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GUIDELINES

2024 European Thyroid Association Guidelines on diagnosis and management of genetic disorders of thyroid hormone transport, metabolism and action

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Abstract

Impaired sensitivity to thyroid hormones encompasses disorders with defective transport of hormones into cells, reduced hormone metabolism, and resistance to hormone action. Mediated by heritable single-gene defects, these rare conditions exhibit different patterns of discordant thyroid function associated with multisystem phenotypes. In this context, challenges include ruling out other causes of biochemical discordance, making a diagnosis using clinical features together with the identification of pathogenic variants in causal genes, and managing these rare disorders with a limited evidence base. For each condition, the present guidelines aim to inform clinical practice by summarizing key clinical features and useful investigations, criteria for molecular genetic diagnosis, and pathways for management and therapy. Specific, key recommendations were developed by combining the best research evidence available with the knowledge and clinical experience of panel members, to achieve a consensus.

Keywords: clinical practice guideline; deiodinase; diagnosis and management; impaired sensitivity to thyroid hormones; resistance to thyroid hormone; selenoprotein; thyroid hormone receptor; thyroid hormone transporter

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Introduction

Membrane transporters are rate-limiting for cellular entry of thyroid hormones (TH; T4 and T3) into some tissues, with selenocysteine-containing deiodinase enzymes (D1, D2) converting T4 to the biologically active hormone T3. THs exert their physiological effects principally by regulating the expression of target genes via hormone-inducible nuclear receptors (TRα and TRβ).

A consensus statement after the 12th International Workshop on resistance to thyroid hormone widened the definition of disorders with impaired sensitivity to thyroid hormones to include conditions with defective cellular uptake of TH via membrane transporters, reduced intracellular hormone metabolism generating T3 from T4, as well as resistance to thyroid hormone action via nuclear receptors (1, 2, 3).

Accordingly, these guidelines focus on the diagnosis and management of genetic disorders of thyroid hormone transport, metabolism, and action comprising resistance to thyroid hormone β (RTHβ), resistance to thyroid hormone α (RTHα), monocarboxylate transporter 8 (MCT8) defects, selenoprotein deficiency, and iodothyronine deiodinase 1 defects.

Methodology and grading of evidence

Following consultation with its Guidelines Board, the Executive Committee of the ETA commissioned the development of this guideline by a team of experts led by one chairperson (KC). For each disorder, designated task force members with knowledge and expertise of this condition (one or more primary reviewers), were assigned. Following a review of the literature based on a systematic search of the MEDLINE database via the PubMed search engine, primary reviewers formulated clinical features and key investigations, guidance on diagnosis and management, together with statements of key recommendations. This information was assessed by secondary reviewers, with dialogue between primary and secondary reviewers, amending the guidance. Finally, the guidance was further refined (and amended if necessary) by all members of the task force to achieve a common consensus.

We have used the GRADE system to assess and sort out the quality of the evidence (4). The strength of each statement has been classified as strong (S, a recommendation or clinically important best practice applicable to most patients) or weak (W, a suggestion – to be considered by the clinician and applicable best practice in particular patients or contexts). The quality of the evidence concerning each aspect of the statement has been graded as: level 1, high quality (RCT evidence/meta-analysis (ØØØØ)); level 2, moderate quality (intervention short of RCT or large observational studies (ØØØO)); level 3, low quality (case-control studies, case series (ØØOO)); level 4, very-low quality (case reports, expert opinion (ØOOO)) using modified GRADE criteria (5). Boxes 1, 2, 3, and 4 summarise key recommendations for differential diagnosis of raised thyroid hormones and non-suppressed TSH as well as the diagnosis, management, and treatment of each disorder.

Differential diagnosis of raised thyroid hormones and non-suppressed TSH

The finding of thyroid hormones {(free) T4 and/or (free) T3} above the reference interval with non-suppressed thyrotropin (TSH) can be one of the most challenging patterns of discordant thyroid function tests (TFTs) to resolve. A systematic approach (Fig.1) is required to prevent inappropriate further investigations and unnecessary treatments, while at the same time ensuring rare genetic and acquired disorders are diagnosed in a timely manner.

A key first step in the evaluation of a patient with hyperthyroxinemia and non-suppressed TSH is to

Box 1. Summary of key recommendations – Differential diagnosis

Differential diagnosis of raised thyroid hormones and non-suppressed TSH

- Potential confounding effects of medications and intercurrent illness should be carefully considered when assessing a patient with raised thyroid hormone concentrations and non-suppressed TSH (**Recommendation: S; Quality of evidence:** ØØOO).
- Laboratory assay interference in the measurement of thyroid hormones (T4, T3) and TSH should be excluded before screening for rare genetic and acquired disorders of thyroid hormone transport, metabolism, and action (**Recommendation: S; Quality of evidence:** ØØØO).
- Dynamic endocrine tests (TRH stimulation (if available), L-T3 suppression), pituitary imaging (MRI, PET), and trial of depot somatostatin receptor ligand may aid in the distinction of RTHβ and thyrotropinoma (**Recommendation: S; Quality of evidence:** ØØOO).

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Box 2. Summary of key recommendations – Resistance to thyroid hormone

Recommendations in resistance to thyroid hormone β

Diagnosis

- We **recommend** considering a diagnosis of RTHβ in cases with a discordant pattern of thyroid function tests (TFTs), comprising genuinely elevated, circulating free (or total) T4, raised free (or total) T3, and nonsuppressed TSH (**Recommendation: S; Quality of evidence**: ØØØØ).
- We recommend suspecting RTHβ only when failure to normalize TSH in hypothyroidism is accompanied by high FT4 (**Recommendation: S; Quality of evidence:** ØØØO).
- If RTHβ is suspected, we **recommend** measuring TFTs in first-degree relatives. Finding abnormal TFTs in first-degree relatives strengthens the likelihood of RTHβ (**Recommendation: S; Quality of evidence:** ØØØØ).
- We **recommend** *THRB* sequencing to confirm the diagnosis of RTHβ in cases with genuinely raised thyroid hormones (T4 and T3) with nonsuppressed TSH (**Recommendation: S; Level of evidence:** ØØØØ).
- When a *THRB* variant of unknown significance (VUS) is identified by sequencing (e.g. next generation) in an index case or families, **we recommend** checking segregation with abnormal thyroid function tests in affected individuals to establish the pathogenicity and confirm RTHβ (**Recommendation: S; Quality of evidence:** ØØØO).
- In cases with a VUS in *THRB* where this is not possible (e.g. sporadic cases, unavailable family members, borderline abnormalities in thyroid function), **we suggest** *in vivo* assessment with a T3 suppression test as well as functional studies of the TRβ variant *in vitro* (less sensitive) (**Recommendation: W; Quality of evidence:** ØØOO).
- Following the diagnosis of RTHβ in an index case, **we recommend** testing (biochemical, then genetic) of first-degree relatives (**Recommendation: S; Quality of evidence:** ØØØØ).
- If a *THRB* mutation is absent with conventional sequencing (especially in cases with the transmission of abnormal thyroid function to progeny), **we recommend** next-generation sequencing of tissues other than blood to exclude RTHβ due to somatic mosaicism (**Recommendation: S; Quality of evidence:** ØOOO).

