

Syndromes of Resistance to Thyroid Hormone

Roy E. Weiss and Samuel Refetoff

Key Points

Syndromes of resistance to thyroid hormone are a heterogeneous group of disorders.

RTH is mostly caused by mutations in the thyroid hormone receptor β gene.

Diagnosis is based on persistent elevations of serum free thyroxine and often triiodothyronine levels in absence of thyroid-stimulating hormone (thyrotropin) suppression.

The key clinical feature is goiter, followed by palpitations and attention-deficit/hyperactivity disorder.

The best treatment is to ensure that inadvertent thyroid gland ablation or surgical removal is not done.

Resistance to thyroid hormone (RTH), a syndrome of reduced end-organ responsiveness to thyroid hormone (TH), was described in 1967.¹ Various mechanisms to explain the syndrome were postulated, including defects in TH transport, metabolism, and action.² Subsequent to the identification of TH receptor (TR) β gene mutations,^{3,4} the term *RTH* became synonymous with defects of the TR.⁵ The recent discoveries of genetic defects that reduce the effectiveness of TH through altered cell membrane transport (see Chapter 22) and metabolism⁶ have broadened the definition of TH insensitivity to encompass all defects that can interfere with the biologic activity of a chemically intact hormone secreted in normal amounts. In this chapter, use of the acronym *RTH* is limited to the syndrome produced by reduced intracellular action of the active TH, triiodothyronine (T_3).

Expression of TH effects requires the presence of sufficient amount of the active hormone T_3 within the cell. Rapid nongenomic action is exerted at the level of the plasma membrane and cytoplasm.⁷ However, the principal, best-studied, and characterized effect requires the translocation of the hormone into the nucleus, where it interacts with TRs to activate or repress transcription of specific target genes. These genes contain nucleotide sequences at or near their promoter regions (TH response elements, or TREs) recognized by TRs for binding. In the absence

of TH, TRs associate with other molecules, most notably the coregulator retinoid X receptor (RXR), and corepressors. These complexes have silencing effect on genes positively regulated by TH. The latter undergo conformational changes initiated by T_3 binding, which in turn trigger a chain of processes including release of the corepressor and recruitment of coactivators and a large number of other proteins. In positively controlled genes, this results in making the DNA more accessible for transcription.⁸

The cardinal features of RTH are elevated serum levels of free thyroxine (T_4) and often free T_3 , normal or slightly increased serum thyrotropin (TSH), and absence of typical symptoms and metabolic consequences of TH excess.^{5,9} Theoretically, interference at any step in the pathway following hormonogenesis that leads to hormone action would result in resistance. Whereas those caused by defective transport into the cell, subsequent metabolism, and action at the TR have been identified, defects in cytosolic action, translocation into the nucleus, and cofactors interacting with the TR remain to be elucidated (Fig. 21-1). If the defect responsible for TH action were restricted to specific organs or tissues, then the particular tissue would be hypothyroid relative to unaffected tissues, despite normal TH levels. More commonly, the hyposensitivity of the pituitary to TH produces an increase in TSH secretion, causing an increase in the circulating levels of TH

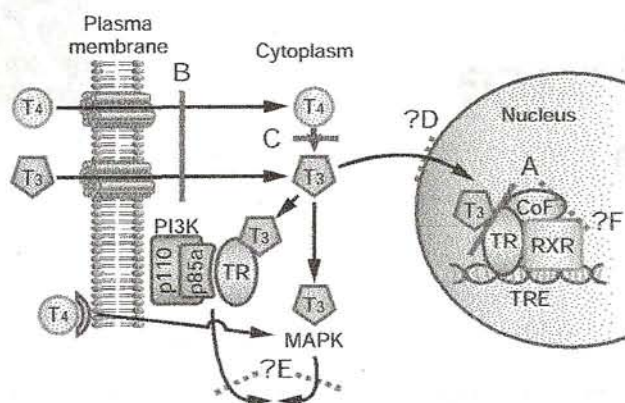


Figure 21-1 Sites of disruption of posthormonogenesis pathways involved in thyroid hormone (TH) activity. The most common cause of resistance to thyroid hormone (RTH), as described in this chapter, is impaired action of the TH receptor (A). However, a defect in transport of TH into the cell (B) as seen in *MCT8* mutations (see Chapter 22) or a defect in the conversion of thyroxine (T_4) to triiodothyronine (T_3), as seen in *SECISBP2* mutations,⁶ can occur (C). Although possible but not yet described, impaired T_3 and TR translocation to the nucleus (D) or defects in nongenomic pathways of TH action (E) can be hypothesized. In addition, a defective cofactor interaction with thyroid hormone receptor (TR) (F) may also be responsible for non-thyroid hormone receptor resistance to thyroid hormone.

(Fig. 21-2). This provides compensation to tissues that are equally resistant whereas other tissues, such as the heart, which are primarily dependent on the $TR\alpha$ isoform, manifest signs of TH hormone excess.

The two TRs encoded by different genes, $TR\alpha$ and $TR\beta$, are of similar structure.¹⁰ They are members of the nuclear receptor superfamily that include, among others, receptors for vitamin D, glucocorticoids, mineralocorticoids sex hormones, retinoic acid, retinoid X (RXR), and the peroxisome proliferator-activated receptor (PPAR).¹¹⁻¹⁵ Defects in all these receptors produce syndromes reflecting the resulting reduced sensitivity to the cognate hormone.¹⁶⁻²¹ The lack of other mechanisms causing resistance in hormones other than the thyroid likely reflects our inability to predict the clinical consequences resulting from transport and activation defects for most hormones. In the case of RTH, 85% of affected individuals have a mutation of the *TR\beta* gene. The other 15% are presumed to have defects in cofactors or coregulators involved in the mediation of TH action at the nuclear level, although their precise nature remains unknown.²²⁻²⁴

Careful clinical evaluation of subjects with RTH-like syndromes can be helpful in determining the site of the defect (see later). For example, administration of incremental doses of T_3 and T_4 can identify a defect in iodothyronine metabolism when T_3

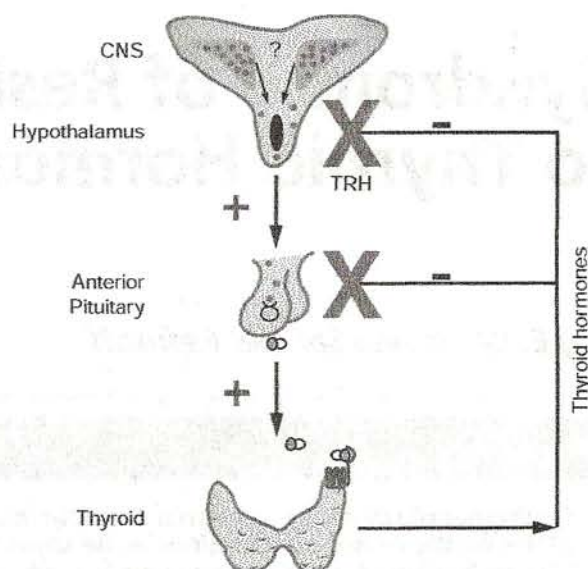


Figure 21-2 Regulation of thyroid hormone synthesis and secretion by the hypothalamus and pituitary. In resistance to thyroid hormone (RTH) syndrome, impaired feedback of thyroid hormone to the thyrotropes in the anterior pituitary and thyrotropin-releasing hormone (TRH) neurons in the hypothalamus result in increased stimulation of the thyroid gland to produce excess amounts of triiodothyronine and thyroxine. CNS, central nervous system. (Courtesy of Dr. Fredric Wondisford.)

but not T_4 appropriately suppresses the serum TSH.⁶ RTH, in contrast, will show resistance to the suppressive effects of both iodothyronines. Proper interpretation of seemingly paradoxical thyroid function tests is necessary for appropriate diagnosis. The purpose of this chapter is to present the methods available for diagnosis of RTH and suggest options for management of this condition.

