THYROID DYSFUNCTION IN CHILDREN BORN TO MOTHERS WITH AUTOIMMUNE THYROID DISEASE

*Ljiljana Šaranac, Mirjana Miljković, Hristina Stamenković,  
Radmila Mileusnić-Milenović, Goran Petrović, Borislav Kamenov*

*Pediatric Clinic, University Clinical Centre, Niš, Serbia*

**Summary.** *We report two rare cases of autoimmune dysthyroidism in children born to mothers with autoimmune thyroid disease. The first female baby was admitted with the clinical signs of overt hyperthyroidism that occur on 25<sup>th</sup> day of life: irritability, incessant crying, hyperreflexion, dysphonia, tachycardia, tachypnoe, poor weight gain and ocular signs, including stare, eyelid retraction and even proptosis. The mother suffered from Chronic Autoimmune Thyroiditis (CAT) and received Na-l-thyroxine during pregnancy. Her hormonal status was normal, as well as that of her newborn. Determination of hormones using fluoroimmunometric assay (Delfia kits) revealed a high level of free T4 on 40<sup>th</sup> day of life. A small and soft goiter was found and the ultrasound examination showed a slightly enlarged thyroid with hypoechogeneity of the structure. A short course of propylthiouracil, corticotherapy and propranolol administration proved effective.*

*The second baby, also euthyroid at birth, was born to a hyperthyroid mother and examined at 2.5 months of age because of feeding difficulties. The baby presented "mixed dysthyroidism": retardation of growth, the length <P5 and weight +400 g over ideal, dysphonia, low position of umbilicus, as well as hyper-reflection, irritability and stare. Hormonal determination showed subclinical hypothyroidism. A five-month Na-l-thyroxin substitution therapy eliminated the clinical signs of dysfunction and improved growth to P50.*

*Transient thyroid dysfunction of the type opposite to maternal thyroid disease was in both cases caused by transplacental passage of TSH receptor antibodies with polyclonal activity and different half-life. These transient forms should be early diagnosed, treated and distinguished from persistent thyroid disease.*

**Key words:** *Transient hyperthyroidism, transient hypothyroidism*

### Introduction

Neonatal hyperthyroidism is a rare disease, probably because of the low incidence of thyrotoxicosis in pregnancy (1 to 2 cases per 1,000 pregnancies) and the fact that neonatal disease occurs only in about 1:70 cases of thyrotoxic pregnancy (1,2). In a majority of cases, the disease is due to transplacental passage of TRAb (Thyroid-stimulating hormone receptor antibody) from a mother with an active or inactive Grave's disease or Chronic Autoimmune Thyroiditis (CAT) (3,12). The prediction of neonatal hyperthyroidism from the maternal clinical status is, therefore, not always possible.

"Grave's disease" was not reported in neonates and children until earlier in the past century, and the observation that the neonatal form was transient suggested that the disease was mediated by a humoral factor originally believed to be the thyroid-stimulating hormone. As the activity of this factor, measured by an in vivo radio receptor assay in mice, showed a later peak and longer activity than TSH, it was termed the long acting thyroid stimulator. Subsequently, the activity was found to be that of an immunoglobulin

(IgG1) binding to the TSH receptor (TRAb) (2,12). It may stimulate or block the TSH receptor. In some instances, especially in neonates, the autoimmune thyroid disease (AITD) is polyclonal, and more than one population of TRAbs is found (3).

This autoimmune and transient form of congenital hyperthyroidism should be distinguished from the persisting one which contains no detectable autoantibodies, due to a hereditary or de novo germline mutation of the thyrotropin receptor gene (5,6,7).

Maternal-to-fetal transfer of TSH receptor-blocking antibodies can lead to transient perinatal hypothyroidism (18). Although rare, this condition has been reported in the neonates of women with euthyroid or hypothyroid autoimmune thyroid disease (18,19), but not with hyperthyroid.

Transient congenital hypothyroidism must be differentiated from transient hyperthyrotropinaemia and persistent congenital hypothyroidism because of thyroid dysgenesis or dysmorphogenesis (2).

