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Authors:	Corina Maria VASILE Alice Elena GHENEA Oana IANA Vlad Dumitru BĂLEANU Anca UNGUREANU Mihaela POPESCU

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Medical Sciences

CHILDHOOD-ONSET GRAVES' DISEASE

Corina Maria VASILE[1]
Alice Elena GHENEA[2]
Oana IANA[3]
Vlad Dumitru BĂLEANU[4]
Anca UNGUREANU[5]
Mihaela POPESCU[6]

ABSTRACT:
HYPERTHYROIDISM IS CAUSED BY A THYROID-STIMULATING HORMONE (TSH) RECEPTOR THAT STIMULATES AUTOANTIBODIES THAT CAUSE EXCESS PRODUCTION AND GROWTH OF THYROID HORMONES. HYPERTHYROIDISM IN CHILDHOOD IS OFTEN CAUSED BY GRAVES-BASEDOW DISEASE. APART FROM CASES OF TRANSIENT NEONATAL HYPERTHYROIDISM THAT DEVELOP FROM MOTHERS WITH ACTIVE GRAVES-BASEDOW DISEASE, HYPERTHYROIDISM OCCURS LESS IN PRESCHOOL CHILDREN AND RARELY IN CHILDHOOD. SYMPTOMS OF HYPERTHYROIDISM INCLUDE EXCESS PHYSICAL ACTIVITY, TREMOR, TACHYCARDIA, FLUSHING, PALPITATIONS, WEIGHT LOSS, ACCELERATED LINEAR GROWTH, REDUCED BONE MINERALIZATION, AND POOR SCHOOL PERFORMANCE. IN CHILDHOOD GRAVES' DISEASE, OPHTALMOPATHY OCCURS IN LESS THAN 50 PERCENT OF PATIENTS AND IS USUALLY MILD WHEN PRESENT. WE'RE PRESENTING THE CASE OF A 2,8 YEARS OLD GIRL WITH BASEOW-GRAVES DISEASE HOSPITALIZED FOR BILATERAL EXOPHTHALMIA. SHORTLY AFTER THE FIRST YEAR, THE BABY GIRL DEVELOPED SIGNS OF HYPERTHYROIDISM, BUT THE MOTHER NEGLECTED THE PRESENTATION TO THE DOCTOR. THE MOST PROMINENT FEATURES WERE THE ACCELERATION OF SKELETAL MATURATION, LINEAR GROWTH AND CHARACTERISTIC APPEARANCE OF THE FACE. LATE MANIFESTATIONS WERE REVERSIBLE FOLLOWING TREATMENT WITH ANTITHYROID SYNTHESIS.

KEYWORDS: GRAVES- BASEDOW DISEASE, BILATERAL EXOPHTHALMIA, HYPERTHYROIDISM, ANTITHYROID TREATMENT

[1] Phd - Department of Pediatric Cardiology, University of Medicine and Pharmacy of Craiova, Romania, corina.vasile93@gmail.com
[2] * Corresponding author, Lecturer- Department of Bacteriology - Virusology - Parasitology, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania, gaman_alice@yahoo.com
[3] C.I. Parhon National Institute of Endocrinology Bucharest Romania
[4] "Sf. Pantelimon" Emergency Clinical Hospital, General Surgery Department, 340 Sos. Pantelimon, 021659, Bucharest, Romania
[5] Associate Professor of Bacteriology - Virusology - Parasitology, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania, ancaungureanu65@yahoo.com
[6] Lecturer - Department of Endocrinology, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania, mihaela.n.popescu99@gmail.com

INTRODUCTION

Hyperthyroid Graves disease is one of the most common autoimmune disorders affecting about 1% of women. Graves' disease is unique among autoimmune conditions in that the target tissue is stimulated by immune response rather than progressively destroyed by it. This, coupled with the early identification of circulating thyroid-stimulating autoantibodies as the immunological hallmark of the condition, has led to Graves' disease acting as a paradigm for research into autoimmune endocrinopathy[7]. In infants, Graves Disease is much rarer than in adults. However, it can also occur in very young children under 5 years of age (about 10% of cases).

