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ORIGINAL ARTICLE

Variable clinical presentation and outcome in pediatric patients with resistance to thyroid hormone (RTH)

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Abstract Resistance to thyroid hormone (RTH) is characterized by elevated levels of thyroid hormones, normal or slightly increased TSH levels respondent to TRH, resistance to thyroid hormone administration, and variable clinical expression. To describe the diverse clinical and biochemical findings of six children from five unrelated families with molecular diagnosis of RTH (0.5–12.7 years) and their follow-up (3–20 years). All RTH patients and 4 affected parents' harbored mutations in exons 9 or 10 of the thyroid receptor β gene: p.M313T (de novo), pN331D, p.L341P, p.L346F, and p.P453L. At consultation 5/6 had goiter, 4/6 tachycardia, and 3/5 learning disabilities. Median hormone levels were: T_4 257.4 nmol/l (NR: 77.2–180.2); FreeT_4 39.9 pmol/(NR:10.3–28.3); T_3 4.28 nmol/l (NR:1.23–3.39) TSH 2.8 mUI/l (NR: 0.5–5) always responsive to TRH. TSH levels remained detectable after supraphysiologic T_3 administration while SHBG levels showed a paradoxical decrease in 4/6. Thyroid antibodies, initially present in two subjects, became positive in other two during follow-up. All patients grew normally and presented variable symptoms that were treated according to need. Two patients developed psychiatric disorders. Only one of the four affected parents exhibited clinical signs of RTH (tachycardia and depression). Parent's thyroid profile showed similar TSH and T_3 levels but lower T_4 and FT_4 than their children. RTH has a distinctive biochemical profile with highly variable clinical manifestations and outcomes. Its recognition and molecular characterization avoid misleading diagnosis. Treatment has to be instituted according to each subject's own clinical requirements.

Keywords Thyroid hormone resistance · Pediatric patients · TSH · Outcome · TRβ gene

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Introduction

Resistance to thyroid hormone (RTH) is a genetic disease characterized by elevated thyroid hormones in serum and failure to suppress pituitary thyroid stimulating hormone (TSH) secretion with variable refractoriness to hormone action in peripheral tissues resulting in diverse clinical expression [1, 2].

This syndrome has been described up to now in approximately 2,000 patients that belong to 372 families with an estimated incidence of 1:40,000 live births [1, 3–6].

RTH is associated with diverse mutations in the thyroid hormone receptor β gene (TRβ) localized in chromosome 3 [7]. This nuclear receptor is a ligand-dependent transcription factor and its function relies on a complex dynamics of binding and release of co-activators and co-repressors. The structure of TRβ includes two functional domains, the ligand binding domain (LBD) which recognizes T_3 at the carboxy-terminus, and the DNA binding domain (DBD) near the middle of the molecule. Mutations are usually located in the last 4 exons of the TRβ gene, which code for

the hinge region and the LBD and are part of clusters 1, 2, and 3 at codons 429–461, 310–353, and 234–232, respectively [7]. Molecular alterations of other components that influence the normal receptor function as altered ligand dissociation, inhibition of activator binding or defective release of co-repressors have also been described [8–11].

With few exceptions, the majority of cases described are inherited as autosomal dominant disorders. Excluding the rare cases of homozygous families, heterozygous patients carry only one mutated TRβ allele that interferes with the wild-type receptor's function by a dominant negative mechanism [12, 13]. Families present with multiple affected members while 15–20% of reported cases occur as a result of de novo mutations [1]. Both genders are equally affected.

Clinical phenotype of RTH is highly heterogeneous and ranges from subclinical to highly symptomatic. The majority of affected individuals are euthyroid without clinical abnormalities. They achieve normal growth and mental development and are able to lead a normal adult life as RTH is compensated by high thyroid hormone levels.

In other patients, signs of thyroid hormone deficiency, sufficiency, and excess may coexist depending on the level of TRβ gene expression in various tissues [1]. Some individuals exhibit clinical evidence of hyperthyroidism as hyperactivity and tachycardia along with signs of hypothyroidism as delayed growth or learning disabilities. More rarely high endogenous thyroid hormones can produce toxic effects on peripheral tissues [1].

Clinical expression may vary too in the same patient as tissues and organ systems maybe differently affected or change their involvement over the years [2, 4].

