CONGENITAL HYPERTHYROIDISM – CASE REPORT

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INTRODUCTION

Graves’ disease and Hashimoto’s thyroiditis represent the two most common autoimmune thyroid disorders during pregnancy affecting fetal and neonatal development. The immunological mechanisms involved in these diseases are closely related, the differences between the two disorders are made by antibody titre determination. High TSI levels are found in Basedow disease, while they are absent in Hashimoto. In Hashimoto, antibodies against...
thyroid peroxidase and/or thyroglobulin cause gradual destruction of cells in the thyroid gland.\textsuperscript{1,2}

The endocrine pathology of the newborn can seriously affect his health status and, not recognized and treated properly, can be life-threatening.

Fetal hyperthyroidism may be associated with intrauterine growth retardation, nonimmune fetal hydrops, craniosynostosis and intrauterine death. Features of this condition in the neonate include hyperkinesis, diarrhoea, poor weight gain, vomiting, ophthalmopathy, cardiac failure and arrhythmias, systemic and pulmonary hypertension, hepatosplenomegaly, jaundice, hyerviscosity syndrome, thrombocytopenia, craniosynostosis and death in the severe form thyrotoxicosis.\textsuperscript{3}

Fetal and neonatal hyperthyroidism are usually produced by transplacental passage of TSI (80%).\textsuperscript{1,3,4} Most commonly, TSI are a component of active maternal Graves’ disease. However, such antibodies may continue to be produced after ablation of the thyroid by surgery or radioiodine treatment. Other mechanisms that have produced fetal and neonatal hyperthyroidism include activating mutations of the stimulatory G protein in McCune-Albright syndrome and activating mutations of the thyrotropin (TSH) receptor “nonautoimmune hyperthyroidism”\textsuperscript{1,5-7}

The incidence of neonatal Graves’ disease is 1 to 2 per 1,000 births from affected mothers. The cause for concern is that the infant mortality rate is 16% to 25%.\textsuperscript{7,8} Cause of death could be heart failure and/or dyselectrolytemia produced by intestinal hyperperistalsism and diarrhoea. Remission by 20 weeks is most common in neonatal Graves’ disease; remission by 48 weeks is nearly always seen, due to “clearance” of maternal antibodies from the newborn circulation.

The treatment for neonates is driven by the clinical symptoms and laboratory values. If the patient has obvious clinical symptoms (goiter, cardiac failure, exophthalmia) with significant TSH suppression, the infant should receive a beta blocker and an antithyroid drug. If the laboratory values show minimal changes and the patient has no obvious clinical symptoms and good growth, observation alone may be sufficient. Monthly follow-up, with laboratory evaluation, is recommended.\textsuperscript{2,4,7}

\section*{CASE REPORT}

The patient, P.A., 2 weeks old, male was admitted in our hospital for: hyperkinesis, poor weight gain, jaundice. During the 20\textsuperscript{th} week of gestation the mother was diagnosed with Graves’ disease. Thiamazol until 37 weeks of gestation was instituted, followed by Propithyouracil.

Immunological and hormonal monitoring during pregnancy had shown high TSI level: 18.8 IU/ml (Normal values < 2 IU/l), in the 31\textsuperscript{st} week of gestation.

At delivery, TSI and TSH cord blood values were high (20 UI/l respectively 26.530 µU/ml), and FT4 value (1.27 ng/ml) was in normal range.

After 5 days, TSH value maintained high (25.812 µU/ml) and FT4 normal (1.69 ng/ml). The patient left maternity without clinical and hormonal follow-up recommendations.

At the age of two weeks the newborn presented psychomotory agitation, growth retardation, jaundice – reasons for hospital addmision.

Birth history revealed the child’s order of birth (second child), gestational age 39 weeks, birth weight 3250 g (50 percentile), length 50 cm (50 percentile), cranial circumference 34 cm (25 percentile), Apgar score 9, immunized with BCG and Engerix.

Positive familial history was stated for endocrinological disease: maternal grandmother with Graves’ disease, mother diagnosed during pregnancy with the same disease.

\begin{table}[h]
\centering
\caption{Immunological and hormonal evaluation at 2 weeks.}
\begin{tabular}{ll}
\hline
\textbf{Hormones} & \textbf{Values} \\
\hline
TSH & 0.086 µU/ml  \\
(0.49-4.97 µU/ml) &  \\
FT4 & 2.31 ng/ml  \\
(0.71-1.85 ng/ml) &  \\
\hline
\end{tabular}
\end{table}

At the hospital addmision clinical examination revealed a newborn with gain loss from birth (3120g), pallor, jaundice, cutaneous trophic alterations, polipneea, tachycardia – 190-210 bpm; accelerated intestinal transit – 7 stools/day, hipereexcitability, clonus, incomplete archaic reflexes.