EPIDEMIOLOGY, RISK FACTORS, PATHOGENESIS

The precise incidence of RTH is not known because it is usually not detected by routine neonatal screening for hypothyroidism, using blood spot TSH determination. A limited screen for high T_4 values found a prevalence of 1 in 40,000 live births.²⁵ Equal number of males and females are affected, although the prevalence of RTH without TR mutations is more common in females.²⁶

In most cases, RTH is caused by mutations in the *TR\beta* gene, located on chromosome 3. Mutations have been found in the carboxyl terminus of the $TR\beta$ covering the ligand-binding domain and adjacent hinge domain of the $TR\beta$ protein (Fig. 21-3).²⁷⁻²⁹ They are contained within three clusters rich in CG hot spots, separated by areas devoid of mutations (cold regions). The latter are located

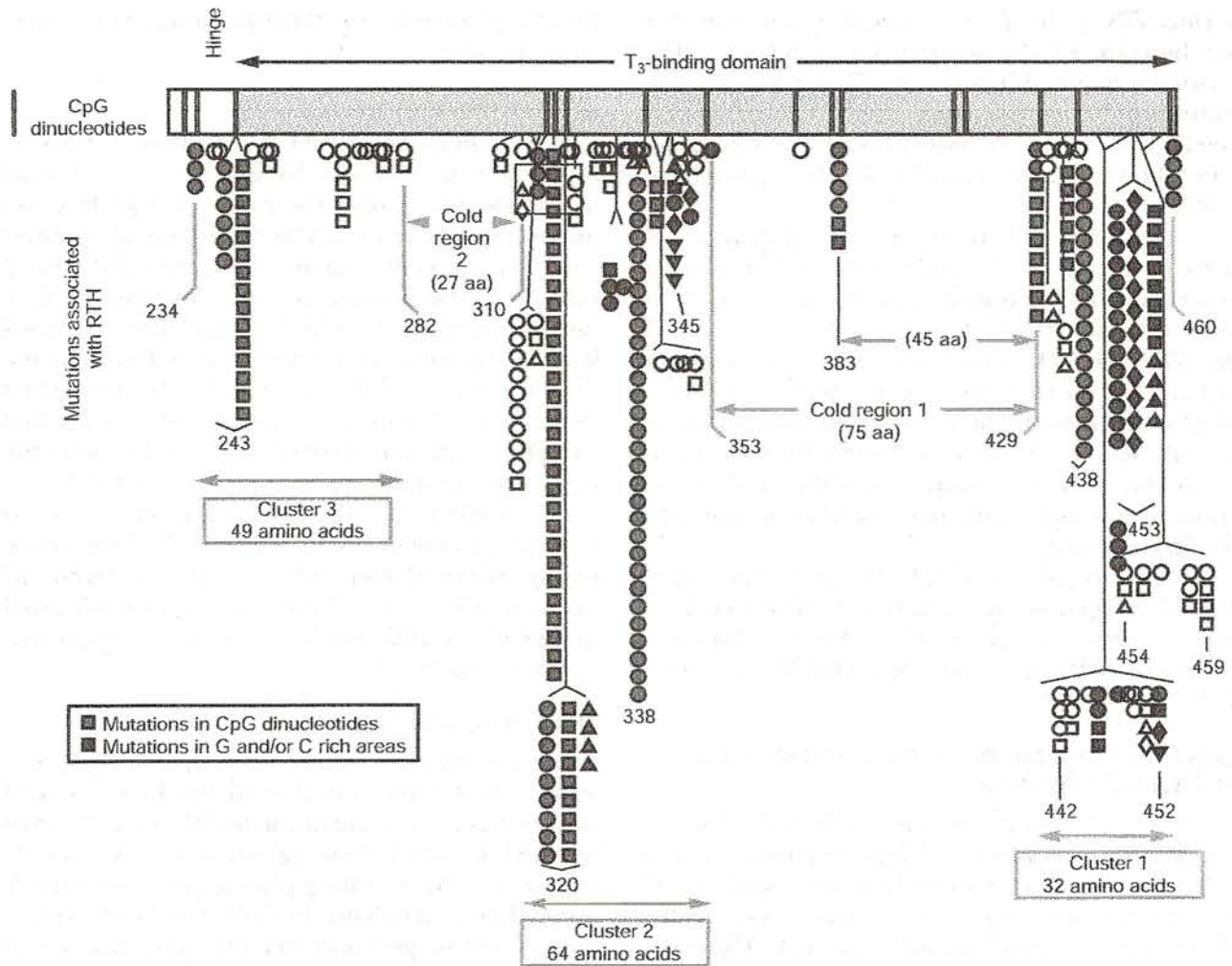


Figure 21-3 Location of natural mutations in the thyroid hormone receptor β (TR β) molecule associated with resistance to thyroid hormone (RTH). The triiodothyronine (T₃)-binding domain and distal end of the hinge region, which contain the three mutation clusters, are expanded and show the positions of CpG dinucleotide mutational hot spots in the corresponding TR β gene. The location of the 121 different mutations detected in 299 unrelated families are each indicated by a symbol. Identical mutations in members of unrelated families are represented by the same shading pattern of vertically placed symbols. Cold regions are areas devoid of mutations associated with RTH. (Adapted from Refetoff S: *Defects of Thyroid Hormone Transport in Serum*, 2007. Available at <http://www.thyroidmanager.org/Chapter16/16c-frame.htm>.)

between codons 282 and 310 and, with the exception of 383, codons 353 and 429. No mutation has been reported upstream of codon 234. Because cold regions are not devoid of hot spots, the lack of mutations reflects the observation that mutations in the second cold region do not impair TR function and therefore are not expected to produce a phenotype.³⁰

TR β gene defects have been identified in 344 families, comprising 124 distinct mutations. We have found mutations in 148 families (a partial listing is available online at <http://www.receptors.org/cgi-bin/nrmd/nrmd.py>). Although mostly missense mutations, nucleotide deletion and insertions producing frame shifts have created nonsense proteins with two additional amino acids in five cases. In four cases,

single nucleotide deletions have produced truncated receptors. In only one family, complete TR β gene deletion resulted in recessively inherited RTH.³¹ The following mutations have been identified in more than 10 unrelated families, often the consequence of de novo mutations: R243Q (15 families); A317T (29 families); R338W (30 families); R438H (17 families); P453T (17 families); and P453S (12 families). Of these frequently observed mutations, all are in CG hot spots or long stretches of Cs (see Fig. 21-3).

The mutant TR β molecules have reduced affinity for T₃^{27,28} or impaired interaction with one of the cofactors involved in the mediation of thyroid hormone action.^{28,32-34} Because TR mutants are still able to bind to TREs on DNA and dimerize with

normal TRs or the RXR partner, they interfere with the function of the normal TRs, explaining the dominant mode of inheritance. Therefore, it is not surprising that in the single family reported with a deletion of all coding sequences of the *TRβ* gene, only homozygotes manifested the phenotype of RTH.³¹

A family with two de novo *TRβ* gene mutations occurring in the same nucleotide has been reported.³⁵ The probanda with apparent de novo missense mutation (GTG to GGG) in codon 458 of the *TRβ* gene (*V458G*) transmitted this mutation to her affected son. The mutant allele underwent another de novo mutation that was transferred to her affected daughter as GAG (*V458E*). This apparent attempt of repair is more likely the result of the creation of a mutagenic three-guanine sequence by the first mutation.

No mutations in the *TRα* gene have been identified so far in humans. Based on observations in transgenic mice (see later, "Animal Models"), a putative *TRα* gene mutation should not cause RTH.

Non-Thyroid Hormone Receptor Resistance to Thyroid Hormone

In 1996, we reported a family in which RTH manifested in the absence of *TRβ* gene mutation and a *TRβ* gene transcript of normal size and abundance.²⁴ Nevertheless, fibroblasts were resistant to the in vitro effect of TH. Recombinant wild-type (WT) *TRβ* interacted aberrantly with nuclear extracts of fibroblasts from affected individuals of the family but not from normal individuals or subjects with complete *TRβ* gene deletion, and far-Western analysis has revealed an additional 84-kD band. More families with non-TR RTH were subsequently reported.^{22,36-38} We have identified non-TR RTH in 27 out of 175 families with RTH studied. Similarly, glucocorticoid and androgen resistance have now been described in the absence of mutations in the respective receptors,^{39,40} as well as partial resistance to several steroid hormones in the same subjects.⁴¹ It should be noted that mosaicism should be considered in any subject with phenotypic RTH in whom no mutation can be demonstrated in a particular cell lineage.⁴²

Animal Models

The generation of mice with *TRβ* deletion (knockout [KO]) and with mutations (knock-in [KI]) replicating those observed in humans have been important in understanding TR function and the pathophysiology of RTH. Similar manipulations of the *TRα* gene have allowed the prediction of a

putative phenotype for corresponding human gene abnormalities.⁴³

TRβ GENE MANIPULATION

TRβ KO mice manifest all the features of humans with *TRβ* gene deletion. Heterozygotes are normal and homozygotes have the typical thyroid function test abnormalities as well as sensorineural deafness and monochromatic vision.⁴⁴ Thus, deaf mutism and color blindness in humans can be fully explained by the *TRβ* deficiency.¹ *TRβ* KO mice have increased heart rate that can be corrected with reduction of the TH level. This finding, together with the lower heart rate in *Tra1* KO mice,⁴³ supports the concept that TH affects heart rate through *TRα1*, and explains the tachycardia observed in some patients with RTH.

