Thyroid hormone resistance

N K Agrawal, R Goyal, A Rastogi, D Naik, S K Singh

Department of Endocrinology and Metabolism, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India

Correspondence to:
Dr N K Agrawal, A-5 Krishna Bag Apartments, N-1/69 C, Nagwa, Varanasi- 221005, India;
drnkavns@gmail.com

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ABSTRACT

Thyroid hormone resistance (THR) is a rare syndrome of reduced end organ sensitivity. Patients with THR have elevated serum free thyroxine (FT_4), free triiodothyronine (FT_3), but normal or slightly elevated serum thyrotropin values. The characteristic clinical feature is goitre without symptoms and metabolic consequences of thyroid hormone excess. THR can be classified on the basis of tissue resistance into pituitary, peripheral or generalised (both pituitary and peripheral) types. Mutations in the TRβ gene, cell membrane transporter and genes controlling intracellular metabolism of thyroid hormone have been implicated. THR is differentiated from thyroid stimulating hormone (TSH) secreting pituitary adenoma by history of THR in the family. No specific treatment is often required for THR; patients with features of hypo- or hyperthyroidism are appropriately treated with levo-triiodothyronine (L-T_3), levo-thyroxine (L-T_4), dextro-thyroxine(D-T_4) or 3,3,5 triiodo-thyroacetic acid (TRIAC). The diagnosis helps in appropriate genetic counselling of the family.

Thyroid hormones regulate growth, basal metabolic rate, myocardial contractility and functional differentiation of the central nervous system. Their synthesis is stimulated by thyrotrophin releasing hormone (TRH) and thyroid stimulating hormone (TSH), and suppressed by its negative feedback effect. Thyroid hormones act on the carboxy-terminal domain of steroid nuclear receptors called thyroid receptors (TR), which bind to thyroid response elements (TRE) located in the promoter regions of target genes. Although TR can bind TRE as a monomer or homodimer, it usually interacts preferentially as a heterodimer with the retinoid X-receptor (RXR). Many promoters are repressed or "silenced" by unliganded receptor; hormone binding results in relief of repression and ligand dependent activation of gene transcription. Reduced end organ response to circulating thyroid hormones or thyroid hormone resistance (THR) was first recognised in 1967 by Refetoff.[1] Many patients and families have since been identified.

The present review highlights the classification, pathogenesis, clinical features, diagnosis and treatment for THR, with a view to enable appropriate genetic counselling.

CLASSIFICATION

THR is characterised by elevated concentrations of free thyroxine (FT_4) and free tri-iodothyronine (FT_3), with inappropriately normal thyrotropin (TSH). On the basis of tissue response to thyroid hormones, THR has been classified into generalised, pituitary and peripheral resistance.[2 3]

Generalised thyroid hormone resistance (GTHR)—The patient is clinically euthyroid. There may be low IQ without an effect on bone (normal stature) or vice versa due to variable tissue resistance.[2] The euthyroid state is maintained by a compensatory increase in thyroid hormone concentrations.

Pituitary thyroid hormone resistance (PTHR)—The patient presents with hyperthyroidism. The inappropriately high pituitary TSH secretion causes overproduction of T_4 and T_3, thus establishing a new equilibrium with high T_4 and T_3 together with a non-suppressed TSH. The signs and symptoms are subjective; differentiating selective pituitary resistance from generalised resistance can be difficult.[2]

Peripheral thyroid hormone resistance (PerTHR)—In this rare entity, the patient may present with clinical hypothyroidism.[4 5] The TSH value is normal. The sensitivity of peripheral tissues to thyroid hormones is decreased relative to that of the pituitary. However, the distinction is unclear as a variable degree of resistance can be found in pituitary and peripheral tissues of the same individual.[6]

PATHOGENESIS

In humans there are two subtypes of TR, TRα and TRβ (encoded by genes on chromosomes 17 and 3, respectively) and three main isoforms: TRα1 (most abundant in the central nervous system, myocardium, and skeletal muscle), TRβ1 (predominant in liver and kidney), and TRβ2 (highly expressed in the pituitary and hypothalamus) generated by alternate splicing.

