Pediatric Endocrinology Diabetes and Metabolism
Endokrynologia, Diabetologia i Choroby Przemiany Materii Wieku Rozwojowego

Case Raport | Praca kazuistyczna
Pediatr Endocrinol Diabetes Metab 2017;23,4:208-213
DOI: 10.18544/PEDM-23.04.0095

redakcja@pediatricendocrinology.pl
www.pediatricendocrinology.pl
www.pteidd.pl

Thyroid hormone resistance syndrome – own experiences

Zespół oporności na hormony tarczycy – doświadczenia własne

Tomasz Jackowski, Elżbieta Petriczko, Anita Horodnicka-Józwa, Mieczysław Walczak

Klinika Pediatrii, Endokrynologii, Diabetologii, Chorób Metabolicznych i Kardiologii Wieku Rozwojowego PUM

Abstract
Thyroid hormone resistance syndrome, also known as Refetoff syndrome, is a rare disease associated with decreased reaction of body tissues to thyroid hormones (TH). Patients with Refetoff syndrome tend to have elevated free TH concentrations and normal or inadequately elevated TSH (caused by thyrotropic cells in the pituitary gland insensitivity to TH). The cause of the disease is the mutation in TR-beta receptor gene. Depending on the clinical presentation generalised and pituitary resistance to TH are described. The syndrome is often misdiagnosed as hyperthyroidism and unnecessarily treated with anti-thyroid drugs. Some patients receive l-thyroxine treatment for apparent hypothyroidism. In this report, three patients are presented with a long history in our Clinic and Outpatient Clinic.
Key words
thyroid hormone resistance syndrome, thyroid hormones, hypothyroidism, hyperthyroidism, treatment

Streszczenie
Zespół oporności na hormony tarczycy, znany także jako zespół Refetoffa, to rzadka choroba związana z obniżoną reakcją tkanek na działanie hormonów tarczycy (HT). U osób dotkniętych zespołem Refetoffa oznacza się wysokie stężenia wolnych HT oraz prawidłowe lub nieadekwatnie podwyższone stężenie TSH (wynikające z niewrażliwości komórek tyreotropowych przysadki na HT).Przyczyną choroby jest mutacja w genie receptora TR-beta, Zależnie od obrazu klinicznego wyróżnia się uogólnioną i przysadkową oporność na HT. Zespół rozpoznawany jest często mylnie jako nadczynność tarczycy i niepotrzebnie leczony lekami przeciwtarczycowymi. U części chorych leczenie prowadzone jest jak dla pacjentów z pierwotną niedoczynnością tarczycy, jednak obserwuje się brak istotnego wpływu l-tyroksyny na stężenia HT i TSH. Opisywane są przypadki trojga pacjentów pozostających w wieloletniej obserwacji w Klinice i Przyklinicznej Poradni Endokrynologicznej.
Słowa kluczowe
zespół oporności na hormony tarczycy, hormony tarczycy, niedoczynność tarczycy, nadczynność tarczycy, leczenie

Introduction

Thyroid hormone resistance syndrome, also known as Refetoff syndrome, is a rare (about 1:40000 births [1, 2]) disease associated with decreased reaction of body tissues to thyroid hormones (TH). Patients with Refetoff syndrome tend to have elevated free TH concentrations and normal or inadequately elevated TSH (caused by thyrotropic cells in the pituitary gland insensitivity to TH). Clinically, the patients present a vast array of symptoms, because of varying sensitivity of tissues to TH. In partial resistance for example, goitre can be the only symptom the patient presents. The cause of the disease are point mutations in the carboxyl end of theTHRB gene, coding the TR-beta receptor. As of today, over 120 mutations are known, most of which are inherited autosomally dominant. Mutation in these region tend to retain the receptor's critical functions, such as DNA dimerisation and binding, but disrupt T3 binding [3–7]. Due to its rarity, the syndrome is often misdiagnosed and unnecessarily treated as hyper- or hypothyroidism.