There is a significant predominance of cases in females, as in all thyroid pathologies and in adults.Predisposition to the disease is considered to be polygenic. GD has been reported to be associated with the human leukocyte antigen gene on chromosome 6p, the cytotoxic T lymphocyte antigen-4 gene on chromosome 2q33, and PTPN22 (lymphoid tyrosine phosphatase) chromosome gene 1p13. It has been presumed that the insufficiency of T suppressor lymphocytes makes the expression of T helper lymphocytes sensitized by TSH antigens that react with B lymphocytes. Antibodies bind to the TSH receptor and activate AMPc-like TSH[8]. Data from the twin studies and the higher incidence of GD in first-degree relatives of patients with this disease compared to the control group suggest that about 80 percent of GD is present in patients diagnosed. The overall GD predisposition is influenced by genetics[9].Thyroid-stimulating immunoglobulin binds and stimulates the thyroid-stimulating hormone (TSH) receptor on the thyroid cell membrane , resulting in follicular cell growth, increased vascularity, and excessive synthesis and secretion of thyroid hormone. Thyroid gland typically exhibits lymphocytic infiltration, T-lymphocyte abnormality and lack of follicular destruction. T cells activate local inflammation and tissue remodeling by producing and releasing cytokines, leading to B-cell dysregulation and increased autoantibody production. The imbalance between pathogenic and regulatory T cells is thought to be associated with both the expansion of GD and its severity[10]. There is a genetic predisposition to Graves' disease, determined by alleles in the major histocompatibility complex, cytotoxic T-lymphocyte-associated antigen, protein tyrosine phosphatase non-receptor 22, and other less well-defined chromosomal loci.

Additional, non-genetic factors that influence are pregnancy, estrogen use, and stressful life , smoking (especially associated with ophtalmopathy), sex (most commonly in women), postpartum, iodine (including amiodarone), lithium, and rare factors such as alpha-interferon therapy, antiretroviral therapy,It may be associated with autoimmune endocrine diseases (Addison disease, type I diabetes mellitus, primary gonadic insufficiency, Hashimoto, lymphocytic hypophysitis) and non-endocrine diseases (celiac disease, vitiligo, aerated alopecia, myasthenia gravis, pernicious anemia, thrombocytopenic purpura,

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rheumatoid arthritis) along with other diseases (periodic hypokaliemic paralysis, mitral valve prolapse).

Clinical manifestations in children are similar to those in adults. Most of the children have diffuse goiter and eye marks. They suffer behavioral changes such as decreased attention span, difficulty concentrating, hyperreactivity, restless sleep, tachycardia, tremor, weight loss, despite increased appetite and sometimes diarrhea. Ophthalmopathy is a specific autoimmune organ process in Graves-Basedow disease. Although hyperthyroidism can be successfully treated, ophthalmopathy can cause problems in these children. Eyelide retraction, protrusion (defined as an antero-posterior protrusion of the eyeball>19 mm, or any discrepancy between the two eyes > 1 mm), periorbital edema, chemosis, and motility problems may constitute functional sequelae of the disease. In some cases , the disease may result in vision loss due to keratopathy or optic neuropathy [8,9].Several studies suggest that ophtalmopathy in children has a benign character compared to adults, with a very low frequency of extraocular myopathy. Increased intraocular tension is one of the criteria of thyroid myopathy. Most children with Graves ophtalmopathy require only eye lubricating drops[11].

Hyperthyroidism can be confirmed by the measurement of pituitary thyrotropic, free thyroxine and triiodothyronine. However, there is no need for 24-hour radioiodocapture in young patients because, although there are other diagnostic possibilities, hyperthyroidism at this age almost always shows Graves' disease (more than 95% of cases)[12].