The THR usually is dominantly inherited.[2] The current estimate of de novo mutation is approximately 22.5% in which TRβ gene mutation is excluded in the parents. Recessive transmission is very rare and was clearly demonstrated only in the first family reported by Refetoff.[3]

THR phenotype can result from TR and non-TR defects. The TRβ mutations have been strongly associated with THR.[7] Genetic studies in 300 families with this syndrome showed 122 different point mutations or frame shift mutations (insertions and deletions) localised to three mutation clusters within the hormone binding domain of the receptor, except one which was having complete deletion of the TRβ gene.[8] Affected individuals are heterozygous for mutations in the TRβ gene; this occurs in approximately 10% of sporadic cases. The same receptor mutation can result in PTHR in some individuals and GTHR in others within a single family or unrelated kindreds.[9] Another reported family had the father with mosaicism in some cell lineages, including his germline for R338W mutation, but not in the fibroblasts. This mosaicism is without apparent TRβ gene mutations.[10] In a few cases there may be limited expression of somatic TRβ1 mutation which is undetectable in peripheral blood leucocyte DNA.

THR phenotype could also result from non-TRβ defects. In some families or sporadic cases, mutations in TR locus have been excluded, raising the possibility of new, non-receptor mechanisms to produce THR phenotype called non-TR THR.[11] So far 29 affected subjects from 23 different families have been identified.[3 12] They are clinically similar to subjects with TRβ gene mutations but have a high female-to-male ratio (2.5:1) and high prevalence of sporadic cases.[3] Genetic and clinical studies have highlighted two novel defects giving rise to THR. The first one involves transport of thyroid hormone and the second defect lies in its intracellular metabolism (SECISBP2 gene mutation affecting synthesis of selenoproteins).[13] The psychomotor abnormalities in males have been associated with X linked monocarboxylate transporters (MCT8) mutation.[14 15]

The location of an abnormality in the hormone binding domain of the mutant receptor determines the strength of T_3 binding affinity to the receptor and its ability to activate or repress target genes. A subset of receptor mutations that involve residues critical for mediating TRβ interaction with co-activators result in notably reduced transcriptional function with normal hormone binding.

In the first documented family with THR, which was recessively inherited, the two affected siblings were homozygous for complete deletion of the TRβ receptor gene.[16] Significantly, their heterozygous parents harbouring a deletion of one TRβ allele were completely normal. In the dominantly inherited THR, mutant receptors are not only functionally impaired but can also cause inhibition of wild type receptor (dominant negative inhibition).[17] A case of compound effect of two dominant negative mutant receptors has been reported in a child with severe biochemical resistance, pronounced developmental delay, growth retardation, and cardiac hyperthyroidism which was fatal due to heart failure following septicaemia. This child showed homozygosity for a point mutation in both alleles of the TRβ gene.[18]

In another form of non-TR THR, the non-T_3 binding mutant homodimer binds to DNA and exhibits constitutive silencing function which cannot be overcome by hormone. Conversely, TR mutants with impaired homodimerisation properties are weaker dominant negative inhibitors when tested directly; some TR mutants either bind co-repressor more avidly or fail to dissociate from co-repressor following receptor occupancy by hormone.[19] The mutant receptor–co-repressor complexes occupy TRE in target gene promoters to mediate dominant negative inhibition. Most of the mutations are located around the hydrophobic hormone binding pocket. The DNA binding, dimerisation and co-repressor binding regions of TR are devoid of naturally occurring mutations perhaps because such mutations elude discovery by lacking dominant negative activity, therefore being clinically and biochemically silent. The ability to exert a dominant negative effect within the hypothalamic–pituitary–thyroid axis is a key property of mutant TRs which characteristically generates abnormal thyroid function tests, leading to the identification of the disorder.

Table 1 Clinical features of thyroid hormone resistance

Findings	Frequency (%)
Goitre	66–95
Emotional disturbances	60
Recurrent ear and throat infections	55
Delayed bone age >2 SD below mean	29–47
Attention deficit hyperactivity disorder	40–60
Tachycardia	33–75
Hyperkinetic behaviour	33–68
Low body mass index (in children)	33
Learning disability	30
Short stature (<5th centile)	18–25
Hearing loss (sensorineural)	10–22
Mental retardation (IQ <70)	4–16

CLINICAL FEATURES

THR was first described in two clinically euthyroid siblings with high circulating thyroid hormone concentrations and other abnormalities including deaf mutism, delayed bone maturation, stippled femoral epiphyses, short stature, dysmorphic facies, winging of the scapulae and pectus carinatum.[1] In some cases, hypothyroid features such as growth retardation, delayed dentition or bone age occurred in children, whereas in adults fatigue and hypercholesterolaemia may coexist with thyrotoxic symptoms in the same individual. Nevertheless, the presence or absence of thyrotoxic symptoms, suggesting either generalised or pituitary resistance to thyroid hormone, is a useful guide to treatment.

