Journal of Clinical Otorhinolaryngology Case Report

Thyroid Pathologies

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Received date: May 06, 2025; Accepted date: May 10, 2025; Published date: May 12, 2025
Citation: Bon E.I., Maksimovich N.Ye., Kazlouski D.A., (2025), Nephrology, Urology, Nephrologists and Urologists, Kidneys and Human Urinary System Reflected by a Number of Collectible Means, Journal of Clinical Otorhinolaryngology, 7(3); DOI:10.31579/2692-9562/152

Abstract
The thyroid gland requires iodine for the synthesis of thyroid hormones. Thyroxine (T4) is the major thyroid hormone directly synthesized by the thyroid gland. In contrast, triiodothyronine (T3), the physiologically active thyroid hormone, is produced either directly by the thyroid gland or after peripheral deiodination of circulating T4 by selenium-containing deiodinases. Thyroid hormones regulate several physiological processes, including growth, development, metabolism, and reproductive function
Purpose of the work: to study in detail the thyroid pathologies in children and adults
Key words: thyroid gland, thyroid hormone, physiological processes.

Introduction

The thyroid gland requires iodine for the synthesis of thyroid hormones. Thyroxine (T4) is the major thyroid hormone directly synthesized by the thyroid gland. In contrast, triiodothyronine (T3), the physiologically active thyroid hormone, is produced either directly by the thyroid gland or after peripheral deiodination of circulating T4 by selenium-containing deiodinases. Thyroid hormones regulate several physiological processes, including growth, development, metabolism, and reproductive function [1].

Thyroid hormone synthesis is enhanced by thyroid-stimulating hormone (TSH), produced by the pituitary gland, which in turn stimulates iodine uptake and oxidation by thyrocytes, thyroglobulin synthesis, iodothyronine binding, and thyroid hormone release from the gland [2]. Thyroid avidity and iodine uptake are increased in iodine deficiency and suppressed in cases of iodine overexposure.

Iodine deficiency results in inadequate production of T4. In response to decreased blood T4 levels, the pituitary gland increases TSH to restore circulating T4 levels. When TSH is persistently elevated, this results in thyroid enlargement (hyperplasia) and multinodular goiter [2]. Because adaptation is insufficient to provide the body with sufficient thyroid hormones, iodine deficiency can lead to primary hypothyroidism.

Overview of Thyroid Hormone Synthesis

Thyroid hormone synthesis requires two proteins: thyroglobulin (TG) and thyroid peroxidase (TPO). Both are synthesized under the control of TSH. TG is a 660 kDa glycoprotein secreted into the follicular lumen whose tyrosyl residues serve as substrates for iodination and hormone synthesis. TPO is a heme-containing enzyme expressed on the apical membrane of thyrocytes. TPO reduces H2O2 produced by NADPH oxidase to create iodinating species and catalyzes the iodination of tyrosyl residues of growing TG molecules [2]. Oxidized iodine is incorporated into thyroxine residues to form mono- (MIT) and diiodothyronine (DIT) before they combine to form T3 and T4.

Iodothyronine is a component of TG and is stored in colloid in the follicular lumen for weeks or months depending on individual thyroid hormone requirements.

The first step in thyroid hormone release is endocytosis of colloidal droplets from the follicular lumen into the cytoplasm. Endocytic vesicles fuse with lysosomes, where TG is proteolyzed by endo- and exopeptidases. Following proteolysis, thyroid hormones are released into the cytoplasm of thyrocytes, where specific transporters mediate the release of T4 into the bloodstream [2]. Iodine deficiency decreases the ratios of DIT to MIT and T4 to T3, whereas iodine replacement increases them.

Thyroid Function in Infants and Children

The developing fetus receives maternal T4 via the placenta, particularly during the first trimester of pregnancy, as well as hormones and other factors that affect thyroid function. Many studies of the effects of TG on the developing fetus have been conducted using sheep and rats, and the type of placentation and timing of maturation must be taken into account when evaluating these results. The rat thyroid gland is much less mature at birth than the human thyroid gland, and significant maturation of the rat thyroid gland and the hypothalamic-pituitary-thyroid axis occurs between birth and the first 2 or 3 weeks of life.

