Case Report

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Pituitary Hyperplasia and Overt Hypothyroidism Induced by Methimazole in an Adolescent Girl with Resistance to Thyroid Hormone Accompanying Hashimoto's Thyroiditis: A Case Report

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Abstract

We describe a 13-year-old girl who presented at her local hospital with a diffuse goiter and had discrepant thyroid function test (TFT) of elevated free T4 (FT4), free T3 (FT3) levels with mildly elevated thyroid-stimulating hormone (TSH) and a pituitary magnetic resonance imaging (MRI) report of a pituitary hyperplasia. She was referred to our hospital where a repeat TFT found low FT4 and high TSH levels, and high levels of antithyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibodies, leading to the diagnosis of Hashimoto's thyroiditis (HT) with overt primary hypothyroidism. The girl had a good response after daily 100 μg levothyroxine treatment for 8 months with decreased goiter size along with disappearance of the pituitary mass. However, her FT4 and FT3 levels were elevated while the TSH was in the high normal range, although at this time there were no signs of hyperthyroidism. A genetic study confirmed our provisional diagnosis that the patient had a p.Pro453Thr monoallelic loss-of-function mutation of the thyroid hormone receptor beta (*THRB)* gene, suggesting the diagnosis of coexisting resistance to thyroid hormone-β (RTHβ) and HT in this patient.

Keywords: Hashimoto's thyroiditis, overt primary hypothyroidism, pituitary hyperplasia, resistance to thyroid hormone

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Introduction

Hashimoto's thyroiditis (HT) is a common cause of diffuse goiter in the pediatric and adolescent age groups[1,2]. The diagnosis of HT is based on the clinical characteristics of the presence of a goiter and circulating thyroid autoantibodies of anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibodies. The most common clinical presentation of HT is a goiter with varying thyroid functions of euthyroidism, followed by subclinical hypothyroidism, overt hypothyroidism, and transient hyperthyroidism, known as Hashitoxicosis[1,2].

Resistance to thyroid hormone-β (RTHβ) was first described in 1967 by Refetoff et al. in patients who had elevated serum free thyroxine (FT4) and free triiodothyronine (FT3) with non-suppressed thyroid-stimulating hormone (TSH). Since then, over 1000 cases have been identified with over 100 mutations of the thyroid hormone receptor beta (*THRB)* gene encoding thyroid hormone receptor β (TRβ) reported[3,4]. Most patients have no clinical symptoms while some have goiter and mild symptoms of hyperthyroidism. HT coexisting with RTHβ has rarely been reported and can complicate the diagnosis and treatment[5,6].

We herein report an interesting case of a 13-year-old girl referred to our tertiary hospital for evaluation of an enlarged pituitary gland suspected to be a pituitary adenoma which was later confirmed to be pituitary hyperplasia (PH) from overt hypothyroidism due to Hashimoto's thyroiditis. Persistently elevated levels of FT4 and FT3 with normal TSH after an average dosage of levothyroxine treatment suggested a coexisting RTHβ, later confirmed by the finding of a genetic mutation of the *THRB* gene.

Case report

A 13-year-old girl, who had been raised in an orphanage since the age of 4, presented at a local hospital with a goiter which she had first noticed about 3 months earlier. She had no clinical symptoms related to thyroid or pituitary disorders. She had entered puberty at the average age of Thai girls (thelarche at 10, menarche at 12 years old). A thyroid function test (TFT) at the initial visit to the local hospital showed an FT3 level of 5.76 pg/mL (normal 2.0-4.4), an FT4 level of 2.15 ng/dL (normal 0.90-1.60), and a TSH level of 13.48 mU/L (normal 0.50-4.30). She was initially diagnosed with Graves' disease and was treated with methimazole (MMI) 20 mg/day. After 6 weeks of MMI treatment, the goiter had not decreased in size, but increased, without any clinical symptoms of hyper- or hypothyroidism. At 8 weeks of MMI treatment, her FT3, FT4 and TSH levels further increased to 6.40 pg/mL, 1.96 ng/dL and 30.4 mU/L, respectively, and the MMI was increased to 30 mg/day. After 12 weeks of MMI treatment, her TSH remained high (53.4 mU/L), along with the elevated FT3 (5.27 pg/mL) and FT4 (1.32 ng/dL) levels, and TSHoma was suspected. A pituitary magnetic resonance imaging (MRI) revealed a 9.6x5.1 mm enlarged pituitary gland with mild deviation of the pituitary stalk (Figure 1). The girl was then referred to Songklanagarind Hospital, a tertiary care center and medical school in southern Thailand.