Biological and paraclinical findings were: low hemoglobin value (10.6 g/dl), red blood cells 2,990,000/mm3, hematocrit 31.1%, serie proteins 40 g/l, low serum iron level 8,2 µmol/l and high levels of unconjugated bilirubin (123 mmol/l) and lactic acid (24 mg%).

Immunological and hormonal status at two weeks showed an increase in antibodies values: antithyroidperoxidase (TPO), antithyroglobulin (Tg) and TSI. (Table 1). Thyroid stimulating immunoglobulins were two-fold increased in maternal milk.

Paraclinical investigations (EKG and Holter EKG) revealed the presence of sinusal tachycardia (heart rate up to 255 bpm). Cerebral ultrasonography demonstrated the aspect of diffuse hypoxic-ischemic
encephalopathy with intraventricular hemorrhage. Electroencephalogram showed an irritative trace.

After evaluation, the diagnosis was:
- Moderate transient congenital hyperthyroidism
- Carential anemia
- Hypoxic-ischemic encephalopathy
- Prolonged neonatal jaundice

Treatment in this case was pathogenic and roborant:
- Phenobarbital for enzymatic induction (glucuronono-conjugation);
- Pentoxiphyllin and Tanakan for circulatory modifications; betablocker for tachycardia;
- iron preparation for anemia, vitaminotherapy. At this time the child was mixed fed (adapted milk formula was introduced due to decrease in maternal lactation).

At 6 weeks, weight and antropometric parameters were within the limits of normal growth. Pallor (based on hematological findings), peripheric circulation disfunction, high HR (140-150 bpm during treatment with Atenolol) and lower limbs hypertonia were still present. Values for antibodies levels were lower: TPO (188 IU/ml), TSI (3.7 IU/ml). TSH and FT4 levels were normal (respectively 2.81 µU/ml and 1.26 ng/ml). Holter EKG showed persistent sinusal tachicardia. Cerebral ultrasonography revealed the same aspect.

At the age of three months, weight was 6000g (Pc-75), cranial circumference 39 cm (Pc-25), length 62 cm (Pc-75). Skin was still pale, with atopic dermatitis on the face and skull. Heart rate was still 140-150 bpm during treatment with Atenolol. Hypertonia preserved, while psychological acquisition was age-appropriate. Thyroid-stimulating immunoglobulin level was 0.1 IU/l and TPO antibodies dissapeared. Paraclinic investigations revealed sinusal tachicardia and discrete improvement of cerebral suffering. At this time the infant was entirely artificially-fed.

**DISCUSSION:**

Risks of an infant born from a mother with Graves’ disease are multiple, beginning in utero:
- Mother’s uncontrolled hyperthyroidism can lead to tachycardia, prematurity, intrauterin growth retardation and possible malformations.\(^2\)\(^5\)\(^7\)

- Elevated levels of TSI cross the placenta, bound to TSH receptor, stimulate adenylcyclase, with AMPC overproduction, stimulating the fetal thyroid function.\(^1\)\(^2\)\(^4\)\(^5\)\(^8\)\(^9\) Severe congenital hyperthyroidism caused by maternal TSI is rare, the antithyroidian treatment (used in pregnancy) having an important role. Antithyroidian medication crosses the placenta and has a protective effect against fetal thyroid hyperfunction.\(^3\)\(^7\)\(^10\) Infants born to mother with Graves’ disease treated with radioactive iodine or by surgery, not requiring antithyroidian medication are at higher risk, developing severe hyperthyroidism due to antibodies persistence after thyroid function normalisation.\(^2\)\(^4\)\(^7\)\(^11\)

- Antithyroidian treatment, Methimazole or Propylthiouracil, crosses the placenta and can affect fetal thyroid function leading to hypothyroidism and sometimes goiter. Effect of the dose that leads to maternal hormone normalization is different for the fetus. Because of slower fetal hepatic metabolization of antithyroid drugs, fetal FT4 can be lower then maternal. Fetal TSH level can be elevated by feed-back regulation.\(^3\)\(^3\)\(^12\)\(^13\)

Coroborating these risks, the aim of treatment during pregnancy is to maintain maternal hormone level close to normal with a minimum dose of medication.

In our case, the risk for thyrotoxicosis was present in the 31\(^{st}\) week of gestation (maternal TSI =18.8 IU/l). (Table 2). At this time, intrauterine fetal heart rate monitorization and fetal development are indispensable (no anamnestic data was obtained).

