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Editorial: Treatment of Resistance to Thyroid Hormone—*Primum Non Nocere*

Resistance to thyroid hormone (RTH) is a dominantly inherited condition of impaired tissue responsiveness to thyroid hormone (TH). Of variable severity, the presence of goiter, tachycardia, hyperactivity, or abnormal findings on routine laboratory tests usually lead to further investigation and, ultimately, the diagnosis of RTH. Characteristic thyroid function tests are elevated free thyroxine (FT_4) and free triiodothyronine (FT_3) concentrations with nonsuppressed thyrotropin (TSH). Despite the high serum TH levels, TSH responds to stimulation with TSH-releasing hormone, and the doses of TH required to suppress TSH and to produce metabolic effects on peripheral tissues are higher than normal (1). The incidence of RTH is probably 1 case per 50,000 live births (2), with over 600 known cases [(3) and personal information].

With a single exception (4), RTH is caused by mutations in the thyroid hormone receptor (TR) β gene. Point mutations have been identified in affected subjects belonging to more than 150 families. The mutant TR molecules have either reduced affinity for T_3 (5) or impaired interaction with one of the cofactors involved in the mediation of TH action (6, 7). These mutant TRs interfere with the function of the normal TRs, which explains the dominant mode of inheritance. It is thus not surprising that, in the single family with deletion of all coding sequences of the TRβ gene, only homozygotes manifest RTH (8).

The clinical presentation of RTH is highly variable. The majority of individuals are completely asymptomatic. Some may manifest symptoms suggestive of TH deprivation such as growth retardation, impaired cognitive ability, and hypercholesterolemia, while others show signs of TH excess such as tachycardia, advanced bone age, or hyperactivity (9–11). Not uncommonly, individuals have symptoms of both TH deficiency and excess. Even more often, symptoms are subjective, and the signs are not specific for thyroid dysfunction. Other than assessment of TSH regulation by TH feedback, laboratory tests that measure most tissue responses to TH are insensitive and relatively nonspecific.

Subjects with RTH that appear to be eumetabolic and maintain a near normal serum TSH concentrations have been classified as having generalized resistance to TH (GRTH). In such individuals, the defect seems to be adequately compensated for by the high endogenous levels of TH. In contrast, some patients with TH levels that are not necessarily higher, appear to be hypermetabolic because they are restless, hyperactive, or have a rapid heart rate. Such individuals have been classified as having selective pituitary resistance to TH (PRTH). However this classification, based on clinical impression, is misleading and has no firm physiologic basis. In favor of PRTH are *in vitro* studies showing that some TRβ mutations appear to interfere more strongly with the negative (suppressive) than positive (stimulatory) effects of TH (12, 13). Yet subjects harboring these same mutations, and even belonging to the same family, have been classified as having GRTH and PRTH (14). Clinical studies have been unable to demonstrate that the peripheral tissues of patients with PRTH have different sensitivity to TH than those of patients with GRTH (15). It has been suggested that the subdivision of RTH into these two categories is an artifact arising from the subjective nature of the symptoms and the poor specificity of signs (11). The possibility of variable levels of expression of the mutant allele relative to the normal counterpart has been explored, but results have been inconsistent (16, 17). The most likely explanation for the variable clinical manifestations of this apparently monogenic condition is the genetic heterogeneity of the many cofactors [coactivators and corepressors (18)] that modulate the receptor-dependent action of TH (19).

