## Interpretation, differential diagnosis, and clinical implications of abnormal thyroid function tests in children

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**Cite this article as:** Akın Kağızmanlı G, Demir K. Interpretation, differential diagnosis, and clinical implications of abnormal thyroid function tests in children. Trends in Pediatrics 2023;4(2):61-71.

#### ABSTRACT

In children, abnormal thyroid function tests (TFTs) can present diagnostic difficulty due to the variety of clinical manifestations that may accompany them. Pediatric patients with abnormal TFTs are discussed in this article, along with their differential diagnoses and approaches to management. The most prevalent causes of pediatric hypothyroidism and hyperthyroidism, including Hashimoto's thyroiditis and Graves' disease, are thoroughly reviewed. Additionally, we explore other potential etiologies of abnormal TFTs in children: congenital hypothyroidism, resistance to thyroid hormone, nonthyroidal illness syndrome, medication use, iodine deficiency, and interferences with thyroid function immunoassays. In the setting of the pediatric population, diagnostic assessment and analysis of TFTs involving thyroid-stimulating hormone (TSH), free thyroxine (fT4), and free triiodothyronine (fT3) are addressed.

Keywords: Free thyroxine, free triiodothyronine, hyperthyroidism, hypothyroidism, pediatric, thyroid-stimulating hormone, thyroid function tests

## **INTRODUCTION**

Thyroid function tests (TFTs) are utilized to assess thyroid gland function and establish a diagnosis of thyroid disorders.<sup>1,2</sup> The diagnosis of hyperthyroidism or hypothyroidism based on TFTs is often uncomplicated for clinicians in circumstances where a strong clinical suspicion of thyroid dysfunction exists. However, there are also subclinical forms of thyroid disorders that can manifest as slight alterations in TFTs and situations characterized by inconsistencies between thyroid-stimulating hormone (TSH) and thyroid hormone (TH) levels. The difficulty in diagnosis associated with subclinical and atypical presentations of thyroid disorders highlights the importance of meticulous interpretation of TFT results and consideration of additional diagnostic measures, including specialized laboratory examinations, radiological tests, and, on occasion, genetic analyses.<sup>3</sup> The purpose of this review is to provide a comprehensive overview of the etiology, clinical manifestations, and management strategies for pediatric patients presenting with abnormal TFTs.

#### **Thyroid Physiology**

The thyroid gland plays a pivotal role in maintaining physiological homeostasis in humans. The hypothalamicpituitary-thyroid (HPT) axis regulates the production and secretion of THs. The hypothalamus synthesizes thyrotropinreleasing hormone (TRH), which stimulates the anterior pituitary gland to release TSH. Subsequently, TSH stimulates the production of 3,3',5,5'-tetraiodothyronine (thyroxine, T4) and 3,3',5-triiodothyronine (T3).<sup>4-6</sup>



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 Received:
 22.05.2023
 Accepted:
 19.06.2023

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T4 is the predominant form of TH that is secreted by the thyroid gland, accounting for roughly 85-90% of the total TH stored in the gland. The remaining 10-15% of stored TH is T3, the biologically active form of TH, which is mainly produced by converting T4 in the peripheral tissues through the action of deiodinases. Over 99% of circulating T4 and T3 are bound tightly to carrier proteins, including thyroid hormone-binding globulin (TBG), albumin, and transthyretin. The carrier-bound hormone primarily serves as a reservoir, whereas the unbound fractions, referred to as free T4 (fT4) and free T3 (fT3), enter the cells and employ their physiological actions. Additionally, both fT4 and fT3 play a crucial role in the negative feedback inhibition of TRH and TSH secretion, respectively.<sup>47,8</sup>

In order for THs to exert their genomic effects, they need to be carried into the cells and subsequently bind to nuclear receptors. The THs require transmembrane protein transporters to access specific types of cells. These transporters encompass monocarboxylate transporters 8 and 10 (MCT8 and MCT10), organic anion transporters (OATPs), and L-amino acid transporters (LATS).<sup>4,9,10</sup> Once inside the cell, the activity of THs depends on various deiodinases, which are selenoproteins expressed differently in diverse cell types. Specific deiodinases in the bloodstream and target cells convert T4 to active T3 and inactive 3,3',5'-triiodothyronine (reverse T3, rT3).<sup>4,9</sup>

Most biological activities of TH are mediated by the binding of T3 to nuclear T3 receptors (TRs). The two thyroid receptor genes *THRA* and *THRB* encode TH receptor- $\alpha$  (TR $\alpha$ ) and TH receptor- $\beta$  (TR $\beta$ ), respectively. These genes lead to the production of three TR $\alpha$  and three TR $\beta$  isoforms. TR $\alpha$ 1, TR $\beta$ 1, and TR $\beta$ 2 are the isoforms that bind to T3. TR $\alpha$ 1 primarily in the brain, heart, and bone, and TR $\beta$ 1 primarily in the liver, kidney, and thyroid. TR $\beta$ 2 has a more limited expression pattern but is the predominant isoform expressed in the pituitary gland and is thus critical for the negative regulation of TSH.<sup>4,9,11-13</sup>

