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Case Report

Graves' Disease with Negative Autoantibodies against the TSH Receptor: 5 Cases

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Abstract

The diagnosis of GD is based on the detection of suppressed plasma TSH and TRAb [4]. However, there are patients in whom TRAb are not detected despite of having a highly suggestive clinic, hormonal profile and imaging tests. We describe 5 pediatric cases of this still little studied and understood clinical situation. The diagnosis of GD is based on the detection of suppressed plasma TSH and TRAb [4]. However, there are patients in whom TRAb are not detected despite of having a highly suggestive clinic, hormonal profile and imaging tests. We describe 5 pediatric cases of this still little studied and understood clinical situation.

Keywords: Graves Disease (GD); Thyroid Stimulating Hormone Receptor (TSHR); Anti-thyroid

Introduction

Graves disease (GD) is the leading cause of hyperthyroidism in childhood. It is an autoimmune disease with production of autoantibodies directed to the thyroid stimulating hormone receptor (TSHR) and progressive infiltration of the thyroid by T and B lymphocytes [1].

There are three types of antibodies that bind to TSHR (TRAb): stimulants (TSAb); blockers (TBAb), and the so-called "neutrals" [1]. Its detection can be carried out by immunoassays, with a sensitivity of up to 98% in third-generation ones [1,2], or by biological tests, which detect functional activity, being even more sensitive [1-3].

The diagnosis of GD is based on the detection of suppressed plasma TSH and TRAb [4]. However, there are patients in whom TRAb are not detected despite of having a highly suggestive clinic, hormonal profile and imaging tests [3]. We describe 5 pediatric cases of this still little studied and understood clinical situation.

Case Report

Case 1: Pubertal patient with a personal and family history of autoimmune disease who presents with clinical hyperthyroidism with suppressed TSH and free T4 in the upper limit of normality in successive laboratory controls in the two subsequent months. Increased anti-TPO and anti-TG antibodies, as well as ultrasound compatible with thyroiditis. Currently controlled with anti-thyroid treatment.

Case 2: 14-year-old adolescent who consulted for initial symptoms of hypothyroidism: asthenia, malaise, drowsiness, abdominal pain, constipation and anorexia. In the laboratory test, suppressed TSH with initially normal free T4, evolving within a month to more characteristic symptoms of hyperthyroidism: palpitations, agitation,

insomnia, palpebral retraction, with increased goiter and elevated free T4.

Case 3: A 10-year-old girl with hyperthyroidism symptoms and biochemistry. In the evolution, stands out thyroid hypofunction with low doses of methimazole. Therefore, after 1.5 years it was suspended, observing relapse and finally receiving radioiodine. The TRAbs were slightly positive for the first generation techniques three years after the onset of the clinic and were subsequently clearly positive with the second generation immunoassays.

Case 4: New born with transient neonatal hyperthyroidism. His mother had a history of thyroidectomized GD due to papillary carcinoma. TRAbs by second generation immunoassays were negative in both the mother and the child.

Case 5: Patient with early-onset and persistent hyperthyroidism, with a family history of hyperthyroidism and negative TRAb. Genetic study to detect TSHR activating mutations was negative. Received radioiodine as definitive treatment.

	Case 1	Case 2	Case 3	Case 4	Case 5
Age*	12 years	14 years	10 years	20 days	3 years
Sex	F	F	F	M	F
Family history	Mother with GD hypothyroidism from the 2n gestation	Maternal aunt with acquired hypothyroidism	Without interest	Mother with TCM GD, later thyroidectomised	Older sister and paternal aunt with hyperthyroidism
Past history	Juvenile idiopathic arthritis from 3 years old	Mite allergy. Mild intermittent asthma.	Without interest	PTNB 29 weeks Neonatal sepsis, IVH, osteopenia	Without interest
Present illness*	Goiter, nervousness, insomnia, hunger, weight loss	Goiter with hypothyroid symptoms. Subsequently, goiter increase and hyperthyroidism symptoms (insomnia, tremor, tachycardia, weight loss)	Goiter, insomnia, palpitations, agitation	Jaundice, cholestasis, tachycardia	Goiter, nervousness, insomnia, tachycardia
TSH* (0,64- 6,27 mU/l)	0,01	0,426 → 0,23	0,01	0,02	Suppressed***
T4L* (0,8- 1,76 ng/dl)	2,09	1,42 → 2,31	1,71	>7,77	High***
T3L* (2,3- 4,2 pg/ml)	7,58	3,83 → 4,58			
Anti-TPO* (0-35 UI/ml)	2669	84,2	61		Negative***
Anti-TG* (0-40 UI/ml)	292	1812	70		Negative***
TRAb* (0 - 1,8 UI/ml)	<0.3UI/L	<0.3UI/L	**TSI-lats: 5.2 (VN: 0-15 UI/L)	<0.3UI/L (mother and patient)	<0.3UI/L
Echography	Heterogeneous Doppler hyperflux	Diffuse magnification Doppler hyperflux	Diffuse magnification Doppler hyperflux	Normal	Diffuse magnification, heterogeneous