Clinical and laboratory investigations and the more recent studies of molecularly engineered mice have provided some understanding regarding the apparent paradoxes in the expression of RTH. The reason for the nonsuppressed serum TSH levels in children and adults with RTH is evident given that their pituitary glands express the defective TRβ, which blunts the suppressive effect of TH. Studies of TRβ deficient mice further showed that the TRβ molecule is not necessary for the upregulation of TSH, but it is required for TH to exert its full suppressive effect (20). It has been less obvious how TSH levels within the normal range can produce a goiter and stimulate the thyroid gland to produce and secrete an increased amount of TH. Work from Professor Beck-Peccoz's laboratory, described by Persani et al. (21), has shown that the TSH circulating in subjects with RTH has an increased biological potency. Another explanation could be an augmented thyrocyte sensitivity to TSH through increased density of TSH receptor units. While elevated TH levels with normal or slightly increased TSH concentrations are present from birth (22–24) and persist throughout the life span of subjects with RTH, nothing is known regarding the state of these hormones during fetal life. Again, Professor Beck-Peccoz's group, in their report by Asteria et al., published in this issue of *JCEM* (see page 405), provides a preliminary look into the fetal pituitary-thyroid axis in a mother with RTH carrying a fetus expressing the same mutant TRβ molecule. Very high levels of TSH were found in the fetus, even though the mother was treated with triiodothyroacetic acid (TRIAC).

Although hearing defects are occasionally found in association with congenital hypothyroidism, severe sensorineural deafness is the hallmark of homozygous deletion of the

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TRβ gene in both humans and mice (25, 26). Mild forms of hearing impairment, due to recurrent ear infections, is more common in the dominantly inherited form of RTH (27). Careful evaluation of subjects with RTH has shown that one half have learning disabilities, often associated with attention deficit hyperactivity disorder (ADHD) and, on the average, lower intellectual quotients (IQ) (10, 28, 29). However, frank mental retardation (IQ $<$60) occurs in only 3% of the cases. Tachycardia occurs in 80–90% of subjects with RTH and, when symptomatic, is the reason that leads to the diagnosis of PRTH (11). It is caused by the excess of TH acting on the TRα gene. Indeed, TRβ-deficient RTH mice have a normal TH dependent increase in heart rate (30), while mice deficient in TRα1 manifest bradycardia (31). The only instance of death attributed to RTH is that of an 8-yr-old child, homozygous for a deletion of one amino acid in the TRβ molecule (32). The child succumbed to heart failure and sepsis.

No treatment is available to fully correct the defect causing RTH. The majority of individuals, if left alone, adequately compensate for the abnormal TRβ through increased TH secretion. By and large, treatment with TH is reserved for those who, due to misdiagnosis, have received ablative therapy and have, as a consequence, limited thyroidal reserve and for subjects in whom the compensation appears to be incomplete due to the concomitant presence of autoimmune thyroid disease. The optimal dose of TH is variable among individuals, and doses of L-T_4 as high as 1,000 μg per day may be necessary to achieve the desired effects. Reduction of the serum TSH concentration to normal is a convenient guide to therapy.

Some investigators have suggested that due to TSH hypersecretion such individuals may be more prone to develop thyrotropic adenomas. This has not been observed in RTH. The thyrotropic hyperplasia reported in a patient with RTH who received radioiodide rapidly regressed by treatment with sufficient amount of L-T_4 to normalize the serum TSH level (33). Using the same logic, the possible proneness of the hyperstimulated thyroid gland to neoplasia has been also considered. However, there is no increased incidence of thyroid cancer in RTH. Goiters are usually small, are rarely obstructive, and should be left alone.

More difficult is the treatment of patients with RTH in whom apparent hypothyroidism at the level of peripheral tissues is not accompanied by an increase in the serum TSH concentration. In such individuals, the judicious administration of supraphysiological doses of TH requires careful monitoring. Markers of TH action such as serum sex hormone binding globulin, cholesterol, and ferritin, basal metabolic rate, bone density, and urinary hydroxyproline should be carefully monitored. Treatment with L-T_3 may improve the symptoms of ADHD in a significant proportion of children that also have RTH (34).