Currently the diagnosis of RTH is based on clinical findings, standard laboratory tests, and genetic studies.

Recognition and diagnosis of these patients during childhood represent a challenging task because of the extreme variability of the disorder. Moreover, pediatric endocrinologists are faced with the paucity of information on the natural history of affected individuals and their follow-up, and with controversies on the therapeutic approach.

Here we report the clinical and biochemical characteristics and long-term follow-up of six children with molecular confirmed RTH with the aim of pointing out some features that are common to the disorder and that would help in the diagnosis and care of these patients.

Patients and methods

Data of six children aged 0.52–12.7 years from five unrelated families who consulted the Endocrinology Division, Hospital de Niños Dr. Ricardo Gutiérrez, Buenos Aires, were retrospectively analyzed.

Relevant history data, cause of consultation, clinical findings, height, and body mass index (BMI) expressed as standard deviation score for the Argentine population (SDS), bone age assessed by Greulich & Pyle method and initial levels of TSH, T_4, FreeT_4 (FT_4), and T_3 determined by electrochemiluminiscence (Eleycsys, Roche Diagnostic Corporation Indianapolis IN) were retrieved from medical records.

Presence of antithyroid peroxidase antibodies (AbTPO) measured by CLIA Immulite DPC (Diagnostic products Corporation LA, CA) at the beginning and during follow-up was also registered.

After the finding of elevated thyroid hormones with inappropriate detectable TSH levels every patient underwent a TRH stimulation test measuring TSH before and after 7 μg/kg IV TRH administration. Afterwards, a T_3 inhibition test was performed according to Sarne et al. [14] using a short-term administration of incremental doses of LT_3 for 3 days (50, 100, and 200 μg/1.70 m^2) followed by another TRH/TSH test performed after the higher dose interval. High levels of thyroid hormones with detectable levels of TSH and normal or exaggerated response to TRH were distinctive of RTH. SHBG levels were determined by chemiluminescent immunoassay (Immulite DPC Diagnostic products Corporation LA, CA) after each incremental period and responses were expressed as the absolute change from basal levels.

Genomic DNA was isolated from blood samples of children and parents, and exons 9 and 10 of the TRβ gene (corresponding to the T_3 binding domain) including their flanking regions were amplified by PCR. The obtained fragments were sequenced using specific forward and reverse primers.

Data from affected parents were obtained retrospectively searching for clinical signs, academic achievement, puberty, current job or problems in social adaptation as well as attention deficit disorder (ADD), psychiatric or endocrine diseases in other family members.

TSH, T_4, FT_4, and T_3 levels of RTH parents (n:4) were compared with those of their children (Wilcoxon paired test).

Time of follow-up, height, and BMI SDS at the last clinical visit, target height and relevant data concerning need of treatment, drugs employed to ameliorate symptoms, changes in clinical status and evolution were documented in the pediatric cohort.

Informed consent was obtained from children and parents for molecular studies. The retrospective study was approved by the Ethical Committee of Hospital de Niños Dr. Ricardo Gutierrez, Buenos Aires.

Table 1 Clinical and biochemical features of six patients with RTH at consultation

Patient	Gender	Age (years)	Bone age (years)	Height SDS	BMI SDS	History	Previous treatment	Cause of consultation				Clinical observations at diagnosis		
								Goiter	Tachycardia	Learning disabilities	Familiar screening	Goiter	Tachycardia	Learning disabilities
1	M	6.3	5.5	−1.4	0.8	Misdiagnosed hyperthyroidism	Lugol	+	−	−	−	+	+	−
2	M	13	10.5	−0.9	−2.2	Celiac disease. Congenital subaortic stenosis	LT_4 celiac diet	+	−	−	−	+	+	−
3	F	9.1	10	2.3	1.5			+	−	+	−	+	+	+ ADD
4	F	10	NA	−0.9	−1	Tachycardia		−	+	−	−	+	+	+ ADDH
5	M	12.5	NA	0.9	1.5	Misdiagnosed hyperthyroidism	MMI	+	−	−	−	+	−	+
6	M	0.5	NA	0.2	0.54	Affected brother		−	−	−	+	−	+	−