TRβ KI mice, produced according to human *TRβ* gene mutations, are true models of the dominantly inherited form of RTH. Heterozygous KI mice manifest many of the abnormalities observed in humans. In addition, homozygotes develop metastatic thyroid cancer.⁴⁵

TRα GENE MANIPULATION

TRα gene deletions, total or only *α1*, do not produce important alterations in thyroid function.⁴⁶ Several human mutations occurring in the *TRβ* gene⁴⁷⁻⁴⁹ were targeted in homologous regions of the *TRα* gene of the mouse. The resulting phenotypes were variable but had no resemblance to RTH. The heterozygotes showed severe postnatal development and growth retardation, as well as increased body fat and insulin resistance. Decreased heart rate and reduced fertility were also observed. All *TRα* KIs were lethal in the homozygous state, in agreement with the noxious effect of unliganded *TRα1*.

COMBINED *TRα* AND *TRβ* GENE DELETIONS

Deletion of both *α* and *β* TRs is compatible with life.^{50,51} This contrasts with the complete TH deficiency as in the athyreotic *Pax8* KO mouse that, if untreated, dies prior to weaning. Removal of the *TRα* gene rescues the *Pax8* KO mice from death.⁵² Deletion of the *Tra1* gene also prevents the development of cerebellar abnormalities during TH deprivation.⁵³ Although the unliganded *TRα* is not required for the upregulation of TSH, it allows TH-mediated suppression in the absence of *TRβ*.

COFACTOR AND COREGULATOR DELETION

Mice deficient in the coactivator SRC-1 have resistance to TH in addition to sex hormones.⁵⁴ Mice deficient in RXR γ , the dimerization partner of TR, are also mildly resistant to TH.⁵⁵



Figure 21-4 Two children with resistance to thyroid hormone (RTH) syndrome showing clinical manifestations at the extremes of the spectrum. **A**, 1-month old infant homozygous for a single amino acid (Thr 337) deletion in the *TRβ* gene showing emaciation and a stare caused by lid retraction or hydrocephalus, giving the appearance of thyrotoxicosis. **B**, 7-month old infant with typical cretinoid and hypothyroid appearance, including narrow forehead, pug nose, large tongue, thin extremities, pot belly, and umbilical hernia. (A from Ono S, Schwartz ID, Mueller OT, et al: *Homozygosity for a dominant negative thyroid hormone receptor gene responsible for generalized resistance to thyroid hormone*. *J Clin Endocrinol Metab* 73:990-994, 1991; B from Refetoff S, Weiss RE, Usala SJ: *The syndromes of resistance to thyroid hormone*. *Endocr Rev* 14:348-399, 1993.)

CLINICAL FEATURES

Presenting Complaints

RTH lacks specific clinical manifestations. When present, they are variable and signs of TH deficiency and excess often coexist.^{5,56} Investigation may be initiated when hypothyroidism is suspected in a child with short stature, learning disability, or mental retardation. In contrast, thyrotoxicosis may be the reason for investigation in a hyperactive youngster or an adult with tachycardia. The detection of a goiter has been also a reason for thyroid testing in children and adults. Formerly, the diagnosis was often missed because of failure to recognize the normal or elevated TSH, leading to treatment aimed at normalizing the elevated TH levels. In such patients, symptoms of fatigue, somnolence, depression, and weight gain associated with bradycardia have ensued. More dramatic is the growth retardation resulting from treatment of children with antithyroid drugs. This has been less common in the last decade with wider recognition of RTH.

Although most patients with RTH are clinically euthyroid, presentation can range from a stare suggestive of exophthalmos to hypotonia, umbilical hernia, and cretinoid facies (Fig. 21-4). Symptoms and sign and their frequency are shown in Table 21-1.

Table 21-1 Clinical Features: Frequency of Symptoms and Signs

Findings	Frequency (%)
Thyroid gland	Goiter (66-95)
Heart	Tachycardia (33-75)
Nervous system	Emotional disturbances (60) Hyperkinetic behavior (33-68) Attention-deficit/hyperactivity disorder (40-60) Learning disability (30) Mental retardation, IQ < 70 (4-16) Hearing loss, sensorineural (10-22)
Growth and development	Short stature, less than 5th percentile (18-25) Delayed bone age > 2 SD (29-47) Low body mass index (in children) (33)
Recurrent ear and throat infections	Viral (55)

IQ, intellectual quotient.

(Data from Refetoff S, Weiss RE, Usala SJ: The syndromes of resistance to thyroid hormone. *Endocr Rev* 14:348-399, 1993; Beck-Peccoz P, Chatterjee VK: The variable clinical phenotype in thyroid hormone resistance syndrome. *Thyroid* 4:225-232, 1994; and Brucker-Davis F, Skarulis MC, Grace MB, et al: Genetic and clinical features of 42 kindreds with resistance to thyroid hormone. The National Institutes of Health Prospective Study. *Ann Intern Med* 123:572-583, 1995.)

THYROID GLAND

Goiter is by far the most common abnormality. In several studies, its prevalence has been reported to range from 66% to 95%. Large goiters are, however, rare.⁵ One severely affected RTH newborn presented with tracheal compression and respiratory difficulty⁵⁷ and one subject had esophageal constriction secondary to a goiter.⁵⁸

GROWTH AND DEVELOPMENT

Failure to thrive and growth delay are not uncommon. However, this rarely results in short stature. More often, children have delay in bone age and low body mass index. Permanent short stature is associated mental retardation (IQ < 70).

PSYCHOLOGICAL PROFILE

Emotional disturbances are found in two thirds of subjects with RTH. Most common is the occurrence of attention-deficit/hyperactivity disorder (ADHD), identified in 40% to 60% of cases. Although ADHD is common in individuals with RTH, the latter is

rarely found in subjects with the primary diagnosis of ADHD. It is of note that children with combined RTH with ADHD have a lower IQ than those with ADHD only.⁵⁹ Learning disabilities alone or in combination with ADHD pose significant problems in school, and many children requiring special classes and treatment with methylphenidate.

HEART

Tachycardia has been reported in 33% to 75% of cases. Together with hyperactivity, it is a common finding suggestive of thyrotoxicosis. It is the consequence of TH excess acting on the heart that expresses the mutant *TRβ* at a very low level. The resulting symptom of palpitations prompts 25% of adults with RTH to seek medical advice.

EARS

Deafness is rare and has been reported only in three affected members of one family homozygous for *TRβ* gene deletion.³¹ On the other hand, mild hearing impairment as result of recurrent ear infections has been reported 50% of cases.⁶⁰

OSTEOPOROSIS

Bone is a $TRα$ -dependent tissue.^{61,62} Subjects with RTH have increased bone marker turnover⁶³ and therefore are at risk for decreased bone mineral density.

MISCELLANEOUS FINDINGS

Various physical findings that cannot be explained on the basis of TH deprivation or excess have been noted. These include major or minor somatic defects, such as winged scapulae, vertebral anomalies, pigeon breast, prominent pectoralis, birdlike facies, scaphocephaly, short fourth metacarpals, and craniosynostosis as well as Besnier's prurigo, ectodermal dysplasia, and congenital ichthyosis. Bull's eye-type macular atrophy, resulting in color blindness, is on the other hand caused by TR deletion, as in mice.⁶⁴ The following conditions have been reported in individuals with RTH: enuresis, schizophrenia, recurrent pneumonia, seizures, rheumatic fever, empty sella, medullary cystic disease of the kidney, types 1 and 2 diabetes mellitus, migraine, and proptosis.⁵

Concurrent Thyroid Disease

Clinically challenging is the diagnosis of RTH when it occurs in combination with other thyroid conditions that independently alter TH concentrations. RTH has been reported with concurrent autoimmune hypothyroidism⁶⁵⁻⁶⁷ and in a patient with thyroid dysgenesis.⁶⁸ The resulting limited thyroidal reserve prevents full compensation, and subjects present

with very high TSH levels, despite normal TH concentrations. *TRβ* gene sequencing is important in confirming the diagnosis of RTH in such cases. We have found autoimmune hyperthyroidism in two individuals with RTH (unpublished findings).