Management

- We **recommend** ultrasound evaluation of the thyroid/goiter (undertaken by a specialist with expertise in the classification (e.g. TIRADS) of thyroid nodules) at diagnosis and periodically thereafter (**Recommendation: S; Quality of evidence:** ØØØØ).
- We **recommend** the management of any thyroid nodule using standard practice (**Recommendation: S; Quality of evidence:** ØØØO).
- We **recommend** the assessment of concurrent anti-thyroid antibodies (Anti-TPO/TRAb) at diagnosis and during follow-up, whenever a change in thyroid status (circulating TSH or free TH) or symptoms (hypothyroid/thyrotoxic) is observed (**Recommendation: S; Quality of evidence:** ØØOO).
- In childhood, **we suggest** a careful evaluation of growth and development by a pediatric endocrinologist (**Recommendation: W; Quality of evidence:** ØOOO).
- We **suggest** treating ear, nose, and throat infections promptly to avoid or reduce complications (**Recommendation: W; Quality of evidence:** ØØOO).
- At diagnosis, **we suggest** undertaking audiometry to detect hearing deficit (**Recommendation: W; Quality of evidence:** ØØOO).
- When RTHβ is diagnosed in children, **we suggest** neuropsychological assessment and psychometric testing to diagnose ADHD and cognitive deficits that could cause learning difficulties (**Recommendation: W; Quality of evidence:** ØØOO).
- In children with RTHβ, **we suggest** considering educational support to manage learning disabilities and/or attention deficit hyperactivity disorder (**Recommendation: W; Quality of evidence:** ØØOO).
- In adult RTHβ patients, **we suggest** initial assessment and subsequent monitoring of bone density and markers of calcium homeostasis (serum calcium, PTH, 25OH-vitamin D) (**Recommendation: W; Quality of evidence:** ØØOO).
- We **recommend the** assessment of cardiovascular risk in all RTHβ patients over the age of 30 years (or younger in patients with cardiac symptoms or signs) at diagnosis, with an ongoing surveillance. This should include the measurement of blood pressure, electrocardiogram, and echocardiography, with cardiac telemetry and markers of cardiac function (e.g. NT-proBNP) in symptomatic cases (**Recommendation: S; Quality of evidence:** ØØØO).
- We **recommend** a metabolic assessment, including fasting lipids (total LDLc, HDLc, triglycerides), glucose, and HbA1c, in RTHβ patients at diagnosis, with periodic, ongoing monitoring (**Recommendation: S; Quality of evidence:** ØØØO).

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- In RTHβ patients, **we suggest** monitoring the risk of metabolic dysfunction-associated steatotic liver disease (MASLD) (e.g. with fibroscan) (**Recommendation: W; Quality of evidence:** ØØOO).
- Due to increased risks (miscarriage, SGA, and LBW of neonates), **we suggest** multidisciplinary (endocrinologist, obstetrician) team management of all women with RTHβ embarking on pregnancy. (**Recommendation: W; Quality of evidence:** ØØOO).
- We **recommend** careful monitoring of fetal parameters (growth, heart rate) in all RTHβ women during pregnancy, with antithyroid drug treatment being considered in cases of fetal tachycardia or growth restriction (**Recommendation: S; Quality of evidence:** ØØOO).
- With the possible risk of SGA and LBW in normal offspring of mothers with RTHβ, **we suggest** considering antithyroid drug treatment during pregnancy when the maternal FT4 exceeds 150% of the upper limit of normal. Such intervention could be preceded by prenatal genetic diagnosis to identify unaffected fetuses, and this approach should ideally be undertaken in the context of a clinical trial (**Recommendation: W; Quality of evidence:** ØOOO).

Treatment

- We **recommend** avoiding treatment with antithyroid drugs or thyroid ablation (surgery or radioiodine) for RTHβ patients in the absence of significant comorbidities (see below) (**Recommendation: S; Quality of evidence:** ØØØO).
- We **recommend** limiting thyroid ablation to RTHβ cases with severe, uncontrolled, or life-threatening hyperthyroidism (e.g. heterozygous RTHβ and thyroid autonomy due to Graves' disease/toxic nodule, or homozygous RTHβ with thyrotoxic cardiomyopathy) or large goiters with compression symptoms or thyroid malignancy. Post-ablation, levothyroxine therapy should aim to restore thyroid function tests to their original level (**Recommendation: S; Quality of evidence:** ØØOO).
- We **recommend** periodic, ongoing surveillance for comorbidities (thyroid autoimmunity, tachyarrhythmias, low bone density, dyslipidemia) (**Recommendation: S; Quality of evidence:** ØØØO).
- We **recommend** beta-blockade alone or, rarely, TRIAC therapy to control thyrotoxic symptoms (e.g. anxiety, tremor, palpitations) and signs (tachycardia) (**Recommendation: S; Quality of evidence:** ØØØO).
- We **recommend** that a decision to treat with TRIAC be made only made after discussion with centers with expertise in its use in this disorder (**Recommendation: S; Quality of evidence:** ØØØO).
- We **recommend** administering TRIAC twice or thrice daily. The dosage of TRIAC is titrated to control hyperthyroid symptoms and signs and lower circulating free T4 concentrations (TRIAC cross-reacts in immunoassays but not LC-MS/MS assays of T3) (**Recommendation: S; Quality of evidence:** ØØØO).
- We **recommend** considering cardioselective beta blockade to control tachycardia, atrial fibrillation, and supraventricular tachyarrhythmias in heterozygous RTHβ patients or cardiac hyperthyroidism in homozygous RTHβ (**Recommendation: S; Quality of evidence:** ØØOO).
- We **recommend** seeking expert cardiological advice on the management of atrial fibrillation in RTHβ, as chemical (e.g. amiodarone, flecainide) and electrical cardioversion or cardiac ablation may not be successful (**Recommendation: S; Quality of evidence:** ØØOO).
- We **suggest** that attention deficit-hyperactivity disorder, which interferes with daily activities of life, should be formally diagnosed by a neuropsychiatrist to decide on the most appropriate intervention. This can either be standard intervention or treatment with TRIAC (not yet licensed for RTHβ in all countries, but available on an individual basis) (**Recommendation: W; Quality of evidence:** ØØOO).
- In levothyroxine treatment of hypothyroidism (autoimmune or congenital) with coexisting RTHβ, elevated circulating TSH with normal free TH concentrations signify under replacement. In this context, we **recommend** that levothyroxine therapy be titrated to achieve FT4 concentrations comparable to other family members (with RTHβ alone) or maintain concurrent high-normal TSH and high free TH concentrations, monitoring cardiac function to avoid overtreatment (**Recommendation: S; Quality of evidence:** ØØOO).

Recommendations in resistance to thyroid hormone α

Diagnosis

- When considering a diagnosis of RTHα, we **recommend** full clinical assessment, including measurement of head circumference, standing height, sitting height, and subischial leg length, with a comparison of these results to age-appropriate population ranges to determine whether any of the recognized clinical phenotypes are present (**Recommendation: S, Quality of evidence:** ØØOO).
- If RTHα is suspected, we **suggest** undertaking additional investigations, which include (but are not limited to): full blood count, T4, T3, TSH, reverse T3, creatine kinase, skeletal and dental radiographs (**Recommendation: W, Quality of evidence:** ØØOO).

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- We **recommend** that *THRA* sequencing be **performed** in any patient with:
  i. three or more of the following major criteria: macrocephaly, short stature, constipation, typical biochemical profile (TSH within reference interval/mildly raised and low/low-normal T4 and raised/high-normal T3, with low reverse T3, if available), developmental delay (all unless otherwise explained) (**Recommendation: S, Quality of evidence:** ØØOO).
- We **suggest** that *THRA* sequencing be **considered** in any patient with:
  two major criteria, as listed above (**Recommendation: W, Quality of evidence:** ØØOO)
  i. one major criterion, as listed above, plus two or more of the following minor criteria: unexplained anemia, clinical features of hypothyroidism (dysmorphic facies), neurocognitive features (dyspraxia), skeletal dysplasia (**Recommendation: W, Quality of evidence:** ØØOO)
  ii. three or more minor criteria, as listed above. (**Recommendation: W, Quality of evidence:** ØØOO)
- We **suggest** that *THRA* sequencing be performed even if the criteria above are not met but clinical suspicion of RTHα remains (**Recommendation: W, Quality of evidence:** ØØOO).
- If a variant of uncertain significance (VUS) in *THRA* is identified, we **suggest** that the following methods can be used to determine whether it is pathogenic, recognizing that such evaluation will require liaison with clinical genetics services or international laboratories/clinical services with expertise in the diagnosis and/or management of RTHα:
  i. Determination of variant genotype–phenotype segregation in families
  ii. Assessment of whether there is a *THRB* mutation known to cause RTHβ homologous with the *THRA* variant in the patient.
  iii. Structural modelling of the variant in TRα and assessment whether the change in protein structure is predicted to affect the normal function of TRα
  iv. Testing the TRα variant in assays of receptor function
  (**Recommendation: W, Quality of evidence: ØØOO**)
- We **do not recommend** the sole use of predictive algorithms (e.g. PolyPhen, SIFT, REVEL, CADD) to determine the pathogenicity of a VUS in *THRA* (**Recommendation: S, Quality of evidence:** ØØOO).
- As the phenotypic spectrum of this disorder is not fully defined, we **do not recommend** making a definitive diagnosis of RTHα in individuals who do not have a pathogenic *THRA* mutation (**Recommendation: S, Quality of evidence:** ØØOO).