Equally difficult is the treatment of subjects with RTH who complain of symptoms suggestive of hypermetabolism. Because the findings are often subjective and nonspecific, it is difficult to assess to what extent these symptoms are caused by the high TH levels acting predominantly on peripheral tissues. The first line of treatment of these patients should be symptomatic. Atenolol is very effective in treating tachycardia and tremor without affecting the conversion of T_4 to T_3. Antianxiety drugs can help alleviate symptoms of nervousness. Treatment with agents with the potential to decrease the levels of TH through suppression of TSH has received much attention. Dopaminergic drugs and somatostatin analogs have had limited use because of side effects and low success rate in maintaining TSH suppression. TRIAC has been used successfully to decrease the serum TSH and TH levels, to reduce goiter size, and to alleviate some of the symptoms attributed to the effect of TH on peripheral tissues (35). However, the concomitant effects of TRIAC on markers that measure TH action on peripheral tissues (see above), as well as on heart rate, are minimal (36) probably because the decrease in TH levels is offset by the intrinsic thyromimetic effect of TRIAC (37). The ability of TRIAC to suppress TSH without an increase in the thyromimetic effect on peripheral tissues is due to two properties of this TH analog: its higher affinity for the β but not α TR as compared with T_3, and the more rapid degradation of TRIAC (38, 39). The mechanism mediating a similar effect attributed to D-T_4 is less well understood.

RTH is more frequently being diagnosed in infancy owing to routine neonatal screening programs that measure both TSH and T_4 and to hormonal and DNA analyses performed in infants born to parents known to have RTH. Early diagnosis provides the opportunity for early treatment, although the wisdom of such treatment is controversial as there are no data regarding the long-term outcome. General guidelines for the treatment with TH, usually L-T_4, are: 1) elevated serum TSH levels; 2) failure to thrive that cannot be explained on the basis of another illness or defect; 3) unexplained seizures; 4) developmental delay; and 5) history of growth or mental retardation in affected members of the family. It has been hypothesized that the development of a fetus that has inherited RTH from the father may be jeopardized because of the exposure to lower levels of TH derived from his normal mother. In fact, there is a significantly higher prevalence of goiter and short stature in children with RTH born to normal mothers compared with those born to affected mothers (10).

In a bold study in this issue of *JCEM* (see page 405), Asteria *et al.* (40) present a 29-yr-old pregnant woman with RTH in whom treatment with TRIAC before pregnancy, was successful in controlling symptoms of TH excess. Symptoms recurred after the discontinuation of TRIAC for fear of adverse effect to the fetus. When genotyping of the fetus, through chorionic villi sampling, established that it shared the maternal mutant TRβ allele, the authors felt justified to reinstate TRIAC treatment to the mother at 20 weeks gestation. The mother's symptoms were controlled, but fetal goiter, not seen at 24 weeks, appeared on ultrasound examination at 29 weeks of intrauterine life. In addition the fetus showed mild growth retardation. This prompted fetal blood sampling by chordocentesis, which revealed a very high TSH level of low bioactivity compared with normal fetuses. The authors interpreted these findings as indicative of fetal hypothyroidism and acted by increasing the dose of TRIAC given to the mother, in an attempt to suppress fetal TSH by increasing the amount of TRIAC transferred to the fetus. At 33 weeks the goiter had decreased in size; however, acute life-threatening fetal complications during repeat chordocentesis necessitated a prompt delivery by cesarean section.

After a stormy early life, complicated by multiple organ failure, the infant made a remarkable recovery and, at 2 yr of age and on no treatment, has normal stature and mental development and no goiter.