Thionamide, radioiodine, or thyroid surgery may be used to treat Graves' disease. No treatment is perfect and every treatment has its pros and cons. Recent isolation of monoclonal human TSH receptor antibodies may result in more sensitive tests for thyroid-stimulating autoantibodies. Thionamide antithyroid drugs, propylthiouracil, carbimazole, and its active substance metabolite methimazole has been used to treat Graves' disease for > 50 years . Approximately 50% of those treated[13] induce hyperthyroid remission after prolonged administration. Thionamides act as preferential substrates for iodination by TPO[14], competing with thyroglobulin to prevent iodotyrosine formation, and as the iodinated drug derivative is peripherally metabolized, thyroid iodine stores are gradually depleted[15]. Initial treatment with methimazole or carbimazole is preferable to propylthiouracil, as drugs can be taken once or twice daily, rather than 8 hours, and the longer half-life leads to more rapid control[16]. Most pediatric endocrinologists recommend thionamids as a treatment for an average period of about 3 years. The second option is different: therefore, thyroidectomy is preferred in Europe, leaving at least 4 g of remaining tissue, while radiotherapy is required in North America. Radioactive iodine has been successfully used in adolescents as the first line of treatment or

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when medical treatment has been contraindicated[17]. The key challenge is to define new treatments that contribute to safe and secure remission of hyperthyroidism without the removal of thyroid function.

MAIN TEXT

We present the case of a 2,8 years old girl, admitted in our Endocrinology Clinic for bilateral exophthalmia. From her personal history,she was the first born, at term, with birth weight=2980 g, scoring an Apgar =9, artificially fed. There is strong family history of thyroid disease. Patient's mother had hyperthyroidism ,following no treatment.

At the time of the presentation, the girl was 93 cm tall and weighs 12 kg, with a head circumference of 46 cm. Parents noticed a girl's attention deficit, hyperreactivity, moody appetite, weight loss, sweating, restless sleep. Objective examination guides the diagnosis, revealing bilateral exophthalmia, tachycardia 130 b / min, fine skin, velvety, vivid reflexes, discreet mitral systolic blast. Blood pressure of 105/55 mm Hg. Hand examination revealed fine tremor and sweating. The chest examination showed an equal air intake with no added sound. The cardiac exam was unremarkable. There was no hepatosplenomegaly, there were no skin changes. Child had a normal tone of muscle and power. The child could walk with no difficulty. The musculoskeletal examination had no modification.the Tanner stage examination showed a pre-pubertal stage.The anterior fontanela had been closed and had no frontal boses or carinostenosis.

Anamnesis revealed signs immediately after birth, but accentuated after 1 year of age. Psychoneuro behavioral development was normal at the time of presentation, with the exception of linear growth and advanced bone age compared to chronological age. Patient was not on medication. There is no past medical and surgical history. Vaccination was up to date. Developmental parameters were appropriate for age. No consanguinity between parents. Hormonal dosages and biochemical analyzes are presented in Table 1.

	Results	Normal values
TSH	<0,03	0,2-4,2 mUI/l
FT4	68,3	9,1-23,8 pmol/l
FAL	173	145-200 UI/l
CALCEMY	2,5	2,1-2,6 mmol/l
GOT	20	<40 UI/l
BILIRUBIN	9	3-21µmol/l
UREA	5,5	2,5-6,6 mmol/l
ATPO	2	< 13 (UI/mL)
TRAb	6	>1 UI/l

Table 1. Test results

Investigations showed Hemoglobin 13,5 g dl, white blood cell (WBC) 9 x10 ^{3}/µL. Serum urea and electrolytes were normal.

[17] Rivkees/SA, Aklarck, Freemark M.-clinical review 99. *The management of Graves' disease in children with special emphasis on radioiodine treatment* J. Clin. Endocrinol Metab. 1998;83;3767-76

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The ophthalmological examination revealed optic papillae, retina and vessels within normal limits and increased ocular tension. It was classified in group 3/4, considering the NOSPECS classification.

