East African Scholars Journal of Medical Sciences
Abbreviated Key Title: East African Scholars J Med Sci
ISSN: 2617-4421 (Print) & ISSN: 2617-7188 (Online)
Published By East African Scholars Publisher, Kenya

Volume-3 | Issue-1 | Jan-2020 | DOI: 10.36349/EASMS.2020.v03i01.02

OPEN ACCESS

Case Report

Syndrome of thyroid hormone resistance

Oukit Loubna*[1], Rafi Sana[1], El Mghari Ghizlane[1], El Ansari Nawal[1]

[1]Department of endocrinology, Mohammed VI university hospital, Marrakesh, Morocco

Article History
Received: 04.12.2019
Accepted: 11.12.2019
Published: 17.01.2020

Journal homepage:
https://www.easpublisher.com/easjms

Quick Response Code

Abstract: A disturbed thyroid check-up is a frequent reason for consultation in endocrinology. The typical situations of hypo or hyperthyroidism encountered lead to classical etiological investigations, to define whether the cause is central or peripheral. In certain unusual situations, the profile encountered may be atypical. We report the case of a 6 years old girl hospitalized for a homogeneous goiter, a tachycardia evolving for a year without thyrotoxicosis or compression. There was strong consanguinity in the family and the mother had a history of thyroidectomy. The assessment found a normal TSH with a high LT4 level, and her mother had the same hormonal profile. Neck ultrasound found a homogeneous goiter with normal vascularization and thyroid scintigraphy, a moderate goiter with very intense fixation, without nodules. Biological examinations found normal prolactin and cortisol levels. The pituitary MRI was without abnormality. The diagnosis of central hormone resistance syndrome was retained. This autosomal dominant transmission syndrome is a rare entity with poor symptomatology. It is important to think about it as a differential diagnosis of a thyreotropin-secreting pituitary adenoma when it results to an increased peripheral hormone level with a normal or elevated TSH, especially in patients with strong consanguinity. The diagnosis is made by genetic tests but it is rarely practice. The treatment is not codified. It ranges from abstention to thyroidectomy and it depends signs of thyrotoxicosis are identified.

Keywords: Goiter, Resistance to thyroid hormones, Pituitary adenoma.

INTRODUCTION

A disturbed thyroid check-up is a frequent reason for consultation in endocrinology. The typical situations of hypometabolism or thyroid hypermetabolism, encountered lead to classic etiological investigations: whether peripheral or central hypothyroidism, peripheral or central hyperthyroidism. In some unusual situations, the profile encountered may be atypical. Syndrome of resistance of thyroid hormones is an inherited disease with autosomal dominant transmission. The index cases were diagnosed in 1967 by Samuel Refetoff in an inbred family. It is, indeed, important to evoke it when an increase of peripheral thyroid hormones with an inappropriate, normal or even high, TSH level is encountered. Its pathophysiology is still poorly understood in a large number of cases. Usually, patients have poor or no symptoms, but goiter can be the reason for consultation. The aim was to shed light on this rare syndrome based on a case encountered in our practice.

OBSERVATION

We report the case of a 6 years old girl hospitalized for a goiter check-up, her parents were consanguineous at first degree, with strong consanguinity in the family, and her mother had a history of total thyroidectomy without necessity of substitution and without signs of dysthyroidism. The interrogation found good psychomotor development, hyperactivity, poor school performance and a goiter progressing for a year without signs of thyrotoxicosis or compression and no hearing loss. On examination, a grade 3, soft, homogeneous goiter (Fig1), without thrill was found, a tachycardia at 111 bpm, a weight at 16kg, in the average and a slight stature advance.

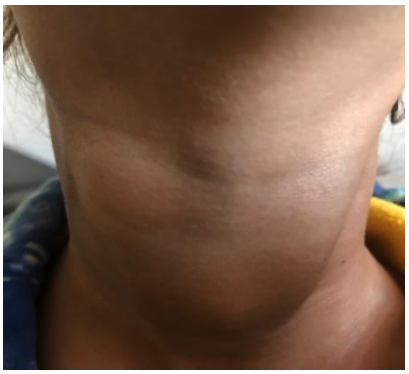

Figure 1: Goiter grade 3, soft, homogeneous

***Corresponding Author:** Oukit Loubna Email: loubna.ok [at]gmail.com

The biological assessment found a normal TSH with an elevated LT4 rate four times, with ascending values on the different samples (Table 1).

