Graves' hyperthyroidism following primary hypothyroidism due to Hashimoto's thyroiditis in a case of thyroid hemiagenesis

Marek Ruchała, Ewelina Szczepanek, Agnieszka Skiba, Rafał Czepczyński and Jerzy Sowiński

1. Department of Endocrinology, Metabolism and Internal Medicine, University of Medical Sciences, Poznań, Poland

Correspondence to: Marek Ruchała, ul. Przybyszewskiego 49, 60-355 Poznań, Poland.
TEL. +48 61 869 15 93, FAX +48 61 869 16 82, MOB. +48 601 748 905
E-MAIL: mruchala@ump.edu.pl

Submitted: 2008-01-20 Accepted: 2008-01-27 Published online: 2008-02-22

Key words: **thyroid dysgenesis; Graves disease; Hashimoto thyroiditis; thyroid-stimulating immunoglobulins; autoantibodies**

Neuroendocrinol Lett 2008; **29**(1):55–58 **PMID:** 18283259 NEL290108C01

Abstract

Thyroid hemiagenesis (TH) is a rare inborn anomaly, resulting from failure of one thyroid lobe development. It is usually detected incidentally during investigation of concomitant thyroid disorders.

The reported patient first presented hypothyroidism at the age of 49, when Hashimoto's thyroiditis (HT) and left thyroid lobe agenesis was diagnosed. L-thyroxine (LT_4) replacement therapy restored hormonal balance. Two years later, the patient developed features of Graves' hyperthyroidism. The antithyroid pharmacotherapy by thiamazole was used. However, due to severe side-effects it was discontinued, and radioiodine treatment was applied. Four months after ^{131}I administration, symptoms of hypothyroidism appeared, so thyroid hormone substitution was re-introduced. The patient, whose observation period has now reached 5 years, under LT_4 replacement therapy, remains both clinically and biochemically euthyroid.

The described case displays a very rare coincidence of hypothyroidism due to HT converted into Graves' hyperthyroidism, accompanying TH. Each of these three entities, may influence the thyroid function in a different way, hence, systematic follow-up and individual therapeutic management is required.

Abbreviations:

AITD	– autoimmune thyroid disease
anti-Tg	– anti-thyroglobulin antibodies
anti-TPO	– anti-thyroid peroxidase antibodies
FT_4	– free thyroxine
GD	– Graves' disease
HT	– Hashimoto's thyroiditis
^{131}I	– radioiodine
LT_4	– levothyroxine
RIA	– radioimmunoassay
TBII	– thyrotropin binding inhibitory immunoglobulins
TH	– thyroid hemiagenesis
TRAb	– thyrotropin receptor antibodies
TSH	– thyroid-stimulating hormone
TSI	– thyroid stimulating immunoglobulins

INTRODUCTION

Thyroid hemiagenesis (TH) is a rare inborn anomaly occurring if one of the thyroid lobes fails to develop. The underlying cause of this defect is a disturbance in the descent or lateral migration of cells from the distal part of the thyroglossal duct during an early phase of embryogenesis. The incidence of TH is estimated at about 0,05% of population, with women predominance [8,12]. The anomaly was first described by Handfield-Jones in 1866 [12]. Since then, about 300 cases have been reported in

CASE REPORT

the literature. Though a number of pathologies developing in a single thyroid lobe were described, Hashimoto's thyroiditis (HT) is relatively seldom seen among patients with TH [6,10,17]. It has also been observed, that a low percentage of patients with primary hypothyroidism, caused by chronic lymphocytic thyroiditis, eventually develop hyperthyroidism due to Graves' disease (GD) [18,19], but the similar sequence of events in a patient with TH is an extreme rarity.

The subject of this report is a patient with TH, who initially exhibited hypothyroidism due to HT and subsequently developed Graves' hyperthyroidism. To our knowledge, it is a second case of such conversion, coupled with TH, described in the literature. However, unlike previously reported one [1], our patient had a left-sided thyroid agenesis and GD treated with radioiodine.

CASE REPORT:

A 49-year-old woman was referred to The Department of Endocrinology with suspicion of hypothyroidism. At admission, the patient complained of weight gain, sleepiness and general malaise. There was no past or family history of thyroid disease. On palpation, the right thyroid lobe was firm in consistency, while the left lobe was not palpable. The rest of physical examination did not reveal any abnormalities. The results of laboratory tests were as follows: TSH: 4.32 μIU/ml [normal: 0.27–4.2], anti-TPO: >3000 IU/ml [normal: <60], anti-Tg: 258 IU/ml [normal: <60] and TRAb: 0.01 IU/l [normal: <1.5]. The thyroid autoantibodies concentration were detected with anti-TPO, anti-Tg and TRAK RIA Kit, by B.R.A.M.H.S, Berlin, Germany. The technetium thyroid scintigraphy revealed homogeneous radiotracer distribution exclusively in the right lobe and isthmus, but no uptake on the left side (Figure 1). Ultrasonography disclosed the right thyroid lobe (21×19×41 mm, thyroid volume V=8.6 ml) with heterogeneous, markedly decreased echogenity, an isoechogenic isthmus (8mm) and confirmed the left lobe agenesis. Hence, subclinical hypothyroidism due to HT was diagnosed. In the presence of clinical symptoms and laboratory tests results, the decision to introduce hormonal therapy was made. The patient received a 25 μg dose of L-thyroxine (LT_4), gradually increased up to 75 μg/day, what resulted in improvement of the patient's clinical state. Throughout a two-year course of treatment, the following TSH levels were observed: 2.5 μIU/ml; 0.76 μIU/ml; 1.0 μIU/ml.