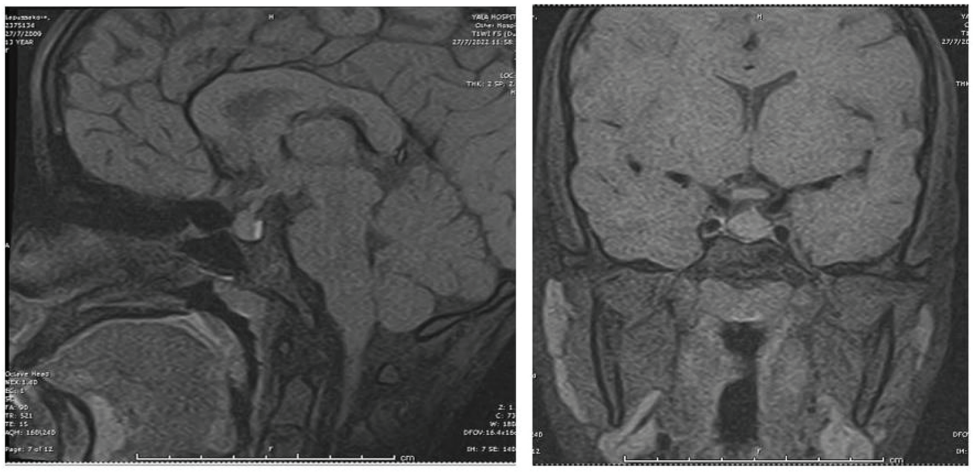
A physical examination at Songklanagarind Hospital found a pulse rate of 76/minute and blood pressure of 92/56 mmHg. Her weight was 44 kg (25^{th}-50^{th} percentile), and her height was 153 cm (25^{th}-50^{th} percentile). She had no puffy face or dry skin. A neck examination found a visibly enlarged diffuse thyroid gland of 9x3 cm without nodules. A neurological examination was unremarkable, including no visual field defects. Her breasts were Tanner stage IV and pubic hair of Tanner III. The TFT, after she had been taking MMI 30 mg/day for 3 months from the local hospital, found serum FT3 of 3.54 pg/mL, FT4 0.53 ng/dL and TSH >100 mU/L. The thyroid autoantibodies were elevated with serum anti-TPO of 165 IU/mL (normal <26) and anti-TG 205 IU/mL (normal<64), and a low level of TSH-receptor antibody (TRAb) at 0.98 IU/L (normal <1.75). Serum prolactin (PRL) was low at 8.81 ng/mL (normal 5-23). Hashimoto's

thyroiditis with overt primary hypothyroidism was diagnosed. Therefore, the MMI treatment was discontinued and she was put on a low dosage of levothyroxine at 50 μg/day for 4 weeks and later increased to an average dosage of 100 μg/day.

After 4 months of the levothyroxine treatment, the thyroid gland gradually reduced in size to 5x1.5 cm. The serum TSH declined to 3.09 mU/L while FT4 remained elevated at 3.46 ng/dL. At 8 months, she had weight gain to 48 kg and her height increased to 155 cm. She had a normal pulse rate of 80/min and BP 100/66 mmHg. A brain MRI at this time showed the disappearance of the pituitary mass, but a TFT showed persistently elevated FT4 at 3.27 ng/dL and TSH at 1.04 mU/L. As the FT4 was persistently elevated while the TSH had returned to a normal level, with the regression of PH after the levothyroxine treatment, RTHβ accompanying Hashimoto's thyroiditis was suspected. After obtaining informed consent, exons 7–10 of the *THRB* gene were sequenced according to previously described protocol[7,8]. A monoallelic missense mutation at codon 453, which resulted in a substitution from proline to threonine (c.1357C>A, p.Pro453Thr), was found (Figure 2), thus confirming the diagnosis of RTHβ in this patient. This mutation has been previously described in RTHβ patients[9].

Discussion

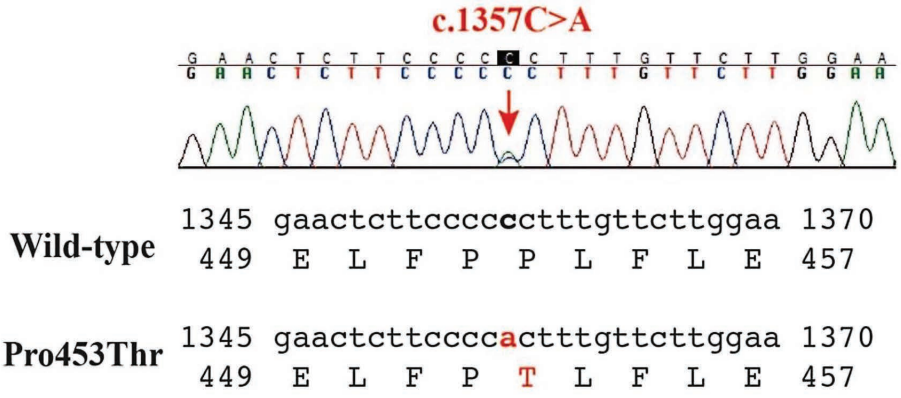
At the first visit to our hospital, the girl had a large goiter, low FT4, and markedly high TSH levels with positive thyroid autoantibodies, compatible with HT with overt primary hypothyroidism. At that time, the elevated FT4, FT3 and TSH levels previously found at the local hospital were thought to be from the transition of Hashitoxicosis to the hypothyroid stage of HT. The pituitary enlargement could be simply explained by thyrotroph hyperplasia from the loss of inhibitory feedback of the hypothalamic–pituitary–thyroid (HPT) axis due to very low FT4 and FT3 levels caused by both the HT and the MMI treatment. The other most likely cause of elevated FT4 and FT3 with elevated TSH was