Patient	Gender	Age (years)	Bone age (years)	Height SDS	BMI SDS	Biochemical characteristics						
						T_4 nmol/l	FT_4 pmol/l	T_3 nmol/l	TSH mUI/l Basal/30'post TRH		SHBG Δ nmol/l with T_3	AbTPO
									Initial	With T_3		
1	M	6.3	5.5	−1.4	0.8	257.4	72.1	5.20	1/11.5	2.1/10	−2.8	Negative
2	M	13	10.5	−0.9	−2.2	166.2	30.7	3.42	15.2/100	0.7/11.8	−18	Positive
3	F	9.1	10	2.3	1.5	256.1	41.2	3.66	2.9/28	0.22/2.2	+17	Positive
4	F	10	NA	−0.9	−1	314	66.9	6.55	3.6/17	0.38/2.15	−7.5	Negative
5	M	12.5	NA	0.9	1.5	257.4	40.8	3.73	2.7/17.3	0.21/2.38	−19	Negative
6	M	0.5	NA	0.2	0.54	265.1	39.5	4.8	2.4/7.6	0.77[a]	+11[a]	Negative

Normal reference values: Basal TSH:0.5–5 mU/l; 30 min post TRH: 4.5–25 mU/l; T_4:77.2–180.2 nmol/l; FT_4:10.3–28.3 pmol/l; T_3:1,23–3,39 nmol/l

M Male, *F* female, *BMI* body mass index, *ADD* attention deficit disorder, *ADDH* attention deficit disorder with hyperactivity, *NA* non available, *AbTPO* antithyroid peroxidase antibodies

[a] Only first dose

Table 2 Molecular findings in the studied population and biochemical and clinical data of RTH affected parents

Patient	Exon	Genomic DNA mutation	Protein change	TSH mU/l	T_4 nmol/l	FT_4 pmol/l	T_3 nmol/l	Ab TPO	Clinical signs	Employment	Academic achievement	Puberty	Adult life	Other affected relatives
1	9	C.838 T > C (ATG > ACG)	P.M313T (de novo)											
2	9	C.991 A > G (AAG > GAT)	P.N331D (mother)	5.7	176.3	30.8	3.8	Neg#	No		High school	Normal	Normal	No
3	9	C.1022 T > C (CTG > CCG)	P.L341P (mother)	2.1	173	32.7	3.1	Neg	Mild ventricular arrhythmia	Housewife	Learning difficulties	Normal	Depression	NA
4	9	C.1036 C > T (CTT > TTT)	P.L346F (mother)	1.67	166	30	NA	NA	No	Housewife	Elementary school	Normal	Normal	NA
5 and 6[a]	10	C.1358 C > T (CCT > CTT)	P.P453L (father)	1.68	195.6	32.1	3.1	Neg	No	Rural employee	Incomplete elementary school	Normal	Normal	Aunt and uncle's not well-characterized hyperthyroidism

Normal reference: TSH:0.5–5 mU/l; T_4:77.2–180.2 nmol/l; FT_4:10.3–28.3 pmol/l; T_3:1.23–3.39 nmol/l

Neg# negative, *NA* not available data

[a] Siblings

Results

Table 1 shows the relevant clinical and biochemical data of the six patients at consultation. Five patients were healthy with no significant previous conditions while one had a well-controlled celiac disease and a well-treated congenital subaortic stenosis.

Initial height was always normal. Bone age, available in three patients, was close to chronological age in two and retarded by 2.5 years in the celiac patient. BMI SDS was normal in all patients except in the subject with celiac disease.

Consultation was prompted for goiter in 4/6 patients. Two had been misdiagnosed as hyperthyroid and were treated with antithyroid drugs [Methymazole (MMI) and Lugol's solution] and in another TSH resistance to L-T_4 treatment was noted during follow-up of celiac disease and thyroiditis. Tachycardia with learning impairment and familiar screening led to diagnosis in the remaining two patients.

Initial physical examination revealed goiter in five, tachycardia in four and learning disabilities in three. The learning impairment was assessed in two patients as attention deficit disorder (ADD), ADD with hyperactivity (ADDH) and was related to iatrogenic hypothyroidism in the third.

Table 1 shows the initial thyroid studies and results obtained after T_3 administration. Basal Median (range) levels were: T_4 257.4 nmol/l (166–314) [Normal reference (NR): 77.2–180.2) FT_4 39.9 pmol/l (30.9–72)(NR: 10.3–28.3); T_3 4.28 nmol/l (3.42–6.55) (NR:1.23–3.39) Basal TSH 2.8 mUI/l (1–15.2) (NR:0.5–5): and after TRH administration 17.5 mUI/l (7.6 > 100)(NR:4.5–25).