## Thyroid-Stimulating Hormone (Thyrotropin, TSH)

TSH is a hormone that plays a crucial role in regulating thyroid gland function. It is produced by the anterior pituitary gland and acts on the thyroid gland to stimulate the production and release of THs. TSH is controlled by a feedback mechanism that involves the hypothalamus and the thyroid gland. When the levels of THs in the blood are low, the hypothalamus releases TRH, which stimulates the pituitary gland to produce and release more THs, which helps raise the levels of THs in the blood.<sup>5,8</sup> TSH secretion is very sensitive to even minor changes in TH levels. Specifically, the relationship between TSH and free TH is characterized as being inversely log-linear. This suggests that

even small reductions in fT4 levels can result in a substantial exponential increase in TSH secretion.<sup>3</sup>

TSH secretion exhibits a circadian pattern, with its highest levels typically observed in the early hours of the morning. Studies have demonstrated that TSH concentrations can differ by as much as 2 mIU/mL between morning and evening measurements. As a result, it is advised to perform TSH assessments in the morning and to repeat measurements if necessary.<sup>2</sup> Additionally, It is important to acknowledge that when interpreting TSH levels in children, it is necessary to take into account that the normal range is not the same as that of adults, in whom the upper limit value is approximately 4  $\mu$ U/mL or lower.<sup>8</sup>

## Thyroxine (total T4 and free T4)

T4 is the major hormone produced by the thyroid gland. T4 is formed through the merging of two diiodothyronine (DIT) molecules. T4 is synthesized and secreted into the circulation in response to TSH released from the pituitary gland. T4 binds to transport proteins such as TBG, albumin, and transthyretin, which prevent its clearance and facilitate its distribution throughout the body. Once T4 enters cells, it undergoes deiodination to produce the active hormone T3, which binds to nuclear THRs to modulate gene expression and cellular metabolism.<sup>8</sup>

Abnormal levels of T4 can lead to significant physiological changes in the body. Hypothyroidism, a condition characterized by decreased thyroid hormone production, is commonly associated with low T4 levels. Conversely, hyperthyroidism, a condition characterized by increased thyroid hormone production, is commonly associated with high T4 levels.<sup>2,3</sup>

Assessment of T4 levels is an important diagnostic tool for the evaluation of thyroid function. Measurement of total T4 levels was commonly used in clinical practice, but fT4 levels, which represent the unbound, biologically active form of the hormone, provides more accurate reflection of thyroid status. Additionally, measurement of fT4 levels in combination with TSH levels aids in the differential diagnosis of primary and secondary thyroid dysfunction.<sup>3,7,8</sup>

## Triiodothyronine (total T3 and free T3)

T3 is the bioactive TH that is essential for normal growth and development. Like T4, the production of T3 is regulated by the hypothalamus and pituitary. T3 is formed by the conversion of T4 in various tissues through the action of the enzyme deiodinase.<sup>8</sup> Type 2 deiodinase generates T3 through the outer ring deiodination process of T4. Conversely, type 3 deiodinase performs inner ring deiodination, which results in

the inactivation of T3 by converting it into 3,3'-diiodothyronine (T2) or inhibiting T3 synthesis from T4 by converting T4 to rT3. Type 1 deiodinase, depending on the substrate, carries out inner or outer ring deiodination, leading to the generation of T3, rT3, or T2.<sup>5</sup>

Measuring T3 in most clinical situations is unnecessary, and it should not be included as part of the initial screening for thyroid dysfunction. T3 measurements are only appropriate in certain clinical circumstances. If the clinical concern is primary hypothyroidism, T3 measurements should not be done as a routine test. T3 levels remain normal in primary hypothyroidism because of the increase in peripheral deiodinases and optimal thyroid stimulation resulting from elevated TSH levels.<sup>2,3</sup> fT3 measurements should only be carried out in patients suspected to have hyperthyroidism or in certain diseases among the group of impaired sensitivity to THs.<sup>14</sup>

## DIAGNOSTIC APPROACH TO ABNORMAL THYROID FUNCTION TESTS

In Figure 1, a general approach based on fT4 is presented. Certain conditions or diseases may be found in multiple subgroups. Table 1 shows typical TFT findings of major diseases classified according to TSH levels.