In this report, three patients are presented, who were diagnosed with Refetoff syndrome based on clinical presentation and laboratory results.

lek. Tomasz Jackowski
Klinika Pediatrii, Endokrynologii, Diabetologii, Chorób Metabolicznych
i Kardiologii Wieku Rozwojowego PUM
ul. Unii Lubelskiej 1 71-252 Szczecin tel. 914253166
e-mail: thomas.jackowski@gmail.com

Received: 10.01.2018
Accepted: 30.01.2018
Conflict of interests: none declared.

Pediatr Endocrinol Diabetes Metab 2017;23,4:209-214

Case presentation

Patient K.T., male, 16,5-years-old. Born from 7th pregnancy, in 38Hbd, with body weight 3100g , in good general condition (Apgar 9/10). Family history: nodular goitre in the mother. The patient has been under Endocrinological Outpatient Clinic's observation since may 2011, where he was first admitted due to improper thyroid function laboratory results and thyroid gland enlargement in palpation. Upon admission he was taking 25μg L-thyroxine daily. In physical examination: enlarged thyroid, smooth, with homogenous consistence, without any audible murmurs. No tachycardia present. On the first visit, both TSH and FT4 were elevated (TSH 6.63 μIU/ml, N: 0.51–4.3; FT4 2.30 ng/dl, N: 0.93–1.70). The patient denied symptoms of hyperthyroidism. In ultrasound examination (March 2011) the thyroid was described as enlarged – RL 19x21x61 mm, LL 21x21x63 mm, volume 24.97 ml (N<9ml); echostructure heterogeneous, decreased, with many connecting hypoechogenic areas and strands of connective tissue, without any focal lesions – presentation of chronic thyroiditis. The dose of L-thyroxine was increased and the patient was seen again after 3 months, with control of anti-thyroid antibodies performed. Upon upcoming admissions the doses of L-thyroxine were modified according to laboratory results – table I.

Based on the received results and instability of TH concentration despite the treatment, the diagnosis of Refetoff syndrome was proposed, the patient was admitted to the Clinic for further diagnostics. In ultrasound examination: thyroid enlarged RL 21x22x65 mm, LL 20x23x65 mm, isthmus 4–5 mm, volume 28.6 ml (N<16ml); echostructure heterogenous, with many connected hypo- and hyperechogenic areas and strands of connective tissue, without any focal lesions and obvious congestion in Doppler analysis – the presentation may suggest chronic thyroiditis. In laboratory results antiTG, antiTPO and TRAb were negative. Concentrations of gonadotropins, sex hormones, cortisol, ACTH and prolactin adequate to age. Blood sample for genetic testing was taken. The patient remains under the observation in the Outpatient Clinic. As of today, he's not taking any medication. Without the treatment TSH and TH levels remain comparable to those measured during the treatment – the patient remains in clinical euthyrosis. He develops well, with body height and weight between 50th and 75th percentile.

Patient M.P., female, 10-years-old. Born from 1st pregnancy, in 41Hbd via caesarean section (risk of intrauterine hypoxia), with body weight of 2560 g, in good general condition (Apgar 10). Neonatal period uncomplicated. Psychomotor development in the first year of life normal. Family history:

Table I. Patient K.T., control thyroid tests

Date	TSH [μIU/ml] N: 0.51-4.3	FT3 [pg/ml] N: 2.53-5.22	FT4 [ng/dl] N: 0.93-1.7	aTPO [IU/ml] N: 0-26	L-thyroxine [μg/day]
V 2011	6.63	-	2.30	-	37.5
VIII 2011	6.66	-	2.41	-	50
I 2012	5.45	-	2.18	7.32	5x50, 2x75
VII 2012	8.25	5.03	2.55	-	75
XI 2012	4.88	3.36	2.07	-	1x100, 6x75
III 2013	5.26	-	2.29	-	1x100, 6x75
VIII 2013	5.6	4.4	2.46	-	2x100, 5x75
XI 2013	7.38	4.51	2.08	11.24	5x100, 2x75
III 2014	6.33	5.14	2.09	-	5x100, 2x75
VIII 2014	5.59	5.27	2.11	-	5x100, 2x75
VII 2015	6.25	6.1	1.77	-	75
XI 2015	5.24	5.07	1.88	12.78	50/75
IV 2016	5.07	5.24	1.88	-	50
I 2017	7.18	5.08	1.99	-	0
III 2017	6.33	4.88	1.81	-	0
XI 2017	6.9	5.25	1.98	-	0

thyroid tumour in father's sister. In physical examination: massive tooth decay, systolic murmur above the heart. No tachycardia present. Thyroid 0 stage WHO. She was admitted to the Outpatient Clinic because of hypothyroidism – first TSH concentration 8.66 μIU/ml (N: 0.51–4.3). Since the first elevated TSH result she has been treated with L-thyroxine, in the beginning 12.5μg/day, then successively increased under the care of the Outpatient Clinic – table II.