Management and treatment

- Following the diagnosis of RTHα, we **recommend** a trial of levothyroxine therapy in all patients (**Recommendation: S, Quality of evidence:** ØØOO).
- We **recommend** the continuation of levothyroxine therapy long-term in all patients unless concerns of side effects or tolerability arise (**Recommendation: W, Quality of evidence:** ØOOO).
- We **suggest** all patients with RTHα remain under the care of an endocrinologist lifelong (**Recommendation: S, Quality of evidence:** ØOOO).
- We **suggest** referral to other specialities, as necessary, including neurology, neuropsychology, gastroenterology, hematology, dental services, physiotherapy, speech and language therapy, and occupational therapy (**Recommendation: S, Quality of Evidence: Quality of evidence:** ØOOO).
- In children with RTHα and impaired GH secretion or low baseline IGF-1 concentrations, we **recommend** reassessment of GH status after levothyroxine therapy (**Recommendation: W, Quality of evidence:** ØØOO).
- There is insufficient data to provide recommendations on the dosage of levothyroxine (though it should be above the usual replacement dose), or to specify clinical or biochemical targets of therapy (**Recommendation: W, Quality of evidence:** ØOOO).
- There is insufficient data to recommend for or against the use of liothyronine in RTHα at present (**Recommendation: W, Quality of evidence:** ØOOO).
- There is insufficient data to provide recommendations on the management of RTHα during pregnancy; however, we **suggest** continuation of levothyroxine therapy during pregnancy (**Recommendation: W, Quality of evidence:** ØOOO).
- We **recommend** against the use of liothyronine during pregnancy (**Recommendation: S, Quality of evidence:** ØOOO).

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Box 3. Summary of key recommendations - MCT8 deficiency.

Diagnosis

- When considering a diagnosis of MCT8 deficiency, we **recommend** a full clinical assessment to determine whether the patient exhibits any recognized clinical phenotypes and a physical examination, including neurological assessment (**Recommendation: S, Quality of evidence:** ØØOO).
- If MCT8 deficiency is suspected, we **recommend** additional investigations including (but not limited to) serum (free) T3, (free) T4, reverse T3 (rT3) and TSH concentrations (interpreting results in the context of age-specific reference intervals), (**Recommendation: S, Quality of evidence:** ØØOO**)**.
- We **recommend** that *SLC16A2* sequencing be **performed** in any male patient with:
  i. the following 'major criteria'; typical biochemical profile (TSH within normal range or mildly raised, low or low-normal (F)T4, raised (F)T3, low reverse T3, and/or elevated (F)T3/(F)T4 or T3/rT3 ratio) in combination with either global developmental delay, hypomyelination on MRI, clinical signs of movement disorder (e.g. dystonia, bradykinesia), persistent primitive reflexes, or a positive family history for MCT8 deficiency (**Recommendation: S, Quality of evidence:** ØØOO).
- We **suggest** that *SLC16A2* sequencing be **considered** in any patient with:
  ii. characteristic thyroid function tests (TSH within normal range or mildly raised, low or low-normal T4, raised T3, low reverse T3, and/or elevated T3/(F)T4 or T3/rT3 ratio) and subtle developmental delay or behavioral abnormalities (**Recommendation: W, Quality of evidence:** ØOOO).
- We **suggest** that *SLC16A2* sequencing be **considered** prenatally (through villus sampling or amniocentesis) in pregnancies with male fetal sex if the family history is positive for MCT8 deficiency and genetic segregation indicates a risk of the fetus carrying the mutant allele (**Recommendation: W, Quality of evidence:** ØOOO).
- If a variant of uncertain significance (VUS) in *SLC16A2* is identified, we **recommend** using the following methods to determine pathogenicity:
  i. segregation of genotype with phenotype in families.
  ii. testing the function of novel variants in transfected cells or patient-derived cells
  iii. structural modeling.
  (**Recommendation: W, Quality of evidence:** ØOOO)
- We **do not recommend** the sole use of predictive algorithms (e.g. PolyPhen, SIFT, REVEL, CADD) to determine the pathogenicity of a VUS (**Recommendation: S, Quality of evidence:** ØOOO).
- The pathways described above may require liaison with clinical genetics services or international laboratories/clinical services with expertise in the diagnosis of MCT8 deficiency.

Management and treatment

- Post-natal treatment with levothyroxine monotherapy is **not recommended** (**Recommendation: S, Quality of evidence:** ØØOO).
- We **recommend** treatment with TRIAC (**Recommendation: S, Quality of evidence:** ØØØO) or DITPA (**Recommendation: W, Quality of evidence:** ØØOO).
- We **recommend** titrating the dosage of TRIAC (or DITPA), aiming to reduce serum T3 concentrations to a target range between 1.4 and 2.5 nmol/L to alleviate the peripheral thyrotoxic state, unless limited by the occurrence of dose-related side effects (**Recommendation: S, Quality of evidence:** ØØØO). A higher dosage of TRIAC can reduce serum T3 concentrations to the lower end or below the age-specific reference range, potentially benefiting neurodevelopment (**Recommendation: W, Quality of evidence:** ØOOO).
- We **recommend** long-term therapy with TRIAC (or DITPA) in all patients unless concerns about drug side effects or tolerability arise (**Recommendation: W, Quality of evidence:** ØØOO).
- If thyroid hormone analogs are unavailable, we **suggest** that a combination of levothyroxine and PTU treatment could be considered (**Recommendation: W, Quality of evidence:** ØØOO).
- Given the rare but potentially severe and life-threatening side effects of PTU and the unknown long-term effects of thyroid hormone analogs, we acknowledge that the risks versus benefits of such therapies should be considered carefully, particularly in patients whose baseline liver function is already deranged (1) (**Recommendation: S, Quality of evidence:** ØØOO).
- We **recommend** all patients with MCT8 deficiency remain under the care of a (pediatric) endocrinologist and a (pediatric) neurologist (**Recommendation: S, Quality of evidence:** ØOOO).
- We **recommend** the discussion of cases by a multidisciplinary team, comprising (pediatric) endocrinologists, neurologists, cardiologists, dietitians, occupational, speech and physiotherapists, physicians in rehabilitation medicine (physiatrists), orthopedic surgeons, and medical daycare centers (**Recommendation: S**); oversight of multidisciplinary team outcomes by a case manager is valuable (**Recommendation: S, Quality of evidence:** ØOOO).
- We **recommend** careful evaluation of dietary intake to maintain body weight that is adequate for age, and addressing feeding problems to prevent undernutrition. We **suggest** initiating percutaneous enteral tube

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feeding and the input of a dietitian to ensure adequate caloric intake at an early stage to prevent malnutrition (**Recommendation: S, Quality of evidence:** ØØOO).
- We **suggest** that all patients should be offered empirical symptomatic treatment for neurological symptoms, including dystonia/hypertonia (spasmolytic drugs), drooling (e.g. anticholinergic drugs), and true epilepsy (carefully distinguished from a paroxysmal movement disorder); and should be referred to rehabilitation physicians/orthopedic surgeons/physiotherapists for measures anticipating contractures, scoliosis, a hip subluxation (**Recommendation: S, Quality of evidence:** ØØOO).
- We **suggest** treating frequently occurring gastrointestinal issues such as gastroesophageal reflux and/or gastroparesis, as well as constipation in accordance with standard practice (**Recommendation: S, Quality of evidence:** ØØOO).