High TSH level and normal FT4 level at birth and 5 days after in our case can be explained by a transient subclinical hypothyroidism determined by:
- Transplacentar passage and fetal slow metabolism of antithyroidian medication;\(^1\)\(^4\)

- Possible concomitent presence of inhibing (that inhibit adenylcyclase) or TSH binding antibodies. In 80% of patients with antireceptor TSH antibodies, they act like agonists and in 20% of cases they play an antagonist role.\(^2\)\(^7\)\(^11\)

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**Table 2. Treatment, immunological and hormonal monitorization during pregnancy.**

<table>
<thead>
<tr>
<th></th>
<th>20 weeks gestation</th>
<th>31 weeks gestation</th>
<th>34 weeks gestation</th>
<th>38 weeks gestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT4 (0.71-1.85 ng/dl)</td>
<td>5.82 Œ</td>
<td>1.67</td>
<td>1.85</td>
<td>1.63</td>
</tr>
<tr>
<td>FT3 (1.8-4.6 pg/ml)</td>
<td>-</td>
<td>5.84 0</td>
<td>5.77 0</td>
<td>5.58 0</td>
</tr>
<tr>
<td>TSH (0.49-4.67 µU/ml)</td>
<td>0.002 Œ</td>
<td>0.001 Œ</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TSI (&lt;2 IU/l)</td>
<td>-</td>
<td>18.80</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mothers medication</td>
<td>Thyrozol</td>
<td>Propilthiouracil</td>
<td>15 mg/day</td>
<td>150 mg/day</td>
</tr>
<tr>
<td></td>
<td>40 mg/day 1 month</td>
<td>20 mg/day</td>
<td></td>
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</tbody>
</table>
- Perinatal cerebral injury (illustrated by neurological signs, cerebral ultrasound and EEG), affecting pituitary-thyroid axis: anterior pituitary gland hypersecretion in a first phase and/or quick reduction of circulant T3 level with short term increasing of TSH.\textsuperscript{7,14}

From the age of two weeks, thyroid stimulating antibodies led to an increased FT4 level with TSH downregulation; 6 weeks after birth, antibodies titre decreased followed by hormone normalization. (Table 3, Fig. 2)

At the age of six weeks TPO antibodies titre decreased two-fold, and, at 3 months, there was no antibodies titre. Thyroid stimulating immunoglobulins evolution was also descendent. Presence of TSI in maternal milk were sett off rising questions about TSI’s intestinal absorption and metabolization of the infant. (Table 3, Fig. 1) Clinical, hormonal and immunological monitorization in newborns from mothers with Graves’ disease is required to prevent possible complications starting from intrauterine period untill 3-6 months after birth. (Fig. 3)

In the case presented above, the follow-up plan was initiated at the first admission in our clinic (at the age of 14 days).

Further neurological and psychosomatic evaluation is required for preventing long term modifications. Genetic counseling is important, taking into account the risk of developing autoimmune pathology.

Case particularity was defined by association of hypo- and hyperthyroidism, evolutive atopy and
persistence of tachycardia after hormonal status normalization. Antiperoxidase antibodies, forming circulating immune complexes and participating in cytotoxic reactions, could play a role in damaging cardiac fibre by injuring the endothelium producing cardiac rhythm disturbances.\textsuperscript{2,11,15}

Presence of atopic dermatitis at the age of three months may be an association with another autoimmune pathology; time and further evaluation will or not confirm that aspect.\textsuperscript{2,11,14}

**CONCLUSIONS**

Fetal and neonatal hyperthyroidisms are usually produced by transplacental passage of TSI. Most commonly, TSI are a component of active maternal Graves’ disease. However, such antibodies may continue to be produced after ablation of the thyroid by surgery, radioiodine, inducing a severe form of neonatal hyperthyroidism.

Treatment with high doses of antithyroid drugs during pregnancy increases the risk of transient neonatal hypothyroidism.

The follow-up for hyperthyroidism in newborns from mothers with Graves’ disease starts in the intrauterine period up to 3-6 months, cases needing to be verified afterwards, taking into account the risk of developing autoimmune pathology.

Given the children’s particular growth dynamics, the challenges in diagnosis, follow-up, and correct treatment require a wide amount of knowledge in pediatrics, as well as other fields. In this matter, collaboration between adult endocrinologists, obstetricians, neonatologists and endocrine pediatricians leads to best results in terms of evolution.

**ACKNOWLEDGEMENTS**

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**REFERENCES**