Two years later, first clinical symptoms suggesting hyperthyroidism such as anxiety, heat intolerance and palpitations, appeared. Laboratory tests revealed a significantly decreased concentration of TSH: 0.01 μIU/ml, while the level of anti-TPO still remained above 3000 IU/ml. That was the reason for LT_4 dosage reduction, however, TSH level still remained undetectable. Therefore, LT_4 administration was discontinued, and treatment with propranolol was started (3×20 mg/day). Despite therapy, the clinical symptoms of thyrotoxicosis persisted and a further increase in free thyroxine (FT_4) level, as well as total thyrotropin suppression were observed; therefore, the level of thyrotropin receptor antibody was measured (TRAb: 2.89 IU/l). On the basis of these findings, GD was diagnosed, however no signs of orbitopathy were noted. The antithyroid treatment with thiamazole was started (3×20 mg/day), yet, it had to be discontinued after a four-week period, due to severe allergic reaction in the form of nettle-rash and granulocytopenia (granulocytes: 0.43 G/l; normal: 1.8–7.7). The ultrasound examination demonstrated heterogeneous, extremely decreased echogenity of the right thyroid lobe (26×24×52 mm, V=17 ml). The radioiodine uptake was 24% after 5 h and 33 % after 24 h. In the presence of persistent clinical symptoms of hyperthyroidism and increasing level of thyrotropin receptor antibodies (TRAb: 4.32 IU/l), the patient was subjected to radioiodine treatment. The patient received a 5 mCi dose of ^{131}I. Six weeks after isotope administration, clinical symptoms regressed and the patient was found to be in remission, with the level of TSH: 0.76 μIU/l, FT_4: 10.0 pmol/l (normal: 11.5–21.0) and lower titer of TRAb: 2.45 IU/l.

Four months later, a considerable increase in the TSH level up to 30.4 μIU/ml, accompanied by clinical features of hypothyroidism, was observed. Thus, the replacement therapy with LT_4 was reintroduced, starting with a 25 μg dose, gradually augmented to 75 μg/day. After three months of treatment, hormonal balance was achieved (TSH: 0.797 μIU/ml, FT_4: 23.05 pmol/l). The check-up examination performed 18 months after radioiodine therapy revealed markedly reduced thyroid volume (2.2 ml) and a gradual decrease in the titer of TRAb: 1.67 IU/l, in comparison with pre-treatment examination.

The patient, whose observation period has now reached five years, continues to be followed-up in the outpatient clinic and on a current replacement dose of LT_4 (125 μg/day) remains both clinically and biochemically euthyroid.

DISCUSSION

The incidence of TH presented in the literature is highly variable, and ranges from 1/20 to 1/9073, depending on the population studied [12]. However, the true occurrence of this defect is difficult to evaluate, and, due to a mostly asymptomatic course, probably underestimated. This anomaly is usually detected accidentally, during the investigation of concomitant abnormalities of the thyroid function or structure. Hence, the prevalence of women with TH, reported in the literature, might be a result of better detectability due to a higher frequency of thyroid diseases in the female sex.

Agenesis, as in the case of our patient, in majority (68–80%) concerns the left thyroid lobe [2,14]. In ap-

proximately half of cases, the isthmus is present with a characteristic scintigraphic appearance (Figure 1), resembling the shape of a hockey stick [11].

Hormonal production of a single thyroid lobe is usually sufficient to maintain euthyroidism. Thus, the thyroid function is disturbed only when some other thyroid disease is superimposed. The most frequently described pathology, concomitant with TH, is Graves' hyperthyroidism [13]. However, HT, is relatively uncommon among patients with an unilateral thyroid agenesis and only few cases have been described so far [6,10,17]. In the majority of cases, it proceeds with hypothyroidism, although some patients might develop symptoms of transient thyrotoxicosis, especially in the initial phase of the disease as a result of excess hormone release from damaged thyroid tissue. Exceptionally, as in the described case, hyperthyroidism in the course of HT, is a result of thyroid stimulation with TRAb, due to GD development [18,19].

