RESISTANCE TO THYROID HORMONES: A NOVEL MUTATION OF THE THYROID HORMONE RECEPTOR β GENE IN AN ALGERIAN FAMILY

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Abstract

Resistance to thyroid hormone (RTH) is an inherited disease transmitted in an autosomal dominant manner. The diagnosis is suspected when peripheral thyroid hormones are increased contrasting with normal or increased levels of thyroid stimulating hormone. Usually, people harboring the rare syndrome have few or no symptoms. However, in some patients signs of hyperthyroidism may be the revealing anomalies as in the following case: A 75 year-old woman was referred to our department for a benign adrenal incidentaloma. In her medical history she was treated for systemic hypertension and diabetes mellitus for 15 years. Clinical examination did not show any sign of adrenal secretion, but discovered rapid irregular cardiac rhythm with some hyperthyroidism features such as increased sweating and upper limbs and jaw tremor. Electrocardiogram showed atrial fibrillation. Hormonal assessment confirmed hyperthyroidism as FT4 levels were high (mean value: 30.2pmol/L (n= 9–23)), contrasting with non-suppressed TSH levels (13.8μU/mL (n = 0.2 – 4)).

Cerebral magnetic resonance imaging was normal. Genetic testing revealed a new heterozygous mutation on exon 10 in the THR β gene (c.1366T>G) compatible with RTH syndrome. Screening of her children showed the same hormonal profile in five out of ten. These results confirmed RTH and the familial character.

Key words: thyroid hormone resistance, hyperthyroidism, cardiothyreosis, new mutation.

INTRODUCTION

Resistance to thyroid hormone (RTH) or thyroid hormone resistance (THR) was reported for the first time by Refetoff *et al.* in 1967. It is a very rare inherited syndrome characterized by reduced tissues' responsiveness to thyroid hormones (1). There are 3 types of THR (2): generalized resistance (pituitary and other tissues), pituitary resistance, and selective peripheral resistance. The diagnosis and treatment vary

according to the type of resistance.

The syndrome is transmitted mainly on an autosomal dominant mode (3, 4). Its incidence is about 1/40.000 live births. Its diagnosis is based on biological assessment showing increased circulating free T4 (FT4) and/or free T3 (FT3) levels along with normal or increased levels of thyroid stimulating hormone (TSH) (3, 5). Generally, patients with THR present no or few hyperthyroidism symptoms. However in very few cases, hyperthyroidism and/or its heart complications can be the revealing symptoms (3). Our aim was to describe a patient with pituitary resistance to thyroid hormones with cardiothyreosis as a revealing symptom: a very rare condition diagnosed incidentally while exploring an adrenal incidentaloma.

CASE REPORT

A 75 year-old Algerian woman was referred to our department for a small adrenal tumor whose exploration pleaded for a non secreting incidentaloma.

In her past medical history, she was diagnosed and treated for systemic hypertension and diabetes mellitus for 15 years. She did not report any similar problems in her family. Clinical examination showed rapid and irregular cardiac rhythm (100 beats per minute) associated with hyperthyroidism features consisting in increased sweating and upper limb and jaw shakiness, but without any sign of heart insufficiency. Electrocardiogram showed atrial fibrillation (Fig. 1).

Echocardiography showed atrial enlargement (left atrial measuring 51mm) with moderate enlargement of the right ventricle. The left ventricle was normal in size with normal ejection fraction (EF) = 67%.

Hormonal assessment demonstrated hyperthyroidism profile as FT4 and FT3 levels were high. FT4 = 30.2pmol/L (N= 9–23) and FT3 = 6.68 pmol/L (N=2.63–5.70), contrasting with non-suppressed TSH levels (13.8μU/mL (N= 0.2 – 4)).

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Figure 1. Atrial fibrillation

Cerebral magnetic resonance imaging (MRI) was normal excluding a pituitary tumor secreting TSH. Screening of her children showed the same hormonal profile in five out of ten. This result confirmed the familial character. Genetic testing was done in an accredited laboratory in the department of Genetics and Biochemistry at Angers Teaching Hospital (France). Direct sequencing analysis of the full *THRβ* gene for *THRβ* mutation was performed and revealed the presence of new heterozygous mutation on the exon 10 (c.1366T>G) (Fig. 2). This nucleotide change results in the amino acid substitution of Leucine by Valine in position 456 (p.Leu456Val) which explains RTH syndrome.

Cervical ultrasound showed a multi-nodular goiter. The predominant nodule, measuring 18 x 17mm, was markedly hypo echoic. It has well defined margins and normal vascularization and was classified as TIRADS 4. On Thyroid scintigraphy all the nodules were cold as they did not show any fixation. Fine needle aspiration was not done because of anti coagulant treatment prescribed for rhythmic troubles.

Screening for bone mineral density showed severe osteoporosis as the T-score was very low: -3.2 on the lumbar spine site and -2.1 on the upper part of the left hip.

This patient was treated with beta-blockers to control tachycardia and tremor. She was given propranolol 40 mg twice a day. The result was good as these symptoms disappeared after eight weeks. Biphosphonates' treatment and follow-up by rheumatologists was also proposed for osteoporosis.

DISCUSSION

RTH is associated in the majority of cases with mutations in the thyroid hormone receptor beta

Figure 2. New mutation of thyroid hormone receptor. Presence of a new heterozygous mutation on the exon 10 (c.1366T>G). This nucleotide change results in the amino acid substitution of Leucine by Valine in position 456 (p.Leu456Val).