Table II. Patient M.P., control thyroid tests

Date	TSH [μIU/ml] N: 0.51-4.3	FT3 [pg/ml] N: 2.53-5.22	FT4 [ng/dl] N: 0.93-1.7	L-thyroxine [μg/day]
VI 2011	8.66	-	-	12.5
XI 2011	5.7	-	2.17	2x25, 5x12.5
IV 2012	7.8	6.0	1.98	12.5
IX 2012	6.07	6.55	1.78	12.5
I 2013	19.62	4.97	1.61	25
I 2013	33	-	-	37.5
II 2013	53.7	-	1.4	37.5/50
III 2013	32	5.26	1.46	5x50, 2x37.5
V 2013	6.4	5.98	1.96	50
VIII 2013	19.2	5.04	1.82	50
IX 2013	27	-	1.6	5x50, 2x75
X 2013	6.6	-	2.26	50
XII 2013	2.8	-	-	50
III 2014	3.36	-	2.22	5x50, 2x37.5
IV 2014	12.7	-	2.04	5x50, 2x37.5
V 2014	9.96	5.7	1.99	4x50, 3x75
X 2014	4.55	5.0	1.95	5x50, 2x75
I 2015	4.72	5.7	2.12	5x50, 2x75
II 2015	4.69	5.69	1.9	5x50, 2x75
V 2015	9.5	5.51	1.78	6x50, 1x75
XII 2015	8.87	5.39	1.76	5x50, 2x75
I 2016	11.88	-	1.78	4x75, 3x50
VI 2016	5.96	5.02	1.74	4x75, 3x50
VII 2016	5.98	5.08	1.73	4x75, 3x50
XI 2016	13.07	5.63	1.69	4x75, 3x50
XII 2016	12.23	5.47	1.71	5x75, 2x50
II 2017	9.410	5.64	1.66	5x75, 2x50
X 2017	12.34	5.14	1.93	75
XI 2017	7.6	5.8	1.66	75

Pediatr Endocrinol Diabetes Metab 2017;23,4:209-214

According to the mother the child was hyperactive, unable to focus. Because of that she was diagnosed psychologically – admission to elementary school was delayed, correction, compensation and speech therapy were implemented. The girl had to retake class "0" in elementary school. Because of learning difficulties and speech impairment audiometry was performed, which first suggested sensory hearing loss. However, when the test was repeated after her upper respiratory tract infection was healed, the result was normal.

During the observation in the Outpatient Clinic the patient grew symmetrically, with body height along the 3rd percentile, body weight 3–10th percentile. No goitre was ever noticed. Clinically the patient presented no symptoms of thyrotoxicosis or hypothyroidism. In all the ultrasounds performed (I 2013, VI 2016, XII 2016, X 2017) thyroid not enlarged (last measurement RL 13x12x41mm, LL 16x13x35mm, volume 6.68 ml, N<6.9) with decreased, heterogeneous echostructure, with strands of connective tissue, with no focal lesions – presentation like in chronic autoimmune thyroiditis. During the patient's observation slightly elevated antiTG antibodies concentration was marked, with negative antiTPO and TRAb. In control tests anti TG was negative.

The girl was hospitalised many times in our Clinic, last time in November 2017. According to the mother her psychological state has worsened, she has difficulties sleeping and nightmares. Consulting psychiatrist diagnosed her with mental retardation, organic disruption of emotion and behaviour. Puberty assessment was also needed in the patient – first symptoms appeared in the 8th year of life (pubarche). From then on growth acceleration was noticed, which presented as pubertal growth spur. Menarche appeared at the age of 10. Bone age described as that for the girl at the age of 12. Currently in auxological measurements: body height 50–70th percentile, body weight 75–90th percentile. The patient remains in observation of the Clinic and Outpatient Clinic. More thorough diagnostics, including neuroimaging, is planned in the future. A blood sample for genetic testing was taken. Due to intellectual disability the decision was made to keep supplementing the girl with L-thyroxine until the diagnosis is genetically confirmed.