Fertility and Pregnancy

An accurate evaluation of fertility and pregnancy outcome in RTH had been difficult to obtain until the discovery of a large Azorean kindred harboring the *TRβ* mutation *R343Q*.^{69,70} A three- to fourfold increase in the rate of miscarriages was observed in affected women as compared with that in spouses of affected fathers or unaffected first-degree relatives. Fertility was not impaired in affected couples, regardless of whether women or men harbored the mutant *TRβ* gene. The difference in genotype frequency in the progeny of affected mothers (20 affected vs. 11 unaffected offspring), combined with a significantly higher miscarriage rate, suggests that these women tend to lose more normal than affected fetuses. This was not found in the progeny of affected fathers, whose spouses had almost equal number of affected and unaffected offspring (15 and 12, respectively). Because the mothers with RTH were not thyrotoxic and had no thyroid autoantibodies, it may be concluded that miscarriages were the consequence of the fetal exposure to the high levels of TH. This is supported by the improved survival of the affected fetuses for whom high TH levels were physiologic, as in their affected mothers. Contrary to findings in uncontrolled maternal hyperthyroidism, women with RTH have no increased frequency of premature labor, preeclampsia, stillbirths, or perinatal loss.

Unaffected infants born to affected mothers have a significantly lower weight at birth than their affected siblings. This suggests that the high maternal TH level was able to induce a catabolic state during fetal life, similar to what happens in children and adults with uncontrolled hyperthyroidism. That these infants were thyrotoxic is supported by their suppressed blood TSH level at birth (Fig. 21-5).

DIAGNOSIS

Baseline Thyroid Function Tests

RTH should be considered in subjects with elevated TH levels and nonsuppressed TSH values (Fig. 21-6). The differential diagnosis of euthyroid hyperthyroxinemia includes transport defects as well as T_4 to T_3 conversion defects. The presence of a goiter with elevation of free T_4 and, in most cases, free T_3 concentration with normal or elevated TSH levels is diagnostic of RTH. The presence of autoantibodies raises the suspicion that circulating substances may

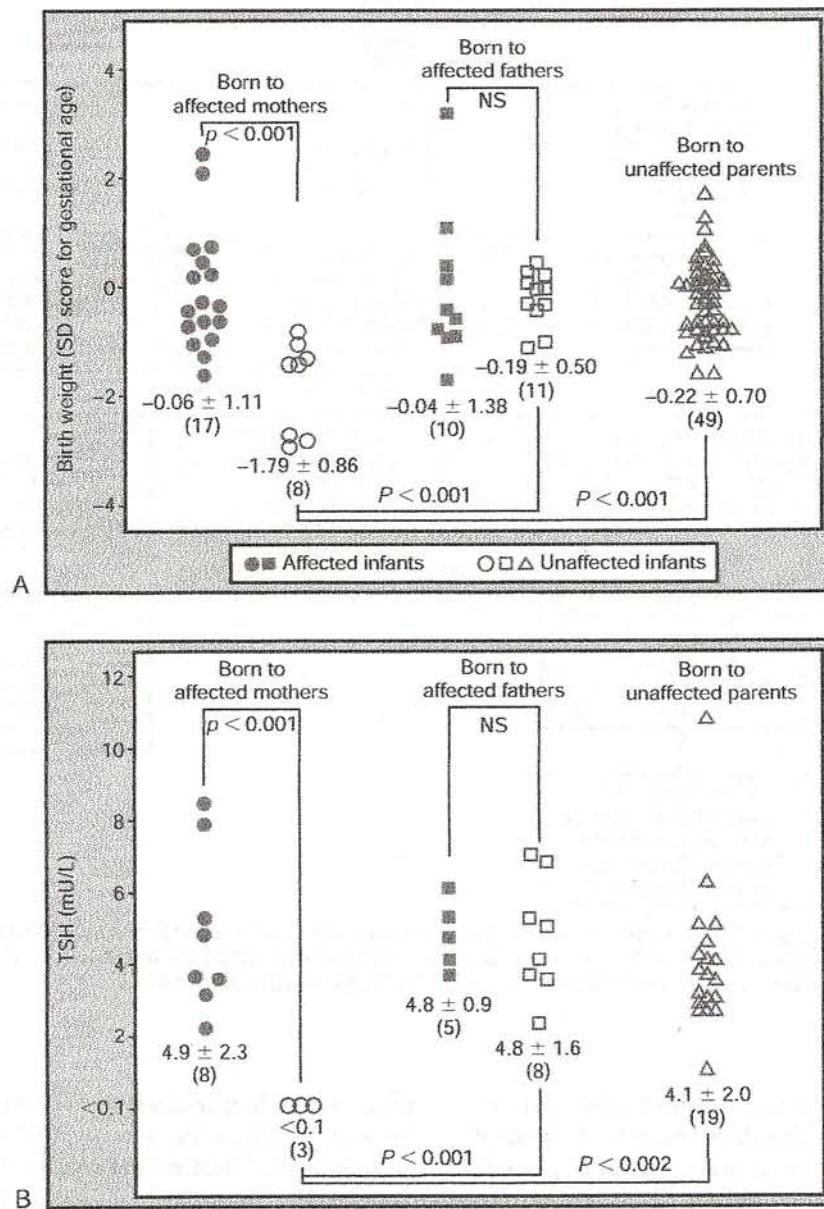


Figure 21-5 **A**, Birth weights in the different groups according to genotype. Data are expressed as mean SD score for gestational age using a chart obtained for singleton infants born to the Portuguese population and adjusted for the sex of the infant. A highly significant reduction in birth weight was found only in unaffected infants born to affected mothers. In additions, 3 of the infants in this group are of low birth weight, according to World Health Organization criteria. **B**, Neonatal blood TSH concentrations in the different groups and according to genotype. Only unaffected infants born to RTH mothers had undetectable blood TSH values. (Adapted from Anselmo J, Cao D, Karrison T, et al: Fetal loss associated with excess thyroid hormone exposure. *JAMA* 292:691-695, 2004.)

interfere with measurement of THs or, more rarely, of TSH. Exclusion of such antibodies by direct testing or confirmation using different assays is advisable. Reverse T_3 (rT_3) concentrations are also high and the levels of thyroglobulin (TG) reflect the degree of serum TSH elevation. Thyroidal radioiodide uptake is increased and ultrasound of the thyroid gland demonstrates the presence of gland enlargement, diffuse or multinodular. The finding of goiter in the presence of normal serum TSH

levels is explained by the increase of TSH bioactivity in RTH.⁷¹

Distinction between RTH and a TSH-secreting pituitary adenoma (TSH-oma) can be challenging. No single test is conclusive and diagnosis of RTH must rest on a combination of tests and observations: (1) absence of an elevated serum concentration of the alpha pituitary glycoprotein subunit; (2) stimulation of TSH following the administration of TSH-releasing hormone (TRH);