### Case 1

A female baby, 40 days old, was admitted to the Intensive Care Unit of the Niš University Pediatric Clinic because of irritability, vomiting, poor weight gain and tachycardia. Fifteen days prior to admission, the mother noticed a stare appearance and twitching of the arms. The child was then treated in the local hospital, but the therapy (intravenous crystalloids and antibiotics) was not successful.

This is the first baby of a 45-year-old mother who conceived after a seven-year treatment for sterility. The mother has been suffering from Chronic Autoimmune Thyroiditis since 1984 and received Na-I-thyroxine substitution therapy for hypothyreosis. Her hormonal status during pregnancy was euthyroid. The newborn's hormonal status, checked on the third day of life, was also normal. It was a "small for date" baby, born by "sectio Caesarea" at 39<sup>th</sup> week of gestation. The APGAR score was 5. The birth weight was 2,300 g, the head circumference - 33 cm, and the length - 45 cm.

On admission, the female baby had a slightly reduced weight of 3,030 g (-320 g from the ideal weight) and a normal length of 49 cm (P10). The head circumference was 35 cm. She presented irritability, flushing, incessant crying, dysphonia, hypotonia, hyperreflexion, adequate hydration, tachycardia (178 beats per minute) and tachypnea (46 respirations per minute).

Marked ocular signs were present: stare, eyelid retraction, and even mild proptosis. A small and soft goiter (Ib size) was detected, and the ultrasound examination of the gland's volume and structure showed a slightly enlarged thyroid and hypoechogeneity.

The hormonal status ( $T_4$ ,  $T_3$ ,  $fT_4$ ,  $fT_3$ , ultra TSH), determined by fluoroimmunometric assay (Delfia kits), was normal, with the exception of  $fT_4$  value (Table 1). Neither thyroglobulin autoantibodies (radioimmunoassay, Inep-RIA-h-Tg-Ab) titer nor TPO-Ab titer was elevated. Unfortunately, TRAb determination was not available.

Table 1. Hormonal status of Case 1  
(Hyperthyroid child of hypothyroid mother)

Age	$T_4$ (nmol/l)	$fT_4$ (pmol/l)	$T_3$ (nmol/l)	$fT_3$ (pmol/l)	TSH (ultra) (mU/l)
43 days	130	<b>31.0</b>	2.9	2.6	2.3
58 days	103	12.9	1.9	5.2	0.8
3 months	125	12.5	2.2	5.3	1.2
6 months	127	13.0	2.8	5.6	1.6
normal value	58 - 161	(10 - 25)	1.2 - 3.0	(4 - 8)	0.17 - 4.05

We administered a short course of propylthiouracil at 0.5 mg/kg for 2 weeks and propranolol at 1 mg/kg/day. Corticotherapy was used for only 5 days at a 1 mg/kg dose in order to reduce  $T_4$  to  $T_3$  conversion.

The treatment eliminated the clinical signs of hyperthyroidism and gradually decreased the ocular signs. Weight gain became adequate. Two weeks later, the hormonal status was restored to normal. Periodical measurements of hormonal levels were performed and we

could confirm a full recovery, no clinical or hormonal signs of hyperthyroidism, and an excellent growth and maturation rate. Exophthalmos disappeared after a month.

### Case 2

The second case was a 2.5-month-old female baby of a hyperthyroid young mother with the aggravation of her hyperthyroid state during pregnancy and severe necrotic vasculitis in both femoral regions of the skin. During the last trimester, the mother had a high titre of antineurophil cytoplasmic antibodies (ANCA), measured by the enzyme-linked immunosolvent assay, and a high titre of TRAbs, measured by the radio receptor assay. She was initially treated with propylthiouracil but, upon development of complications, she received carbimazole.