Table 1. A summary of the conditions primarily classified to typical TSH levels				
	fT4	fT3	Thyroid status	Additional clinical and biochemical features
Low TSH				
Graves' Disease	High	High	Hyperthyroid	Eye disease, goitre, anti-TSH receptor antibody
Neonatal thyrotoxicosis	High	High	Hyperthyroid	Anti-TSH receptor antibody
Hashitoxicosis	High	High	Hyperthyroid	
Euthyroid sick syndrome	Normal/Low	Low	Euthyroid	High serum rT3
Biotin interference	High	High	Euthyroid	Symptoms of hyperthyroidism lacking
Central hypothyroidism	Low	Low/Normal	Hypothyroid	TSH levels may be normal, low, or mildly high
High TSH				
Congenital or acquired hypothyroidism	Low/Normal	Normal	Hypothyroid/ Euthyroid	Additional features according to underlying pathology
Subclinical hypothyroidism	Normal	Normal	Euthyroid	Hashimoto's thyroiditis, obesity, trisomy 21
TSHoma	High	High	Hyperthyroid	High levels of the alpha-glycoprotein subunit
Normal TSH				
Resistance to thyroid hormone β	High	High	Euthyroid/ Hyperthyroid	High rT3 Generally asymptomatic, growth retardation, failure to thrive, goiter, tachycardia
Resistance to thyroid hormone $\boldsymbol{\alpha}$	Low or lower half of normal range	High or upper half of normal range	Hypothyroid	Constipation, short stature, motor retardation, speech delay, bradycardia
MCT8 Deficiency	Low or lower half of normal range	High or upper half of normal range	Cerebral hypothyroidism with peripheral hyperthyroidism	Low rT3, and normal or slightly elevated levels of TSH Developmental delay, hypotonia, poor weight gain, feeding difficulties, tachycardia

\*TSH, thyroid-stimulating hormone; fT4, free thyroxine; fT3, free triiodothyronine; rT3, reverse triiodothyronine; TG, thyroglobulin; TPO, thyroperoxidase; MCT8, monocarboxylate transporters 8



## Low Free T4 Levels

Low levels of THs in the bloodstream can arise from dysfunction anywhere in the HPT axis. Hypothyroidism can manifest either at birth or develop later in life. It can result from intrinsic defects in the thyroid gland, leading to inadequate production of THs. Additionally, hypothyroidism can be of central origin, resulting from reduced secretion of TSH or TRH. Furthermore, abnormalities in TH transport or action can also be associated with low levels of T4.

#### 1. Congenital Hypothyroidism

Congenital hypothyroidism (CH), the commonest neonatal endocrine condition, results from a deficiency of TH production during fetal development. The incidence of CH varies depending on the geographical region, ranging from 1 in 2.000 to 1 in 3.000 live births worldwide. Primary CH can result from developmental abnormalities of the thyroid gland (thyroid dysgenesis) or congenital defects in TH production (dyshormonogenesis). Thyroid dysgenesis is the primary cause of CH, accounting for approximately 80% to 85% of all cases, followed by thyroid dyshormonogenesis. CH can be transient due to reasons linked to the mother or newborn, and the leading cause is an iodine deficiency. Additionally, iodine excess can also lead to transient primary CH through the Wolff-Chaikoff effect. It can also effect newborns via breastfeeding (povidone-iodine douching or iodine-containing tampons for episiotomy antisepsis after vaginal delivery). Furthermore, transient CH may be caused

by the transplacental transfer of maternal antithyroid drugs, transplacental transfer of maternal TSH-receptor blocking IgG antibodies, and DUOX2 mutations.<sup>1,5,8</sup>

It is very important to diagnose and treat CH as soon as possible in early life to ensure normal cognitive and developmental abilities.<sup>1,15</sup> The primary method for detecting CH is newborn screening, which mainly involves measuring TSH levels in capillary whole blood within a few days of birth. In many countries, newborn screening programs for CH have been established as a standard of care, enabling early detection and timely intervention for affected infants.<sup>16</sup> The newborn screening for the diagnosis of CH was initially introduced in both Quebec, Canada, and Pittsburgh, Pennsylvania, in 1974.<sup>17</sup> The optimal approach for performing and optimizing newborn screening for congenital hypothyroidism remains a topic of debate. Essentially, two screening methods are commonly employed: (i) screening with TSH measurement (T4 measurement as required) and (ii) screening with T4 measurement (TSH measurement as required).<sup>15</sup> As of 2006, national screening began in Turkey, utilizing a method based on TSH measurement from blood samples collected by heel-prick and blotted on filter paper (the "Guthrie card").18

Certain groups of children with delayed TSH elevation, such as preterm infants, low-birth-weight newborns, and sick preterm infants who are hospitalized in neonatal intensive care units, may receive neonatal screening results that incorrectly indicate they are healthy, or the results may miss mild cases of CH. In such instances, a post-screening plan that involves collecting a second specimen at 14 days of age or 2 weeks after the initial test may be considered.<sup>15,18</sup>

