A Perplexing Case of a DUOX2 Mutation and Graves' Disease

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Abstract: It is commonly accepted that DUOX2 mutations may cause congenital hypothyroidism and thyrotropin resistance, thus its combination with Graves' disease would be unusual. In this case, our patient's serum thyroid function tests suggested a high probability of thyroid hormone resistance syndrome, but genetic testing did not suggest gene mutations of THRα or THRβ. This is a rare case report of thyroid hormone resistance.

Keywords: Graves' Disease; DUOX2 Mutations; Thyroid Hormone Resistance Syndrome

Introduction

The effects of the thyroid hormone are mediated by thyroid hormone receptors (TRs). There are two different subtypes of TR, TRα, and TRβ. Therefore, the syndrome of resistance to thyroid hormone (RTH), which is characterized by the reduced response to thyroid hormone in various tissues, should include RTH due to TRα mutation (RTHα) in addition to RTH due to TRβ mutation (RTHβ).

In this case, the patient's thyroid function level suggested a high probability of thyroid hormone resistance syndrome, but genetic testing did not suggest mutations in the THRα or THRβ genes. Interestingly, however, in previous studies, it was found that (1) the probability of patients with thyroid hormone resistance syndrome without THRα or THRβ gene mutations is about 15%, and (2) DUOX2 gene mutations are often likely to be nonsense mutations. Combining the above 2 points, we suspect that the mutation in this patient may be a nonsense mutation, and this patient belongs to the 15% non-mutation scenario.

Case report

In May 2009, a 15-year-old young woman presented to a local hospital with neck swelling, heat intolerance, sweating, excessive hunger, panic, and hand tremors with no apparent cause. Based on serum thyroid function testing, she was diagnosed with Graves' disease and treated with anti-thyroid drug therapy. However, her thyroid function remained uncontrolled, thus she was treated with three repeated doses of 131I (doses unknown) in January 2013, June 2013, and October 2014. The patient's hyperthyroidism recurred within six months after the first two 131I doses, then she became hypothyroid after completion of the third 131I dose.

The patient's father had a history of mild asymptomatic hyperthyroidism that was not treated with any medication.The patient then showed unexplained changes in her serum thyroid function tests starting in January 2016. Serum free triiodothyronine (FT3) and free thyroxine (FT4) values were both elevated when the serum thyrotropin (TSH) was normal; yet when the FT3 and FT4 levels were low, the TSH levels could be extremely high.

In August 2020, repeat serum thyroid function tests showed: FT3 4.26 pmol/L (reference, 3.1-6.8 pmol/L) , FT4 27.87 pmol/L (reference, 12-22 pmol/L) , TSH 23.38 μIU/ml (reference, 0.27-4.20 μIU/ml) , thyroglobulin antibody 137 IU/ml (reference, 0-115IU/ml) , thyroid peroxidase antibody 132 IU/ml (reference, 0-34IU/ml). She was confirmed to have a third pregnancy. She was depressed, weak, and dizzy, had a foreign body sensation in the neck, and reported paroxysmal pain in the abdomen. There was no heat intolerance, blurred vision, recent memory loss, weight loss, nor abnormal bowel movements. Physical examination revealed a normal-sized thyroid gland that was mobile and non-tender.

Considering that the patient's thyroid function abnormalities were difficult to explain, the patient and her immediate family were advised to have a thorough evaluation to include genetic testing. The patient's father remained asymptomatic and had no signs of hyperthyroidism. Her mother and brother had no abnormalities in their serum thyroid function tests.

Genetic testing suggested that the patient had a heterozygous mutation in the DUOX2 gene (c.127A>T), resulting in a pathogenic mutation (p.N43Y). Treatment was begun with levothyroxine (Eugenol) 175 μg once daily and hydrocortisone 10 mg once daily. She was also begun on calcium and vitamin D supplementation, progesterone, and dydrogesterone fetal preservation therapy. On this therapy, the patient was able to deliver a baby boy, who had a mildly elevated serum TSH on a heelstick blood screen and for which further follow-up will be needed.

Discussion

In this case, the patient had a foreign body sensation in the neck as the main clinical manifestation, and no enlargement of the thyroid gland was seen on physical examination, and the patient was treated with "hyperthyroidism" at the local hospital. However, from January 2016, all hospital tests of thyroid function suggested some kind of resistance relationship between TSH levels and FT3 and FT4, which was inconsistent with the common clinical regression of hyperthyroidism. The patient's father had mildly elevated serum FT3 and FT4, but had been in good health since childhood without any discomfort. Combining the patient's medical history, treatment history and family history, it was highly suggested that the patient had a combination of thyroid hormone resistance syndrome, so full gene sequencing was performed, which revealed that both the patient and his father had DUOX2 gene mutation.

This case reports a female patient who suffered from chronic thyroid function abnormalities. The following 3 points should be focused on in this case: (1) Cases of Graves Disease and resistance of thyroid hormone have been reported, but cases of Graves Disease and resistance of thyroid hormone combined with DUOX2 mutation has not been reported; (2) Most resistance of thyroid hormone has a genetic mutation, but there is a small percentage without a mutation; (3) Most reported DUOX2 mutations are associated with hypothyroidism, but whether DUOX2 is significant in this case needs to be further explored.