Differential diagnosis of resistance to thyroid hormone

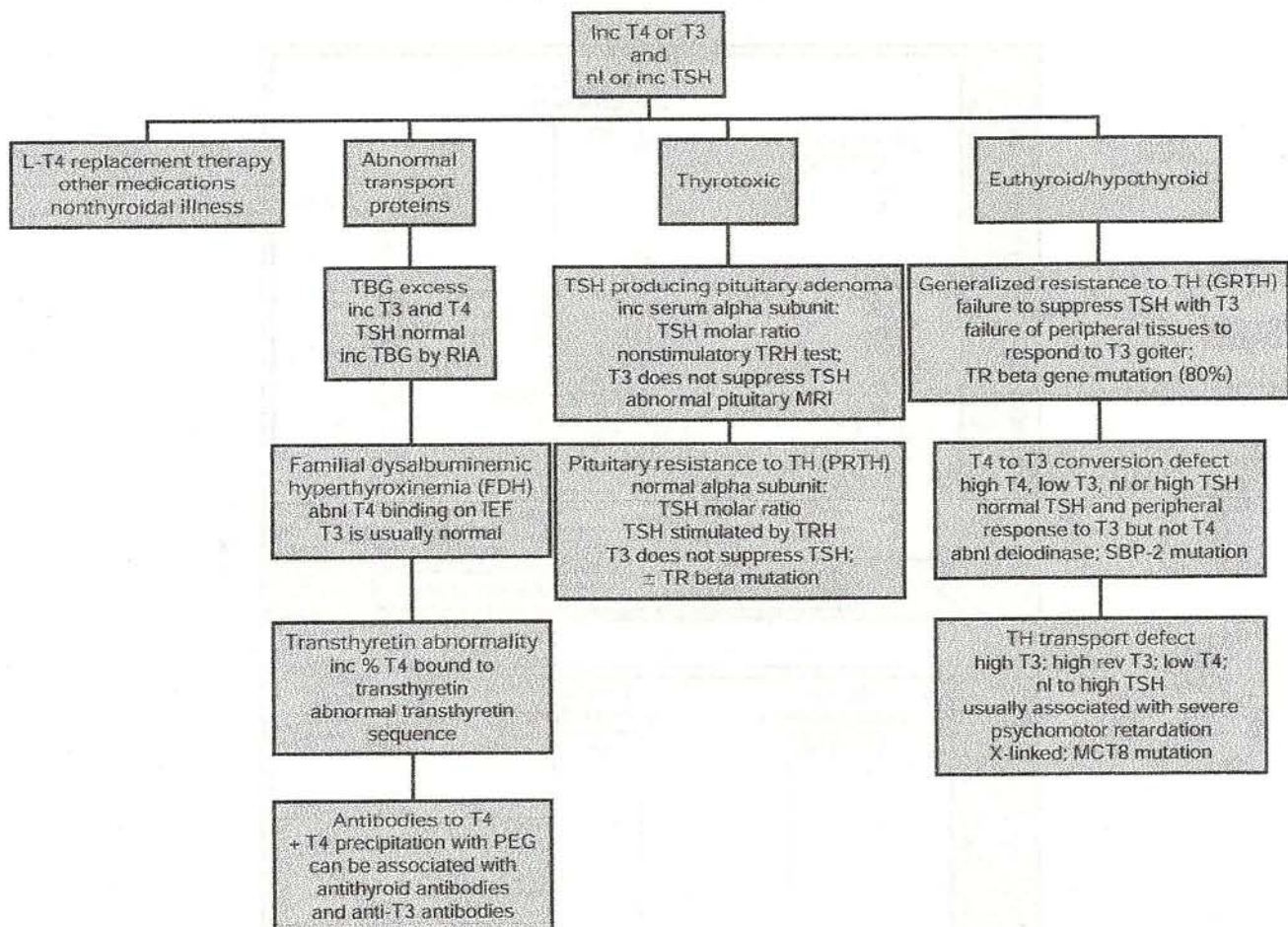


Figure 21-6 Differential diagnosis of resistance to thyroid hormone (RTH) syndrome. IEF, isoelectric focusing; L-T₄, levothyroxine; PEG, polyethylene glycol; RIA, radioimmunoassay; T₃, triiodothyronine; T₄, thyroxine; TBG, thyroxine-binding globulin; TH, thyroid hormone; TR, thyroid hormone receptor; TSH, thyroid-stimulating hormone.

(3) presence of thyroid test abnormalities compatible with RTH in other family members; (4) absence of elevated serum sex hormone-binding globulin (SHBG) concentration, reflecting a euthyroid state; and (5) ability to suppress serum TSH with supraphysiologic doses of levotriiodothyronine (L-T₃).

Thyrotropin-Releasing Hormone Stimulation Test

The TRH stimulation test measures the increase in TSH in serum in response to the administration of synthetic TRH. The magnitude of the response is modulated by the thyrotropic suppressibility by TH and is inversely proportional to the concentration of free TH in serum. The response is exquisitely sensitive to minor changes in the level of circulating TH, which may not be detected by direct measurement. The main use of the test is for the differential

diagnosis of inappropriate TSH secretion, in particular when a TSH-oma is suspected. TSH is usually not stimulated by TRH in TSH-omas.^{72,73}

The standard test uses a single TRH dose of 200 µg/1.73 m² body surface area, given by rapid intravenous injection. Serum is collected before the test, at 15 minutes, and then at 30-minute intervals over a period of 120 to 180 minutes. Many clinicians obtain blood for TSH measurements before and a single postinjection sample at 15, 20, or 30 minutes. Normal peak TSH response is at 15 to 40 minutes (i.e., on average, or five times the basal level). The decline is more gradual, with a return of serum TSH to the preinjection level by 3 to 4 hours.⁷⁴ Determination of TSH before and 30 minutes after the injection of TRH provides information concerning the presence or absence of TSH responsiveness but cannot detect delayed or prolonged responses. At the time

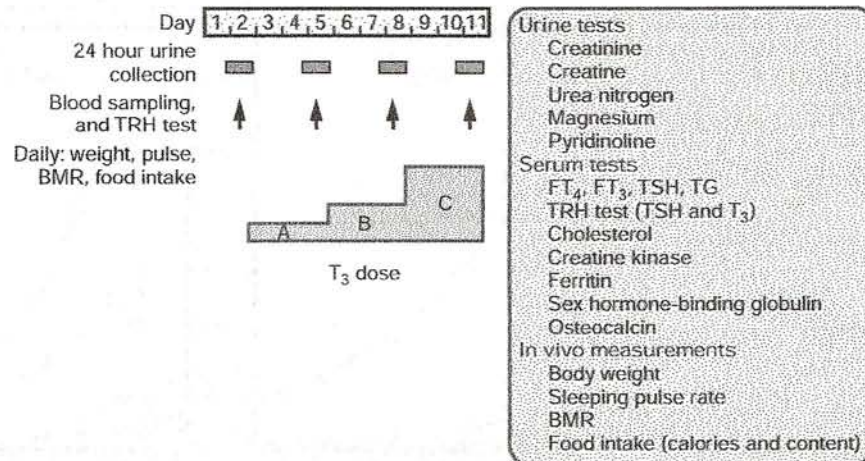


Figure 21-7 Schematic representation of a protocol for the in vivo assessment of thyroid hormone action used at the University of Chicago. It is used to establish the diagnosis of resistance to thyroid hormone (RTH) syndrome. See text for details. BMR, basal metabolic rate; FT₄, free thyroxine; T₃, triiodothyronine; TG, thyroglobulin; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

of this writing, TRH is not available here but can be obtained for use in the United States (from Ferring Arzneimittel, GmbH, Kiel, Germany) after submitting an investigational new drug (IND) application from the U.S. Food and Drug Administration (FDA).

Levothyronine Suppression Test

The measurement of responses to the administration of incremental doses of TH is the best method to assess the presence and magnitude of the hormonal resistance and obtain a clinical diagnosis of RTH. The rationale for the use of L-T₃ rather than L-T₄ is its direct effect on tissues, independent of variations in T₄ metabolism. The rapid onset of L-T₄ action reduces the period of hormone administration and the shorter half-life of this hormone decreases the duration of symptoms that may arise in hormonally responsive subjects. The protocol is outlined in Figure 21-7 and a detailed description has been published.⁵ It involves the administration of three incremental doses of L-T₃, each for 3 days. Amounts range from just below to three times above replacement. Hospitalization for 11 days is required for the detailed study, which includes measurement of sleeping pulse, basal metabolic rate (BMR), and calorie balance, for which food intake is controlled and urinary nitrogen excretion is measured.

Dosages of L-T₃ for adults are 50, 100, and 200 µg/day, each given for three consecutive days in a split dose every 12 hours, a total of six doses per increment. Corresponding doses for children, adjusted for size and age to obtain similar serum levels of T₃, are available.⁵ A TRH test is performed at baseline and at the time of the administration of the last L-T₃ dose

of each increment. Blood samples drawn over 180 minutes are used to measure the TSH and prolactin responses, as well as the nadir and peak of serum T₃ levels achieved with each incremental dose. Measurements of TG and T₄ assess the magnitude of thyroid gland suppression, whereas those of serum cholesterol, creatine kinase, ferritin, SHBG, and osteocalcin (OC) assess the responses of peripheral tissues to the hormone. Figure 21-8 shows typical results obtained in a normal subject as compared with those of subjects with RTH and with and without TRβ gene mutations.