TSH levels and its response to TRH remained always measurable (>0.02 mU/l) after the administration of the higher dose of T_3. SHBG decreased paradoxically in four out of six patients.

During T_3 test three patients remained asymptomatic; two increased their heart rate, body temperature an emotional lability. These symptoms disappeared few days after the test was over. The younger patient presented overt signs of hyperthyroidism with the lowest dose of T_3, and the test had to be stopped. AbTPO was initially positive in two patients.

Direct sequence analysis revealed four novel missense mutations in exon 9 (one de novo) and a novel mutation in exon 10 that were previously reported and are listed in Table 2 along with the data of affected parents. [15, 16].

RHT parents led a normal adult life without problems in social adaptation or work performance. Only the mother of patient 3 referred learning problems as a child and mild ventricular arrhythmia and depression in adulthood. An uncle and aunt of patients 5 and 6 have been treated for a not well-characterized hyperthyroidism.

Table 3 Treatment and outcome of six patients with RTH. Status at last visit

Patient	Age (follow up) (years)	Height SDS	Target height SDS	BMI SDS	Puberty	Goiter treatment (Evolution)[#]	Tachycardia treatment (Evolution)	IQ	Learning treatment (Evolution)	Psychiatric treatment (Evolution)	Academic achievement	AbTPO	Current treatment
1	26 (20)	1	−0.46	−0.01	Normal	No Bromocriptine (I)[#]	No L-T_4 (W)[#] TRIAC (I)	93	Normal	Phobia Anxiety Depression Clonazepam (I)	University graduate	Positive	TRIAC Clonazepam
2	22 (9)	−1.7	NA	−3.4	Late and slow	Mild TRIAC (RS)[#]	No TRIAC (I)	111	Normal	Normal	University graduate	Positive	TRIAC celiac diet
3	13 (4)	0.25	NA	2.3	Normal	No (I)	No (I)	Normal	ADD Disabled	Lost to follow up		Positive	None
4	12.8 (2.8)	−0.6	−1.4	−0.33	Normal	Big TRIAC (RS) MMI (W)	Yes MPhe (W) β blockers (I)	73	ADDH disabled MPhe (W)	Aggressive disorder (W)	Special education	Positive	Antipsychotic drugs
5	17.8 (5.3)	−1.5	−1.24	−0.29	Slow delayed	No MMI withdrawal (I)	No	Normal	Normal (I)	Normal	High school	Negative	None
6	4.3 (3.7)	0.48	−1.24	−2	–	No	Yes (RS)	Normal	Normal	Normal	Normal	Negative	None

AbTPO Antithyroid peroxidase antibodies, *TRIAC* triiodothyroacetic acid, *MMI* metylmercaptoimidazole, *MPhe* Methylphenidate, *ADDH* attention deficit disorder with hyperactivity. *NA* not available, *Evolution*[#] I improved, *RS* remained stable, *W* worsened

Parental median levels of TSH: (1.89 mU/l) and T_3 (3.1 nmol/) in the affected parents showed no significant differences with their children while median levels of T_4: (175 nmol/l) and FT4 (31.5 pmol/l) were significantly lower ($P < 0.05$).

The treatment aim was to maintain clinical euthyroidism and to reduce TSH levels and goiter size; different treatments were used to ameliorate individual symptoms.

Cardiac β blockers were needed to control tachycardia only in one patient.

Triiodoacetic acid (TRIAC) therapy was installed at a dose of 0.02 mg/kg/day to normalize thyroid profile in three patients with initial good results, lowering TSH levels but the long-term response was variable and subjective. This therapy was successful in patients 1 and 2 as it diminished TSH levels and produced clinical subjective improvement but failed in the severely affected girl (patient 4).

Bromocriptine (BC) was used to reduce TSH levels and diminish thyroid size in patient 1. After a short test as reported by Bajorunas et al. [17] in which TSH levels dropped from 4.2 to 1 mU/l, a 2 month course of 2.5 mg/day followed by another 2 months of 5 mg/day was administered. Initially TSH levels dropped but after 2 months TSH recovered previous levels while thyroid hormones remained unchanged. Concomitantly nocturnal TSH secretion assessed before and after BC treatment showed a decrease of 38% in the TSH nocturnal surge and 36% in the TSH nadir. Without any adverse effects, goiter size diminished markedly and even after BC withdrawal remained of normal size.