Patient P.M., male, 23-year-old. Until adulthood he remained in the care of the Endocrinological Outpatient Clinic. Born from 2nd pregnancy, in 39Hbd, with body weight 3650g, in good general condition (Apgar 10). The adaptation period was uncomplicated. Family history clear. The boy was first put in the Outpatient's Clinic care due to elevated TSH in neonatal screening – 35.55mU/l (N<20). In control tests in the first months of life: TSH – 5.32 mU/l (N: 0.4–4.0), FT4 – 51.78 pmol/l (N: 8.5–19.0), FT3 – 16.46 pmol/l (N: 3.5–7.9). At the age of 12 months the boy was hospitalised for further diagnostics. His general condition was assessed as good. Physical and psychomotoric development was adequate to age. In physical examination enlarged thyroid was described. No tachycardia present. Basic laboratory tests within the norm for the age. In thyroid tests: TSH – 2.94 mU/l (N: 0.4–4.0), FT4 – 60.92 pmol/l (N: 8.5–19.0), FT3 – 19.64pmol/l (N: 3.5–7.9). Thyreoglobulin concentration normal. TRH-TSH stimulation test was performed, with results presented in table III.

Table III. Patient P.M., TRH-TSH stimulation test

Minute	TSH concentration [mU/l]
0'	3.38
30'	18.88
60'	11.64

In ultrasound enlarged, homogenously hypoechogenic thyroid was described. No irregularities in neuroimaging. Clinically the patient presented no symptoms of thyroid dysfunction. In psychological assessment his intellectual development was described as good. Based on those results Refetoff syndrome was diagnosed. The patient remained under care of the Outpatient Clinic, no treatment was introduced. During the whole observation the boy remained in clinical euthyrosis despite elevated TSH and TH levels. Last hospitalisation in 2011. In thyroid tests: TSH 5.32 μIU/ml (N: 0.51–4.3), FT3 9.73 pg/ml (N: 2.53–5.01), FT4 4.31 ng/dl (N: 0.93–1.7). No abnormalities in physical examination. Physical development normal – body height 50–75th percentile, body weight 75–90th percentile. Clinical euthyrosis. Thyroid ultrasound normal. No abnormalities in MRI of the brain and pituitary gland. The patient is now under care of Endocrinological Outpatient Clinic for adults. He still does not require any treatment. He is currently getting a degree at a technical university.

Discussion

Refetoff syndrome, since its description in 1967, has been diagnosed in over 1000 patients, more than 120 genetic mutations responsible for its existence have been identified. The differences in tissue sensitivity to TH and the vast variety of possible mutations are the reason for the heterogeneity of the syndrome's clinical presentation. However, two main phenotypes can be described – generalised TH resistance (GRTH) and pituitary TH resistance (PRTH). The main difference is the existence of hyperthyroidism symptoms in patients with PRTH and euthyrosis or slight hypothyroidism in patients with GRTH. Molecular examinations have shown that in related patients the same mutation can be responsible for both GRTH and PRTH, which suggests that both phenotypes are a spectrum of the same genetic disorder. Familial occurrence of the symptom has been described in 70% of the cases, *de novo* mutations rate is estimated at 17% [4, 6, 13, 14, 21].

Despite the syndrome's heterogeneity, some common symptoms are described:

- Sinus tachycardia – according to some authors present in as many as 80% of patients; its presence is explained by

the myocardium's sensitivity to TH due to the presence of TR-alfa receptors [5–8, 21]
- Neurocognitive disorders,described in many patients, such as the disruption of development, speech impairment, dyslexia, ADHD [5, 8, 9, 11]
- Hearing impairment [5, 8]

Patient K.T. presents goitre, elevated free TH, without the symptoms of hyperthyroidism. No problems with mental development or bone development were diagnosed. Substitution treatment with L-thyroxine did not cause satisfactory suppression of TSH production.