In their conclusions, the authors "advocate prenatal diagnosis of RTH" and treatment of maternal "hyperthyroidism, to avoid thyrotropic hyperplasia" and "reduce fetal goiter." We believe that it is incorrect to advocate such aggressive management of pregnant women and their feti with RTH, especially given the current report. The treatment efforts to control maternal symptoms, the importance of which are difficult to assess without objective measurements of metabolic parameters, and the measures taken to monitor the effect of the treatment on the fetus have resulted in morbidity well beyond that expected to occur without any intervention under the same circumstances. The challenging suggestions made by the authors pose very important questions that need to be answered before condoning their approach. How can the metabolic status of the fetus be assessed when we lack specific markers to evaluate adults and children? How can we be sure that goiter, which has been observed at birth in many infants with RTH, is not more prominent and a common finding during the second third of fetal life? Is a high fetal TSH concentration a common occurrence in RTH as a consequence of reduced bioactivity? The absolute bioactive level of the fetal TSH was close to the upper limit of normal for gestational age if one takes into account the measured 11- and 7-fold reduction in bioactivity, at 29 and 33 weeks gestation, respectively. Finally, to what extent treatment with TRIAC has affected the fetal findings when the amount of TRIAC transferred to and metabolized by the fetus are unknown? While answers to these questions cannot be obtained by simple, noninvasive means, serial ultrasonograms of feti with RTH should provide data on the frequency and evolution of goiter. Intrauterine growth and development of feti with and without RTH in affected or unaffected mothers can be assessed and retrospectively analyzed upon determination of the genotype and phenotype after birth.

Until such information is gathered, we propose treatment of symptomatic mothers with a β-blocker, recognizing that the small risk is not comparable with that of chordocentesis. Whereas the goal of management of subjects with RTH, pregnant or not, is to maintain a normal serum TSH level and an eumetabolic state, it would seem premature to advocate intrauterine diagnosis without the knowledge of how to interpret the results of the tests. Proper diagnosis, noninvasive follow-up, and symptomatic treatment fulfill the enduring dictum "*primum non nocere.*"

In this age of rapidly advancing knowledge, it is reasonable to expect that the not too distant future will bring specific treatments for RTH. This will probably not be in the form of gene therapy as the dominant expression would require excision of the defective gene. The most simple genetic approach, one within the realm of current technology, is the selection of an oocyte from the affected mother that does not harbor the abnormal allele for *in vitro* fertilization followed by implantation into the donor. This insures a fetus without RTH but does not guarantee a normal pregnancy and fetal development. The development of TH agonists and antagonists that are TR-isoform specific would allow the stimulation or blockade of specific tissue effects that are perturbed in a given individual with RTH.