Box 4. Summary of key recommendations – Disorders of thyroid hormone metabolism.

Recommendations in selenoprotein deficiency

Diagnosis

- We **recommend** measurements to identify raised serum FT4, normal or low FT3, raised reverse T3, and low plasma selenium concentrations (**Recommendation: S, Quality of evidence:** ØØOO).
- When making a genetic diagnosis, we **recommend** next-generation (whole exome or genome) sequencing of *SECISBP2*, enabling identification of intronic mutations as recorded in several cases. In cases of proven selenoprotein deficiency with an apparent, monoallelic, gene defect, we **recommend** analysis of SECISBP2 cDNA to identify missplicing events due to cryptic intronic mutations involving the other allele. Reduced expression or function of selenoproteins in patient-derived cells is also informative (**Recommendation: S, Quality of evidence:** ØØOO).

Management

- We **recommend** monitoring for growth retardation and delayed development in childhood (**Recommendation: S, Quality of evidence:** ØØOO).
- We **recommend** periodic magnetic resonance imaging and **suggest** muscle biopsy in selected cases to identify and monitor the evolution of muscular dystrophy, with measurements of vital capacity and polysomnography to detect nocturnal hypoventilation (**Recommendation: S, Quality of evidence:** ØØOO).
- We **recommend** surveillance of patients for progressive, sensorineural hearing loss and aneurysmal dilatation of the thoracic aorta (**Recommendation: S, Quality of evidence:** ØØOO).
- We **suggest** monitoring patients for cutaneous photosensitivity, and male infertility (**Recommendation: W, Quality of evidence:** ØØOO).

Treatment

- We **recommend** liothyronine therapy in patients with subnormal FT3 concentrations (**Recommendation: S, Quality of evidence:** ØØOO).
- We **do not recommend** selenium supplementation in SECISBP2 deficiency (**Recommendation: S, Quality of evidence:** ØØOO).
- We **suggest** that antioxidant (e.g. alpha-tocopherol) treatment to prevent oxidative stress-induced tissue damage can be considered (**Recommendation: W, Quality of evidence:** ØØOO).

Recommendations in iodothyronine deiodinase defects

Diagnosis

- When considering a diagnosis of a D1 defect, we **recommend** first documenting raised serum rT3 concentrations and an elevated rT3:T3 ratio in the absence of non-thyroidal illness (see Supplementary figure 3) (**Recommendation: W, Quality of evidence:** ØOOO).
- As inheritance is dominant, testing other family members, in particular the parents, is very helpful (**Recommendation: S, Quality of evidence:** ØØOO).
- As with other disorders, such as the *SECISBP2* mutation, which can exhibit the same thyroid hormone abnormalities, demonstrating a mutation in the *DIO1* gene is paramount (**Recommendation: S, Quality of evidence:** ØØOO).
- New *DIO1* mutations would require demonstration of a functional abnormality (**Recommendation: W, Quality of evidence:** ØOOO).
- There are no other reported clinical or biochemical manifestations, but the loss of D1 function can alter the thyroid tests associated with other thyroid defects (**Recommendation: W, Quality of evidence:** ØOOO).

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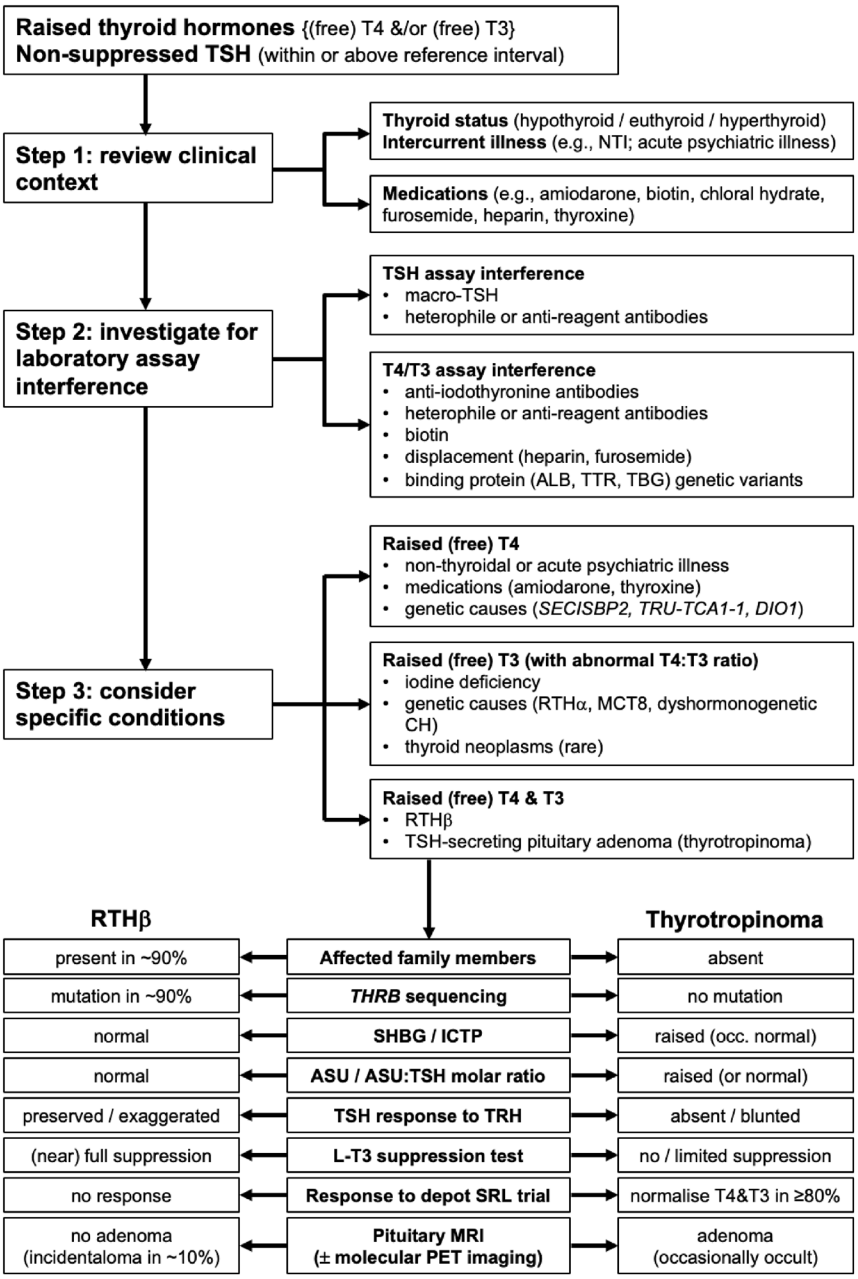

Figure 1

Algorithm for differential diagnosis, showing stepwise approach to the investigation of raised thyroid hormones (T4 and/or T3) with non-suppressed TSH. Key: ALB, albumin; ASU, alpha subunit; CH, congenital hypothyroidism; DIO1, deiodinase type 1; ICTP, serum carboxy-terminal telopeptide of type 1 collagen; L-T3, liothyronine; MCT8, monocarboxylate transporter 8; MRI, magnetic resonance imaging; NTI, non-thyroidal illness; PET, positron emission tomography; RTHα, resistance to thyroid hormone alpha; RTHβ, resistance to thyroid hormone beta; SECISBP2, selenocysteine insertion sequence binding protein 2; SHBG, sex hormone binding globulin; SRL, somatostatin receptor ligand; T3, triiodothyronine; T4, thyroxine; TBG, thyroxine binding globulin; THRB, thyroid hormone receptor beta gene; TRH, thyrotropin releasing hormone; TRU-TCA1-1, tRNA selenocysteine (anticodon TCA) 1-1; TSH, thyrotropin; TTR, transthyretin.

exclude potential confounding factors (including intercurrent non-thyroidal physical or psychiatric illness) and medications (e.g. amiodarone, thyroxine). At the same time, the patient's clinical thyroid status should be determined (Fig. 1, Step 1) (6, 7).