Gammagraphy		Slight increase diffuse increased uptake	Diffuse increased uptake		
Treatment	Metimazole (>1,5 years)	Propranolol (6 weeks) Metimazole (>1 year)	Metimazole Levotiroxine Radioiodine	Lugol 5 days Levotiroxine 8 months	Metimazole (>10 years) +/- Levotiroxine
Present age	14 years	15 years	17 years	4 years	13 years
Evolution	End of symptoms and stable thyroid function with treatment	End of symptoms and stable thyroid function with treatment	Bad control. TRAb + 3 years after debut	Hypothyroidism secondary to lugol → euthyroidism	Relapses that do not allow methimazole withdrawal
Legend. Between parentheses "( )" the normal reference values are expressed in the corresponding units used in our laboratory. (*) At the time of diagnosis. (**) The TRAb detection method at that time was not the one currently used. (***) Patient followed in another center until she was 10 years old, missing data in the reports provided. IVH: Intraventricular Hemorrhage. MTC: Medullary Thyroid Carcinoma. GD: Gestational Diabetes. AC: Antibody Concentrations. PTNB: Preterm New-Born					

Table 1: Summary of the symptoms, complementary examinations, treatment and evolution.

Discussion

Although we have few studies in the pediatric population, it seems that patients with hyperthyroidism compatible with GD but with undetectable levels of TRAb tend to have clinically and biochemically less severe thyrotoxicosis [3]. In this sense, our findings are consistent with previous studies: none of the 5 cases presented ophthalmopathy or pretibial myxedema, and FT4 levels at diagnosis were not extremely high.

In cases 2 and 3, with a very silent evolution, we could consider the coexistence of TSAb and TBAb during the evolution of the disease. Recent studies have demonstrated the coexistence and changes in the proportions of TSAb and TBAb in the same patient, which occur mainly during pregnancy and in up to 10% of patients with GD treated with antithyroid drugs [4]. Owing to this reason and its greater sensitivity, some authors recommend using biological tests to diagnose cases in which a low level of autoantibodies is expected, such as in pregnant women or in neonatal hyperthyroidism [2].

In a patient with hyperthyroidism and negative TRAb, we must make the differential diagnosis with the thyrotoxic phase of Hashimoto's thyroiditis (compatible ultrasound and antibodies, with a FT4 that will decrease in a few weeks). Despite being very rare (only 4.5% of patients with hyperthyroidism, diffuse goiter and negative TRAb [5]), in cases of early-onset hyperthyroidism with a family history and poor response to anti-thyroid treatment (case 5) , we must consider activating mutations of the TSHR. Other causes of thyrotoxicosis can be ruled out by anamnesis, physical examination, and ultrasound.

Having ruled out other diseases, one hypothesis to explain why TRAbs are negative is that the sensitivity of the assays is too low to capture low antibody concentrations. Another possible explanation is that TRAb production is limited to the thyroid gland, without reaching the systemic circulation. This hypothesis is based on the fact that lymphocytes isolated from the thyroid gland of a patient with autoimmune thyroiditis without plasma thyroid autoantibodies have shown that can produce anti-thyroid autoantibodies [3,6].

Conclusion

In conclusion, in the presence of a TRAb negative hyperthyroidism, Graves' disease cannot be ruled out. It is important to consider this clinical situation to start anti-thyroid treatment as early as possible.

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