NOSPECS classification:
class 0 – No signs or symptoms;
class 1 - Only signs no symptoms;
class 2 – Soft tissue involvement;
class 3 – Proptosis;
class 4 – Extraocular muscle involvement;
class 5 - Corneal involvement;
class 6 – Sight loss/ optic nerve involvement.

Thyroid ultrasound revealed diffuse hypoecogenity with increased vascularization on the Doppler exam. Few submental lymph nodes have been enlarged.

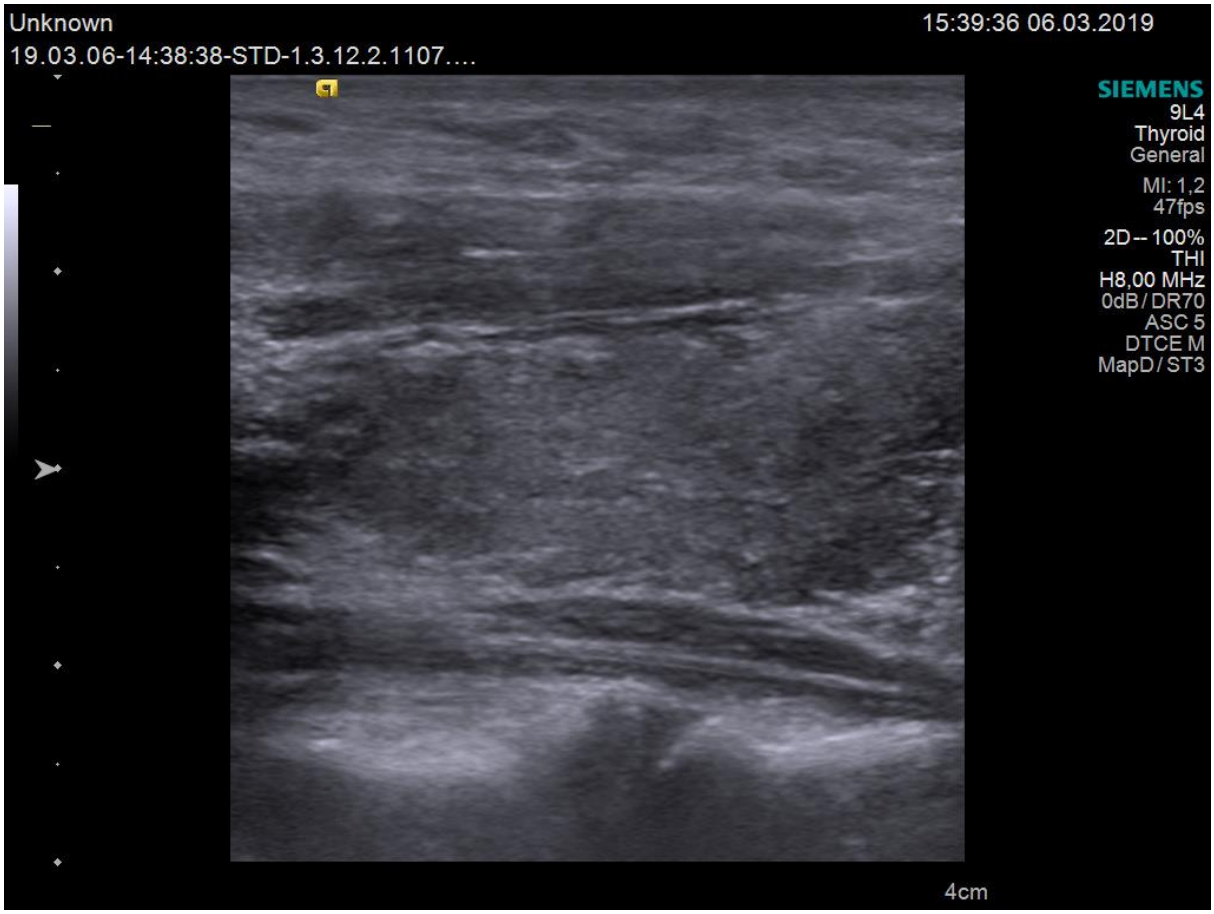

Fig 1. Thyroid ultrasound- revealing diffuse hypoecogenity (longitudinal section)