Hormonal determination revealed no hormonal change in her mature newborn. The first endocrine examination at 2.5 months of age, because of feeding difficulties, showed the clinical signs of "mixed dysthyroidism": retardation of growth; the length (51.5 cm) was below P5; the "height age" was only 15 days; the weight was 3,800 g (400 g over the ideal weight-to-length ratio); the head circumference was 38 cm; there were present dysphonia, low position of umbilicus, hyperreflexion, irritability and the child was surprisingly stare. Thyroid hormonal status, determined by the fluoroimmunometric assay (Delfia kits), revealed subclinical hypothyroidism ( $T_4$ : 103 nmol/l;  $fT_4$ : 12.9 nmol/l;  $T_3$ : 2.2 nmol/l;  $fT_3$ : 7.1 pmol/l; and TSH was elevated to 6.7 mU/ml). TRAb titre was elevated (33.5 U/ml) and HTG-Ab titre was negative. Substitution therapy with Na-I-thyroxine was initiated (25 µg/day) and the benefit was soon obvious; after 2 weeks the feeding difficulties disappeared and dysphonia became milder, after 6 weeks the baby's length reached 59.5 cm (P5), the weight was ideal (5450 g) relative to the length, and she had no sign of dysthyroidism. Hormonal control confirmed euthyroid state ( $T_4$ : 136.0 nmol/l,  $fT_4$ : 17.4 nmol/l,  $fT_3$  6.4 pmol/l and TSH: 3.3 mU/l. After 3 months the treatment was temporarily discontinued because of growth acceleration; the length was 65 cm and reaching P50, and the weight was 850 g below the ideal body weight. Hormonal levels were checked without substitution, but subclinical hypothyroidism was still present (Table 2).

Table 2. Hormonal status of Case 2 (Subclinically hypothyroid child of hyperthyroid mother)

Age (months)	$T_4$ (nmol/l)	$fT_4$ (pmol/l)	$T_3$ (nmol/l)	$fT_3$ (pmol/l)	TSH (ultra) (mU/l)
2.5	103	12.9	2.2	7.1	<b>6.7</b>
3.5	136	17.4	1.7	6.4	3.3
5	104	14.1	2.3	5.7	<b>7.4</b>
6.5	128	14.3	1.9	5.9	0.26
7.5	132	12.1	1.7	7.2	1.24
normal value	58 - 161	(10 - 25)	1.2 - 3.0	(4 - 8)	0.17 - 4.05

A full clinical and hormonal recovery occurred after 5 months of substitution. Periodical controls of the hormonal status showed no further need for hormonal replacement.

## Discussion

The fetal pituitary-thyroid axis develops independently of the maternal system (8,15). The placenta is impermeable to TSH and relatively impermeable to  $T_4$  and  $T_3$ . In addition, the placental tissue contains an active inner ring - iodotyronine deiodinase - that deiodinates  $T_4$  to inactive  $rT_3$  and deiodinates  $T_3$  to inactive  $T_2$ . In humans, therefore, little active maternal hormone is transferred to the fetus (15). Recent observations suggest an important role of maternal thyroid hormones in fetal brain development. Experimental data, mainly from studies on rats, suggest that nuclear receptors of thyroid hormones are present in a developing embryo before the onset of fetal thyroid functions (8).  $T_3$  is essential to normal development of the fetal brain. During this time, however, the fetus is incapable of utilising maternal  $T_3$  and is entirely dependent on adequate levels of maternal  $T_4$  that convert to  $T_3$  in the fetal brain (9). When fetal thyroid function starts, there is a rapid rise in extra-thyroidal stores of  $T_4$  and  $T_3$  derived from the fetus. Maternal-to-fetal transfer of thyroid hormones does not cease but, as pregnancy continues, the stores become predominantly fetal in origin (8).

The human placenta is freely permeable for maternal thyroid autoantibodies and some antithyroid drugs. In infants born to mothers with autoimmune thyroid disease, both TSH receptor-stimulating and TSH receptor-blocking antibodies are acquired through the mother. The blocking antibodies have been also reported to block the effect of the stimulating antibodies for 4-6 weeks, such that the infant develops late-onset neonatal hyperthyroidism (12,13). The stimulating activity does not cause clinical disease until the blocking TRAbs have been metabolized. These data explain the late onset of hyperthyroid state in Case 1.