In the absence of a readily explainable physical or pharmacological cause for the abnormal TFTs, close cooperation with the clinical biochemistry laboratory is necessary to investigate possible interference in one or more assays (Fig. 1, Step 2). Here, information from the clinical assessment helps guide the approach to excluding artefactual elevation in T4, T3, or TSH (e.g. in a patient with clinical features of hyperthyroidism, initial suspicion should focus on the reliability of TSH measurement). The presence of interfering antibodies (including both analyte-specific (e.g. macro-TSH, anti-iodothyronine) and those targeting reagents in commonly used immunoassays (e.g. heterophile or anti-animal immunoglobulins)) requires specific exclusion. Demonstration of discrepant findings using different assay platforms (method comparison) is strongly suggestive of interference, but additional steps may be required for detection/confirmation (e.g. dilution studies, polyethylene glycol (PEG) precipitation, or gel filtration chromatography for suspected TSH interference; equilibrium dialysis or ultrafiltration for suspected T4 or T3 interference) (7, 8).

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Once laboratory assay artefact has been excluded, and genuine hyperthyroxinemia with non-suppressed TSH is confirmed, judicious use of additional tests (including (free) T3 if not already measured (with calculation of the T4:T3 ratio), reverse T3 (rT3), thyroid autoantibodies, sex hormone-binding globulin (SHBG)) can provide important clues to the underlying diagnosis (Table 1) and guide the next phase of investigation (Fig. 1, Step 3) (7).

Distinction between resistance to thyroid hormone beta (RTHβ) and TSH-secreting pituitary adenoma (thyrotropinoma or TSHoma) typically requires a multimodal approach, including biochemical investigation, genetic screening, dynamic endocrine testing, pituitary imaging, and a possible trial of depot somatostatin receptor ligand (SRL) therapy (Fig. 1, Step 3) (9, 10).

Resistance to thyroid hormone β

Diagnosis

- The key characteristic of resistance to thyroid hormone beta (RTHβ) (OMIM 188570: Thyroid hormone resistance, generalized; OMIM 145650: Thyroid hormone resistance, pituitary; ORPHA: 566243) is a combination of genuinely raised (total and free) thyroid hormones (T4, T3), with non-suppressed TSH (11, 12, 13, 14)). The diagnosis is also suspected based on other phenotypes described below (and summarized in Table 2).
- After excluding assay interference or other causes of this abnormal hormone pattern, distinguishing between RTHβ or a pituitary TSH-secreting adenoma (TSHoma) is made based on clinical, dynamic endocrine, and radiological investigations outlined above.
- Heterozygous pathogenic variants in *THRB* are identified by conventional (Sanger) gene sequencing (which may not be available in resource-limited settings) in most suspected RTHβ cases and confirm the diagnosis (Supplementary Figure 1, see section on supplementary materials given at the end of this article), but in 10% of individuals with this clinical and biochemical phenotype, a *THRB* defect cannot be identified. Somatic mosaicism for a *THRB* variant that is not expressed in all tissues may account for a subset of such negative cases, and next-generation sequencing at higher read depth may enable the diagnosis of RTHβ in this context (15, 16).
- Consistent with the autosomal dominant inheritance of RTHβ, mutant TRβ inhibits the function of its normal (or wild-type) receptor counterpart in a dominant negative manner (17). Receptor loss-of-function is usually due to reduced hormone binding affinity (18, 19), but some TRβ mutants exhibit impaired corepressor dissociation (20) or coactivator recruitment (21, 22, 23).
- When treating autoimmune hypothyroidism (24, 25, 26, 27) or congenital hypothyroidism (28, 29, 30, 31), the inability of thyroxine replacement (even in supraphysiological dosages) to normalize circulating TSH can suggest underlying coexistent RTHβ.
- Hyperthyroidism (due to Graves' disease, thyroiditis, or amiodarone-induced) can mask underlying RTHβ, which is suspected when antithyroid drug or other treatment results in a marked or exaggerated rise in TSH concentrations in the face of normal circulating thyroid hormones (25, 32, 33).

Clinical features

RTHβ patients can exhibit features of hypothyroidism or hyperthyroidism, reflecting either hormone resistance in TRβ-expressing tissues or approximately normal sensitivity to elevated circulating thyroid hormones in TRα-expressing tissues.

Thyroid

- A goiter, with eventual nodular change, can often be present in RTHβ (34), possibly due to enhanced bioactivity of circulating TSH in this disorder (35).
- Rarely, cases of RTHβ with thyroid cancer (generally papillary microcarcinoma; one metastatic) have been reported (36, 37, 38, 39) with favorable clinical outcomes despite incomplete TSH suppression following thyroid ablation (38).
- Patients with RTHβ have a higher risk of developing thyroid autoimmunity (40).

Cardiovascular phenotype

- Hyperthyroid cardiac manifestations, mediated by the action of elevated thyroid hormones on TRα-expressing myocardium, include tachycardia/tachyarrhythmias (in most cases), atrial fibrillation, and cardiac insufficiency (41, 42, 43, 44). RTHβ patients are at significantly higher risk of adverse cardiovascular outcomes (atrial fibrillation, myocardial infarction, heart failure) and of earlier mortality (45).

Metabolism

- Resistance to hormone action in TRβ-expressing liver likely mediates normal serum SHBG (46, 47), mixed dyslipidemia (raised cholesterol, triglyceride), and increased liver fat (MASLD) in RTHβ patients (48, 49, 50, 51). The respective roles of muscle or liver insulin resistance in the metabolic picture are not clearly delineated. Similarly, whether adverse cardiovascular outcomes are due to dyslipidemia and insulin resistance causing increased atherosclerosis or represent a direct, thyrotoxic cardiomyopathy or a combination remains unknown.

Neurological and audiovisual phenotypes

- Neurocognitive manifestations of RTHβ include anxiety and sleep disturbance, attention deficit

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Table 1 Key biochemical and clinical features in genetic disorders of thyroid hormone transport, metabolism, and action.

	Disorder				
	RTHβ	**RTHα**	**MCT8 deficiency**	**SP deficiency**	**DIO1 deficiency**
Gene	*THRB*	*THRA*	*SLC16A2*	*SECISBP2 or TRU-TCA 1-1*	*DIO1*
Biochemical signature					
Free T4	High	Low-normal or low	Low-normal or low	High	Normal or slightly high
Free T3	High	High-normal or high	Usually high or high-normal	Low or normal	Normal
Reverse T3	High	Normal or low	Low	High	High
TSH	Normal or high	Normal (or mildly raised)	Normal (or mildly raised)	Normal	High
SHBG	Normal	Normal or high	High	High	–

DIO1, deiodinase type 1; MCT8, monocarboxylate transporter 8; RTHβ, resistance to thyroid hormone beta; RTHα, resistance to thyroid hormone alpha; SP, selenoprotein.

hyperactivity disorder (52, 53), mild intellectual disability (lower nonverbal intelligence), language difficulties (54), and poorer academic outcomes (55). Severe intellectual disability in homozygous cases (56) suggests that either mutant TRβ can interfere with the function of TRα1 or a role for TRβ pathways in brain development.
- Hearing loss in RTHβ is due to a combination of conductive deficit (secondary to frequent ear infections in childhood) and cochlear dysfunction (34, 57).
- Impaired color perception is present in heterozygous RTHβ patients (58) with frankly abnormal color vision only in rare homozygous cases (59, 60). Macular dystrophies have been recorded in patients with a *THRB* splice variant (61).

Fertility and pregnancy

- An increased rate of miscarriage has been reported in maternal RTHβ patients (62, 63). Following exposure to high maternal TH during gestation, unaffected infants born to RTHβ females are small for gestational age, have a suppressed TSH, and exhibit low birth weight (62, 63, 64, 65).

Genotype-phenotype correlation

- The clinical phenotype of RTHβ is highly variable, ranging from asymptomatic individuals to patients with thyrotoxic features (66). The magnitude of elevation in circulating free T4 (67), resting energy expenditure (68), or LDL cholesterol (50) correlates with the *THRB* genotype, for a subset (so-called type 1) of TRβ mutations whose loss-of-function is proportional to their degree of impairment in hormone binding (67). Rare cases with homozygous deletion (59) or variants (56, 69) in *THRB* exhibit features including dysmorphic facies and audiovisual abnormalities (59) or intellectual disability, tachyarrhythmias, and thyrotoxic cardiomyopathy (56, 69, 70).