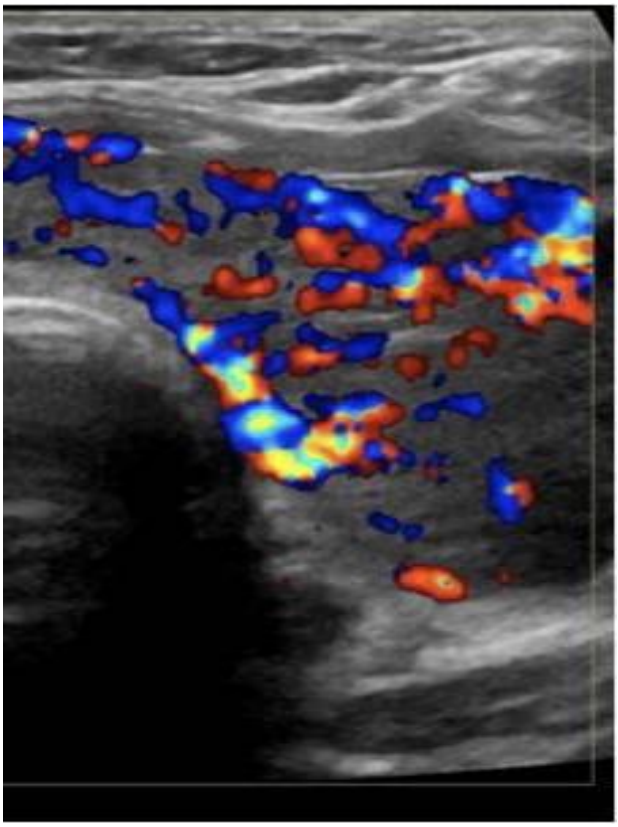

Fig 2. Left Lobe- increased vascularizationn on the Doppler exam

Orbital ultrasound was also performed, which showed the participation of the extrinsic eyeball muscles and the appearance of buphthalmia, excluding the retroorbital tumor.

Once diagnosis of Graves' disease has been established, treatment with antithyroid synthesis (Methimazole 10 mg / z) and B-adrenergic blocker (propranolol 5 mg / day) has begun. In children, the dose of antithyroid attacks is 0.4-1.6 mg / kg body / day and the maintenance dose is 0.1-0.5 mg / kg body / day.

Clinical symptomatology recovered within a few months, propranolol was interrupted and maintained a therapeutic dose of 5-2.5 mg Thyrozole. There were no complications during treatment. The little girl is still undergoing treatment. She underwent surgery for congenital glaucoma in April 2020.

DISCUSSION

In some cases, neonatal hyperthyroidism does not subside and persists in childhood. These patients have a family history of hyperthyroidism, although circulating antibodies may sometimes be absent.

Hyperthyroidism is caused by a thyroid-stimulating hormone (TSH) receptor that stimulates autoantibodies that cause excess production and growth of thyroid hormones. Peroxidase of the thyroid autoantibodies are also commonly found and could be important in the destruction of thyrocytes and the perpetuation of autoimmunity[18].

Elevation of one or both serum-free thyroid hormones together with undetectable TSH (3rd generation assay) confirms the diagnosis of thyrotoxicosis. In the presence of clear

[18] A. P. Weetman © Humana Press, Totowa, NJ: Contemporary Endocrinology: *Autoimmune Diseases in Endocrinology* 2008; eISBN: 978-1-59745-517-6

extrathyroid signs of Graves' disease (e.g., protosis, Dermopathy), no further testing beyond free thyroid hormone(s) and TSH is required. In the absence of these features, an attempt should be made to ensure an etiological diagnosis.

