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Professional Paper

ALTERNATING HYPOTHYROIDISM AND HYPERTHYROIDISM IN AN ADOLESCENT BOY – DO WE ALWAYS UNDERSTAND WHAT DRIVES THE SWITCH?

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SUMMARY – Alternating hypothyroidism and hyperthyroidism is a rare phenomenon, especially among pediatric patients. It is usually related to simultaneous, unbalanced presence of stimulating and blocking thyroid stimulating hormone receptor antibodies (TRAbs). Herein we describe thyroid stimulating hormone (TSH) and thyroid hormone fluctuations in an adolescent boy with negative TRAbs. A 12-year-old healthy boy exhibited alternating thyroid function, with several switches between hypothyroidism and hyperthyroidism during almost six years of follow-up. He had persistently elevated thyroid peroxidase antibodies, while TRAbs were repetitively negative. Due to a mild clinical presentation, most of the time he did not require any medication. This case contributes to the spectrum of alternating hypothyroidism and hyperthyroidism in the pediatric age and raises the question of mechanisms involved in fluctuating thyroid function. Therapeutic decisions should be individualized and guided by clinical manifestations and thyroid function tests, irrespective of the underlying pathophysiology.

Key words: *Alternating thyroid function; Thyroid stimulating hormone receptor antibodies; Pediatric age*

Introduction

The most frequent cause of acquired thyroid dysfunction in the pediatric age is immune-mediated thyroid disease. Hypothyroidism due to Hashimoto's thyroiditis and hyperthyroidism due to Graves' disease are commonly encountered in the clinical setting as the opposite sides of the autoimmune thyroid disease spectrum. On the other hand, alternating hypothyroidism and hyperthyroidism (hypo-/hyperthyroidism) is a rare clinical entity that has been reported in children and adolescents sporadically[1,2]. While the pathophysiological background of this phenomenon is not entirely clear, it has been speculated that thyroid stimulating hormone receptor antibodies (TRAbs) play a major role in fluctuating thyroid function. It is thought that both stimulating and blocking TRAbs coexist in a patient, and the alterations in their balance in a given moment determine whether a subject is hypothyroid, euthyroid or hyperthyroid[3,4].

Herein, we describe an adolescent with fluctuating thyroid function and negative TRAbs, pointing out that the mechanisms responsible for alternating hypo-/hyperthyroidism are not always obvious.

Case Report

In October 2014, a previously healthy 12-year-old boy presented to the endocrine outpatient department

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for evaluation of weight gain due to suspected thyroid dysfunction. His body mass index (BMI) was 23.6 kg/m^2 (94th percentile, 1.55 SDS), he was pubertal (Tanner stage 2), with unremarkable physical examination, including no significant thyromegaly. His serum thyroid function tests (TFTs) were consistent with subclinical hypothyroidism and thyroid peroxidase antibodies (TPOAbs) were positive (Table 1, Fig. 1). Ultrasonographic examination revealed thyroid volume of 10.9 mL and mildly heterogeneous parenchyma without thyroid nodules. The boy had a positive family history of thyroid disease. His mother had euthyroid Hashimoto's thyroiditis and her sister was receiving levothyroxine (L-T4) replacement therapy for hypothyroidism. Father's sister and grandfather were thyroidectomized for multinodular goiter.

In December 2014, the boy's thyroid stimulating hormone (TSH) and free thyroxine (FT4) levels normalized without medication (Table 1, Fig. 1). In March 2015, he complained of palpitations with elevated resting heart rate (110 beats/min), but was otherwise feeling well. His BMI was 22.7 kg/m^2 (91st percentile, 1.33 standard deviation score [SDS]), he had no palpable goiter and no ophthalmopathy. His TFTs confirmed hyperthyroidism, TPOAbs were positive and thyroglobulin antibodies

Table 1. Change in thyroid function tests, thyroid autoantibodies and body mass index over time