Treatment of RTHβ

- Case reports and small case series have shown that TRIAC (triiodothyroacetic acid), a central thyromimetic which inhibits TSH secretion to lower circulating TH, when used alone or in combination with beta blockade, controls thyrotoxic signs and symptoms in RTHβ, both in adults (71) and children (72, 73). A dosage of 1.4 to 2.8 mg administered twice or three times daily is most effective (74), in keeping with its half-life (75), and ameliorates ADHD symptoms (76, 77). The combination of antithyroid drug and TRIAC can control thyrotoxic cardiomyopathy without a rise in TSH and goitrogenesis (70). Although not yet licensed for this indication, TRIAC can be prescribed in individual RTHβ cases via the manufacturer's managed access programs or via Galenic formulations of the drug made by pharmacists.
- Alternate day T3 administration was reported to reduce large goiter volume in one RTHβ patient (78). Liothyronine (but not methylphenidate) therapy ameliorated ADHD symptoms (79).
- Coexistent RTHβ complicates the treatment of hypothyroidism, with thyroid hormone replacement needing to balance restoration of normal thyroid status with avoidance of tissue (e.g. cardiac) hyperthyroidism (80). Chronic underreplacement with levothyroxine in hypothyroid RTHβ cases risks the development of pituitary thyrotroph hyperplasia (81).

Areas of uncertainty

- Whether prenatal diagnosis or antithyroid drug therapy to alter maternal TH concentrations in an RTHβ pregnancy is warranted.

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Table 2 Clinical features and investigations in resistance to thyroid hormone β.

System	Clinical features	Investigation[a]
Thyroid	Goiter, nodules, thyroid cancer, thyroid autoimmunity	**Ultrasound scan of thyroid; FNA cytology of radiologically indeterminate/suspicious nodules; thyroid autoantibodies**
Metabolic	Abnormal thyroid function, failure to thrive; low body mass index; dyslipidemia, MASLD, insulin resistance	**TSH, Free T4, Free T3** (reverse T3, TBG); resting energy expenditure; muscle creatine kinase, SHBG, angiotensin-converting enzyme; **fasting lipid profile**; fibroscan; **fasting glucose,** HbA1c, insulin
Skeletal	Growth retardation, osteopenia/osteoporosis, stippled epiphyses (biallelic cases)	Pelvis and long bone radiographs, spine radiograph: vertebral fractures; **DXA**: reduced bone mineral density (hip, spine); **calcium**, **25OH-vitamin D**, **PTH;** Markers of bone formation or resorption: P1NP/CTX/BAP (osteocalcin/NTX) (unlike conventional thyrotoxicosis, bone turnover markers are usually normal)
Audiovisual function	Recurrent ENT infections; hearing loss; altered color vision sensitivity	Audiometry; AABR tests; Farnsworth–Munsell 100 Hue test with calculation of total error score; light- and darkness-adapted electroretinograms (ERG), with cone-specific chromatic stimuli.
Neurological and cognitive	Peripheral tremor, ADHD, emotional disturbance (anxiety; insomnia), learning disabilities/memory loss; mental retardation (especially homozygous cases)	**Neuropsychological testing for ADHD** (Rating Scale-IV or Conners Rating Scales) and other cognitive deficits; Wechsler IQ scale.
Appearance	No typical facial features or body habitus (except goiter)	–
Pregnancy	Increased miscarriage rate in the first trimester; LBW/SGA (unaffected babies)	**Expert ultrasound monitoring of fetal growth and development** (as for follow-up of Graves' disease), Monitoring of maternal thyroid hormones
Cardiovascular	Tachycardia, atrial fibrillation, cardiac insufficiency	**Resting ECG**; **cardiac telemetry**; echocardiography: hyperthyroid indices of cardiac contractility; BNP or NT-pro-BNP

AABR, automated auditory brainstem response; ADHD, attention deficit hyperactive disorder.
[a]Key investigations are in bold.

- Whether neonatal diagnosis and early intervention can improve neurological or behavioral phenotypes of RTHβ.
- Whether lipid-lowering or TRIAC therapy, alone or in combination, can alter adverse cardiovascular outcomes in this disorder.
- Whether low bone density in RTHβ increases fracture risk; do antiresorptive or other therapies prevent bone loss or affect fracture risk?
- Further evaluation of therapies (e.g. TRIAC, liothyronine) for ADHD or other neuropsychological phenotypes is warranted.
- Whether the disorder can be caused by heterozygous (or homozygous) variants in *THRB*, outside the recognized mutation hotspots or clusters in its hormone-binding domain.
- Whether genome-wide sequencing should be considered in suspected RTHβ cases without a germline or somatic mosaic mutation in TRβ, looking for either an abnormality in the non-coding region of *THRB* or a defect in an unrelated gene, causing this phenotype.

Resistance to thyroid hormone α

Clinical features and making a diagnosis

Resistance to thyroid hormone α (OMIM 614450: Congenital Nongoitrous Hypothyroidism 6; ORPHA: 566231) is a rare disorder, with 41 affected individuals reported to date (Supplementary Table 1) (82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100). Although the phenotype is highly variable, many patients exhibit similar clinical features, summarized in Table 3. As knowledge of the phenotypic spectrum of RTHα is changing and will probably expand in the future, it is not possible to provide definite criteria that warrant *THRA* sequencing to make a diagnosis. However, to aid physicians' decision-making when considering this diagnosis, we propose using criteria (which may evolve as more cases are described) to direct further investigation. A definitive diagnosis of RTHα is made following the identification of a pathogenic mutation in *THRA*. We acknowledge that *THRA* sequencing is not

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Table 3 Clinical features and investigations in resistance to thyroid hormone α.

System	Clinical feature/phenotype	Investigation[a]
Appearance	Flattened nasal bridge, broad face, thickened lips, macroglossia, coarse facies; skin tags and moles	Photographs
Neurological and cognitive	Delayed childhood milestones; slow speech and initiation of movement; ataxic gait; dysdiadochokinesis; fine and gross motor incoordination (dyspraxia)	MRI scan: .cortical and cerebellar involution; Wechsler IQ scale: reduced perceptual reasoning, processing speed, and visuomotor integration
Skeletal	Growth delay; short stature (often disproportionate); macrocephaly: increased head circumference (SDS or centile); delayed tooth eruption	**Growth chart:** reduced total height; normal sitting height (upper segment); reduced subischial leg length. **Head circumference:** increased (Centile chart or SDS); Skull radiograph; thickened calvarium; delayed fontanelle fusion; excessively serpiginous lambdoid suture (wormian bones); pelvis and long bone radiographs; femoral epiphyseal dysgenesis, cortical hyperostosis; spine radiograph: scalloped vertebral bodies; dental radiograph: delayed tooth eruption; wrist radiograph: delayed carpal bone maturation (bone age)
Gastrointestinal	Constipation	Abdominal radiograph: dilated bowel loops, fecal impaction; measurement of colonic transit time using radio-opaque markers or other locally available investigations; colonic manometry: reduced peristalsis frequency
Cardiovascular	Bradycardia (mild); low BP for age/gender; pericardial effusion (n2)	Cardiac telemetry (average sleeping heart rate); echocardiography: high pre-ejection period, low cardiac index, low E/A ratio, low LV ejection fraction; pericardial effusion; spectral analysis of cardiac autonomic tone[b]
Metabolic	Low metabolic rate; thyroid function tests often borderline abnormal (but can be normal)	**Muscle creatine kinase:** often raised; **SHBG:** often raised; **TSH:** within reference range or borderline elevated; **Free T4/Free T3 ratio**: often low Reverse T3: often low; **serum IGF-1:** may be low; DXA: body composition (fat mass and fat-free (lean) mass[b]; indirect calorimetry: resting energy expenditure[b]
Hematological	Mild anaemia	**Full blood count:** red cell mass and hematocrit can be low; hematinics (iron, B12, folate, hemolytic indices, EPO concentrations) usually normal

[a]Key investigations are in bold; [b]Indicates investigations that are often only available on a research basis.

available in all countries and also that some cases of RTHα have been described in whom *THRA* mutations have not been identified (87).