The prevalence of THR is approximately 1 in 40 000.[6] Table 1 enumerates the clinical features and their frequency of occurrence.

The clinical phenotypes may be attributable to variable peripheral resistance in different individuals, as well as in different tissues within a single subject. This may be due to variable distribution of TR isoforms in different tissues. As hypothalamus, pituitary and liver express predominantly TRβ whereas TRα is mainly expressed in the myocardium, TRβ mutations are likely to be associated with pituitary and liver resistance, as exemplified by normal sex hormone binding globulin (SHBG) and non-suppressed TSH concentrations with retained myocardial sensitivity to thyroid hormones. Another factor, which may regulate the degree of tissue resistance, is the relative expression of mutant versus wild type TRβ alleles.

Goitre, generally diffuse, is present in up to 65% of individuals. Goitre is especially found in adult women. Thyroidectomy tends to be unsuccessful and it aggravates multinodularity and thyroid dysfunction.[20] As TSH shows significantly enhanced biological activity, it may lead to a large goitre, high serum T_4 and T_3 values, but normal concentrations of immunoreactive TSH in some cases.[21]

Before the advent of sensitive TSH assays, a combination of goitre, palpitations and tachycardia (in 75% of patients with generalised resistance and nearly all with pituitary resistance) often led to a misdiagnosis of Graves' disease.[20]

A history of childhood short stature (height <5th centile) and delayed bone age (>2 SD below mean) is found in nearly 18% and 29% adult patients, respectively, with normal height and GTHR or PTHR. About a third of affected newborns have low birth weight. The basal metabolic rate is variably altered in THR, being normal in many cases but elevated particularly in childhood.

Two studies have documented neuropsychological abnormalities in THR patients. Hauser *et al* found attention deficit hyperactivity disorder (ADHD) in childhood more frequently (75%) as compared to their unaffected relatives (15%).[22] Mixson *et al* showed that both children and adults with THR exhibited problems with language development manifested by poor reading skills and problems with articulation.[23] Frank mental retardation (IQ <60) is quite uncommon but 30% of patients show mild learning disability (IQ <85).

A significant degree of hearing loss has been documented in 21% of patients. Conductive defect (probably related to an

increased incidence of recurrent ear infections in childhood) was seen in half of such cases. TRβ subunit has also been identified on the cochlea, mutation of which might contribute to auditory dysfunction.[24] Cochlear dysfunction was found in 50% of all THR patients, with or without hearing loss. Retrocochlear function was normal. No morphological cochlear abnormalities were detected on computed tomography of the temporal bone.[24]

Recurrent pulmonary and upper respiratory tract infections occur more often in THR and the affected individuals have reduced circulating immunoglobulin concentrations.

LABORATORY FINDINGS

THR and thyroid hormone deficiency or excess may be clinically similar; therefore, distinguishing these has a large impact on the choice of treatment modality. With the advent of highly specialised hormonal assays, the diagnosis of such problems, however, has been simplified.

The sine qua non for making a diagnosis in the patient with TRβ defects are high FT_4 with non-suppressed TSH. There is a corresponding rise in serum T_3 and reverse T_3 (rT_3). In contrast to thyrotoxicosis, the ratio of T_4 to T_3 is normal. Thyroid hormone values can be "borderline" elevated if pituitary resistance is mild, but such values should not be ignored. Patients who have undergone thyroidectomy, however, pose a diagnostic challenge. Other supportive findings are raised thyroglobulin, normal or exaggerated response of TSH to TRH, and high thyroidal radioiodine uptake. The titres for thyroid antibodies are negative, thereby ruling out autoimmunity. For thyroid hormone action on central and peripheral tissue a protocol using administration of liothyronine has been standardised.[2] Inability to suppress TSH, cholesterol and creatine kinase and an impaired rise in the concentrations of SHBG and ferritin are in agreement with the diagnosis of THR. Low T_4 and rT_3 with high FT_3 and normal or high TSH are the characteristic laboratory findings in thyroid hormone cell transport defect (THCTD). In individuals with SECISBP2 gene mutation, findings are comparable with TRβ mutation in terms of FT_4, rT_3 and TSH except for low FT_3.

DIFFERENTIAL DIAGNOSIS

The causes of elevated total T_4 with non-suppressed TSH are listed in box 1.

