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Autoimmune alternating hyper- and hypo-thyroidism: a rare condition in pediatrics

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Summary

Alternating between hyper- and hypo-thyroidism may be explained by the simultaneous presence of both types of TSH receptor autoantibodies (TRAbs) – thyroid stimulating autoantibodies (TSAbs) and TSH blocking autoantibodies (TBAbs). It is a very rare condition, particulary in the pediatric age. The clinical state of these patients is determined by the balance between TSAbs and TBAbs and can change over time. Many mechanisms may be involved in fluctuating thyroid function: hormonal supplementation, antithyroid drugs and levels of TSAbs and TBAbs. Frequent dose adjustments are needed in order to achieve euthyroidism. A definitive therapy may be necessary to avoid switches in thyroid function and frequent need of therapeutic changes. We describe an immune-mediated case of oscillating thyroid function in a 13-year-old adolescent. After a short period of levothyroxine treatment, the patient switched to a hyperthyroid state that was only controlled by adding an antithyroid drug.

Learning points:

- Autoimmune alternating hypo- and hyper-thyroidism is a highly uncommon condition in the pediatric age.
- It may be due to the simultaneous presence of both TSAbs and TBAbs, whose activity may be estimated *in vitro* through bioassays.
- The clinical state of these patients is determined by the balance between TSAbs and TBAbs and can change over time.
- The management of this condition is challenging, and three therapeutic options could be considered: I-131 ablation, thyroidectomy or pharmacological treatment (single or double therapy).
- Therapeutic decisions should be taken according to clinical manifestations and thyroid function tests, independent of the bioassays results.
- A definitive treatment might be considered due to the frequent switches in thyroid function and the need for close monitoring of pharmacological treatment. A definitive treatment might be considered due to the frequent switches in thyroid function and the need for close monitoring of pharmacological treatment.

Background

Autoimmune thyroid disease is one of the most common autoimmune conditions, affecting 2–4% of women and 1% of men (1). Although its prevalence is higher in adults, it is also the most frequent etiology of acquired thyroid dysfunction in pediatrics. In this population, it is most common in girls and generally occurs in early and mid-puberty (2).

Autoimmune thyroid disease encompasses an ample spectrum of thyroid disorders from which Hashimoto's

thyroiditis and Graves' disease are the most common presentations. They represent the two ends of the autoimmune thyroid disease spectrum once they have opposite phenotypes and distinct immunologic mechanism. At first, there is T-cell infiltration of the gland leading to its destruction and clinical signs of hypothyroidism; finally, the gland is chronically stimulated by agonist antibodies of thyroid-stimulating hormone (TSH) receptor, produced by local B cells, causing hyperthyroidism.

However, there is an interrelationship between the various autoimmune thyroid disorders that could be explained by a common pathophysiological mechanism and antibody production. The thyroid gland releases antibodies against specific antigens, more frequently against thyroglobulin, thyroid peroxidase and TSH receptor. Elevated levels of antithyroglobulin and antithyroid peroxidase antibodies may not only be found in patients with autoimmune thyroid disease but also in healthy individuals, with a prevalence of 5–30% in the general population. The TSH-receptor antibodies (TRAbs) are more specific for autoimmune thyroid disease. Their prevalence in Graves' disease and autoimmune thyroiditis is 80–95% and 10–20%, respectively (3).

There are two types of TRAbs: thyroid-stimulating autoantibodies (TSAbs) that cause Graves' disease and TSH-blocking autoantibodies (TBAbs), competitive inhibitors of TSH binding sites without agonistic activity. TBAbs are found in a significant number (18.5%) of adult patients with untreated Graves' disease; however, TBAbs-induced hypothryoidism is a very rare condition (4, 5). Some patients may have TBAbs and TSAbs sequentially and evolve from hypo- to hyperthyroidism or vice versa. In very few adult patients, both antibodies may be present simultaneously, leading to a rapid oscillation in thyroid function as TBAbs or TSAbs become dominant (5). This situation is even more uncommon in pediatric population (4). The TRAbs activity may be estimated *in vitro* through bioassays. The more sophisticated ones involve chinese hamster *ovary* cells (CHO cells) transfected with the recombinant human TSH-receptor. The biological activity is deduced through cyclic adenosine 3′,5′-monophosphate (cAMP) production (6, 7).