Management and treatment

- To date, thyroid hormone therapy (almost always levothyroxine, with liothyronine only used in one case (89)), is the only treatment described for RTHα. Although data are restricted to case reports or case series and therapeutic responses are variable, thyroxine treatment in RTHα seems safe and well tolerated and provides beneficial effects for most patients.
- The dosage of levothyroxine used varies (up to 3.8 mcg/kg/day), with serum TSH remaining normal in some T4-treated patients (95, 101), but suppressed TSH with elevated TH concentrations being recorded in other cases (82, 84, 85, 86, 90, 93, 97, 98, 101).
- Levothyroxine therapy has proven beneficial for constipation (82, 84, 86, 93, 95, 98, 99, 101) and growth (82, 84, 90, 93). Cardiac responses to therapy are also mixed, with improvement in contractile function (85, 86) and a rise in heart rate (84, 85), without resultant tachycardia (84, 85, 102). Anaemia, if present, has consistently shown little or no change following levothyroxine (85, 86, 93, 98, 101). Change in neurocognitive function is variable, with improved emotional affect reported in some patients (86, 90, 93, 97, 101), but no benefit in other cases (84, 99). Where tested, nerve conduction improved in a single case (84). Low baseline IGF-1 concentrations in many children with RTHα may (82, 84), or may not (101) normalize following levothyroxine therapy. GH response to provocation can be normal (82) or subnormal (84).
- It is recognized that levothyroxine therapy, in dosages causing suppressed TSH and elevated TH concentrations, may be required to overcome hormone resistance in TRα-expressing tissues, with the potential for thyrotoxicosis in TRβ-expressing tissues (103). Overall, it is likely that an individual RTHα patient's response to levothyroxine therapy depends on the severity of the underlying receptor defect, timing and dosage of drug therapy, and TH concentrations achieved (93).

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Areas of uncertainty

- Optimal biomarkers to diagnose RTHα and assess its response to levothyroxine therapy are undefined.
- Appropriate treatment targets and whether these should be different in childhood (e.g. linear growth, neurodevelopmental outcome) versus adult life (hypothyroid symptoms) are uncertain.
- Whether levothyroxine therapy, in apparent supraphysiological dosage, is associated with tissue thyrotoxicosis and adverse outcomes is unknown.
- There is no information to guide the management of maternal RTHα prior to conception or during pregnancy.
- Whether the diagnosis of the disorder and commencement of levothyroxine therapy at birth can prevent adverse neurodevelopmental outcomes is unknown.

Monocarboxylate transporter 8 deficiency

Clinical features

MCT8 deficiency (OMIM 300523: Allan–Herndon–Dudley syndrome or MCT8 deficiency; ORPHA:59) is characterized by a varying neurodevelopmental delay due to cerebral hypothyroidism, and a wide range of clinical sequelae secondary to chronic peripheral tissue thyrotoxicosis caused by elevated serum T3 concentrations (104) (summarized in Table 4).

Making a diagnosis

- Individuals with MCT8 deficiency have been identified by targeted sequencing of *SLC16A2*, on the X chromosome, in selected individuals (usually male) with clinical and biochemical characteristics, or by exome sequencing strategies (including specific gene panels, e.g. global developmental delay, hypotonia, spasticity, and seizures).
- Definitive diagnosis of MCT8 deficiency requires identification of a known pathogenic mutation, either by reliable *in silico* prediction and/or functional studies of novel variants in transfected cells or patient-derived cells.
- Although the presence and severity of disease features in individuals with mutations in *SLC16A2* can vary, several core characteristics (Table 4) are consistently present and necessitate *SLC16A2* sequencing.

Management and treatment

- Treatment of MCT8 deficiency should ideally aim to
  i. increase thyroid hormone action in the hypothyroid brain.
  ii. ameliorate the thyrotoxic state of peripheral tissues.
- Thus far, treatments with levothyroxine (alone or in combination with propylthiouracil (PTU)), and the T3 analogues diiodothyropropionic acid (DITPA) and triiodothyroacetic acid (TRIAC) have been described.
- Knowledge of response to thyroxine (alone, or in combination with PTU) and DITPA is limited to case reports and case series, whereas the effects of TRIAC have been studied in a phase 2 clinical trial and a prospective cohort study.
- Treatment with levothyroxine in a wide dose range (2.5–15 mcg/kg/day), commenced at the age of 0.5 to 36 months, did not improve neurodevelopment and, in some cases even aggravated the hyperthyroid state in peripheral tissues (105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118).
- Combination therapy with propylthiouracil (PTU–given to block T4 to T3 conversion) and levothyroxine reduced signs of hyperthyroidism in peripheral tissues in some patients, increasing body weight, reducing heart rate, and serum sex hormone-binding globulin (SHBG) concentrations, but had no beneficial effects on neurocognitive development (119, 120, 121, 122).
- Treatment with DITPA (dose range: 2.1–2.5 mg/kg/day) normalized serum T3 and TSH without reduction of T4 concentrations (4/4 cases) and had mixed effects on peripheral symptoms, including a reduction in heart rate (3/4 cases) and improvement in body weight (2/4 cases). Commencement of treatment between 8.5 and 25 months did not improve neurocognitive development (122).

- TRIAC therapy (dose range: 6.4–84.3 mcg/kg/day) has proven to have beneficial effects for some features:
  - Increases body weight (123, 124).
  - Cardiovascular endpoints, including lower resting heart rate, number of premature atrial contractions, and systolic blood pressure (124).
  - Decreases serum T3 concentrations and markers of thyroid hormone status in peripheral tissues (e.g. SHBG) (123, 124).

A formulation of TRIAC (Emcitate®) that has been trialed in MCT8 deficiency is available in several countries; in other countries, Galenic formulations of the drug made by pharmacists may be available.

- The neurocognitive response to TRIAC treatment is unknown (123, 124), and is currently under investigation (NCT02396459).
- Appropriate treatment targets may vary with age. For example, improved neurodevelopmental outcomes may be the most important goal in neonates but not adults; however, gaining body weight is beneficial to patients of all ages. Attaining these treatment targets may require different therapeutic strategies.

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Table 4 Clinical phenotype and investigation of MCT8 deficiency[a].

System	Clinical feature/phenotype	Investigation[b]
Appearance	Myopathic facies, dystrophic	Photograph
Neurological and cognitive	Severely delayed cognitive and motor development; central hypotonia (e.g. poor head control); dystonia; spasticity (later in life); persistent primitive reflexes; seizures	**Neuropsychological tests** (Bayley scales of infant and toddler development; gross motor function measure); MRI scan: can show hypomyelination; EEG
Endocrine	Thyrotoxic features (increased perspiration, tachycardia, low body weight)	**TSH, (F)T4, (F)T3, reverse T3 Free T4/free T3 ratio**: often low; serum markers of thyroid status[c]: SHBG (n/↑), CK (n/↓), creatinine (n/↓), total cholesterol (n/↓), ALAT (n/↑)
Skeletal	Scoliosis; hip subluxation; osteoporosis	Radiographs of spine and hip; DEXA
Cardiovascular	Tachycardia, conduction abnormalities; systolic hypertension	**ECG**; Cardiac telemetry; Blood pressure
General	Low body weight; gastroesophageal reflux; feeding problems; constipation	**Nutritional assessment by dietitian; measure body weight** every 3 months in infants and children

[a]An X-linked disorder usually affecting male individuals; [b]Key investigations are in bold; [c]For recommended serum measurements, changes typically observed in individuals with MCT8 deficiency are indicated between parentheses.
↑ raised, ↑↑ very raised, ↓ low, ↓↓ very low, n, normal; TFTs, thyroid function tests.