Table1: Evolution of TSH, T4 and T3 values during hospitalization

	TSH (mU/l)	T4 (pmol/l)	T3 (pmol/l)
(J-7from hospitalization)	0,63	29,32	
(J1 hospitalization)	1,88	55,2	17,5
(J2 hospitalization)	2,92	58	
(J9 hospitalization)		56,2 (taking 10mg carbimazol)	17,7

Neck ultrasound suggested a homogeneous goiter and normal vascular evaluation on Doppler.

Lipid balance was normal, hormonal pituitary exploration found a normal prolactin level at 3.19 ng / ml, a cortisol at 16.91 µg / dl. His bone age matched chronological age. The ophthalmologic examination found no exophthalmos and papillas were normal (no edema). The thyroid scintigraphy noted a moderate goiter and very intense fixation (rate of fixation at 185%), without individualizable nodule. A pituitary MRI did not reveal any abnormality.

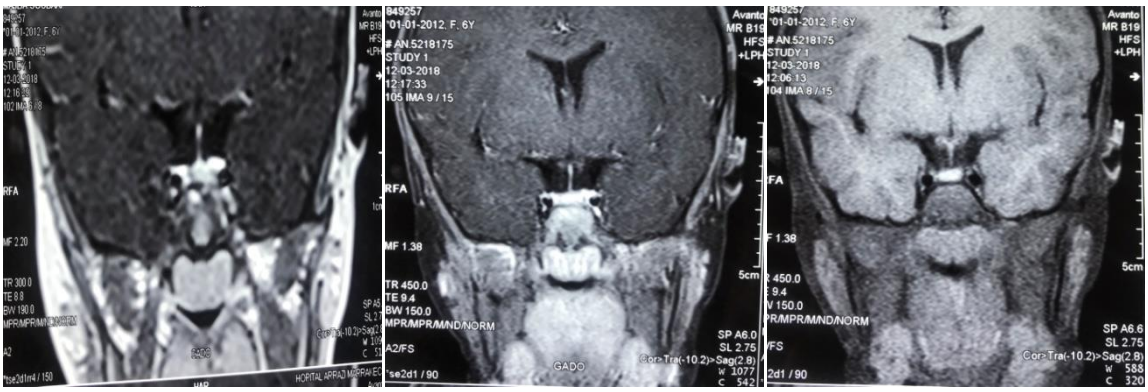

Figure 2: Normal pituitary MRI, no pituitary adenoma

An assessment, for the mother, found the same profile: a normal TSH at 1.74 mU / l, an elevated LT4 level at 41.9 pmol / l and a T3 at 11.3 pmol / l. At thyroid ultrasound the gland was normal (whereas the patient had had a total thyroidectomy 10 years ago).

Regarding to these elements, a pituitary resistance syndrome to thyroid hormones has been retained. And the management has been symptomatic treatment of tachycardia with propanolol and regular monitoring.

DISCUSSION

The thyroid profile often points clearly to one etiology rather than another. However, in our case, the normal or even elevated TSH profile with elevated peripheral hormone level brings to mind two situations, both very rare: thyrotropin-secreting pituitary adenoma representing 0.5% of pituitary adenomas, an incidence of 1 case per million (Rodin P *et al*, 2018), and the pituitary resistance syndrome to thyroid hormones (Table 2) 1 case per 50,000 births (Refetoff S *et al*, 1993; Weiss RE *et al*, 2000).

In the first situation, a pituitary adenoma, most often a microadenoma, secretes excess TSH by thyrotropic cells. TSH stimulates thyroid cells which secrete large amounts of peripheral hormones.