In the same patient a short course of 3 μg/kg/day of LT_4 led to overt hyperthyroidism (tachycardia, profuse sweating, and anxiety) and had to be stopped.

Regarding treatment to improve learning and psychiatric manifestations, a methylphenidate trial to improve school performance in patient 4 worsened tachycardia and had little effect on attention. Assuming that central hyperthyroidism might account for her abnormal behavior, and in an attempt to smooth her aggressive disorder, MMI plus T_4 treatment was installed as proposed by Kim [18]. A large goiter developed and antithyroid drugs were stopped. Goiter decreased after withdrawal. Now the patient is receiving atenolol and antipsychiatric treatment, and undergoing special education. On the other hand, clonazepam on patient 1 has improved attention and shown to be useful to treat his anxious disorder.

Patients were followed over a period of 3–20 years with one patient lost after 4 years. Evolution and treatment during follow-up are shown in Table 3.

Height achieved was always normal in accordance to target height and BMI was in the normal range except in the celiac patient. Five patients went into puberty during

follow-up. In three (two girls and a boy), puberty started and progressed normally while two boys had a late and slow progression of pubertal development.

IQ was normal in five patients and borderline (73) in one. In this girl, ADDH worsened with age with striking learning problems due to aggressive psychiatric symptoms and poor attention. Attention was altered too but without affecting learning in a patient who developed a mild phobic anxious-depressive psychiatric disorder.

AbTPO, initially positive in two patients, became positive in another two subjects during follow-up.

Discussion

RTH has to be suspected in children with the characteristic thyroid profile of high thyroid hormone levels with inappropriate detectable TSH. In them, clinical findings will vary depending on the degree of resistance in the pituitary and peripheral tissues [1–4].

In five of our six patients clinical findings were scarce and three of them underwent erroneous treatments for misinterpreted thyroid abnormalities. Likewise, the four affected parents showed more subtle alterations of the thyroid profile, with lower levels of thyroid hormone needed to keep TSH in almost the same levels as their children, and three of them were completely asymptomatic.

This situation points out to the already described variability and rather benign condition of RHT in some patients and the fact that RHT is sometimes found when thyroid function is included in the routine evaluation of some patients.

After the finding of the characteristic thyroid profile, evaluation of the effect of T_3 to determine the sensitivity of central and peripheral tissues to thyroid hormone was used to reach diagnosis.

This test has the disadvantage of the high peripheral marker variability of thyroid hormone action as was observed in our patients' SHBG response. Moreover, the discomfort produced by reversible hyperthyroidism of variable degree may prevent its use in childhood [3, 19].

Genetic testing for RTH allowed for a definitive diagnosis in all our patients and four affected parents. The four mutations found were placed in exon 9 (4/5) and 10 (1/5) of the THβ gene affecting the T_3 binding domain [15, 16].

Nowadays, with the availability of molecular studies and more sensitive hormone determinations and when considering RTH diagnosis, parents should be investigated and molecular testing is required. The extensive diagnostic testing as performed in our cohort maybe reserved for patients with de novo RTH and without mutations in TRβ beta gene or to complete the differential diagnosis between RTH and TSH-secreting pituitary adenoma [19].

As reported, RTH clinical phenotype varied [20, 21]. In four of our patients RTH seemed to be a benign condition but two patients without signs or data that could predict their evolution developed severe psychiatric manifestations.

However, although with different manifestation severity, goiter, tachycardia, and learning disabilities were the most frequent signs in our pediatric patients, and tachycardia and depression the main features in the most-affected mother.

Goiter was always diffuse, and the coexistence of tachycardia in two patients induced to misleading diagnoses of Graves' disease and erroneous treatment with antithyroid drugs. This treatment invariably rendered patients hypothyroid and worsened goiter. This happened also during follow-up in patient 4 in whom MMI was administered following Kim and Travers experience [18]. The large goiter developed without significant clinical improvement points towards the risk of this therapeutic approach, which has to be used with caution in RTH.

On the other hand, BC was useful to treat goiter. In RTH, this antidopaminergic drug modulates TSH production and enhances bioactivity [22]. In our patient, TSH nocturnal secretion was lowered but thyroid profile did not normalize. Unfortunately bioactivity was not measured.