Grave's disease and CAT are usually polyclonal and patients may have both stimulating and blocking antibodies. The management of the fetus and neonates depends on the biological activity of maternal TRAbs as reported in the study on an infant who had congenital hypothyroidism at birth but developed clinical thyrotoxicosis through transient Grave's disease beginning at approximately 40 days of age (11).

The physiological significance of the neonatal hyperthyroid state remains speculative, but it has been shown that the increased thyroid hormone levels stimulate catecholamine-mediated BAT-thermogenesis and mobilization of fatty acids from the body's fat stores, as well as catecholamine-mediated nonshivering thermogenesis (15,16).

Thyroid hormones also facilitate the activity of catecholamines; increased catecholamine effects are prominent manifestations of the hyperthyroid state. These

effects are mediated via increased beta-adrenergic receptor binding and postreceptor responsiveness, and are manifest despite the normal or lowered circulating concentrations of catecholamines. The beta-adrenergic effects in our patient, such as tachycardia, tremor and lid lag, should be blocked by propranolol, a beta-receptor blocking agent, which is exactly what we did. However, propranolol does not alter thyroid function or the basal level of cellular activity (10,15,16).

Early treatment is important as hyperkinetic behaviour could persist for several years if treatment is delayed (4).

Fortunately, this form of autoimmune neonatal hyperthyroidism is transient, because TRAb disappears from the child, having a half-life of about one month (similar to other IgG molecules), which coincides with a spontaneous remission of the disease. The usual clinical course of neonatal Grave's disease extends 3-12 weeks. In our patient, the hyperthyroid state was present for 5 weeks (including the period at home from the first signs attributable to hyperthyroidism).

Arrhythmias, cardiac failure and death may occur if thyrotoxicity is severe and treatment is inadequate, even in the transient form. Mortality approaches 25% in a disease severe enough to be diagnosed (2,10,14).

The disease should be distinguished from persisting congenital hyperthyroidism, with no autoantibodies, due to an active germline mutation of the thyrotropin receptor gene. The clinical picture includes thyromegaly, eyelid retraction, hepatosplenomegaly, lymphadenopathy and petechiae, as well as trombocytopenia and hepatic cholestasis, and clinical signs similar to sepsis (5,6,7).

Transient neonatal hypothyroidism is commonly seen in premature infants, particularly in iodine deficient areas. It is not necessarily severe and, by definition, resolves spontaneously (4).

Maternal-to-fetal transfer of TSH receptor-blocking antibodies can also lead to transient perinatal hypothyroidism (18). This condition is also rare, but has been reported in the neonates of women with euthyroid or hypothyroid autoimmune thyroid disease (19,20), but not in the child of the woman with severe hyperthyroidism as we described. In such infants, TR-Abs are detectable in maternal and cord blood.

Thyroid hormones play a critical role in brain development during the last fetal trimester and the first 2 years of life. They are necessary for normal maturation, arborisation and myelination of neurons and for glia development (17,25). Thyroid dependency of brain is manifest within this period and untreated children became powerless cretins (4,15,23).

Somatic growth, bone growth and maturation, tooth development and eruption are also thyroid dependent (16). These effects are mediated, at least in part, by stimulation of growth hormone (GH) and IGFs synthesis and action. Our patient with transient hypothyroidism had severe growth retardation, despite the subclinical form of hypofunction. Substitution therapy with Na-I-thyroxine showed a real "catch up" growth and optimal height velocity was

achieved. In the hypothyroid state, GH secretion is attenuated and IGF level is low (24); GH binding to cell membranes of various tissues is disturbed, as well as the synthesis of numerous tissue growth factors: EGF, NGF, IGFs (21, 22).

Transient congenital hypothyroidism must be differentiated from transient hyperthyrotropinaemia and persistent congenital hypothyroidism due to thyroid dysgenesis or dysmorphogenesis. Even the transient form of the subclinical type of hypofunction should be treated in this vulnerable period.