HT and GD are extreme cases of a complex disorder, named autoimmune thyroid disease (AITD) [9,20]. The hypothesis concerning a similar etiopathogenesis of those two, is supported by the fact of alternating occurrence in families [9]. There are also several genes identified, partially common for both these diseases, which together with external factors are responsible for an immune reaction targeted at thyroid autoantigens [20]. Hence, cases of coexistence or progression from one form of AITD into another within an individual are possible, though not very frequent. Moreover, the observed clinical expression and severity of symptoms, is a result of several kinds of not only strictly thyroid-related autoantibodies action and individual variation of responsiveness towards, on the other hand [16].

The following factors are thought to be responsible for the conversion from hypothyroidism to hyperthyroidism in AITD: 1) emergence or increase in stimulating-type TRAb titer 2) disappearance or decrease in blocking-type TRAb titer or 3) recovery from transient hypothyroidism concomitant with hyperthyroidism [21]. In the reported case, the first mechanism is the most probable.

In the study, the titer of thyrotropin binding inhibitory immunoglobulins (TBII) was determined by a commercially available method, which, as the research show, significantly correlates with the concentration of thyroid stimulating immunoglobulins (TSI) [5]. Hence, measurement of TBII in a credible way reflects the degree of thyroid stimulation with TRAb, presenting stimulating activity. It was compatible with a proportional increase of TBII along with intensification of clinical symptoms of hyperthyroidism, and its decrease after treatment, which was observed in our case and previously reported by Bando et al. (1999). In the previous report, the patient exhibited slightly elevated TSI and TBII levels during the hypothyroid state [1]. Though, in our case, TRAb became positive only with the emergence of symptoms of hyperthyroidism, but were negative in the initial hypothyroid phase. However, our patient as well as the formerly reported one [1], showed high titration of anti-TPO persisting throughout the whole observation period.

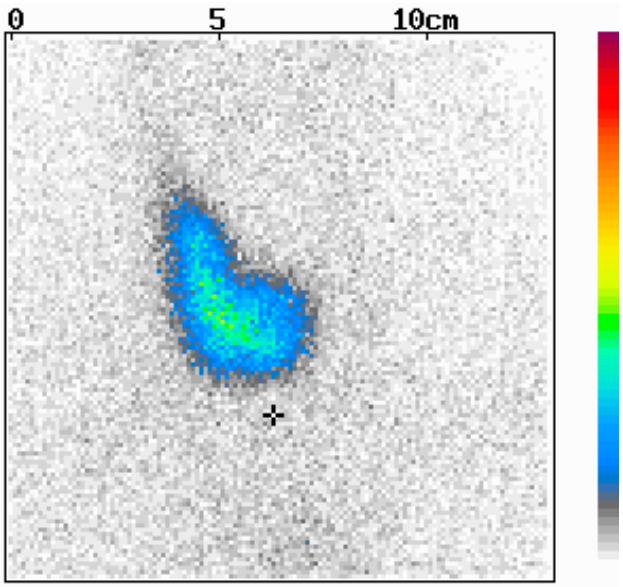

Fig. 1. A Tc-99m thyroid scintiscan showing radiotracer uptake exclusively in the right lobe and isthmus.

There are numerous reports suggesting a genetic contribution towards developmental anomalies as well as autoimmunological and other functional disorders, concerning thyroid gland [7,9,15,20]. However, despite presence of three phenomena, all of which hereditary, at least partially, our patient did not report any other family member with thyroid problems. Nevertheless, there are also studies indicating, that genetic background is not the only one, which determines the final phenotype, suggesting significant participation of epigenetic or environmental factors [4,9].

The occurrence of severe side-effects resulted in the cessation of initially applied thyreostatic pharmacotherapy with thiamazole. Following escalating symptoms of thyrotoxicosis and an increasing level of TRAb, the patient was subjected to radioisotope treatment. A small initial thyroid volume (the absence of one thyroid lobe), relatively low TRAb concentration, notably reduced in comparison with the pre-treatment thyroid volume and small residual thyroid volume after radioiodine treatment, were, in case of our patient, markers of a favorable prognosis for suppressing hyperthyroidism symptoms after a single course of radioisotope treatment, as well as risk factors for development of early hypothyroidism [3]. The administered therapy resulted in subsidence of thyrotoxicosis; however, four months after radioiodine treatment, clinical and laboratory signs of hypothyroidism were observed, simultaneous with continuously positive TRAb. This phenomenon could be explained by radioiodine-induced substantial

destruction of active thyroid tissue, serving as an effector for these antibodies [3,18]. Hormonal balance was soon achieved with LT_4 substitution. Normalization of TSH and FT_4 levels was noted, what was reflected in the improvement of the patient's clinical state. In a twenty-eight-month observation period after radioiodine therapy, no relapse of hyperthyroidism was detected, and a slow, gradual decrease in the TRAb level was observed.

The reported patient displays a very rare coincidence of hypothyroidism due to HT converted into Graves' hyperthyroidism, accompanying TH. Each of these three entities, may influence the thyroid function in a different way, hence, systematic follow-up and individual therapeutic management is required.

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