Thyrotropin-secreting pituitary adenoma, very rare, but more and more diagnosed because of the generalization of hormonal assays. It corresponds to an abnormally high secretion of TSH by the thyrotropic cells of the adenoma, leading to an increase in the level of peripheral thyroid hormones, which will, in turn, lower the level of TSH by negative feedback. Clinically, the patient is most often asymptomatic, but signs of thyrotoxicosis may be evident, like tachycardia. At pituitary MRI, a clearly identifiable adenoma, or even macroadenoma, makes the diagnosis. Otherwise, it can simply be a pituitary incidentaloma, which frequency is higher than TSH-secreting adenoma. Biologically, the ratio of the alpha-TSH subunit is increased in patients with TSH-secreting adenoma. Treatment in this case is based on surgery. Somatostatin analogues find indications in long-term treatment.

The second entity, the thyroid hormone resistance syndrome, is that encountered in our young patient. It is a pathology affecting several members of the same family, given its transmission in an autosomal dominant mode. It is caused by a mutation in a gene on

chromosome 3, which codes for the β receptor of thyroid hormones.

Clinically, a goiter is characterized and biochemically an increased rate of peripheral thyroid hormones and inappropriate TSH secretion (elevated or normal). Hypophyseal and hypothalamic hyposensitivity to elevated levels of these thyroid hormones (Beck-Peccoz *et al*, 2002) is noted. The signs of thyrotoxicosis may be evident, suggesting that hormonal sensitivity can be maintained in peripheral tissues.

Indeed, three categories are to be distinguished: Generalized, pituitary and peripheral (extra-pituitary). They correspond, however, to several forms of the same pathology, explained by the same genetic mutation. These different forms have been found among members of the same family, and may even constitute the progression of the syndrome in the same patient (Weiss RE *et al*, 2000; Refetoff S *et al*, 1997).

Table 2: Various profiles of inappropriate TSH secretion

	Tumor origin: Pituitary adenoma	**Non-tumor origin: Resistance to thyroid hormone**		
		Generalized	Pituitary	peripheral
Pituitary gland	Adenoma	Normal	Normal	Normal
TSH	Normal or increased	Normal or increased	Normal or increased	Normal
Thyroid	Goiter	Goiter	Goiter	Normal
Thyroid hormones	increased	increased	increased	Normal
Metabolic status	Thyrotoxicosis	Eumetabolism	Thyrotoxicosis	Hypometabolism

In generalized resistance, a very large production of thyroid hormones tries to counteract tissue resistance, giving a clinically normal appearance: the patient is in euthyroidism. The clinical status also includes hyperactivity syndrome with attention deficit, various neuro-psychic and morphological signs (language acquisition deficit, thoracic deformities, etc.). On the biological level, thyroid hyperhormonemia (high free T4 and T3), on the other hand, TSH is normal or moderately increased, inappropriate for hormonal status. The α subunit of TSH compared to TSH is not increased, as in pituitary adenoma, thus, making differential diagnosis. Also, thyroid scintigraphy is normal (Vlaeminck-Guillem *et al*, 1997).

In pituitary resistance, which is less often present, central origin of hyperthyroidism is explained by the absence of feedback on the production of TSH. Symptoms are less obvious. The thyroid profile is also similar to the first category. In the case of our young patient it was the pituitary resistance which was found.

In peripheral resistance, which remains exceptional, the patient is in hypometabolism because despite the maintenance of feedback on the pituitary gland, this is not enough to counter the deficit in periphery. The biological assay may return to normal TSH and normal free peripheral hormone levels.

This resistance is based on mutations in receptors: TRβ1 receptor and, or rarely, TRα1 receptor (Rodin P *et al*, 2018). Also, resistance to thyroid hormones is characterized by variable phenotypes. Each form of resistance manifests itself differently regarding to the presence of signs of dysthyroidism, other clinical signs or the response to different treatments. Phenotypic variability is not correlated to the type of mutation (Weiss RE *et al*, 2000; Beck-Peccoz P *et al*, 2005). Indeed, it has been noted that between two families suffering from the same form of resistance, the clinical presentation may be different even if they carry the same mutation.

How to diagnose thyroid hormone resistance syndrome?