Cardiac involvement, the most consistent finding in adults with RTH, affected our patients too. Myocardium expresses mostly TRα that are usually normal in the affected individuals and responsive to high levels of thyroid hormones [2, 21]. Nevertheless, although almost all our patients had tachycardia, only one, the most severely affected, needed permanent β blockade.

Finally, regarding learning disability produced by attention disorder one of our patients was classified as ADD, another as ADDH, and in the third patient learning was impaired while hypothyroid under MMI treatment.

ADD was found to be frequent in RTH children and it was reported that 70% of them and 50% of RTH adults met criteria for ADDH [23]. Nevertheless, a previous study has suggested that RTH only reduces the threshold for a predisposition for ADDH [21, 24].

MMI withdrawal recovered attention and learning capacity in one patient but in the others ADD and ADDH were very difficult to treat.

The same happened with psychiatric manifestations in which the use of antipsychiatric drugs has to be careful. While the patient with the anxious disorder improved with anxiolytic treatment, methylphenidate was useless and potentially harmful in patient 4 considering her cardiac involvement.

Although failure to thrive has been described in THR, our patients grew normally and those who attained final height are within their genetic target range. BMI was abnormal only in the celiac patient in whom other causes of poor weight gain maybe present [21].

Coinciding with previous reports, AbTPO became positive during evolution in four of our patients [25, 26]. The prevalence of AbTPO found is higher than the one expected for the pediatric population of iodide-sufficient areas [27, 28]. Recently Barkof et al. have demonstrated the autoimmune coexistence in RTH proposing the stimulation of the immune system at TRα's level as the underlying mechanism [26]. Frequently associated autoimmunity delays diagnosis, as happened in our celiac patient, and complicates the correct follow-up because the thyroid profile may change reflecting a variable hypothyroid state [29].

No treatment is available yet to correct the underlying defect in RTH. Therapy has to be evaluated carefully with the aim of producing no further harm and decisions depend on the individual characteristics of each patient. Moreover, treatment of RTH in childhood requires careful monitoring to avoid growth retardation and/or cognitive impairment.

Asymptomatic individuals do not need treatment and depending on clinical features patients may require thyroid hormone supply, cardiac β blockers, dopaminergic agonists or analogs of thyroid hormone as TRIAC, anxiolytic or antipsychiatric medications.

Regarding TRIAC, it has been proposed for RTH treatment with generally good results. Its higher affinity for mutant TRβ than T_3 helps to overcome the dominant negative effect. Evidence on improvement of the clinical picture without changes in the thyroid profile of some RTH patients suggests normalization of TSH bioactivity as well. Reported benefits vary from decrease in TSH levels to subjective changes. Nevertheless, due to some intrinsic metabolic activity some changes opposite to that expected were observed in some cases. [20, 30–32]. Two of our patients experienced subjective improvement but it is difficult to assess who would be candidates for this treatment.

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 [33]. Moreover, molecular engineering may provide novel therapeutic approaches and it is possible to speculate that genetic strategies prompted to inhibit mutated TRβ gene expression maybe considered as a specific and individual therapy for RTH patients [34].

Our observations indicate that RTH has a distinctive biochemical profile. Molecular diagnosis, currently more available, allows fast and definitive diagnoses.

Clinical variability involved thyroid gland; heart and learning in our cohort pointed out that these symptoms have to be looked in patients with suspected RTH.

Severity of outcome or response to treatment could not be predicted either on molecular or clinical bases. Moreover, in the majority of cases as well as in RTH parents, the disorder seemed to be benign and without any significant clinical burden.

Due to the heterogeneous nature of RTH each patient has to be evaluated individually and followed up. This should also be kept in mind when deciding to treat or not to treat, how and when to initiate, modify or halt therapy.