Month/ year	TSH (mIU/L)	FT4 (pmol/L)	T4 (nmol/L)	FT3 (pmol/L)	T3 (nmol/L)	TPOAb (kIU/L)	TgAb (kIU/L)	TRAb (IU/L)	BMI (kg/m^2)	BMI z-score	Treatment
10/2014	8.08		79			373.2			23.6	1.55	
12/2014	4.51	11.7									
03/2015	0.01	20.3		8.72		505.0	108.0	0.67	22.7	1.33	
03/2015	0.01	8.7		6.9							
05/2015	35.1	6.7							24.0	1.52	L-T4 0.4 μg/kg/day
07/2015	8.78	9.6		7.8							L-T4 0.6 μg/kg/day
10/2015	3.06	14.2							22.7	1.23	L-T4 0.6 μg/kg/day
12/2015	0.02	21.9		8.6							
01/2016	0.01	21.0		9.8		299.6	59.3	0.32	22.4	1.12	Atenolol 25 mg/day
03/2016	15.1	8.8		6.07					23.1	1.25	
04/2016	17.2	10.1		6.97							
06/2016	9.99	11.4		5.59					23.1	1.20	
10/2016	5.4	12.1			1.7						
03/2017	0.017	23.9		11.2					23.7	1.19	
11/2017	5.13	11.9			1.3				23.9	1.13	
05/2018	<0.004*	13.4*			2.1*						
08/2018	11.27*	9.4*			1.4*	276.2	31.3				
02/2019	3.476*	11.3*			1.8*				23.9	0.91	
07/2019	0.006#	25.7#			3.47#	164.6	114.9	0.35	23.3	0.70	
11/2019	7.915*	9.5*			1.78*				25.1	1.05	
06/2020	4.604*	10.8*			1.8*				24.1	0.72	

Method (reference range): Siemens Immulite, CLIA: TSH (0.40-4.00), FT4 (11.5-22.7), T4 (58-161), FT3 (2.76-6.45), T3 (1.3-2.6); Abbott Architect, CMIA*: TSH (0.35-4.94), FT4 (9.0-19.0), T3 (0.98-2.34); Siemens Atellica, CMIA#: TSH (0.48-4.17), FT4 (10.7-18.4), T3 (1.32-2.96); Roche Cobas, ECLIA: TPOAb (0-34), TgAb (0-115); ELISA: TRAb (<2);
TSH = thyroid stimulating hormone; FT4 = free thyroxine; T4 = thyroxine; FT3 = free triiodothyronine; T3 = triiodothyronine; TPOAb = thyroid peroxidase antibody; TgAb = thyroglobulin antibody; TRAb = thyroid stimulating hormone receptor antibody; BMI = body mass index; L-T4 = levothyroxine

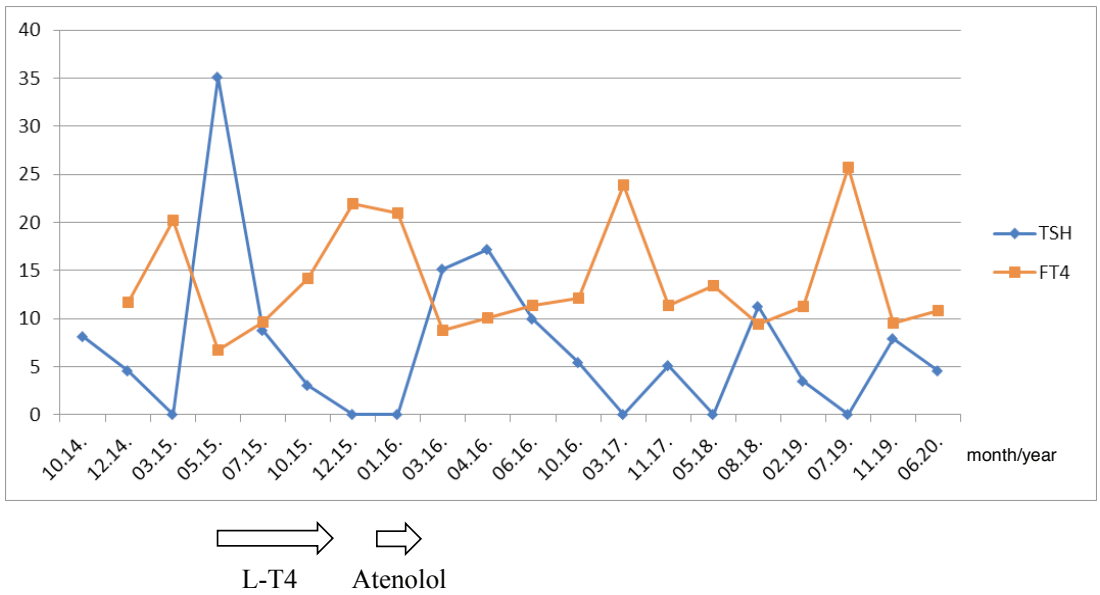

Fig. 1. Alternating thyroid function over time.