A B

MRI=magnetic resonance imaging

Figure 1 Pituitary MRI contrast-enhanced fat-suppressed T1-weighted imaging revealed a 9.6x5.1 mm pituitary gland hyperplasia with mild deviation of the pituitary stalk
(A) coronal view, (B) sagittal view



THRB=thyroid hormone receptor beta

Figure 2 Direct sequencing of exon 10 of the *THRB* gene in the patient revealed a heterozygous missense mutation (c.1357C>A), leading to a substitution of proline to threonine at codon 453 (p.Pro453Thr)

a TSH-secreting pituitary adenoma (TSHoma); however, with a TSHoma the patient normally has obvious clinical symptoms and signs of hyperthyroidism that are very difficult to control by antithyroid drugs[10]. Hence, TSHoma was unlikely in this patient due to the absence of clinical symptoms or signs of hyperthyroidism. The regression of PH after MMI cessation and levothyroxine treatment supported the provisional diagnosis that the enlarged pituitary was from thyrotroph hyperplasia rather than TSHoma. The euthyroid symptoms of our patient with persistently elevated FT4 levels and non-suppressed TSH levels during the standard dose of levothyroxine treatment led us to consider RTHβ. A genetic study revealed a p.Pro453Thr mutation of the *THRB* gene, confirming the diagnosis of RTHβ in this patient. This mutation has previously been identified in RTHβ patients. Previous in vitro studies have confirmed the reduced sensitivity to thyroid hormones of this mutation[7-9].

HT is a common thyroid disorder in the pediatric and adolescent age groups. The most common clinical presentation of HT is a goiter with various thyroid functions at the time of diagnosis, i.e. euthyroidism (57-64% of cases), subclinical hypothyroidism (15-33%), overt hypothyroidism (8-22%), and transient hyperthyroidism (2%)[1,2]. Although one study reported that most HT patients were in a euthyroid state at the time of initial diagnosis, some had fluctuations of thyroid function over time between euthyroidism and subclinical hypothyroidism with a tendency towards thyroid failure and overt hypothyroidism[1]. Fluctuations of thyroid function between hyper- and hypothyroidism in a young HT patient was reported in one study[11]. In addition, Sapkota et al. reported that the enlarged pituitary glands found in overt primary hypothyroidism HT patients were usually more than 10 mm in size as a result of a loss of hypothalamic feedback inhibition, thus leading to compensatory increases in thyrotropin-releasing hormone (TRH) as the stimulatory effect on pituitary thyrotrophs in the anterior pituitary gland and consequent PH[12].

Patients with RTHβ may be misdiagnosed with other forms of hyperthyroidism, including Graves' disease, TSHoma, or Hashitoxicosis because of the elevated serum FT4 and FT3 levels[13,14]. The coexistence of RTHβ with other thyroid disorders, such as Hashimoto's thyroiditis, Graves' disease, and thyroid carcinoma, has been reported[13-15]. Pituitary hyperplasia has also been reported in an RTHβ

adult patient which spontaneously resolved over time[16]. A study by Barkoff et al in 330 individuals from 130 RTHβ families found that individuals affected with RTHβ had an increased likelihood of autoimmune thyroid disease (AITD) compared to unaffected relatives[14]. Gavin et al. proposed a pathophysiologic mechanism suggesting that chronic stimulation of intrathyroidal lymphocytes by persistent elevation of TSH or thyroid hormones in RTHβ might lead to pro-inflammatory cytokine production and thyrocyte destruction[15]. The exact cause of the coexistence of RTHβ with AITD and/or pituitary hyperplasia is still unknown and needs further study.

In our patient, after a retrospective review of the thyroid functions before the MMI treatment, we postulated that she could have had the RTHβ before developing the HT. With the MMI treatment, thyroid hormone synthesis was inhibited, leading to low FT4 levels and inducing overt hypothyroidism with high TSH levels of over 100 mU/L and pituitary enlargement from thyrotroph hyperplasia. The decrease in pituitary size after the levothyroxine treatment supported the postulation that the PH was most likely caused by overt hypothyroidism rather than a TSHoma. Given the orphan status of the patient, we could not obtain DNA from her parents to confirm whether the RTHβ mutation was *de novo* or inherited from one of her parents.

Conclusion

In conclusion, we have added a case of coexisting RTHβ and HT with reactive PH from overt primary hypothyroidism to the literature, and highlighted the distinguishing characteristics between reactive PH and TSHoma. In such cases, carefully monitoring the patient's symptoms, following biochemical and radiological studies, and doing further genetic testing can provide a definite diagnosis and eliminate unnecessary pituitary surgery.

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