T4 measurement by an equilibrium dialysis or by direct two step method may be required to exclude artefactual elevation due to dysalbuminaemia or the presence of anti-iodothyronine and anti-TSH antibodies. Presence of non-thyroidal illness, neonatal age and iatrogenic elevation in thyroid hormone may be excluded by history.

Box 1 Causes of elevated total T4 with non-suppressed thyroid stimulating hormone (TSH)

- Raised serum binding proteins
- Familial dysalbuminaemic hyperthyroxinaemia
- Anti-iodothyronine/anti-TSH antibodies
- Non-thyroidal illness (including acute psychiatric disorders)
- Neonatal period
- Iatrogenic: thyroxine replacement therapy, drugs (for example, amiodarone, heparin)
- TSH secreting pituitary tumour
- Resistance to thyroid hormone

The main differential diagnosis is inappropriate TSH secretion from pituitary adenoma (TSH-oma). The distinction between THR and TSH-oma may be difficult as there are no significant differences in age, gender, FT_4, FT_3 and TSH concentrations in both the conditions. Pituitary imaging may help to differentiate the two conditions. Pituitary adenoma can be differentiated from THR with the help of the Werner test. It is based on the principle that circulating TSH shows a normal or exaggerated response to TRH and is suppressed following T3 administration (80–100 mg orally for 8–10 days) in patients with THR, whereas TSH secretion from autonomous tumours is unresponsive.[25] The family history of a similarly affected first degree relative is virtually diagnostic of THR, as the disorder is familial in 80–90% of cases. Resistance to the thyroid hormone is variable in different tissues, so lack of clinical features of hyperthyroidism does not exclude the diagnosis. Since no single biochemical test is diagnostic, serum SHBG measurement may be of some value, which is often elevated into the thyrotoxic range in TSH secreting tumours but is invariably normal in THR. Co-secretion of other pituitary hormones and measurement of free α-subunits may also help in the diagnosis of thyroid hormone secreting adenoma.

MANAGEMENT

The management of THR is complex, as variable resistance makes it difficult to maintain euthyroidism in all tissues. In general, the presence or absence of overt thyrotoxic or hypothyroid features is a useful guide for treatment. Clinical hypothyroidism may be present in patients in whom hormone resistance at the peripheral tissue level is not compensated by increased thyroid hormone concentrations. This group can be treated by the administration of supraphysiological doses of thyroid hormone, but with careful monitoring of the peripheral markers of thyroid hormone actions to avoid thyrotoxic symptoms. Other circumstances, such as hypercholesterolaemia in adults or developmental delay and growth retardation in children, may also warrant the administration of supraphysiological doses of L-T_4 to overcome a higher degree of resistance in certain tissues.

On the other hand, a reduction in thyroid hormone concentrations may be beneficial in the management of patients with thyrotoxic symptoms. The administration of conventional antithyroid drugs will further raise the TSH with consequent goitre and may also induce pituitary thyrotrophic hyperplasia, with a theoretical risk of inducing autonomy in either organ. Accordingly, agents which inhibit pituitary TSH secretion, yet are devoid of peripheral thyromimetic effects, are used to reduce thyroid hormone values. The most widely used agent is 3,3,5 triiodothyroacetic acid (TRIAC), a thyroid hormone analogue

Current research questions

- Identification of newer defects in mediators of thyroid hormone action, thyroid transporters other than MCT8 and thyroid metabolism to provide further insight into non-receptor mechanisms to produce thyroid hormone resistance phenotype.
- Development of better knock-out and knock-in animal models to elucidate thyroid hormone action.
- Identification of receptor isoform specific agonist and antagonists to help in management of thyroid hormone resistance.

Key learning points

- Thyroid hormone resistance (THR) can be generalised, isolated pituitary, or peripheral in type.
- There is elevated serum FT_4 and FT_3 concentrations and normal or slightly elevated serum thyroid stimulating hormone (TSH) concentration.
- High index of suspicion is important for diagnosing THR in the case of "borderline" hormone values.
- The clinical features include signs of either thyroid hormone deficiency or excess or both.
- Important differential diagnoses are thyroid hormone binding anomalies, TSH secreting pituitary adenoma, and Graves' disease.
- The most common genetic defect is in TRβ; however, thyroid hormone transport and metabolic abnormalities may be the cause in some cases.
- The hypothyroid THR is treated with supraphysiological L-T_4 while thyrotoxic THR may be treated with TRIAC and D-T_4.
- Thyroidectomy for goitre is done for cardiac failure in thyrotoxicosis, otherwise L-T_3 should be used rather than thyroidectomy to suppress goitre.