TSH = thyroid stimulating hormone; FT4 = free thyroxine; L-T4 = levothyroxine

(TgAbs) were negative, as well as TRAbs (Table 1, Fig. 1). Ultrasonographic features of the thyroid were unchanged, including normal gland vascularization. After only one week, a spontaneous decrease in serum thyroid hormones was recorded, with TSH level still supressed (Table 1). In May 2015, the boy had no symptoms of thyroid dysfunction other than weight gain, and his BMI was 24 kg/m^2 (94th percentile, 1.52 SDS). His TFTs revealed hypothyroidism and L-T4 at a dose of 0.4 μg/kg/day was initiated. Six weeks later, due to still elevated TSH, the dose was increased to 0.6 μg/kg/day. For subsequent 6 months under replacement therapy, his TSH and FT4 levels remained within the reference range (Table 1, Fig. 1).

Meanwhile, the boy's father was diagonsed with thyrotoxicosis. He was asymptomatic but had goiter, negative thyroid autoantibodies, and inhomogeneously increased uptake on technetium scan. He became spontaneously euthyroid and required no medication during several years of follow-up.

In December 2015, the boy complained of palpitations again. His TFTs suggested hyperthyroidism (Table 1, Fig. 1), so L-T4 treatment was weaned off. One month later, as resting tachycardia (120 beats/min) persisted along with the appearance of fine hand tremor, TFTs were repeated. At that time, his BMI was 22.4 kg/m^2 (87th percentile, 1.12 SDS), his TSH was still suppressed with high normal FT4 and elevated free triiodothyronine (FT3), TPOAbs were positive, TgAbs and TRAbs were negative (Table 1, Fig. 1). Atenolol at a dose of 25 mg/day was introduced, but as symptoms of hyperthyroidism disappeared after six weeks, the treatment was discontinued.

In March 2016, the boy's BMI was 23.1 kg/m^2 (89th percentile, 1.25 SDS) and his findings were again suggestive of hypothyroidism (Table 1, Fig. 1). Since he was feeling well, he received no replacement therapy. During subsequent four years, TRAbs remained negative, while the boy had three more switching hyper-/hypothyroidism episodes (Table 1, Fig. 1). Due to the absence of significant signs and symptoms of thyroid dysfunction, throughout this period he required no medication.

Discussion

In the case described, a longstanding fluctuation between hypo-/hyperthyroidism in an adolescent boy with negative TRAbs was observed. As alternating thyroid function is usually associated with elevated levels of TRAbs[1-5], the appearance of repetitive switching between hypo-/hyperthyroidism in a TRAb-negative patient encouraged us to consider the possible underlying mechanisms.

At first, the presumptive diagnosis of Hashimoto's thyroiditis was based on elevated TPOAbs and ultrasonographic features compatible with autoimmune thyroid disease, along with suggestive family history. The initial clinical course was in line with this assumption. However, it is highly unusual for patients with Hashimoto's thyroiditis who already developed hypothyroidism, to switch to hyperthyroidism thereafter. To our knowledge, in all the published cases with such clinical course, children and adolescents were TRAb positive[1,2,6]. As previously pointed out, this was not the case in our patient. Therefore, in December 2015, L-T4 overtreatment was considered. However, this option was discarded as hyperthyroidism persisted, and symptoms were even more pronounced a month after L-T4 treatment cessation. Unfortunately, at that point, thyroid scan was not performed due to parental hesitation. As symptoms of hyperthyroidism resolved within a few weeks with symptomatic treatment only, the opportunity to carry out this diagnostic procedure was missed. It should be noted, however, that there are no conclusive data available on scintigraphic findings in patients with alternating thyroid function. Moreover, a report of a homogeneously increased iodine uptake suggesting Graves' disease while the patient was hypothyroid[2] opens up the possibility of a puzzling finding if scintigraphy is performed in a transition phase between hypo-/hyperthyroidism. Interferences in thyroid function testing were also considered in our patient, as they may be unique to an individual and may change over time[7]. However, the boy was not taking food supplements or drugs other than L-T4 and atenolol over a limited time, and he did not have contact with pets. Since there were neither clinical nor biochemical discrepancies suggesting interference as a possible underlying mechanism of swinging TFT results, this option was eventually rejected. Whereas alternating thyroid function is inconsistent with the course of Hashimoto's thyroiditis, and after excluding L-T4 overtreatment and interferences with thyroid function immunoassays, a speculation that switches between hypo-/hyperthyroidism might be induced with the TRAb levels below the cut off for positivity was reviewed. McLachlan and Rapoport expressed the opinion that concentrations of stimulating and blocking antibodies, as well as their affinities for the TSH receptor, play a critical role in their balance and potential activities[4]. Thus, we wondered if clinical status of the patient and his TFTs could be shaped not only by the concentration of TRAbs, but also by different proportions and affinities of stimulating and blocking antibodies for the TSH receptor. In a scenario like this, although the concentration of TRAbs is below the limit of positivity, the higher proportion of or affinity for either stimulating or blocking antibodies would determine clinical presentation and affect the results of TFTs. Such a hypothesis might also explain milder symptoms in our patient when compared to the cases described so far. However, according to the clinical course and laboratory findings, we finally concluded that our adolescent most likely suffered from recurrent painless thyroiditis, which is considered a variant form of chronic autoimmune thyroiditis, and as such is included in the spectrum of thyroid autoimmune disease[8]. Painless thyroiditis is characterized by transient hyperthyroidism, frequently followed by hypothyroidism, and then by recovery. Repetitive episodes of painless thyroiditis were described in the literature[9], but as far as we know, not in the pediatric age.