The diagnosis can be made after having:

- Eliminated a problem in the dosage, laboratory error, repeated dosages.
- Eliminated a pathophysiological situation (treatment with thyroid hormones or amiodarone)
- Eliminated an abnormality of carrier proteins
- Checked for antibodies to thyroid hormones or TSH.
- Eliminated a thyrotropin-secreting pituitary adenoma

How to treat thyroid hormone resistance syndrome?

It is essential to respect, the spontaneous hormonal state, and thus, to stick to the spontaneous balance, and to use only to symptomatic treatments (Refetoff S *et al*, 1993; Weiss RE *et al*, 1999).

Thus, in metabolically balanced situations, abstention is most often indicated. When hypermetabolism is at the forefront, antithyroid drugs,

radioactive iodine therapy, and even goiter reduction surgery may have a place to suppress thyroid hyperfunction. Other methods including dopamine analogs, somatostatin derivatives, T3, TRIAC, or the dextrorotatory form of T4 will help suppress hyperthyreotropism.

The therapeutic arsenal is therefore made up of:

- Abstention: in most situations
- Replacement therapy with thyroid hormones: in case of hypometabolism (hypothyroidism due to tissue insensitivity)
- Symptomatic treatment: Rest, non-cardioselective beta blockers, etc.
- TSH blocking treatments: Bromocriptine, Glucocorticoids, Somatostatin analogues

However, treatments such as antithyroid drugs, surgery or iratherapy which aim to reduce the level of peripheral hormones, can lead to elevated TSH and, therefore, a recurrence of goiter. On the other hand, the administration of somatostatin analogs or dopaminergics aimed at slowing down TSH, can quickly lead to an escape and an elevation of peripheral hormones.

This is why another treatment route has been developed: introducing a T3 analog, with no significant biological activity but binding to the T3 receptors (Weiss RE *et al*, 1999; Pohlenz J, 1996). Beta-blockers are used to control tachycardia, amiodarone is prohibited. The management of associated disorders is essential: hyperactivity and attention deficit disorder, ear infections, etc.

CONCLUSION

Thyroid hormone resistance syndrome is a rare entity, which remains unknown and underdiagnosed. However, with a codified diagnostic approach, its identification is easy: the thyroid profile is characterized by an increase in peripheral thyroid hormones in relation to an increased or normal TSH. Incorrect diagnosis can lead to ineffective or even harmful treatment. The identification of the mutation in the gene encoding the receptor confirms the diagnosis. Therapeutic care is not yet consensual.

REFERENCES

1. Beck-Peccoz P, Mannavola D, Persani L. (2005). Syndromes of thyroid hormone resistance. Ann Endocrinol, 66:264-69.
2. Beck-Peccoz, P., Mannavola, D., & Persani, L. (2002). Syndromes de résistance aux hormones thyroïdiennes par mutations du récepteur T3R beta: avancées dans la compréhension des mécanismes. *Médecine thérapeutique/Endocrinologie*, *4*(1), 27-33.
3. Pohlenz, J., & Knöbl, D. (1996). Treatment of pituitary resistance to thyroid hormone (PRTH) in an 8-year-old boy. *Acta Pædiatrica*, *85*(3), 387-390.
4. Refetoff S. (1997). Resistance to thyroid hormone. Curr Ther Endocrinol Metab, 6:132-34
5. Refetoff, S., Weiss, R. E., & Usala, S. J. (1993). The syndromes of resistance to thyroid hormone. *Endocrine reviews*, *14*(3), 348-399.
6. Rodin P, Prunier-Mirebeau D, Illouz F. (2018). Les syndromes de sensibilité réduite aux hormones thyroïdiennes. *Médecine clinique Endocrinologie et Diabète*, *92* :32-38.
7. Vlaeminck-Guillem, V., & Wémeau, J. L. (1997). Syndromes de résistance aux hormones thyroïdiennes: bases moléculaires et pathogéniques., 13 :1419-27.
8. Weiss RE, Refetoff S. (2000). Resistance to thyroid hormone. Rev Endocr Metab Disord, *1*:97-108.
9. Weiss, R. E., & Refetoff, S. (1999). Treatment of resistance to thyroid hormone—primum non nocere. *The Journal of Clinical Endocrinology & Metabolism*, *84*(2), 401-404.