Newborns who have a positive result on the screening test should undergo clinical evaluation and venous measurements of fT4 and TSH. To ensure prompt administration of necessary treatment, this evaluation should occur within 24 hours of referral. The diagnosis of CH in infants should be based on low serum fT4 levels for age, and TH therapy should be initiated immediately. Etiological investigations should not delay treatment. Measuring serum TH levels is recommended in infants presenting clinical symptoms of hypothyroidism, even if their screening results are normal.<sup>5,15,18</sup>

CH is confirmed when venous fT4 is below the reference range and/or venous TSH is >20 mU/L. In instances where the fT4 is within normal limits and the TSH is between 6 and 20 mU/L beyond 21 days of age, it is recommended to repeat testing and utilize clinical judgment. Typically, the TSH level tends to decrease spontaneously within the normal range. However, if the fT4 level declines or the TSH level remains persistently elevated, initiating levothyroxine therapy is likely to be necessary. It is crucial not to defer treatment initiation while waiting for test results, particularly if the TSH level in the screening whole blood sample exceeds 40 mU/L.<sup>15</sup> It should be noted that in order to calculate approximate serum equivalent, capillary TSH levels should be multiplied by 2.2.<sup>19</sup> Moreover, when the serum fT4 level is low and the TSH level is low, normal, or slightly elevated, the diagnosis of central CH must be considered.<sup>5,15</sup>

## 2. Hypothyroxinemia of Prematurity

Hypothyroxinemia of prematurity (HOP) is a common condition that affects up to 50% of infants born before 28 weeks of gestation and is related to the immaturity of the HPT axis. It is usually transient and resolves within the first few weeks of life, and is characterized by low levels of T4 with normal TSH. As gestational age decreases, thyroxine concentrations in infants become progressively lower normally. Low concentrations of fT4 may serve as an indicator of illness severity or possibly as a protective mechanism to decrease metabolic rate.<sup>5,8</sup>

There are several risk factors that have been identified in studies for this abnormality, including lower gestational age, maternal pre-eclampsia, respiratory distress syndrome, mechanical ventilation, and dopamine infusions. Besides, preterm infants may experience iodine deficiency as a result of inadequate levels in parenteral nutrition and the rapid loss of maternal supply, which can impede recovery from hypothyroxinemia of prematurity. As a consequence, exposure to excessive iodine from sources such as disinfectants or radiological contrast infusions can lead to a decrease in T4 and T3 levels, a phenomenon referred to as the Wolff-Chaikoff effect.<sup>20</sup>

The optimal management of HOP is still a matter of debate, and there is currently no consensus on the best treatment approach for HOP. Close monitoring of TH levels is essential to identify infants who may benefit from treatment. Work up for other pituitary hormones may be performed in order to exclude or confirm central hypothyroidism. Further research is needed to determine the optimal management of HOP and to improve the long-term outcomes of premature infants affected by this condition.<sup>21-23</sup>

## 3. Acquired Primary Hypothyroidism

The most prevalent cause of acquired hypothyroidism in children and adolescents worldwide is severe iodine deficiency, but in areas where iodine is sufficient, it is more frequently caused by chronic autoimmune thyroiditis, also known as Hashimoto's thyroiditis.<sup>13,24</sup> Acquired hypothyroidism can also occur due to other, less common etiologies. For instance, the chronic administration of high doses of iodine from iodinated contrast material, the highly iodinated antiarrhythmic amiodarone, the topical antiseptic povidone-iodine, or iodine-containing thyroid supplements may result in hypothyroidism.<sup>1,5,13</sup> In addition, acute thyroiditis, radiation therapy to the head and neck for certain cancers, total-body irradiation before a bone marrow transplant, as well as several medications, such as lithium.<sup>1</sup>

#### a. Hashimoto's Thyroiditis (Autoimmune Thyroiditis)

Hashimoto's thyroiditis is an autoimmune disorder that affects the thyroid gland, causing it to become inflamed and unable to produce sufficient THs. Although it is more commonly seen in adults, Hashimoto's thyroiditis is the most common acquired thyroid disease in childhood, with an estimated incidence of 1 to 2 cases per 1000 children.<sup>1</sup> Hashimoto's thyroiditis is a condition characterized by the presence of antibodies against thyroglobulin (TG) and thyroperoxidase (TPO), leading to infiltration of the thyroid gland with lymphocytes and subsequent enlargement. Depending on the specific antithyroid antibodies involved, Hashimoto's disease may lead to a euthyroid state, hypothyroidism, or transient hyperthyroidism. The condition typically presents in adolescents and is more prevalent among females than males. Furthermore, Hashimoto's thyroiditis is more commonly seen in patients with type 1 diabetes mellitus, celiac disease, vitiligo, alopecia, rheumatoid arthritis, Down syndrome, Turner syndrome, Klinefelter syndrome, autoimmune polyglandular syndrome, and IPEX (immunodysregulation polyendocrinopathy enteropathy X-linked) syndrome.<sup>5,8</sup>