Color Flow Doppler Sonography

Recently, the use of color flow Doppler sonography of the thyroid gland has been shown to distinguish between patients with TSH-omas and those with RTH.⁷⁵ The test is performed during the course of L-T₃ suppression according to the schedule described earlier. The increased pattern and peak systolic velocity normalized in 8 of 10 patients with RTH, but not in any of the 8 patients with a TSH-oma.

Prenatal Diagnosis

Although prenatal diagnosis of RTH based on genetic testing of amniotic fluid has not been reported, we have successfully identified the genotype of fetuses carried by women with RTH who were known to have TRβ gene mutations.

TREATMENT

There is no available treatment to correct the specific defect. Current treatments are aimed at alleviating symptoms when present. Most important is not to treat asymptomatic fully compensated individuals

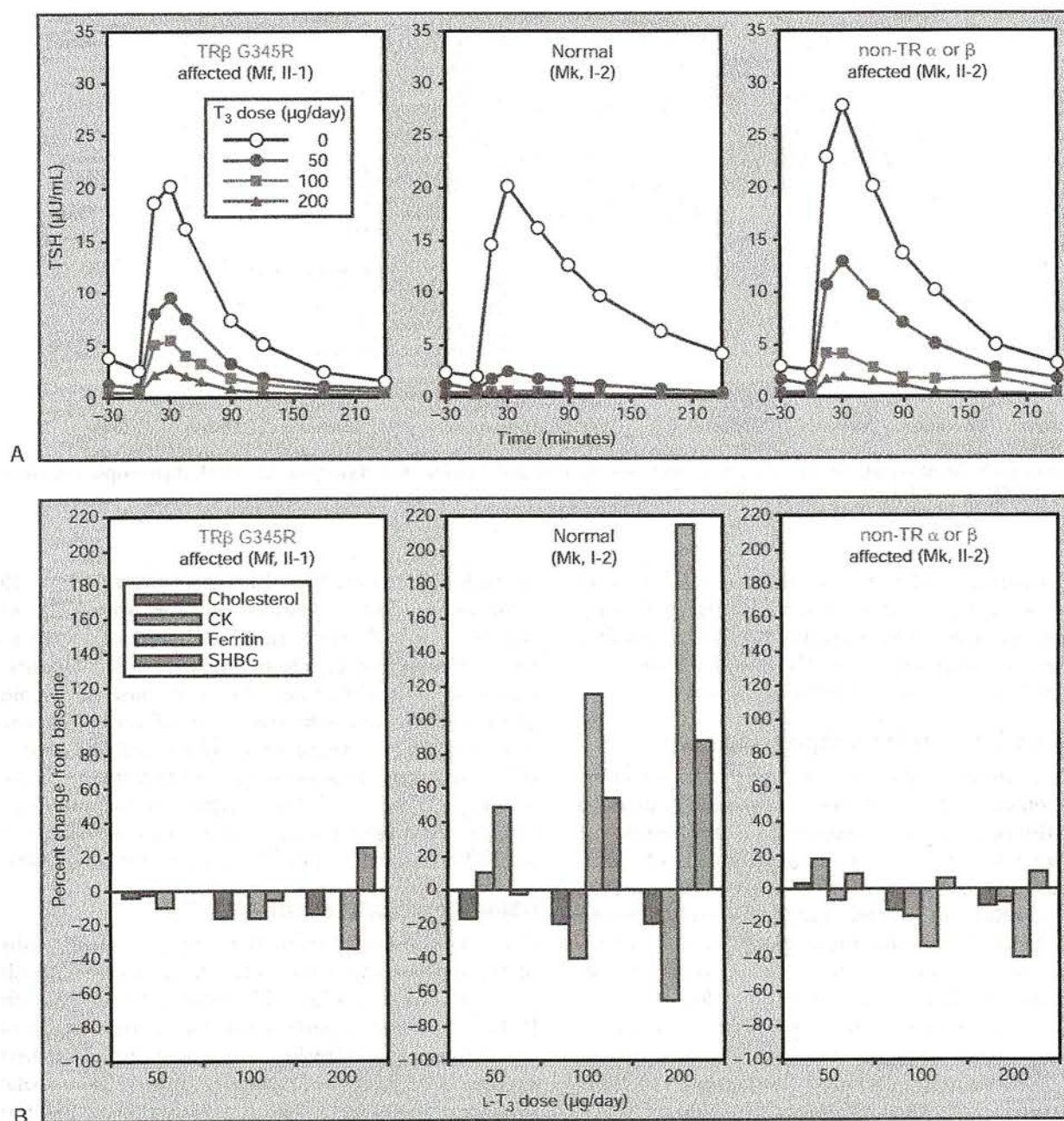


Figure 21-8 A, Thyrotropic responses to thyrotropin-releasing hormone (TRH) stimulation at baseline and after the administration of graded doses of levotriiodothyronine ($L-T_3$). The hormone was given in three incremental doses, each for 3 days, as depicted in Figure 21-7. Results are shown for patients with resistance to thyroid hormone (RTH) syndrome in the presence (left) or absence (right) of a thyroid receptor β ($TR\beta$) gene mutation, together with the unaffected mother of the patient with non- TR RTH (center). B, Responses of peripheral tissues to the administration of $L-T_3$ in the presence or absence of mutations in the $TR\beta$ gene. The hormone was given as described in Figure 21-7. Note the stimulation of ferritin and sex hormone-binding globulin (SHBG) and the suppression of cholesterol and creatine kinase (CK) in the normal subject. Responses in affected subjects, with or without a $TR\beta$ gene mutation, were blunted or paradoxical. TSH, thyroid-stimulating hormone. (Adapted from Refetoff S: *Defects of Thyroid Hormone Transport in Serum*, 2007. Available at <http://www.thyroidmanager.org/Chapter16/16c-frame.htm>.)

with the sole purpose of correcting the laboratory test abnormalities. Prior ablative treatment, resulting from misdiagnosis, requires the administration of TH often in supraphysiologic doses.

WHEN NOT TO TREAT

There is no reason to treat subjects with elevated levels of TH appropriate for the degree of both thyrotropic and peripheral tissue resistance. Although the theoretical probability of developing thyrotropic adenomas caused by a long-standing increase in thyrotropic activity has been suggested, only one case of a pituitary adenoma in a subject with RTH has been reported.⁷⁶ In mouse models of RTH, pituitary pathology consists of thyrotropic hyperplasia only, particularly in homozygotes, which rarely occurs in humans. Using the same logic, the thyroid gland, which is under increased stimulation by TSH, may also be prone to tumor development, but there is no increased incidence of thyroid cancer in RTH and goiters are rarely obstructive. A mouse model homozygous for a mutation in the *TR β* gene will develop papillary thyroid cancer,⁴⁵ but the relevance in humans is unknown. Therefore, the mainstay for the management of RTH patients who are asymptomatic is to recognize the correct diagnosis and avoid antithyroid treatment.

REAL AND APPARENT THYROID HORMONE DEFICIENCY

Intervention is recommended in patients who present with objective findings of TH deprivation, usually because of treatment aimed to decrease the circulating TH level. If the consequence is reversible, such as antithyroid drugs, treatment should be discontinued. In the case of prior ablative treatment (surgery or radioiodide), judicious administration of supraphysiologic doses of TH are usually required. The dose of TH needs to be titrated in an incremental manner to normalize the serum TSH concentration. Dosages of L-T₄ as high as 500 to 1000 μ g/day may be necessary to obtain the desired TH effect. Tachycardia should not be a contraindication for T₄ treatment because it can be managed with atenolol (see later). Most difficult is the treatment of children with apparent hypothyroidism manifesting as growth retardation with delayed bone age and failure to thrive. A guide for TH dosage in such children is growth, bone maturation, and mental development. In addition, it is suggested that BMR, nitrogen balance, and serum SHBG be monitored at each dose increment.

APPARENT THYROID HORMONE EXCESS

The most common symptom suggestive of hyperthyroidism is sinus tachycardia, present in about 50% of patients with RTH. When symptomatic, or limiting

exercise tolerance, treatment with a beta-adrenergic blocking agent is effective. Some beta blockers, such as propranolol (Inderal), have an added effect of inhibiting conversion of T₄ to T₃, which is not desirable in RTH. We prefer to use atenolol, which does not have this added effect of depriving the TH-resistant cells of TH. More generalized symptoms of hyperthyroidism, including tremor, heat intolerance, sweating, and agitation, may also benefit from treatment with atenolol. However, this may not be effective in extreme cases. Two other approaches have been used but experience is limited; these are reduction of TSH secretion and blocking the action of TH.