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References

1. **Refetoff S, Weiss RE.** 1997 Resistance to thyroid hormone. In: Thakker TV, ed. Molecular genetics of endocrine disorders. London: Chapman & Hill; 85–122.
2. **Snyder D, Sesser D, Skeels M, Nelson G, LaFranchi S.** 1997 Thyroid disorders in newborn infants with elevated screening T4. Thyroid. 7(suppl 1):S-29. (Abstract).
3. **Announcement.** 1994 A registry for resistance to thyroid hormone. Mol Endocrinol. 8:1558.
4. **Weiss RE, Hayashi Y, Nagaya T, et al.** 1996 Dominant inheritance of resistance to thyroid hormone not linked to defects in the thyroid hormone receptors α or β genes may be due to a defective co-factor. J Clin Endocrinol Metab. 81:4196–4203.
5. **Hayashi Y, Weiss RE, Sarne DH, et al.** 1995 Do clinical manifestations of resistance to thyroid hormone correlate with the functional alteration of the corresponding mutant thyroid hormone-β receptors? J Clin Endocrinol Metab. 80:3246–3256.
6. **Yoh SM, Chatterjee VKK, Privalsky ML.** 1997 Thyroid hormone resistance syndrome manifests as an aberrant interaction between mutant T_3 receptor and transcriptional corepressor. Mol Endocrinol. 11:470–480.
7. **Liu Y, Takeshita A, Misiti S, Chin WW, Yen PM.** 1998 Lack of coactivator interaction can be a mechanism for dominant negative activity by mutant thyroid hormone receptors. Endocrinology. 139:4197–4204.
8. **Takeda K, Sakurai A, DeGroot LJ, Refetoff S.** 1992 Recessive inheritance of thyroid hormone resistance caused by complete deletion of the protein-coding region of the thyroid hormone receptor-β gene. J Clin Endocrinol Metab. 74:49–55.
9. **Refetoff S, Weiss RE, Usala SJ.** 1993 The syndromes of resistance to thyroid hormone. Endocr Rev. 14:348–399.
10. **Brucker-Davis F, Skarulis MC, Grace MB, et al.** 1995 Genetic and clinical features of 42 kindreds with resistance to thyroid hormone. The National Institutes of Health prospective study. Ann Intern Med. 123:573–583.
11. **Beck-Peccoz P, Chatterjee VKK.** 1994 The variable clinical phenotype in thyroid hormone resistance syndrome. Thyroid. 4:225–232.
12. **Clifton-Bligh RJ, de Zegher F, Wagner RL, et al.** 1998 A novel mutation (R383H) in resistance to thyroid hormone syndrome predominantly impairs corepressor release and negative transcriptional regulation. Mol Endocrinol. 12:609–621.
13. **Safer JD, Langlois MF, Cohen R, et al.** 1997 Isoform variable action among thyroid hormone receptor mutants provides insight into pituitary resistance to thyroid hormone. Mol Endocrinol. 11:16–26.
14. **Adams M, Matthews C, Collingwood TN, Tone Y, Beck-Peccoz P, Chatterjee KK.** 1994 Genetic analysis of 29 kindreds with generalized and pituitary resistance to thyroid hormone: identification of thirteen novel mutations in the thyroid hormone receptor β gene. J Clin Invest. 94:506–515.
15. **Beck-Peccoz P, Roncoroni R, Mariotti S, et al.** 1990 Sex hormone-binding globulin measurement in patients with inappropriate secretion of thyrotropin (IST): Evidence against selective pituitary thyroid hormone resistance in non-neoplastic IST. J Clin Endocrinol Metab. 71:19–25.
16. **Mixson AJ, Hauser P, Tennyson G, Renault JC, Bodenner DL, Weintraub BD.** 1993 Differential expression of mutant and normal beta T3 receptor alleles in kindreds with generalized resistance to thyroid hormone. J Clin Invest. 91:2296–2300.
17. **Hayashi Y, Janssen OE, Weiss RE, Murata Y, Seo H, Refetoff S.** 1993 The relative expression of mutant and normal thyroid hormone receptor genes in patients with generalized resistance to thyroid hormone determined by estimation of their specific messenger ribonucleic acid products. J Clin Endocrinol Metab. 76:64–69.
18. **Koenig RJ.** 1998 Thyroid hormone receptor coactivators and corepressors. Thyroid. 8:703–713.
19. **Weiss RE, Marcocci C, Bruno-Bossio G, Refetoff S.** 1993 Multiple genetic factors in the heterogeneity of thyroid hormone resistance. J Clin Endocrinol Metab. 76:257–259.
20. **Weiss RE, Forrest D, Pohlenz J, Cua K, Curran T, Refetoff S.** 1997 Thyrotropin regulation by thyroid hormone in thyroid hormone receptor β-deficient mice. Endocrinology. 138:3624–3629.
21. **Persani L, Asteria C, Tonacchera M, Vitti P, Chatterjee VKK, Beck-Peccoz P.** 1994 Evidence for secretion of thyrotropin with enhanced bioactivity in syndromes of thyroid hormone resistance. J Clin Endocrinol Metab. 78:1034–1039.
22. **Weiss RE, Balzano S, Scherberg NH, Refetoff S.** 1990 Neonatal detection of generalized resistance to thyroid hormone. JAMA. 264:2245–2250.
23. **Poitrineau P, Malpuech G, Nivelon JL, et al.** 1993 Découverte, à partir du