Herein, we report a case of an adolescent with fluctuating thyroid function associated with elevated levels of antithyroglobulin, antithyroid peroxidase and TSH-receptor antibodies.

Case presentation

A previously healthy 13-year-old girl, referred for evaluation, presented in the clinic with a slightly increased thyroid volume, and a subclinical hyperthyroidism observed in June 2012, with no signs or symptoms (table 1). There was family history of thyroid disease.

On first evaluation, in March 2013, she presented a visible and palpable thyroid gland with no individualized nodules, no adenomegaly, and no exophthalmos. There were no other relevant findings in her physical exam. The TSH and free-thyroxine (fT_4) serum levels were within the normal range, but she presented with elevated levels of antithyroid peroxidase antibodies (Table 1). The thyroid ultrasound confirmed a diffuse glandular enlargement (right lobe 18×16×46 mm; left lobe 16×16×51 mm), with an heterogeneous and hypoechoic parenchymal echo pattern suggestive of thyroiditis. She was started on levoT_4 (LT_4) 0.4 μg/kg per day to reduce goiter volume. However, after 6 months of treatment (in September 2013), she developed subclinical hyperthyroidism, and LT_4 was slowly weaned off.

In June 2014, 4 months after the LT_4 cessation, she gained weight rapidly (2.5 kg in 2 months), but no other signs or symptoms of hypothyroidism were reported and there was no increase in goiter volume. At this time, TSH was 46 μU/ml, fT_4 was 0.5 ng/dl and there was an elevation in the TRAbs adding to elevated TPO (Table 1). After 3 days, a repeat TSH measurement showed a spontaneous decrease in TSH to 14.2 μU/ml, without any treatment, and the scintigraphy showed a homogeneously increased iodine uptake, suggestive of Graves' disease. She was again started on LT_4 at 0.73 μg/kg per day. On follow-up after 2 months of LT_4 treatment (in August 2014), she was noted to have a decrease in TSH and an increase in fT_4, with no signs of hyperthyroidism apart from weight loss (Table 1). She maintained treatment with LT_4. Methimazol was started at a dose of 0.15 mg/kg per day and increased after 2 months to 0.20 mg/kg per day due to laboratory evidence of persistent hyperthyroidism. Thyroid function was controlled with this double therapeutic regimen for a period of time, but after 6 months she again developed hyperthyroidism that demanded another adjustment, with a decrease in LT_4 to 0.37 mg/kg and increase in methimazol to 0.23 mg/kg daily (in July 2015). At this point, on suspicion of the coexistence of TBAbs and TSAbs as a cause of these rapid oscillations in thyroid function, a sample of serum was sent to Hospices Civils de Lyon to perform a bioassay to measure TSAbs and TBAbs activity (the method is described in Table 2). The serum level of TSH was <0.004 μU/ml, fT_4 was 3.1 ng/dl and TRAbs were 20 UI/l. A moderate TSAbs activity was detected (203%), but there was no evidence of blocking activity.

Table 1 Thyroid function tests, autoantibodies and pharmacological treatment during follow-up.