Confirmation of hypothyroidism due to Hashimoto's thyroiditis involves elevated TSH, low fT4, the presence of TPO or TG antibodies, and/or a characteristic ultrasound appearance. However, in some cases of Hashimoto's thyroiditis, the goiter may be the only presenting feature, and half of the children at the time of diagnosis may have normal thyroid function. Children who are younger or have Down syndrome or Turner syndrome are more likely to have abnormal thyroid function at the time of diagnosis.<sup>25</sup>

## **b.** Iodine Deficiency

lodine is an essential micronutrient required for the synthesis of THs, and insufficient dietary intake of iodine may result in hypothyroidism. Inadequate iodine intake is prevalent among people residing in iodine-deficient areas. In developed countries, inadequate dietary intake may arise from self-imposed restrictions on iodized salt consumption, prolonged parenteral nutrition without iodine supplementation, and the use of enteral formulas with low iodine concentration.<sup>26,27</sup> In children and adolescents with iodine deficiency, thyroid function is characterized by a high fT3, low fT4, and a normal or slightly elevated TSH, in addition to high TG levels.<sup>28</sup>

#### c. Iodine-Induced Hypothyroidism

Sufficient iodine intake is necessary for proper thyroid function, but excessive iodine exposure can result in a rapid decline in the release of preexisting TH and hindered TH synthesis, which is referred to as the Wolff-Chaikoff effect. Several factors may lead to excessive iodine intake, including excess consumption of nutritional supplements and cough suppressants containing high amounts of iodine, the use of radiocontrast dyes, amiodarone, and iodinated antiseptics. Moreover, individuals living in iodine-deficient areas may be at increased risk of iodineinduced hypothyroidism due to sudden exposure to high levels of iodine.<sup>29</sup> The diagnosis of iodine-induced hypothyroidism is based on abrupt onset and demonstration of of elevated urinary iodine levels.<sup>5,8</sup>

#### d. Postablative Hypothyroidism

Annual TSH screening is recommended for up to 30% of children who have received irradiation to the head and neck area, as they are at risk of developing primary hypothyroidism in the long-term follow-up. Furthermore, postablative hypothyroidism can occur as a consequence of subtotal or total thyroidectomy or radioactive iodine therapy.<sup>8,28</sup>

# 4. Euthyroid Sick Syndrome (Nonthyroidal Illness or Low T3 Syndrome)

Low fT3 and fT4 along with normal TSH levels can be associated with various moderate to severe non-thyroidal factors, such as the neonatal period, stress, cold exposure, infection, calorie deprivation, surgery, medications (such as propranolol, amiodarone, and diphenylhydantoin), hepatic dysfunction, and renal dysfunction.<sup>28</sup> During critical illness, there is a tendency for T4 to convert into the metabolically inert rT3 instead of the biologically active form, T3. This mechanism serves as a protective response by reducing metabolic demands and conserving energy. Subsequently, fT4 levels also decrease, accompanied by a decline in TSH levels. As the individual recovers, there is an initial increase in TSH levels, which may occasionally exceed the normal range. Eventually, the free TH levels normalize, indicating the restoration of thyroid function.<sup>3</sup> Treatment of euthyroid sick syndrome primarily focuses on addressing the underlying illness rather than directly targeting the TH abnormalities. Administering TH treatment is unnecessary and may have adverse effects that outweigh any potential benefits.<sup>5,28,30</sup>

#### 5. Central Hypothyroidism

Central hypothyroidism is a rare cause of hypothyroidism, accounting for less than 1% of all cases. It may be secondary due to inadequate secretion of TSH from the pituitary gland or tertiary due to inadequate secretion of TRH from the hypothalamus. Central hypothyroidism can be congenital due to various genetic alterations or acquired particularly due to tumors or irradiation.<sup>8,28</sup> Central hypothyroidism can be associated with other pituitary hormone deficiencies. In cases where infants have multiple pituitary hormone deficiencies, they may experience symptoms such as hypoglycemia, cholestatic jaundice, micropenis, and cryptorchidism.<sup>1,5</sup>

In contrast to primary hypothyroidism, diagnosing central hypothyroidism can be challenging. Typically, fT4 levels are low while TSH levels may be normal, low, or slightly high.<sup>5,31</sup> On the other hand, despite being in normal range, progressive decline in fT4 levels to lower quartile of reference range in a patient with known hypothalamopituitary dysfunction suggest central hypothyroidism.<sup>32</sup>

#### 6. Disorders of Thyroid Hormone Transport: MCT8 Deficiency

TH transporter proteins on the plasma membrane play a crucial role in regulating the intracellular availability of THs. Among the identified TH transporters, monocarboxylate transporter