The cause of GD remains unclear, but it is believed to be the result of a complex interaction between genetic background (heredity), external conditions and the immune system[23].The immune system produces an antibody (TRAb, a thyroid-stimulating hormone receptor antibody) that stimulates the thyroid gland to produce excess growth hormone[19], so the gold-standard test is a highly sensitive TSHR-stimulating antibody assay, which will be positive in >95% of subjects with Graves' disease, which is also confirmed in the case presented .

Peroxidase of the thyroid autoantibodies are also commonly found and could be important in the destruction of thyrocytes and the perpetuation of autoimmunity[20], in our case ATPO were not detected in the patient's serum.

Placental passage of thyroid-stimulating immunoglobulins (TSIs) from mothers with hyperthyroidism(usually Graves' disease, but occasionally Hashimoto's disease. The TSIs may persist even after definitive therapy with radioactive iodine or surgery. This is a transient phenomenon which resolves on clearing of maternal antibody from the fetal circulation[21].

Symptoms of hyperthyroidism include flushing, palpitations, tremor, weight loss of tachycardia, accelerated linear growth, reduced bone mineralization, and poor school performance[22]. In pediatric GD, ophtalmopathy occurs in less than 50 percent of patients and is usually mild when present[23], the little girl presentd both ophthalmopathy and other manifestations described in the literature.

In both adults and adolescents, GD is much more prevalent in female than in male subjects. It can occur at any time during childhood, but increases in frequency with age, reaching its peak during adolescence[24]. GD is more common in children with other autoimmune disorders and children with a family history of autoimmune thyroid disease. The disease can appear at any time with highest prevalence during adolescence[25], in our case, the patient's mother is diagnosed with hyperthyroidism.

It has recently been established that there is a gene mutation in these children that encodes the receptor for TSH. Genetic susceptibility to the disease is thought to be polygenic, unfortunately, they could not been realized. In case of germline-activating TSHR mutation, due to suspicion of malignancy the preferred treatment is subtotal thyroidectomy.

The typical signs of hyperthyroidism were noticed in this young girl, but the most prominent aspect was the acceleration of bone maturation. The association of glaucoma may

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be due to the intrauterine action of thyroid hormones on the brain and eye structures, as well as extraocular thyroid myopathy.

The first-line treatment is anti-thyroid drugs to reduce the production of thyroid hormones and b-blockers to control cardiac symptoms. Carbimazole/Methimazole, initially 0,5-1.9 mg/kg body/ day, given as a once-daily dose, which blocks iodine organification. The main side effect are uncommon (rash 8%, granulocytopenia 6%, arthritis 2%), our patient received the maximum dose allowed. Beta-blockers doses (Propranolol): 0,5-1 mg/kg body/ day in 3 divided doses, if there are signs and symptoms associated with tachycardia, so we decided a 5 mg dose of Propranolol for our little girl. All thyrotoxic patients may gain symptomatic benefit from beta blockade, but this is contraindicated in asthma patients.

Most subjects with hyperthyroid disease Graves develop euthyroid (as measured by normal free thyroid hormones) for 4-to 8-week treatment with methimazole (10 mg daily) or carbimazole (10 mg daily). Only those with large goiter, recent exposure to iodide, or poor compliance with treatment may need to be treated for longer or longer doses of thionamide[26].

Once symptoms have been controlled, B-blockers can be withdrawn. We choose to follow the dose titration, once our patient started to feel better, treatment is continued with the anty-thyroid drug, but the dose is gradually reduced to a maintenance level once free T3 and Free T4 fall witinh the normal range. TSH levels may remain suppressed for many months, and sever as an indicator of autoimmune disease activity.

CONCLUSION

Graves-Baseow disease can occur differently in children than in adults, and there are some differences in diagnosis and treatment of this disorder. It is characterized by thyrotoxicosis, goiter and ophtalmopathy. It occurs rarely in infants, affecting 0.8/100,000 infants per year. Of all cases of Baseow disease, only 5% occur in childhood. It's five times more common in girls[27].

The persistent form of Graves-Basedow disease in childhood, as described here, is rare, antithyroid diagnosis and treatment should be initiated early, as any delay may have significant effects on growth and development.

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