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References

1. S. Refetoff, R. Weiss, S. Usala, The syndromes of resistance to thyroid hormone. Endocr. Rev. **14**, 348–399 (1993)
2. S. Refetoff, A.M. Dumitrescu, Syndromes of reduced sensitivity to thyroid hormone: genetic defects in hormone receptors, cell transporters and deiodination. Best Pract. Res. Clin. Endocrinol. Metab. **21**(2), 277–305 (2007)
3. K.K. Chaterjee, Resistance to thyroid hormone. Horm. Res. **48**(4), 43–46 (1997)
4. P. Beck-Peccoz, V.K.K. Chatterjee, The variable clinical phenotype in thyroid hormone resistance syndrome. Thyroid **4**, 225–232 (1994)
5. R.E. Weiss, S. Refetoff, Resistance to thyroid hormone. Rev. Endocr. Metab. Disord. **1**, 97–1086 (2000)
6. S.H. LaFranchi, D.B. Snyder, D.E. Sesser, M.R. Skeels, N. Singh, G.A. Brent, J.C. Nelson, Follow-up of newborns with elevated screening T_4 concentrations. J. Pediatr. **143**, 296–301 (2003)
7. A. Sakurai, A. Nakai, L.J. De Groot, Structural analyses of human thyroid receptor βgene. Mol. Cell. Endocrinol. **71**, 83–91 (1990)
8. M. Alonso, C. Goodwin, X. Liao, T. Ortiga-Carvalho, D.S. Machado, F.E. Wondisford, S. Refetoff, R.E. Weiss, In vivo interaction of steroid receptor coactivator (SRC)-1 and the activation function-2 domain of the thyroid hormone receptor (TR) beta in TRbeta E457A knock-in and SRC-1 knockout mice. Endocrinology **150**(8), 3927–3934 (2009)
9. R.E. Weiss, Y. Hayashi, T. Nagaya, K.J. Petty, Y. Murata, H. Tunca, H. Seo, S. Refetoff, 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. Clin. Endocrinol. Metab. **81**, 4196–4203 (1996)
10. J. Pohlenz, R.E. Weiss, P. Macchia, S. Pannain, I.T. Lau, H. Ho, S. Refetoff, Five new families with resistance to thyroid hormone not caused by mutations in the thyroid hormone receptor β gene. J. Clin. Endocrinol. Metab. **84**, 3919–3928 (1999)
11. B. Hamon, P. Hamon, M. Bovier-Lapierre, M. Pugeat, F. Savagner, P. Rodien, J. Orgiazzi, A child with resistance to thyroid hormone without thyroid hormone gene mutation: a 20 year follow up. Thyroid **18**, 1 35–1 44 (2008)
12. S. Refetoff, Resistance to thyroid hormone: one of several defects causing reduced sensitivity to thyroid hormone. Nat. Clin. Pract. Endocrinol. Metab. **4**(1), 1 (2008)
13. A. Sakurai, T. Miyamoto, S. Refetoff, L. De Groot, Dominant negative transcriptional regulation by a mutant thyroid receptor β in a family with generalized thyroid hormone resistance. Mol. Endocrinol. **4**, 1988–1994 (1990)