REDUCTION OF THYROID-STIMULATING HORMONE SECRETION

Agents in this category include glucocorticoids, somatostatin, and dopaminergic drugs. Although effective at reducing the TSH concentration, glucocorticoids have unacceptable side effects and therefore are not clinically useful. Dopaminergic agents such as bromocriptine or pergolide can reduce the TSH concentration but lose their effectiveness when used for a prolonged period. In addition, patients may not tolerate the gastrointestinal side effects.^{58,77-79} The somatostatin analogue SMS201-995 was studied in three patients with RTH and found to have a weaker and more transient effect when compared with that in patients with TSH-omas.⁸⁰

GOITER

Thyroid gland enlargement is usually modest, but large goiters occasionally occur. Surgical treatment is not effective in the long term because goiters are notorious for their recurrence, and contrary to autoimmune thyroid disease, there is no underlying destructive process. Thus, it is more effective to inhibit thyroid gland growth by suppression of TSH. The latter has been achieved by treating with a single large dose of L-T₃ given every second day (Fig. 21-9). The high levels of serum T₃ produced a few hours after ingestion of the hormone are effective in suppressing TSH but do not persist, so symptoms of TH excess do not develop.⁸¹

REDUCTION THYROID HORMONE ACTION USING ANALOGUES

Triiodothyroacetic acid (TRIAc) is a TH analogue with low hormonal potency but high affinity for the TR⁸² and very rapid turnover, requiring the use of doses more than 1000-fold those of L-T₃. In vitro studies have shown that the binding affinity of TRIAC is almost three times that of T₃ for normal TR β and similar to T₃ for TR α 1.⁸³ TRIAC was also more potent than T₃ in the transactivation of some

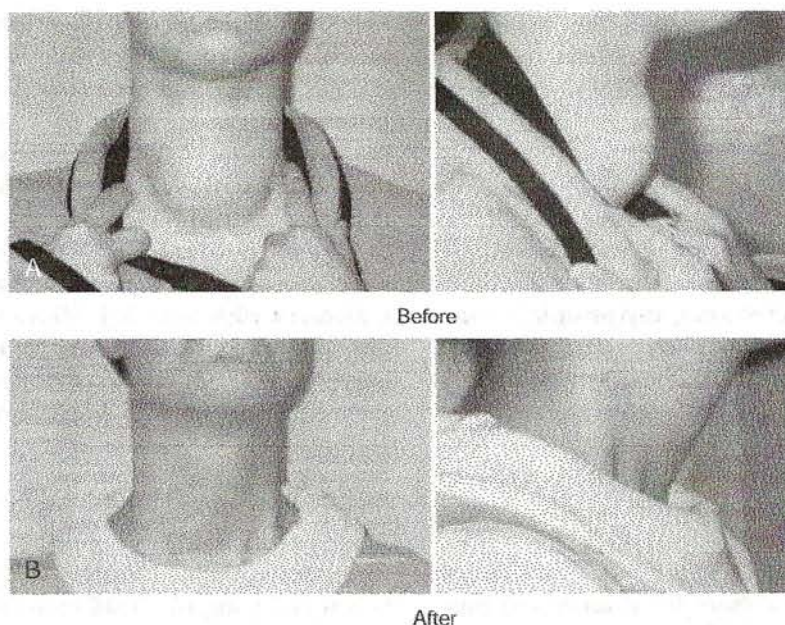


Figure 21-9 Goiter in a patient with resistance to thyroid hormone (RTH) syndrome. **A**, Patient's neck just before beginning of treatment. Although doses of 150 μg of levotriiodothyronine (L-T_3) every other day for 11 months resulted in a decrease in thyroid-stimulating hormone (TSH) level from 1.1 to 0.24 mU/L, there was no decrease in the size of the goiter. **B**, However, treatment with 250 μg L-T_3 every other day for 7 months resulted in disappearance of the goiter and serum TSH levels below 0.08 mU/L, associated with a modest increase in body weight and no symptoms of thyroid hormone excess. (From Anselmo J, Refetoff S: Regression of a large goiter in a patient with resistance to thyroid hormone by every other day treatment with triiodothyronine. *Thyroid* 14:71-74, 2004.)

mutant $\text{TR}\beta$ s, suggesting that TRIAC may overcome a dominant negative effect of these mutant $\text{TR}\beta$ s.⁸³ Long-term studies on the effect of TRIAC have been reported in several subjects with RTH.^{77,79,80,84-91} Although a significant reduction in the basal and TRH-stimulated TSH levels, as well as in serum free T_4 and T_3 levels, were observed in most cases, there was no appreciable change in parameters that measure TH action. This inhibition of TSH secretion without peripheral tissue metabolic effects was seen with TRIAC in normal and hypothyroid patients.⁸⁶ In two children, TRIAC produced normal growth and bone maturation.^{87,89} In several subjects, there was no change in thyroid function after discontinuing TRIAC, questioning the specificity of the observed effect. Most investigators who used TRIAC reported receiving the drug from Laboratories ANA (Neuilly-sur-Seine, France). It is not available in the United States.

Dextrothyroxine (D-T_4) had been thought to be useful in reducing plasma cholesterol without producing adverse thyromimetic effects⁹² in some subjects but not in others.^{93,94} Investigators have tried to treat RTH with D-T_4 in an effort to decrease TSH levels.⁹⁵⁻⁹⁷ Several patients with RTH of various severity have received 2 to 8 mg of D-T_4 daily.⁹⁶⁻⁹⁹ Clinical changes were minimal and

often not supported by objective findings. Given that most preparations contain small amounts of L-T_4 , 2% to 3% of the levo substance could fully account for the thyromimetic effect.⁹⁵ In most cases, D-T_4 (Dynothel, 2-mg tablet) was obtained from Henning (Berlin).

TREATMENT OF CHILDREN AND INFANTS

Infants may be found to have RTH by early testing because of a known affected sibling or parent or, more rarely, because routine neonatal testing revealed an elevated T_4 level and a nonsuppressed TSH. Treatment of these infants is controversial, especially when asymptomatic, because there have been no long-term outcome studies. In general, we tend to treat infants and children with L-T_4 only if any of the following are present: (1) marked elevation of TSH; (2) history of adverse symptoms in other affected family members, such as mental retardation; (3) evidence of failure to thrive; (4) growth retardation; or (5) developmental delays.

There are no guidelines for the treatment of fetuses. Based on the study described earlier,⁶⁹ it seems reasonable to reduce the hormone level in a mother with RTH who carries a normal fetus. Although subjects with RTH born to normal mothers, as compared with RTH mothers, had childhood

short stature,⁶⁰ it is unclear whether treatment with TH during pregnancy would be beneficial in such circumstances.

CLINICAL COURSE AND PREVENTION

There is no evidence to suggest that RTH has an effect on the life span. The few reported infant deaths were from unrelated causes. Only in one subject was RTH thought to have contributed to his demise. This individual,¹⁰⁰ with a homozygous *TRβ* gene mutation and resting heart rate of 190 beats/min, died from a cardiac shock complicating staphylococcal septicemia. Several others with RTH have died from a presumably unrelated illness, the nature of which is unknown, and no information is available from post-mortem examinations.

In humans,¹⁰¹ as in mice¹⁰² with RTH, the serum levels of T_4 and T_3 decline with age, suggesting that the severity of the resistance may improve with time. However, this could represent an exaggerated trend that occurs in normal individuals as well.¹⁰¹

PITFALLS, COMPLICATIONS, AND CONTROVERSIES

CORRECT DIAGNOSIS

A common pitfall in RTH is the failure to make the correct diagnosis. With increased awareness of the syndrome and its inclusion in standard textbooks, ablative therapy is used less frequently. However, clinical and laboratory diagnosis by standard tests is more difficult in patients on TH replacement because of prior surgery or radioiodide treatment. This is particularly important for patients who require higher than the usual replacement doses of TH. In such cases, it is imperative to document carefully that there is a reduced sensitivity to administered TH, to perform genetic testing, and to determine that there are other family members with an RTH phenotype.