Patient M.P. presents a wider spectrum of symptoms, including behaviour disorders, impaired speech, delayed intellectual development, short stature. In laboratory test elevated TH concentrations were noted, with no symptoms of hyperthyroidism.

Patient P.M. was diagnosed early because of diagnostics he had undergone due to neonatal screening results, which allowed for no unnecessary treatment to be introduced. The only symptom was the goitre, which became smaller with age – currently the patient's thyroid's size is normal.

Heterogeneous clinical presentation of the syndrome may cause diagnostic difficulties – PRTH can be suspected in patients with elevated TH and TSH as well as symptoms of hyperthyroidism. Such clinical presentation needs differentiating with TSH-secreting adenoma, which can be excluded by performing TRH test (resulting in increased thyrotropic reaction of the pituitary) and neuroimaging. In TSH-secreting tumours, the TSH response elicited by TRH is blunted. On the contrary, TSH usually rises in response to TRH in thyroid hormone insensitivity and in healthy subjects. Concomitant measurement of α-subunit at each point during the TRH test is helpful because the molar ratio of α-subunit to TRH is high (>1) in almost 85% of patients with TSH-secreting tumours [10, 12, 15, 20]. Because of the laboratory results along with symptoms of hyperthyroidism the disease is often misdiagnosed as primary or secondary hyperthyroidism, causing the patients to be unnecessarily treated with antithyroid medication. Some patients, especially ones with GRTH, are diagnosed by endocrinologists because of elevated TSH levels, and therefore are treated as patients with primary hypothyroidism. Thyrostatics and radical treatment cause only a short-term improvement. Surgical treatment is not effective in the long term because goitres have a tendency to be recurring, because contrary to autoimmune thyroid disease, there is no destructive process involved. It is therefore more effective to inhibit thyroid gland growth by the suppression of TSH, which can be achieved by treating with a single large dose of l-T3, given every other day.

The high levels of serum T3 after the administration of the hormone are effective in suppressing TSH but do not persist due to the short half-life of T3, meaning they do not cause hyperthyroidism syndrome. There are also some reports of satisfactory results of treatment with triiodothyroacetic acid (TRIAC), which is a TH analogue with low hormonal potency but high affinity for the TR and very rapid turnover, requiring the use of doses more that 1,000-fold those of l-T3. In long term studies describing the effect of TRIAC on TH resistance patients there was a significant reduction in the basal and TRH-stimulated TSH observed in the majority of cases. However, there was no appreciable change in parameters that measure TH action. Symptomatic treatment is also justified, such as beta-blockers administration in patients with tachycardia [1–3, 5, 9, 12, 18, 22].

In patients with GRTH the therapy is not certain. In most cases increased TH secretion will compensate the tissue resistance and allow to keep clinical euthyrosis. In some though it is justified to use supraphysiological doses of L-thyroxine (as high as 1000μg/day] to keep proper functioning of the body. In most patients, satisfactory suppression of TSH secretion is impossible in spite of substitution treatment [9].

Patients K.T. and M.P. had thyroid ultrasound image suggesting chronic autoimmune inflammation – a diagnosis which was not confirmed by serology.

Patients K.T. and M.P. had their blood samples taken for genetic testing to find a mutation in the THRB gene – the results still remain under review. The result of genetic tests would, with high probability, allow us to definitely confirm the diagnosis (according to some authors we are unable to genetically confirm less than 13% of the patients) [4]. Due to the inheritance mechanism, this would allow for genetic counselling for the whole family, also taking into account the patients' future children.

Abbreviations:

TSH – thyroid-stimulating hormone, FT3 – free triiodothyronine, FT4 – free thyroxine, AntiTG–anti-thyroglobulin, AntiTPO – anti-thyroperoxidase, TRAb–TSH receptor antibodies, ADHD – attention deficiency and hyperactivity disorder