14. D. Sarne, S. Sobieszczyk, K. Ain, S. Refetoff, Serum thyrotropin and prolactin in the syndrome of generalized resistance to thyroid hormone: responses to thyrotropin releasing hormone stimulation and short term triiodotironine suppression. J. Clin. Endocrinol. Metab. **70**, 1305–1311 (1990)
15. M. di Fulvio, A. Chiesa, Baranzini, L. Gruñeiro-Papendieck, A. Masini Repiso, H. Targovnik, A new point mutation (M313T) in the thyroid hormone receptor beta gene in a patient with resistance to thyroid hormone. Thyroid **7**(1), 43–45 (1997)
16. C.M. Rivolta, M.C. Olcese, F. Belforte, A. Chiesa, L. Gruñeiro-ppaendieck, S. Iorcansky, V. Herzovich, F. Cassorla, G. Gauna, G. Gonzalez Sarmiento, H. Targovnik, Genotyping of resistance to thyroid hormone in South American population. Identification of seven novel missense mutations in the human thyroid hormone receptor b gene. Mol. Cell. Probes **23**(3–4), 148–153 (2009)
17. D.R. Bajorunas, W. Rosner, I.A. Kourides, Use of bromocriptine in a patient with generalized resistance to thyroid hormone. J. Clin. Endocrinol. Metab. **58**(4), 731–735 (1984)
18. T.J. Kim, S. Travers, Case report: thyroid hormone resistance and its therapeutic challenges. Curr. Opin. Pediatr. **20**(4), 490–493 (2008)
19. R.E. Weiss, They have ears but do not hear (Psalms 135:17): non-thyroid hormone receptor beta (non-TRbeta) resistance to thyroid hormone. Thyroid **18**(1), 3–5 (2008)
20. O. Ercan, Thyroid hormone resistance in children. Pediatr. Endocrinol. Rev. **1**(2), 191–197 (2003)
21. F. Brucker Davis, M.C. Skarutis, M.B. Grace, J. Benichou, P. Hauser, E. Wiggs, B.D. Weintraub, Genetic and clinical features of 42 kindreds with resistance to thyroid hormone. Ann. Inter. Med. **123**, 572–583 (1995)
22. L. Persani, C. Asteria, M. Tonacchera, P. Vitti, V.K.K. Chatterjee, P. Beck-Peccoz, Evidence for the secretion of thyrotropin with enhanced bioactivity in syndromes of thyroid hormone resistance. J. Clin. Endocrinol. Metab. **78**, 1034–1039 (1994)
23. P. Hauser, A.J. Zametkin, P. Martinez, B. Vitiello, J.A. Matochik, A.J. Mixson, B.D. Weintraub, Attention deficit hyperactivity disorder in people with generalized resistance to thyroid hormone. N. Engl. J. Med. **328**, 997–1001 (1993)
24. S. Refetoff, H. Tunca, D.L. Wilansky, V.C. Mussey, R.E. Weiss et al., Mutation in the thyroid hormone receptor (TR) β gene (M313T) not previously reported in two unrelated families with resistance to thyroid hormone (RTH). Thyroid **6**(6), 571–573 (1996)
25. C. Gavin, H. Meggison, T.C. Ooi, Proposing a causal link between thyroid hormone resistance and primary autoimmune hypothyroidism. Med. Hypotheses **70**(5), 1024–1028 (2008)
26. M.S. Barkoff, M. Kocherginsky, J. Anselmo, R.E. Weiss, S. Refetoff, Autoimmunity in patients with resistance to thyroid hormone. J. Clin. Endocrinol. Metab. **95**(7), 3189–3193 (2010)
27. M. Kabelitz, K.P. Liesenkotter, B. Stach, H. Willgerodt, W. Stablein, W. Singendonk, E. Jager-Roman, H. Litzenborger, B. Ehnert, A. Gruters, The prevalence of anti-thyroid peroxidase antibodies and autoimmune thyroiditis in children and adolescents in an iodine replete area. Eur. J. Endocrinol. **148**(3), 301–307 (2003)
28. J.G. Hollowell, N.W. Staehling, W.D. Flanders, W.H. Hannon, E.W. Gunter, C.A. Spencer, L.E. Braverman, Serum TSH, T, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III)". J. Clin. Endocrinol. Metab. **87**(2), 489–499 (2002)
29. H.A. Tran, Difficulties in diagnosing and managing coexisting primary hypothyroidism and resistance to thyroid hormone. Endocr. Pract. **12**, 288–293 (2006)
30. T. Takeda, S. Suzuki, R.T. Liu, L. DeGroot, Triiodothyroacetic acid has unique potential for therapy of resistance to thyroid hormone. J. Clin. Endocrinol. Metab. **80 7**, 2033–2040 (1995)
31. P. Beck-Peccoz, G. Piscitelli, M.G. Cattaneo, G. Faglia, Treatment of hyperthyroidism due to non neoplastic pituitary TSH hypersecretion with 3, 5, 3′triiodothyrocatic acid (TRIAC). J. Endocrinol. Invest. **6**, 217–223 (1983)
32. G. Radetti, I. Persani, D. Molinaro, D. Mannavola, D. Cortelazzi, V.K.K. Chatterjee, P. Beck Peccoz, Clinical and hormonal outcome after two years of triiodothyroacetic acid treatment in a child with thyroid hormone resistance. Thyroid **7**(5), 775–778 (1997)
33. G. Chiellini, J.W. Apriletti, H.A. Yoshihara, J.D. Baxter, R.C.J. Ribeiro, T.S. Scanlan, A high-affinity subtype selective agonist ligand for thyroid hormone receptor. Chem. Biol. **5**, 299–306 (1998)
34. H.F. Ye, K.E. O'Reilly, J.T. Koh, A subtype-selective thyromimetic designed to bind a mutant thyroid hormone receptor implicated in resistance to thyroid hormone. J. Am. Chem. Soc. **123**, 1521–1522 (2001)