(*THRβ*) gene and in few cases is associated with mutations in the thyroid hormone receptor alpha (*THRα*) gene. *THRβ* and *THRα* proteins are nuclear hormone receptors for T3.

The THR low incidence may be explained by lack of systematic screening in the whole population. Inheritance of this anomaly is usually autosomal dominant, but sometimes it can be autosomal recessive.

THR is characterized by variable degrees of reduced sensitivity of different tissues to 3,5,3'-l- triiodothyronine, with persistent high levels of circulating free thyroid hormones (TH) (FT3 and FT4 levels) contrasting with non-suppressed serum TSH (3-5).

Symptoms vary according to the type of resistance. Symptoms are usually totally absent in generalized resistance to TH. These cases seem to be eu-metabolic and maintain near normal TSH levels compensated by high levels of TH. In other cases hyper metabolism's symptoms are present such as developmental delay, learning disabilities, attention deficit, hyperactivity disorder, tremor, and sweating. In rare cases sinus tachycardia or atrial fibrillation can be observed as in our case. Osteoporosis can also be present and thyroid enlargement which can develop in response to TSH secretion can be observed too (4). Thyroid enlargement may sometimes lead to upper airway compression. These categories of patients are classified as having selective, central, or pituitary resistance to TH (6, 7).

Isolated peripheral tissue resistance to TH seems to be very rare as to the best of our knowledge; it was reported only in one patient (8). Sometimes THR diagnosis is made after screening patient's relatives

having THR syndrome.

There are several mutations in THR β , Lee *et al.* reported at least 137 different THR β mutations affecting more than 40.000 people worldwide (7). In our study, screening through direct sequencing analysis revealed a novel mutation (c.1366T>G) consisting in substitution of Leucine by Valine in position 456 (p.Leu456Val). Meanwhile bioinformatic analysis indicated the pathogenic role of this variant with conservation of this amino acid between species.

To the best of our knowledge, this mutation has never been reported before in literature or in database. This Novel mutation is worth being known, however more investigations are needed to be known if it exist worldwide or is specific to Algerian population. Regarding treatment, there is currently no definite therapy to correct the molecular defect causing RTH β . On the other hand, most patients do not need any treatment as they are asymptomatic.

In the great majority of cases, high levels of circulating free TH are able to compensate the resistance of peripheral tissues when there is a general resistance, however, a thyrotoxic state may be observed in central resistance as in our patient.

In the cases of general resistance, patients are eumetabolic and the physiological state should be better respected. Therefore therapeutic manoeuvres aiming to reduce high TH levels such as thyroid ablation or anti thyroid drugs should be avoided since they aggravate the hypo metabolic state (9). In the cases of central resistance, patients are hyper metabolic, a reduction of TSH secretion and the consequent reduction of thyroid hormone levels may be benefic. So, several drugs acting at various levels can be used such as corticosteroids, dopaminergic drugs, somatostatin analogs and triiodothyronine or LT3, but with poor beneficial effects (9). Symptomatic treatment is helpful in patients with tachycardia and palpitations at rest; the use of cardio selective β -blockers (atenolol or others) is sometimes necessary. In cases of severe thyrotoxicosis not responding to β -blockers, a reduction in thyroid hormone levels may be beneficial, but this cannot be achieved using anti thyroid drugs, because consequent increase in TSH may lead to goiter enlargement (10). The treatment of choice in such cases consists in administration of thyromimetic compounds, such as 3,5,3'-triiodothyroacetic acid (TRIAC). This treatment was suggested on an empirical basis by Beck Peccoz P *et al.* TRIAC is able to block TH pituitary secretion, but does not have thyromimetic properties on peripheral tissues (11). If medical treatment is dedicated to

reduce hyper metabolism and thyrotoxicosis signs, surgical treatment or total thyroidectomy is reserved to patients presenting uncontrolled tachycardia and atrial fibrillation, and those suspicious of thyroid cancers (12). New attempts have been proposed to develop therapies based on modifications of known agonists to obtain selective ligands capable of compensating the action of the mutant receptors implicated in RTH (13). Moreover, molecular engineering may provide novel therapeutic approaches and it is possible to speculate that genetic strategies prompted to inhibit mutated THR β gene expression may be considered as a specific and individual therapy for RTH patients in the future (14). Systematic screening is recommended for the relatives and families of the affected patients due to the autosomal dominant way of transmission which is the most common way of inheritance in RTH.

The main feature of our case is that it reports a new variant of mutation in THR β gene. It is true that the region where our mutation was found is responsible for RTH β resistance but our variant of mutation is new and has never been reported before. Another important issue in our case is that the profile of symptoms is expressed as a central resistance which is rarely reported as well as that our patient showed a good response to propranolol therapy with amelioration of all major symptoms especially the disappearance of tachycardia and tremor.

In conclusion, although most patients presenting THR syndrome are usually asymptomatic, others can present thyrotoxicosis' manifestations and even cardiac complications or cardiomyopathy as in the case described. Signs of thyrotoxicosis can be explained by a peripheral sensitivity to thyroid hormones whereas the pituitary one is altered, resulting in central resistance. The variant mutation found in our patient: p. L 456 V seems to be a novel one. Further studies should be made to clarify this entity.

Conflict of interest

The authors have no conflicts of interest to declare. The informed consent of the patient was obtained.

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