	Reference values	2012	2013			2014					2015		
		June	March	September	February	3rd June	6th June*	August	October	January	April	July†
TSH (mU/l)	0.6–6.4 μU/l	0.11	1.1	0.026	0.027	46	14.2	0.018	0.016	1.21	0.008	<0.004
T_4 (ng/dl)	0.8–1.99	1.99	1.054	1.5	1.3	0.5	0.6	2.8	2.1	1.0	1.9	3.1
T_3 (pg/ml)	1.4–4.4	–	–	–	–	–	3.5	11.0	6.4	–	5.8	–
TPO Abs (UI/ml)	< 35	496.2	7786.5	10848.7	6235.5	–	>1000	>1000	>1000	–	–	948
TRAbs (UI/l)	< 14	–	–	–	4.1	10.8	–	–	–	32.9	–	20
Levothyroxine (μg/kg per day)	–	–	0.37	0.18	–	–	0.73	0.73	0.73	0.73	0.73	0.37
Methimazole (mg/kg per day)	–	–	–	–	–	–	–	0.15	0.20	0.20	0.20	0.23

*Scintigraphic findings of homogeneously increased iodine uptake, suggestive of Graves' disease.
†Serum sample where bioassay to estimate TSAbs and TBAbs biological activity was performed.

Discussion

In this clinical case, there is an alternation between hyper- and hypothyroidism associated with elevated levels of antithyroglobulin, antithyroid peroxidase and TRAbs, with ultrasonographic and scintigraphic findings compatible both with thyroiditis and Graves' disease, respectively. A hyperthyroid state was evident at the early onset in June 2012, with spontaneous remission, and after the beginning of LT_4 therapy in March 2013, to reduce goiter volume. Effectiveness of LT_4 treatment in reducing goiter volume in euthyroid children and adolescents with autoimmune thyroid disease is not clear yet, although recent data supports its use (8, 9). However, due to the possibility of LT_4 overtreatment as a cause of hyperthyroidism noticed in September 2013, LT_4 was slowly weaned off until its cessation. After a period without treatment, she unexpectedly developed hypothyroidism (in June 2014), associated with elevated levels of TRAbs. Notice also that without any medication, TSH levels decreased significantly within 3 days and that at this point scintigraphic findings were compatible with Graves' disease. LT_4 was restarted and, once again, a switch to hyperthyroidism was noted right after the beginning of LT_4 that was only reverted with the addition of methimazol. Further therapeutic adjustments were needed, due to thyroid function fluctuation over time.

This type of oscillation in thyroid function is extremely rare, especially in the pediatric age, and is only described in a few case reports in literature (4, 5). Takasu & Matsushita (10) admitted that this fluctuation in thyroid function can be explained by the simultaneous presence of TSAbs and TBAbs in the sera of the patient. The balance between both antibodies determines whether a patient has hypo- or hyperthyroidism (10). McLachlan & Rapoport (5) advocate that a number of mechanisms may be behind the pendulum swinging from TBAbs and TSAbs: i) treatment with LT_4; ii) treatment with antithyroid drugs and iii) inherent properties of TSAbs and TBAbs. In some patients, LT_4 therapy may be associated with an increase in autoantibody responses due to the effect of LT_4 in innate and adaptive immune responses (5). This may explain the reason why our patient developed hyperthyroidism in a short period after she was started on LT_4. On the other hand, treatment with antithyroid drugs, in particular methimazole, may lead to a decrease in the levels of thyroid autoantibodies by a direct mechanism of inhibition of its synthesis (5). In this case, no blocking activity was detected during a hyperthyroid state, 1 year after double therapy, which may be due to the influence methimazole in immune responses and antibody

Table 2 Bioassay descriptions for measurement of TRAbs biological activity (6, 7).