Pediatr Endocrinol Diabetes Metab 2017;23,4:209-214

References

1. Rivas AM, Lado-Abeal J. *Thyroid hormone resistance and its management.* Proc (Bayl Univ Med Cent). 2016;29(2):209-211.
2. Philip R, Padikal MK, Alinausad A, Keshavan C. *Not all elevated hormones are toxic: A case of thyroid hormone resistance.* J Family Med Prim Care. 2016;5(2):460-462.
3. Refetoff S, Weiss RE, Usala SJ. *The Syndromes of Resistance to Thyroid Hormone.* Endocr Rev. 1993 Jun;14(3):348-399.
4. Işık E, Beck Peccoz P, Campi I, Özön A, Alikaşifoğlu A et al. *Thyroid hormone resistance: a novel mutation in thyroid hormone receptor beta (THRB) gene – case report.* Turk J Pediatr. 2013;55(3):322-327.
5. Kopp P, Kitajima K, Jameson JL. *Syndrome of resistance to thyroid hormone: insights into thyroid hormone action.* Proc Soc Exp Biol Med. 1996;211(1):49-61.
6. Chatterjee VK. *Resistance to thyroid hormone – an uncommon cause of thyroxine excess and inappropriate TSH secretion.* Acta Med Austriaca. 1994;21(2):56-60.
7. Weiss RE, Weinberg M, Refetoff S. *Identical mutations in unrelated families with generalized resistance to thyroid hormone occur in cytosine-guanine-rich areas of the thyroid hormone receptor beta gene. Analysis of 15 families.* J Clin Invest. 1993;91(6):2408-2415.
8. Usala SJ, Bale AE, Gesundheit N, Weinberger C et al. *Tight linkage between the syndrome of generalized thyroid hormone resistance and the human c-erbA beta gene.* Mol Endocrinol. 1988;2:1217-1220.
9. Weiss RE, Refetoff S. *Treatment of resistance to thyroid hormone – primum non nocere.* J Clin Endocrinol Metab. 1999;84(2):401-404.
10. Olateju TO, Vanderpump MP. *Thyroid hormone resistance.* Ann Clin Biochem. 2006;43(Pt 6):431-440.
11. Kaplan MM, Swartz SL, Larsen PR. *Partial peripheral resistance to thyroid hormone.* Am J Med. 1981;70(5):1115-1121.
12. Banecka B, Jaklińska T, Szewczyk L. *Przysadkowy zespół oporności na hormony tarczycy u chłopca w wieku szkolnym – problemy terapeutyczne.* Endokrynologia Pediatryczna, 2007 Nr 4(21).
13. Refetoff S. *Resistance to thyrotropin.* J. Endocrinol. Invest. 2003,26(8):770-779.
14. Greenspan F. *Gruczoł tarczowy. Zespoły oporności na hormony tarczycy.* W: Greenspan F, Gardner D. *Endokrynologia ogólna i kliniczna*. Red. Lewiński A. Wyd. Czelej, Lublin 2004.
15. Zieleniewski W, Jurczyńska J, Kunert-Radek J. *Przysadkowa oporność na hormony tarczycy – opis przypadku.* Endokrynologia Pol. 2005;56(5):790-793.
16. Krysiak R, Okopien B, Herman ZS. *Thyroid hormone resistance syndrome.* Pol. Merkur. Lekarski. 2006;20(116);214-219.
17. Norlela S, Nor Azmi K, Khalid BA. *Pituitary thyroid resistance syndrome.* Med. J. Malayzia. 2005;60(5):642-643.
18. Radetti G, Persani L, Molinaro G. *Clinical and hormonal outcome after two years of triiodothyroacetic acid treatment in a child with thyroid hormone resistance.* Thyroid. 1997;7(5):775-778.
19. Sato H, Koike Y, Honma M, Yagame M, Ito K. *Evaluation of thyroid hormone action in a case of generalized resistance to thyroid hormone with chronic thyroiditis: discovery of a novel heterozygous missense mutation (G347A).* Endocr J. 2007 Dec;54(5):727-732. Epub 2007 Sep 7.
20. Florkowski CM, Browline BE, Croxson MS et al. *Thyroid hormone resistance: the role of mutational analysis.* Intern. Med. J. 2006;36(11):738-741.
21. McDermott MT, Ridgway EC. *Thyroid hormone resistance syndromes.* Am J Med. 1993;94(4):424-432.
22. Weiss RE, Dumitrescu A, Refetoff S. *Approach to the Patient with Resistance to Thyroid Hormone and Pregnancy.* J Clin Endocrinol Metab. 2010;95(7):3094-3102.