- No available treatment regimen has proven to rescue the neurocognitive phenotype in humans with MCT8 deficiency. Patients require supportive/symptomatic treatment of neurological sequelae (i.e. dystonia, spasticity, drooling, scoliosis, feeding problems, epilepsy) and frequently occurring gastrointestinal symptoms (i.e. gastro-esophageal reflux disease, gastroparesis, constipation) according to common practice. In the context of MCT8 deficiency, the effectiveness of such interventions has not been evaluated.
- Being underweight in early childhood is associated with higher mortality (104), while caloric intake is frequently inadequate due to impaired swallowing function and increased catabolism due to peripheral tissue thyrotoxicosis.
- There is little literature on the management of MCT8 deficiency pre-conception or during pregnancy. A single case of prenatal, intra-amniotic treatment with high dose levothyroxine starting from gestational week 17 suggests intervention may have beneficial effects on neurodevelopmental outcomes (125).

Areas of uncertainty and challenges

- Timely diagnoses allow early intervention with therapies (i.e. thyroid hormone analogs).
- The disorder is not diagnosed in current neonatal screening programs.
- In early life, symptoms can be non-specific.
- Awareness and knowledge of the condition among clinicians are limited.
- Cross-reactivity of TRIAC in most T3 immunoassays precludes precise measurement of serum T3 concentrations during TRIAC therapy. Alternatively, liquid chromatography with tandem mass spectrometry (LC-MS/MS) T3 assays are not susceptible to TRIAC cross-reactivity.
- Effects (and optimal dosage) of TRIAC (and other therapies) on neurocognitive outcomes, particularly when initiated early in life.
- Potential adverse effects of further lowering (F)T4 concentrations with TRIAC treatment.
- Limited access to tools that can determine the pathogenicity of (novel) variants.
- Identification of (rare) female cases with MCT8 deficiency and skewed X-inactivation.

Selenoprotein deficiency

Background

- Selenium, an essential trace element, is incorporated as the amino acid selenocysteine (Sec) into 25 different human selenoproteins, including the iodothyronine deiodinase enzymes. Homozygous or compound heterozygous mutations in factors required for incorporation of Sec into selenoproteins during their synthesis (Selenocysteine insertion-sequence binding protein 2, *SECISBP2*; tRNA selenocysteine (anticodon TCA) 1-1, *TRU-TCA1-1*), mediate multisystem disorders (OMIM 609698: Thyroid hormone metabolism abnormal 1; OMIM 620198: Thyroid hormone metabolism abnormal 3; ORPHA:171706) characterized by abnormal thyroid function and low plasma selenium (126, 127, 128). Diverse phenotypes are caused either by a deficiency of selenoproteins or attributable to tissue oxidative damage secondary to the loss of antioxidant selenoenzymes (129).
- Defects in another factor (O-phosphoserine-tRNA:selenocysteine tRNA synthase, SEPSECS) in this biosynthetic pathway cause a disorder with progressive microcephaly due to cortical and cerebellar atrophy, but normal circulating T4 and selenium concentrations (129).

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- *SECISBP2* is a complex gene, encoding different protein isoforms, within which mutations in both coding and noncoding regions have been described; two unrelated patients with the same homozygous mutation in *TRU-TCA1-1*, have been described (129) (Supplementary Table 2).

Diagnosis, management and treatment

- Deficiencies of selenoproteins result in a multisystem disorder, with diverse features (Table 5) attributable to the lack of tissue-specific selenoproteins, oxidative damage due to the loss of antioxidant selenoenzymes, and disordered thyroid hormone metabolism reflecting reduced activity of selenocysteine-containing deiodinases.
- Raised serum FT4, normal or low FT3, and raised reverse T3 concentrations, together with low plasma selenium concentrations, are biochemical hallmarks of selenoprotein deficiency due to mutations in *SECISBP2* or *TRU-TCA1-1*.
- Short stature and delayed development in childhood, whose basis is not fully understood, have been recorded in most cases (126, 130, 131, 132, 133). Weakness and hypotonia, due to progressive degeneration of specific muscle groups (e.g. sartorius, adductor, axial paraspinal) which resemble muscular dystrophy due to SELENON deficiency, is a major phenotype (129, 130, 131, 134, 135). Other phenotypes include aneurysmal dilatation of the thoracic aorta (133) sensorineural hearing loss, cutaneous photosensitivity, and male infertility (135).
- Liothyronine therapy corrects subnormal circulating FT3 concentrations (130) and improves linear growth when administered alone (130) or in combination with growth hormone (131), but untreated individuals can also attain normal height. Although oral selenium supplementation in SECISBP2 deficiency restores plasma selenium concentrations (130, 134, 136), it does not correct circulating selenoprotein deficiencies or impaired conversion of T4 to T3 (137). Antioxidant (e.g. alpha-tocopherol) treatment protects the patient's cells and protein lipids from oxidative damage (133, 138), without adversely affecting their favorable metabolic phenotype (133, 135).

Areas of uncertainty

- Most patients identified hitherto are children or young adults. Whether chronic oxidative tissue damage, secondary to their known reduced antioxidant defenses, predisposes to other complications (e.g. neurodegeneration, premature aging, neoplasia) at a later age remains unknown.
- Whether selenium supplementation can correct selenoprotein deficiencies in *TRU-TCA 1-1* mutation patients or whether long-term antioxidant therapies can ameliorate or prevent multisystem complications of selenoprotein deficiency remains to be determined.

Iodothyronine deiodinase defects

Background

- The search for mutations in the deiodinase (DIO) genes has intensified after the generation of mice deficient in each of the three deiodinases (DioKOs) (139, 140, 141, 142) (Supplementary Table 3). Until 2021, the only genetic conditions affecting deiodinases were *SECISBP2* and *TRU-TCA1-1*-dependent defects in selenoprotein synthesis (see disorders of thyroid hormone metabolism due to selenoprotein deficiency).
- Only three families with pathogenic *DIO1* mutations (OMIM 619855: Thyroid hormone metabolism abnormal 2; ORPHA:171706) have been reported (143, 144). All affected individuals were heterozygous, causing haploinsufficiency as in

Table 5 Clinical features and investigation of selenoprotein deficiency due to *SECISBP2* mutations.

System	Clinical features	Investigation[a]
Biochemical	Abnormal thyroid function; low circulating selenoproteins	**TSH, raised free T4, normal/low free T3, high reverse T3; free T4/free T3 ratio, high; low plasma selenium;** plasma glutathione peroxidase type 3, serum selenoprotein P
Metabolic	Increased fat mass, increased systemic insulin sensitivity	DXA scan; whole-body MRI scan; fasting glucose, insulin, and lipid profile; low hepatic lipid on MRS
Musculoskeletal	Growth retardation; axial and limb muscular dystrophy; hypoventilation	**Auxology; T1-weighted MRI** (fatty infiltration adductor, sartorius, paraspinal muscles); vital capacity; muscle biopsy (type 1 fiber predominance; disorganized sarcomeres – 'minicores'")
Auditory function	Hearing loss	**Audiometry;** abnormal otoacoustic emissions; normal brainstem auditory evoked responses
Cardiovascular	Thoracic aortic aneurysm	**Serial echocardiography;** MR aortogram
Reproductive	Male infertility	**Semen analysis**
Cutaneous	Photosensitivity; Raynaud's disease	Ultraviolet A irradiation patch testing

[a]Key investigations are in bold

heterozygous *Dio1*KO mice (Supplementary Figure 3), and exhibited abnormalities including elevated circulating reverse T3, a high rT3/T3 ratio, and (in one family) raised total cholesterol concentrations.
- D1, the product of the DIO1 gene, deiodinates the outer and, to a lesser degree, the inner ring of T4, producing T3 and reverse T3 (rT3), respectively.

Management

- Whether specific treatment or intervention is required in DIO1 variant carriers is undetermined.

Areas of uncertainty

- The coexistence of D1 haploinsufficiency with other congenital thyroid defects may require adjustment of thyroxine replacement therapy to ensure adequate bioavailability of T3 in tissues, particularly during development.

Supplementary materials
This is linked to the online version of the paper at https://doi.org/10.1530/ETJ-24-0125.

Declaration of interest
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