Bioassays location	Biology Department of the Hospices Civils de Lyon Sud University Hospital
Procedure	The CHO cells (strain JP-26) are transfected with the recombinant human TSH receptor The CHO JP-26 cells are seeded into 96-well plates (50 000 cells/well), cultured in Ham's F12 medium, containing 5% calf serum, and used for TSAb and TBAb bioassays 24 h after seeding The CHO cells were exposed for 2 h to 4 ml of test serum or control serum in 196 ml with 10 mM HEPES, 0.25 mmol/l isobutylmethylxanthine, and 0.75% bovine seric albumin, pH 7.4 For the TBAb bioassay, the hypotonic medium was supplemented with bovine TSH (0.1 mIU/ml) After incubation, cAMP released from the cells was measured with a commercial RIA Kit (RIA cAMP, IMMUNOTECH, a Beckman Coulter Company, Marseille, France) according to the manufacturer's instructions Pooled TRAb-negative sera (normal sera) were used to measure cAMP basal production, pooled TSAb-positive sera were used as positive controls in TSAb assay and pooled TBAb-positive sera as positive controls in TBAb assay
TRAbs biological activity	TSAb activity was expressed as a percentage of cAMP basal production TSAb activities ranging from: 140–200% were considered as weak 200–400% were considered as moderate $\geq$400% were considered as strong TBAb activity was calculated and expressed as follows: 1 – (*a*/*b*)$\times$100, where: (*a*) is the cAMP generated in the presence of the patient's sample and bovine TSH (*b*) is the cAMP generated in the presence of normal sera and bovine TSH TBAb activities ranging from: 10–20% were considered as weak 20–40% were considered as moderate $\geq$40% were considered as strong The assays were run in triplicate, and results are expressed as the mean of the three data
Variability between assays	TSAb activity: 8.6% TBA activity: 7.1%

production, leading to a decrease of TBAbs to undetectable levels. Another important mechanism that might be involved is the TSAbs' and TRAbs' affinities for the TSH receptor. Clinical status of a patient in a particular point of time may reflect not only the concentration of both antibodies, but also their different affinities for the receptor, and the antibodies with higher concentrations and affinity will dictate the clinical presentation (5).

The bioassays to determine biological activity of TSAbs and TBAbs may be very useful to clarify specific situations, when clinical manifestations suggest the presence of TBAbs. However, once they are not widely available, and there are various mechanisms that may influence TBAbs and TSAbs biologic activity over time, their clinical utility may be limited in situations of alternating thyroid function. McLachlan & Rapoport (5) emphasize that therapeutic decisions should be taken according to clinical manifestations and thyroid function tests, independent of the bioassays results.

The management of this condition is challenging, and three therapeutic options could be considered: I-131 ablation, thyroidectomy or pharmacological treatment (single or double therapy). This last option requires frequent thyroid function monitoring to titrate drugs. Mathew & Moore (4) reported two similar cases, in a 5- and an 8-year-old girl in whom an appropriate single drug regimen failed to control thyroid function. In both cases, and considering their age, patients underwent a total thyroidectomy (4). In this case, double therapy briefly controlled thyroid function, with frequent dose adjustment needed. Definitive treatment with I-131 is being considered as a suitable option for our patient to avoid the switches in thyroid function.

Another unexpected fact in this clinical case is the scintigraphic findings of a homogeneously increased iodine uptake, suggesting Graves' disease, during a hypothyroidism state (in June 2014). There are no data in literature about scintigraphic findings in patients with an oscillation of thyroid function. One possible explanation is that the scintigraphy was done in a transition phase between hypo- and hyper-thyroidism, once TSH decreased significantly within 3 days and TRAbs were elevated. This fact may lead to an overstimulation of the thyroid that could be responsible for the homogeneously increased iodine uptake in scintigraphy. Further studies are needed to confirm this hypothesis and to better understand this phenomenon.

Conclusion

Autoimmune alternating hypo- and hyper-thyroidism is a highly uncommon challenging condition, particularly in

the pediatric age, and is due to the simultaneous presence of both TSAbs and TBAbs. The clinical status of the patient may reflect the balance between these autoantibodies and can be influenced by their concentration, affinities and therapeutic interventions (LT_4 and antithyroid drugs). The bioassays that determine biological activity of TSAbs and TBAbs may be useful; however, their clinical utility is limited in situations of alternating thyroid function. Therapeutic decisions should be taken according to clinical manifestations and thyroid function tests, independent of the bioassays results. Adding an antithyroid drug to LT_4 treatment might be necessary to achieve better thyroid function control. A definitive treatment should be considered due to the frequent switches in thyroid function and the need for close monitoring of pharmacological treatment.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
A written informed consent was obtained from the patients' guardians for publication of the submitted article.

Author contribution statement
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