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which has been shown to be beneficial in both children and adults.[26 27] This compound exerts predominantly pituitary and hepatic thyromimetic effects in vivo and exhibits a higher affinity for TRβ than TRα in vitro. The usual dose of TRIAC is 1.4–2.8 mg once daily. A recent study suggested that twice daily administration might inhibit TSH secretion more effectively.[28] TRIAC in pregnancy controls maternal thyrotoxic symptoms but may induce fetal goitre. Another agent, dextro-thyroxine (D-T_4), has been shown to be effective in some cases where TRIAC treatment is not successful.[29 30] The dopaminergic agent bromocriptine or the somatostatin analogue octreotide have also been used, but unlike TSH-omas, pituitary TSH secretion escapes their inhibitory effects.[31 32] Thyrotoxic symptoms in THR show spontaneous variation, so a periodic cessation of thyroid hormone lowering therapy and re-evaluation of the clinical status of the patient is advisable. Thyroid ablation followed by sub-physiological thyroxine replacement can be used in rare circumstances (THR associated with life threatening thyrotoxic cardiac failure). Some studies have also shown successful suppression of TSH in PTHR with D-T_4 as this does not result in iatrogenic hyperthyroidism.

Patients who have previously been misdiagnosed and have undergone thyroid ablation with surgery or radioiodine to correct the biochemical abnormality end up with recrudescence of the goitre, disruption of the pituitary–thyroid axis, and subsequent hypothyroidism. These patients should be treated with thyroxine in supraphysiological dosage as increased TSH may potentiate the risk of thyrotrophic hyperplasia and possible adenoma formation.

Recently it has been shown that treatment with supraphysiological doses of L-T_3 as a single dose every alternate day is effective in reducing goitre size with remarkable cosmetic benefits and without causing side effects; hence, this seems to be the treatment of choice presently, considering the high incidence of failure of surgery. The dose of L-T_3 should be adjusted according to TSH, thyroglobulin concentrations, and goitre size.[33]

In the future, identification of thyroid hormone analogues with greater thyromimetic activity on TRβ2 and TRβ1 versus TRα1 or receptor isoform specific antagonists might represent a more rational therapeutic approach.[34] Development of better animal models (for example, by targeted disruption of mouse TRβ and TRα loci) should also enable improved understanding of thyroid hormone action.[35]

CONCLUSION

THR is a rare but important differential diagnosis in patients presenting with thyroid disorders. Its clinical presentation is heterogeneous; features corresponding to hypo- or hyperfunction of the thyroid gland, or both, can be found in the same or different individuals. The variability in tissue sensitivity has been attributed to tissue distribution of TR isoforms. Family history, concentrations of TSH, FT_3, FT_4, and an MRI scan of the pituitary are usually sufficient to rule out Graves' disease, thyroid hormone binding anomalies, and TSH secreting pituitary adenoma. The disease is dominantly inherited with defects in TRβ and sometimes may be due to thyroid hormone transport and inactivation abnormalities. Techniques for genetic screening and diagnosis have improved, thereby permitting confirmation of the diagnosis. The screening of family members helps in genetic counselling, thus minimising morbidity in future generations. Treatment for THR can be attempted with supraphysiological T_4 in hypothyroid patients and with TRIAC or D-T_4 in hyperthyroid patients. Treatment with L-T_3 is more appropriate for reducing goitre size than attempting thyroidectomy.

CHOOSE ONE OF THE FOUR OPTIONS FOR EACH QUESTION (ANSWERS AFTER THE REFERENCES)

1. All are sites where TRβ is located except:

A. Liver
B. Pituitary
C. Brown fat
D. Kidney

2. Mode of inheritance of MCT8 mutation is:

A. Autosomal dominant
B. Autosomal recessive
C. X-linked
D. Non-Mendelian

3. All the following are compatible with the diagnosis of THR except:

A. Normal T_3 to T_4 ratio
B. Increased radio-iodine thyroidal uptake
C. Short term liothyronine leads to increased SHBG values
D. Negative anti-thyroid antibodies

4. Differentiation between TSH-oma and THR can be done by:

A. Presence of goitre
B. Tachycardia
C. Werner test
D. Increased uptake on thyroid scan

5. All the following can be tried in the management of THR except:

A. TRIAC
B. Thyroidectomy
C. L-T_3
D. Dextro thyroxine

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Answers

1. C
2. C
3. C
4. C
5. B

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