In both our cases the opposite type of thyroid dysfunction occurred. Obviously, mothers with AITD had polyclonal TR-Abs with a different activity and affinity. High affinity antibodies for the maternal thyroid were attached there, but Abs with a lower affinity and opposite function "overleapt" to their fetuses and showed a remarkable thyroid dysfunction, fortunately transient.

A thorough evaluation is important in pregnant women with a history of autoimmune thyroid disease and those who either have a currently active disease or

were previously treated for hypothyroidism or hyperthyroidism. Thyroid function and antibody tests should be evaluated early in pregnancy, preferably before conception.

## Conclusion

Two rare cases of transient thyroid dysfunction in children born to mothers with AITD are reported: one with clinical signs of overt hyperthyroidism and confirmation of elevated FT4 value (case 1) and the other with retardation of growth and subclinical hypothyroidism (case 2). Transient thyroid dysfunction opposite to maternal was caused by transplacental passage of TSH receptor antibodies with polyclonal activity and different half-life. Both children were euthyroid at birth, so careful monitoring of babies born to mothers with AITD is recommended during the first trimester. These transient forms should be early diagnosed, treated and distinguished from persistent thyroid disease.

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## KASNA FORMA TRANZITORNE TIROIDNE DISFUNKCIJE U DECE MAJKI SA AUTOIMUNSKOM TIROIDNOM BOLEŠĆU

*Ljiljana Šaranac, Mirjana Miljković, Hristina Stamenković,  
Radmila Mileusnić-Milenović, Goran Petrović, Borislav Kamenov*

*Dečja klinika Univerziteta u Nišu*

Kratak sadržaj: Prikazana su dva retka slučaja autoimunskog distiroidizma u dece majki sa autoimunskom tiroidnom bolešću (AITB). U prvom slučaju radilo se o ženskom novorodjenčetu koje je primljeno sa znacima jasnog hipertiroidizma koji se javljaju 25. dana života: razdražljivost, neprekidan plač, hiperrefleksija, dysphonia, tahikardija, tahipneja, loše napredovanje u težini i očni znaci - razrogačen pogled, retrakcija kapaka i čak proptoza. Majka je bolovala od hroničnog autoimunskog tiroiditisa (HAT) i dobijala Na-I-tiroksin u toku trudnoće. Njen hormonski status bio je normalan kao i status njenog novorodjenčeta. Određivanje hormona fluoroimunometrijskom metodom, upotrebom Delfia kitova pokazalo je visoke vrednosti slobodnog T4 u 40. danu života. Pronadjena je mala, mekana struma a ultrazvučno ispitivanje je pokazalo blago uvećanu štitnjacu hipoehogene strukture. Kratkotrajno lečenje propiltiouracilom, kortikoidima i propranololom bilo je efikasno.

Drugo odojče bilo je dete hipertiroidne majke i takodje eutiroidno na rođenju. Ispitivano je u 2,5 mes uzrasta zbog teškoća u ishrani i imalo je "mešoviti distiroidizam"; retardaciju rasta, dužinu <P5, i + od 400 g u odnosu na idealnu telesnu masu, dysphoniui, nisko postavljen umbilicus, ali takodje i hiperrefleksiju, razdražljivost i razrogačen pogled. Određivanje hormona pokazalo je subkličički hipotiroidizam. Supstitucija Na-I-tiroksinom eliminisala je kliničke znake disfunkcije, pospešila rast do P50, a bila je neophodna 5 meseci.

Tranzitorna tiroidna disfunkcija suprotnog tipa od maternalne u oba slučaja izazvana je transplacentarnom pasażom TSH receptornih antitela poliklonalne aktivnosti i različitog poluživota. Ove tranzitorne forme treba da budu rano dijagnostikovane, lečene i razlikovane od perzistentne tiroidne bolesti.

Ključne reči: Prolazni hipertiroidizam, prolazni hipotiroidizam