PRESUMED PERIPHERAL TISSUE RESISTANCE TO THYROID HORMONE VERSUS THYROID HORMONE HABITUATION

A common referral to physicians with expertise in RTH is the apparent requirement of high doses of TH, despite TSH suppression. Such individuals are presumed to have selective peripheral tissue resistance to thyroid hormone (PTRTH). Usually, these patients have elevated serum T_4 and T_3 levels with suppressed TSH but the patient continues to feel hypothyroid. Although theoretically possible, this condition has not been convincingly shown to exist. It is acquired and not associated with demonstrable receptor defects. A typical presentation is that of a patient who has undergone thyroid ablation or had

a history of mild hyperthyrotropinemia, is dissatisfied with their energy level or weight, and attributes it to insufficient TH replacement. Patients have often tried different TH preparations including L- T_3 and desiccated thyroid. In patients on high doses of L- T_4 , the serum rT_3 concentration is disproportionately high relative to T_3 . This shunting of T_4 metabolism to produce an inactive hormone explains the scarcity of signs of TH excess. These patients present a challenge to physicians to determine the cause for their complaints and prevent overmedication with TH.

CONTROVERSIES IN RESISTANCE TO THYROID HORMONE SYNDROME

These include the following:

1. Determination of the cause for the heterogeneous phenotype of subjects with identical mutations across and within the same family
2. Development of treatment to revert the dominant negative effect of the receptor and thus cure RTH
3. Management of maternal and fetal TH levels during gestation
4. Cause of non-TR RTH
5. Identification of humans with $TRα$ mutations

References

1. Refetoff S, DeWind LT, DeGroot LJ: Familial syndrome combining deaf-mutism, stuppled epiphyses, goiter and abnormally high PBI: Possible target organ refractoriness to thyroid hormone. *J Clin Endocrinol Metab* 27:279-294, 1967.
2. Refetoff S, DeGroot LJ, Benard B, DeWind LT: Studies of a sibship with apparent hereditary resistance to the intracellular action of thyroid hormone. *Metabolism* 21:723-756, 1972.
3. Sakurai A, Takeda K, Ain K, et al: Generalized resistance to thyroid hormone associated with a mutation in the ligand-binding domain of the human thyroid hormone receptor beta. *Proc Natl Acad Sci U S A* 86:8977-8981, 1989.
4. Usala SJ, Tennyson GE, Bale AE, et al: A base mutation of the C-erbA beta thyroid hormone receptor in a kindred with generalized thyroid hormone resistance. Molecular heterogeneity in two other kindreds. *J Clin Invest* 85:93-100, 1990.
5. Refetoff S, Weiss RE, Usala SJ: The syndromes of resistance to thyroid hormone. *Endocr Rev* 14:348-399, 1993.
6. Dumitrescu AM, Liao XH, Abdullah MS, et al: Mutations in *SECISBP2* result in abnormal thyroid hormone metabolism. *Nat Genet* 37:1247-1252, 2005.
7. Bassett JH, Harvey CB, Williams GR: Mechanisms of thyroid hormone receptor-specific nuclear and extra nuclear actions. *Mol Cell Endocrinol* 213: 1-11, 2003.

8. Fondell JD, Guermah M, Malik S, Roeder RG: Thyroid hormone receptor-associated proteins and general positive cofactors mediate thyroid hormone receptor function in the absence of the TATA box-binding protein-associated factors of TFIID. *Proc Natl Acad Sci U S A* 96:1959-1964, 1999.
9. Refetoff S, Weiss RE, Usala SJ, Hayashi Y: The syndromes of resistance to thyroid hormone: Update 1994. In Braverman LE, Refetoff S (eds): *Endocrine Reviews Monographs*. Bethesda, Md, The Endocrine Society, 1994, pp 336-343, 1994.
10. Flamant F, Gauthier K, Samarut J: Thyroid hormones signaling is getting more complex: STORMS are coming. *Mol Endocrinol* 21:321-333, 2007.
11. Evans RM: The steroid and thyroid hormone receptor superfamily. *Science* 240:889-895, 1988.
12. Gurnell M, Chatterjee VK: Nuclear receptors in disease: Thyroid receptor beta, peroxisome proliferator-activated receptor gamma and orphan receptors. *Essays Biochem* 40:169-189, 2004.
13. Klier SA, Umesono K, Mangelsdorf DJ, Evans RM: Retinoid X receptor interacts with nuclear receptors in retinoic acid, thyroid hormone and vitamin D₃ signalling. *Nature* 355:446-449, 1992.
14. Lazar MA: Thyroid hormone receptors: Multiple forms, multiple possibilities. *Endocr Rev* 14:184-193, 1993.
15. Mangelsdorf DJ, Evans RM: The RXR heterodimers and orphan receptors. *Cell* 83:841-850, 1995.
16. Arai K, Chrousos GP: Syndromes of glucocorticoid and mineralocorticoid resistance. *Steroids* 60:173-179, 1995.
17. Bouillon R, Verstuyf A, Mathieu C, et al: Vitamin D resistance. *Best Pract Res* 20:627-645, 2006.
18. Hughes MR, Malloy PJ, Kieback DG, et al: Point mutations in the human vitamin D receptor gene associated with hypocalcemic rickets. *Science* 242:1702-1705, 1988.
19. Quigley CA, De Bellis A, Marschke KB, et al: Androgen receptor defects: Histological, clinical, and molecular perspectives. *Endocr Rev* 16:271-321, 1995.
20. Smith EP, Boyd J, Frank GR, et al: Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. *N Engl J Med* 331:1056-1061, 1994.
21. van Rossum EF, Lamberts SW: Glucocorticoid resistance syndrome: A diagnostic and therapeutic approach. *Best Pract Res* 20:611-626, 2006.
22. Pohlenz J, Weiss RE, Macchia PE, et al: 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.
23. Reutrakul S, Sadow PM, Pannain S, et al: Search for abnormalities of nuclear corepressors, coactivators, and a coregulator in families with resistance to thyroid hormone without mutations in thyroid hormone receptor beta or alpha genes. *J Clin Endocrinol Metab* 85:3609-3617, 2000.
24. Weiss RE, Hayashi Y, Nagaya T, et al: Dominant inheritance of resistance to thyroid hormone not linked to defects in the thyroid hormone receptors alpha or beta genes may be due to a defective co-factor. *J Clin Endocrinol Metab* 81:4196-4203, 1996.
25. Lafranchi SH, Snyder DB, Sesser DE, et al: Follow-up of newborns with elevated screening T4 concentrations. *J Pediatr* 143:296-301, 2003.
26. Sadow PM, Reutrakul S, Weiss RE, Refetoff S: Resistance to thyroid hormone in the absence of mutations in the thyroid hormone receptor genes. *Curr Opin Endocrinol Diabetes* 7:253-259, 2000.
27. Adams M, Matthews C, Collingwood TN, et al: 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, 1994.
28. Collingwood TN, Wagner R, Matthews CH, et al: A role for helix 3 of the TR β ligand-binding domain in coactivator recruitment identified by characterization of a third cluster of mutations in resistance to thyroid hormone. *EMBO J* 17:4760-4770, 1998.
29. 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* 91:2408-2415.
30. Hayashi Y, Sunthornthepvarakul T, Refetoff S: Mutations of CpG dinucleotides located in the triiodothyronine (T₃)-binding domain of the thyroid hormone receptor (TR) beta gene that appears to be devoid of natural mutations may not be detected because they are unlikely to produce the clinical phenotype of resistance to thyroid hormone. *J Clin Invest* 94:607-615, 1994.
31. Takeda K, Sakurai A, DeGroot LJ, Refetoff S: 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, 1992.
32. Liu Y, Takeshita A, Misiti S, et al: Lack of coactivator interaction can be a mechanism for dominant negative activity by mutant thyroid hormone receptors. *Endocrinology* 139:4197-4204, 1998.
33. Safer JD, Cohen RN, Hollenberg AN, Wondisford FE: Defective release of corepressor by hinge mutants of the thyroid hormone receptor found in patients with resistance to thyroid hormone. *J Biol Chem* 273:30175-30182, 1998.
34. Yoh SM, Chatterjee VKK, Privalsky ML: Thyroid hormone resistance syndrome manifests as an aberrant interaction between mutant T₃ receptor and transcriptional corepressor. *Mol Endocrinol* 11:470-480, 1997.
35. Lado-Abeal J, Dumitrescu AM, Liao XH, et al: A de novo mutation in an already mutant nucleotide of the thyroid hormone receptor beta gene perpetuates resistance to thyroid hormone. *J Clin Endocrinol Metab* 90:1760-1767, 2005.