dépistage néonatal, de deux families porteuses du syndrome de résistance généralisée aux hormones thyroïdiennes. Ann Pediatr (Paris). 40:396–403.
24. **Wong GWK, Shek CC, Lam STS, Tsui MKM, Leung SSF.** 1995 Detection of resistance to thyroid hormone by cord blood screening. Acta Paediatr. 84:335–336.
25. **Refetoff S, DeWind LT, DeGroot LJ.** 1967 Familial syndrome combining deaf-mutism, stippled epiphyses, goiter, and abnormally high PBI: possible target organ refractoriness to thyroid hormone. J Clin Endocrinol Metab. 27:279–294.
26. **Forrest D, Erway LC, Ng L, Altschuler R, Curran T.** 1996 Thyroid hormone receptor β is essential for development of auditory function. Nature Genet. 13:354–357.
27. **Brucker-Davis F, Skarulis MC, Pikus A, et al.** 1996 Prevalence and mechanisms of hearing loss in patients with resistance to thyroid hormone. J Clin Endocrinol Metab. 81:2768–2772.
28. **Hauser P, Zametkin AJ, Martinez P, et al.** 1993 Attention deficit-hyperactivity disorder in people with generalized resistance to thyroid hormone. N Engl J Med. 328:997–1001.
29. **Weiss RE, Stein MA, Duck SC, et al.** 1994 Low intelligence but not attention deficit hyperactivity disorder is associated with resistance to thyroid hormone caused by mutation R316H in the thyroid hormone receptor β gene. J Clin Endocrinol Metab. 78:1525–1528.
30. **Weiss RE, Murata Y, Cua K, et al.** 1998 Thyroid hormone action on liver, heart and energy expenditure in thyroid hormone receptor β deficient mice. Endocrinology. 139:4945–4952.
31. **Wikstsöm L, Johansson C, Salto C, et al.** 1998 Abnormal heart rate and body temperature in mice lacking thyroid hormone receptor α1. EMBO J. 17:455–461.
32. **Ono S, Schwartz ID, Mueller OT, Root AW, Usala SJ, Bercu BB.** 1991 Homozygosity for a "dominant negative" thyroid hormone receptor gene responsible for generalized resistance to thyroid hormone. J Clin Endocrinol Metab. 73:990–994.
33. **Gurnell M, Rajanayagam O, Barbar I, Keston Jones M, Chatterjee VKK.** 1998 Reversible pituitary enlargement in the syndrome of resistance to thyroid hormone. Thyroid. 7:678–682.
34. **Weiss RE, Stein MA, Refetoff S.** 1997 Behavioral effects of liothyronine ($L\text{-}T_3$) in children with attention deficit hyperactivity disorder in the presence and absence of resistance to thyroid hormone. Thyroid. 7:389–393.
35. **Beck-Peccoz P, Piscitelli G, Cattaneo MG, Faglia G.** 1983 Effectiveness of 3,5,3′-triiodothyroacetic acid (TRIAC), but not bromocriptine, in lowering TSH secretion in one hyperthyroid patient with non-neoplastic pituitary TSH hypersecretion. Ann d'Endocrinol. 44:38A. (Abstract).
36. **Weiss RE.** 1999 Management of patients with resistance to thyroid hormone. Thyroid Today. 12:1–11.
37. **Kunitake JM, Hartman N, Henson LC, et al.** 1989 3,5,3′-triiodothyroacetic acid therapy for thyroid hormone resistance. J Clin Endocrinol Metab. 69:461–466.
38. **Schueler PA, Schwartz HL, Strait KA, Mariash CN, Oppenheimer JH.** 1990 Binding of 3,5,3′-triiodothyronine (T3) and its analogs to the *in vitro* translational products of c-erbA protooncogenes: Differences in the affinity of α- and β-forms for the acetic acid analog and failure of the human testis and kidney α-2 products to bind T3. Mol Endocrinol. 4:227–234.
39. **Takeda T, Suzuki S, Liu R-T, DeGroot LJ.** 1995 Triiodothyroacetic acid has unique potential for therapy of resistance to thyroid hormone. J Clin Endocrinol Metab. 80:2033–2040.
40. **Asteria C, Rajanayagam O, Collingwood TN, et al.** 1999 Prenatal diagnosis of thyroid hormone resistance. J Clin Endocrinol Metab. 84:405–410.