It should be pointed out that the boy did not require any medication from February 2016 to June 2020. During the specified period, he did not have significant symptoms of thyroid dysfunction, although several hypo-/hyperthyroidism episodes were recorded by TFTs at routine check-ups. However, the patient's weight cycled slightly with thyroid function (Table 1) and it was the most consistent sign of pendulum swinging between hypo-/hyperthyroidism, as previously described by Solaimanzadeh *et al.*[10].

Due to the unpredictable course of the disease, management of children and adolescents with alternating hypo-/hyperthyroidism is challenging. Three therapeutic options should be considered, i.e., pharmacological treatment, I-131 ablation, and thyroidectomy. To our knowledge, in all pediatric TRAb positive cases described so far, definitve treatment with either thyroidectomy or I-131 ablation was selected or considered as a suitable option[1,2,6]. However, a mild clinical course in a TRAb negative adolescent boy led us to opt for a conservative therapeutic approach. Considering that, close monitoring of the patient along with regular TFTs were required during the follow-up.

Conclusion

Alternating hypo-/hyperthyroidism is a rare phenomenon in the pediatric age and its' occurrence in a TRAbs negative subject draws attention to the fact that underlying mechanisms are not always obvious.

Frequent fluctuations of thyroid funciton require close monitoring and regular follow up. Therapeutic decisions should be individualized and guided by the combination of clinical symptoms and thyroid function tests. Conservative therapeutic approach should be considered in cases with mild clinical course.

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Sažetak

PONAVLJAJUĆE IZMJENE HIPOTIREOZE I HIPERTIREOZE U ADOLESCENTA – RAZUMIJEMO LI UVIJEK ŠTO POKREĆE PROMJENU?

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Izmjena hipotireoze i hipertireoze je rijetka, osobito u pedijatrijskih bolesnika. Obično je povezana s istodobnim, neuravnoteženim prisustvom stimulirajućih i blokirajućih antitijela usmjerenih na receptor za tireoidni stimulirajući hormon (TRA). U nastavku prikazujemo kolebanja vrijednosti tireoidnog stimulirajućeg hormona i hormona štitnjače u adolescenta s negativnim TRA. U dvanaestogodišnjeg inače zdravog dječaka pratili smo promjenjivu funkciju štitnjače, s nekoliko izmjena hipotireoze i hipertireoze tijekom razdoblja od gotovo šest godina. Dječak je imao trajno povišene vrijednosti antitijela na peroksidazu štitnjače, dok su TRA bila ponavljano negativna. S obzirom na blagu kliničku sliku, većinu vremena nije bilo potrebe za medikamentnim liječenjem. Prikazom ovog bolesnika ukazujemo na širinu kliničkog spektra tireoidne disfunkcije u dječjoj dobi i razmatramo mehanizame odgovorne za promjenjivu funkciju štitnjače. Donošenje terapijskih odluka treba individualizirati, pri čemu ih treba temeljiti na kliničkim manifestacijama i hormonskom statusu, neovisno o podležećoj patofiziologiji.

Ključne riječi: *Promjenjiva funkcija štitnjače; Antitjela na TSH receptor; Pedijatrijska dob*