8 (MCT8; solute carrier family 16A2, *SLC16A2*) stands out as one of the most efficient and specific transporters known to date. MCT8 facilitates the cellular uptake and release of T3, T4, and the inactive metabolite rT3. This protein exhibits wide expression in various tissues, with prominent thyroid, liver, kidney, and brain localization.<sup>33,34</sup> MCT8 deficiency, also known as Allan-Herndon-Dudley syndrome, is a rare and severe disorder that is characterized by neurological and metabolic consequences. It is caused by pathogenic variants in the *MCT8* gene and has an estimated prevalence of 1 in 70,000 males.<sup>35</sup> The malfunctioning MCT8 disrupts the homeostasis of THs in the brain, consequently causing neurodevelopmental delay due to cerebral hypothyroidism. However, the elevated levels of circulating T3 concentrations cause thyrotoxicosis in MCT8independent tissues.<sup>34</sup>

The thyroid biochemistry observed in individuals with MCT8 deficiency is characterized by significantly elevated levels of fT3 (rarely in the upper half of normal), decreased levels of fT4 (either low or within the lower end of the normal range), reduced levels of rT3, and normal or slightly elevated levels of TSH. The majority of patients exhibit elevated serum concentrations of SHBG, indicating the hepatic action of thyroid hormones. Conversely, serum concentrations of creatine kinase (CK), reflecting thyroid hormone action in muscles, are frequently observed to be low within the normal reference range.<sup>34</sup> Brain magnetic resonance imaging scanning reveals a global delay in myelination that improves with age. Additionally, diffuse atrophy is present with concomitant ventricle dilatation.<sup>36</sup>

## 7. Resistance to Thyroid Hormone $\alpha$ (RTH $\alpha$ )

TR $\alpha$ -mediated RTH is caused by heterozygous, dominantnegative, loss-of-function mutations in the *THRA* gene.<sup>5</sup> This condition manifests varying degrees of symptoms similar to that of primary hypothyroidism. However, the TFTs of affected individuals are near normal due to intact TR $\beta$ , which regulates the negative feedback of THs in the hypothalamus and pituitary glands.<sup>11</sup>

Typically, TSH levels are normal, fT4 slightly low or in the lower half of normal range, and fT3 slightly high or at the upper half of normal range, leading to an abnormally low T4/T3 ratio. Additionally, affected individuals commonly present with mild normocytic anemia and elevated levels of muscle CK.<sup>12,37</sup> Diagnosis is important since clinical picture ameliorates with levothyroxine treatment in most of the patients.<sup>12</sup>

#### **High Free T4 Levels**

Elevated serum levels of TH mostly indicate inappropriately increased production or secretion of TH to bloodstream. In this case TSH levels are suppressed. On the other hand, in some cases there is an abnormality in TH metabolism or fT4 levels are falsely found elevated due to interference.

#### 1. Graves' Disease

Graves' Disease (GD) is the most common cause of hyperthyroidism in children, accounting for more than 95% of cases, and the incidence is between 1 and 3/100,000. The onset of GD can occur at any stage of childhood, but its prevalence increases with age and peaks during adolescence. The frequency of GD is higher in children with other autoimmune conditions as well as with some syndromes such as Down syndrome and Turner syndrome, and in children with a family history of autoimmune thyroid disease.<sup>5,38</sup>

GD occurs as a result of the production of TSH receptorstimulating immunoglobulins (TSIs), which are antibodies that activate the TSH receptor on thyroid follicular cells. These TSIs were previously known as long-acting thyroid stimulators and stimulate increased vascularity, follicular hypertrophy and hyperplasia, and excessive synthesis and secretion of THs. This, in turn, leads to diffuse thyroid enlargement and the development of a palpable goiter. Along with TSIs, the body produces neutral and inhibitory thyroid antibodies, whose levels and affinity to the TSH receptor can change, resulting in variations in TH levels and clinical symptoms.<sup>38,39</sup>

When hyperthyroidism is suspected, it is recommended to measure the levels of fT3, fT4, TSH and thyroid autoantibodies, including anti TPO (anti- thyroperoxidase ), antiTG (antithyroglobulin ), and TRAbs (TSH receptor antibodys, preferably TSIs). GD is characterized by increased production of T3 and T4, an increased T3/T4 ratio, and a suppressed TSH level. Unlike the assessment for hypothyroidism, it is crucial to include the measurement of T3 levels in the evaluation for GD since an isolated rise in T3 levels may occur before a rise in T4 levels in the early stages. If clinical presentation suggests GD but thyroid antibodies are not detected, it is recommended to repeat the antibody tests after a few weeks.<sup>1,5,40</sup> If there is still no evidence of thyroid autoimmunity, further investigations such as thyroid ultrasonography, scintigraphy (preferably using Tc-99m-pertechnetate), and additional laboratory tests may be considered.41