Our patient developed unexplained changes in thyroid function and was considered to be resistant for thyroid hormones after being hospitalized in our hospital. Further thyroid-related genetic testing did not reveal mutations in THRα and THRβ. The combination of Graves Disease, thyroid hormone resistance and DUOX2 mutation was thus considered, which has not been reported in the previous literature.

The earliest record of RTH, also known as syndrome of inappropriate TSH secretion (SITSH), was reported by Refetoff [1] et al. in an RTH genetic family presenting with elevated thyroid hormone with thyrotropin levels. Germline mutations in the TRβ gene were first identified in a patient with RTH in 1989 [2]. TRα mutations were first reported in 2012 [3] , and TRα mutations are not present in SITSH. In addition, mutations in TRβ and TRα are not found in some SITSH patients [4] , and these patients are in about 10-15% of RTH [5].

In 2010, Japanese scholar Sato[6] reported a case of hyperthyroidism combined with thyroid hormone resistance. Sato's case report suggests that Graves' disease combined with thyroid hormone resistance syndrome can be completely remitted by methimazole treatment, but there is no standardized control goal, which should be combined with clinical manifestations and

thyroid function levels, maintaining thyroid function at slightly high levels of FT4 and FT3 and normal or slightly high levels of TSH, and avoiding drug overdose as much as possible. If a patient with Graves' disease has normalized FT4 and FT3 after drug treatment but is hypothyroid, this is highly suggestive of a combination of thyroid hormone resistance syndrome.

The thyroid hormone resistance syndrome combined with Graves' hyperthyroidism has been rarely reported, with only 6 cases reported worldwide. There is no unified treatment guideline, and pharmacological treatment is the first choice. Hyperthyroidism can be well controlled, but the control goal should be combined with the patient's clinical performance and thyroid function level.

At present, it is believed that simple thyroid hormone resistance is not suitable for treatment with antithyroid drugs, surgery or radioactive iodine, because lowering the circulating level of thyroid hormone will weaken the negative feedback inhibitory effect of thyroid hormone on the secretion of pituitary TSH cells, resulting in further increase in serum TSH concentration, TSH cell hyperplasia, and even the development of pituitary tumors. However, it is interesting to note that a small number of thyroid hormone resistance syndromes do not have genetic mutations and the molecular mechanisms need to be further investigated.

Another aspect, Congenital primary hypothyroidism (CH) is a state of inadequate thyroid hormone production detected at birth, caused either by absent, underdeveloped or ectopic thyroid gland (dysgenesis), or by defected thyroid hormone biosynthesis (dyshormonogenesis)[7]. The gene DUOX2 or THOX2 encodes the human protein dual oxidase 2 (DUOX2), a member of the NADPH oxidase family. Hydrogen peroxide (H2O2) is essential for thyroperoxidase-mediated thyroid hormone synthesis in the follicular lumen of the thyroid gland. DUOX2 and its maturation factor and essential partner, DUOXA2, play a crucial role in H2O2 generation, necessary for the biological activation of TPO[8]. Previous studies have mostly reported on DUOX2 gene mutations causing hypothyroidism, but in this case, CH was not seen in the patient, nor was it seen in her immediate family. This situation still requires further discussion.

In this case report, the patient's father had a thyroid function presentation consistent with thyroid hormone resistance syndrome, but genetic testing suggested a DUOX2 mutation. This raises the suspicion that the DUOX2 mutation is a nonsense mutation and that in actual clinical studies there is a 15% probability that the thyroid hormone resistance syndrome does not have a mutation.

It is believed that a small proportion of thyroid hormone resistance syndromes are still free of genetic mutations, and the specific molecular mechanisms need to be further investigated.

References

[1] Refetoff S, Dewind L T, Degroot L J. Familial syndrome combining deaf-mutism, stuppled epiphyses, goiter and abnormally high PBI: possible target organ refractoriness to thyroid hormone[J]. J Clin Endocrinol Metab. 1967, 27(2): 279-294.

[2] Sakurai A, Takeda K, Ain K, et al. Generalized resistance to thyroid hormone associated with a mutation in the ligand-binding domain of the human thyroid hormone receptor beta[J]. Proc Natl Acad Sci U S A. 1989, 86(22): 8977-8981.

[3] Bochukova E, Schoenmakers N, Agostini M, et al. A mutation in the thyroid hormone receptor alpha gene[J]. N Engl J Med. 2012, 366(3): 243-249.

[4] Weiss RE, Hayashi Y, Nagaya T, et al. Dominant inheritance of resistance to thyroid hormone not linked to defects in the thyroid hormone receptor alpha or beta genes may be due to a defective cofactor[J]. J Clin Endocrinol Metab. 1996, 81(12): 4196-4203.

[5] Dumitrescu AM, Refetoff S. The syndromes of reduced sensitivity to thyroid hormone[J]. Biochim Biophys Acta. 2013, 1830(7): 3987-4003.

[6] Sato H. Clinical features of primary hyperthyroidism caused by Graves' disease admixed with resistance to thyroid hormone (P453T)[J]. Endocr J. 2010, 57(8): 687-692.

[7] Kostopoulou E, Miliordos K, Spiliotis B. Genetics of primary congenital hypothyroidism-a review[J]. Hormones (Athens). 2021, 20(2): 225-236.

[8] Carvalho DP, Dupuy C. Role of the NADPH Oxidases DUOX and NOX4 in thyroid oxidative stress[J]. Eur Thyroid J. 2013, 2(3): 160-167.