#### 2. Neonatal Thyrotoxicosis

Neonatal thyrotoxicosis is predominantly caused by maternal TRAbs that cross the placenta, leading to neonatal GD. Although this condition is generally temporary and self-limiting, it can result in severe clinical manifestations and long-term complications as well. Neonatal thyrotoxicosis occurs in 1% to 5% of infants born to affected mothers, resulting in an estimated incidence of neonatal GD of 1 in 25,000 neonates.<sup>40</sup> Rarely neonatal thyrotoxicosis will persist, like the GD disease seen in older children.<sup>8</sup> TFTs and TRAbs should be performed on neonates born to mothers with a history of GD (either active or in the past). If neonatal thyrotoxicosis is diagnosed, treatment should be initiated promptly.<sup>18,40</sup> Rarely, activating mutations of TSH receptor gene (TSHR) can lead to neonatal onset hyperthyroidism, in such cases autoimmune markers are negative.<sup>42,43</sup>

#### 3. Hashitoxicosis

Hashitoxicosis, a transient phase of autoimmune thyroiditis, can occur due to the release of stored T4 and T3 from the damaged thyroid gland. The duration of the hyperthyroid phase may last for several weeks to months, and its associated symptoms can be managed with beta-blockers. Unlike GD, there are no eye-related symptoms, and there is no elevation of TSIs.<sup>44</sup> Thyroid scintigraphy can be used to determine the underlying pathology, which is characterized by increased uptake due to TSH receptor stimulation in GD and reduced uptake in hashitoxicosis.<sup>45</sup> Hashitoxicosis typically resolves spontaneously, and consequently, the child may develop hypothyroidism in the future. Therefore, close monitoring of thyroid function is essential.<sup>5</sup>

## 4. McCune-Albright Syndrome

McCune-Albright syndrome is a genetic disorder characterized by spontaneous activation of the alpha subunit of the G protein. Because the TSH receptor is G protein-coupled, somatic mutations of the alpha subunit within the thyroid gland may result in hyperthyroidism. The somatic mutations associated with this condition can also cause various simultaneous endocrine disorders, such as Cushing syndrome, precocious puberty, and growth hormone excess. It is often accompanied by characteristically large café au lait skin pigmentation and polyostotic fibrous dysplasia. Nodular goiter, which is associated with thyroid hyperfunction, can develop at any age, including during the neonatal period. Autoimmune markers are negative. In addition to the excessive production of fT4 due to TSHindependent stimulation, there is also evidence of intrathyroidal deiodinase type 1 and 2 overactivity, which results in an elevated T3/T4 ratio.  $^{\rm 46,47}$ 

#### 5. TSH-Secreting Pituitary Adenoma (TSHoma)

TSHoma is a rare type of pituitary tumor that causes hyperthyroidism by producing excessive TSH. These tumors are usually characterized by macroadenomas. Elevated levels of THs and TSH are common in TSHoma. It is important to distinguish TSHoma from resistance to thyroid hormone  $\beta$  (RTH $\beta$ ), which can have similar biochemical features. Notable distinguishing features of TSHoma include clinically apparent thyrotoxicosis, pituitary tumor, non-responsiveness to TRH stimulation, and elevated levels of the alpha-glycoprotein subunit.<sup>48</sup>

#### 6. Toxic Multinodular Goiters

Toxic multinodular goiter (TMNG) is rare in children; however, affected patients may develop thyrotoxicosis, which is typically correlated with the duration and size of the goiter. In this context, hyperthyroidism occurs when a nodule within the thyroid becomes hyperactive and functions autonomously.<sup>49</sup>

#### 7. Biotin Interference

Biotin, also known as vitamin B7, is a water-soluble vitamin that plays a crucial role in treatment of rare metabolic conditions like biotinidase deficiencies and propionic acidemia. In addition, the popularity of biotin supplementation for promoting hair, skin, and nail health has significantly increased recently. On the other hand, there exist several types of immunoassays for TFTs, which rely on the interaction between biotin and streptavidin. The high affinity between biotin and streptavidin can lead to the formation of biotin-streptavidin complexes, causing falsely elevated fT3 and fT4 levels and falsely low TSH level in subjects using biotin treatment.<sup>50,51</sup> When a child presents with elevated fT4-T3 levels and low TSH levels without symptoms of hyperthyroidism, administration of biotin should be investigated. It is recommended to repeat the measurement after discontinuing biotin use for 2-3 days. Alternatively, if discontinuation is not possible, it is advised to repeat the TFT using an assay that does not rely on biotin as a marker.<sup>50</sup>

#### 8. Familial Dysalbuminemic Hyperthyroxinemia

Familial dysalbuminemic hyperthyroxinemia (FDH) is an autosomal dominant familial condition that was first documented in 1979.<sup>52,53</sup> It arises from an abnormal albumin molecule that exhibits an increased affinity for serum T4, despite normal quantitative levels of serum albumin. FDH does not cause thyroid dysfunction but, depending on the assay used, it can affect serum TH levels. For instance, serum levels of fT4 and fT3 may be falsely elevated while serum TSH levels remain normal, resembling the syndrome of inappropriate secretion of TSH. Since individuals with FDH are clinically euthyroid and asymptomatic, treatment is unnecessary.<sup>5,54</sup>

## 9. Resistance to Thyroid Hormone β (RTHβ)

RTH $\beta$  is a rare disorder characterized by elevated levels of circulating free THs, inappropriately normal or rarely mildly elevated TSH secretion, and impaired peripheral tissue responses to the action of iodothyronines. In families, RTH $\beta$  typically follows an autosomal dominant inheritance pattern (80%), but it can also occur sporadically in individuals without a family history of RTH $\beta$  (20%).<sup>11</sup> Currently, over 3000 cases from approximately 1200 different families have been reported worldwide, with an equal frequency observed in both sexes and an estimated occurrence rate of 1 in 40,000 live births.<sup>11,55</sup>

The hallmark of RTH $\beta$  is the impaired response to TH mediated by the defective  $\beta$  receptor. This leads to resistance to TH action within the HPT axis, causing the persistent and nonsuppressed synthesis of TSH despite elevated levels of circulating TH. Many patients with RTH $\beta$  are asymptomatic and are incidentally diagnosed during thyroid function testing conducted for reasons unrelated to thyroid dysfunction However, the elevated TH levels may result in various degrees of hyperthyroidism in tissues expressing TR $\alpha$ .<sup>35,56</sup>

## Normal Free T4 with Elevated TSH

## 1. Subclinical Hypothyroidism

Subclinical hypothyroidism (SH) is a biochemical definition in which the serum concentration of TSH exceeds the upper limit of the statistically defined reference range, while the serum concentrations of fT4 and fT3 remain within their reference ranges in at least two independent measurements which should be performed 4-12 weeks apart.<sup>28,57,58</sup> The upper limit of TSH for the definition of subclinical hypothyroidism is not clear. TSH levels between the upper limit of the reference range and 9.9 mU/L are classifed as mild or grade 1 SH while levels are equal or above 10 mU/L indicate severe or grade 2 SH.<sup>57</sup>

The prevalence of SH in adolescents is estimated to be around 2%. The majority of individuals with this condition are asymptomatic and do not exhibit any symptoms. In the pediatric population, SH is generally considered a benign and self-resolving condition with a low risk of progressing to overt hypothyroidism depending on the underlying etiology.<sup>59</sup> Risk factors for the progression to overt hypothyroidism include the presence of goiter, being female, experiencing symptoms or signs suggestive of hypothyroidism, and having strongly positive TPO antibodies. Limited data suggest that subclinical hypothyroidism itself does not appear to have any adverse effects on intellectual development, skeletal growth and maturation, or puberty.<sup>60,61</sup> Of note, biochemical evaluation of obese children reveals a high prevalence of elevated TSH levels (up to 7-9 mIU/L) with normal fT4 and fT3 levels. This condition may affect up to 20% of obese children, and studies have demonstrated that TSH levels tend to normalize with weight loss, indicating that thyroid dysfunction is likely a consequence of obesity rather than its primary cause.<sup>5</sup>

## 2. Macro-TSH

Macro-TSH is a distinct condition characterized by the presence of high-molecular-weight complexes of TSH in the bloodstream. These complexes, primarily bound to immunoglobulin G, exhibit low bioactivity and accumulate due to impaired clearance mechanisms. Macro-TSH can be falsely detected as hyperthyrotropinemia using standard immunoassays. The biochemical profile of individuals with macro-TSH resembles that of SH, with elevated serum TSH levels and normal fT4 levels. Therefore, interference should be suspected in a patient with isolated TSH elevation with THs in the upper half of the normal range, and without signs or symptoms of thyroid dysfunction.<sup>50</sup>

The polyethylene glycol (PEG) precipitation procedure, which is commonly used for screening macro-prolactinoma in hyperprolactinemic patients, has also been modified for the detection of macro-TSH. While the PEG precipitation procedure is practical and can be used as an initial screening test for the detection of macro-TSH, it is important to be aware that an increase in globulin concentration can lead to an elevated amount of precipitated TSH, potentially causing misclassification. As a result, gel filtration chromatography (GFC) is widely regarded as the preferred method for the precise identification of macro-TSH. In situations where PEG treatment results in a low recovery, confirmation through GFC is crucial.<sup>50,62</sup>

## Author contribution

Concept: GAK, KD; Design: GAK, KD; Data Collection or Processing: GAK, KD; Analysis or Interpretation: GAK, KD; Literature Search: GAK, KD; Writing: GAK, KD. All authors reviewed the results and approved the final version of the article.

#### Source of funding

The authors declare the study received no funding.

#### **Conflict of interest**

The authors declare that there is no conflict of interest.

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