Neonates and children have a significant increase in TG turnover compared with adults, and their concentrations of T4, free T4, T3, and TSH gradually decline from peak values in the early postnatal period, while serum reverse T3 concentrations remain stable or increase slightly. During the first year of life, serum TG concentrations decline in a similar manner, reaching adult levels by the sixth month. Newborns produce approximately 5–6 mg T4/kg/day; as the child grows, T4 production gradually declines to approximately 2–3 μg/kg/day between ages 3 and 9 years. In contrast, adults synthesize approximately 1.5 μg T4/kg/day. It is therefore critical to use age- specific reference values when estimating serum T3. T4 and TSH Concentrations in Young Children The newborn thyroid gland weighs approximately 1 g, and each lobe is approximately equal in size to the terminal phalanx of a newborn's thumb. The thyroid gland grows slowly during the first few months of life, reaching its mature size of approximately 15–20 g by age 15 years.

Metabolism and function of iodine

Iodine is a non-metallic trace element essential for animals and humans. Iodine accounts for about two-thirds of the molecular weight

of thyroid hormones. According to the official nomenclature system, the term iodide refers to the natural form of the free element (inorganic) in its ionic state (I-), while iodine includes both inorganic iodide and iodine covalently bound to tyrosine [2].
Iodine enters the body as an inorganic ion or organically bound compound, but it is absorbed in the form of iodide after reduction of iodine compounds in the stomach. Enteral absorption of iodide occurs in the stomach and duodenum, where the enteric isoform of the sodium iodide symporter (NIS) is largely expressed [3].

Iodine is stored in the thyroid gland, which therefore contains the largest pool of intracellular iodine in the human body. However, the most significant amount of iodide is retained in the extracellular fluid, where its concentration is about 10–15 μg/L. Circulating iodide undergoes renal clearance, while a small proportion is lost through the skin, intestinal secretions, or expired air.

The mammary gland can also store and secrete iodide, thus offering an additional source of iodide clearance in lactating women [2]. Renal clearance of iodide is 30–50 ml min-1 [4], but is largely dependent on the individual glomerular filtration rate, with no evidence of tubular secretion or active transport [5]. Reabsorption is partial and passive, and renal clearance of iodide depends on total iodide status [6]. The thyroid gland clearance of iodine is about 10–20 ml/min, but it depends on the chronic iodine intake, ranging from 3 ml/min in cases of chronic high iodine overdose (more than 500 μg/day) to 100 ml/min in cases of severe iodine deficiency [7]. The uptake of iodide into the thyroid gland occurs through a specific transporter, NIS. NIS is expressed on the basolateral plasma membrane of thyrocytes. It belongs to the so-called secondary active transporter family, since NIS uses the electrochemical gradient created by the sodium-potassium ATPase to actively transport iodide against the gradient [8]. This mechanism is necessary to maintain the intrathyroidal concentration of free iodide 20–50 times higher than the plasma concentration [9]. NIS expression is enhanced by TSH [10], [11]. There is also an intrinsic autoregulatory mechanism by which iodide transport and intrathyroidal metabolism oscillate inversely with the organic iodine content of the gland. This mechanism, also known as the Wolff- Chaikoff effect, depends on iodine saturation of the transporters and enzymes involved in iodine organification and thyroid hormone synthesis. It is an intrathyroidal defense mechanism to protect against overproduction of thyroid hormones in cases of acute or intermittent iodine overload [11]. Once iodide accumulates in thyrocytes, the passage of iodide from the cytoplasm to the follicular lumen is facilitated by the apical iodide transporter (AIT) [12] and pendrin [13].

Iodide is also formed by intrathyroidal deiodination of iodothyronine following hydrolysis of thyroglobulin. A portion of the circulating iodide pool undergoes reorganization into de novo synthesized iodothyronine, while the remainder is distributed into the systemic circulation (iodide leak). Iodine also arises from the peripheral degradation of thyroid hormones and enters the circulation, where it can either be recycled after subsequent uptake by the thyroid gland or ultimately excreted in the urine.

Natural and Artificial Sources

Iodine occurs naturally as iodide and iodate in igneous rocks and soils. However, iodine can be mobilized from the surface layers of the earth, and rocks such as iodide and iodate are highly soluble in the aqueous phase. Thus, they run off from rainwater into surface waters, seas, and oceans, eventually becoming available for consumption by animals and humans [14]. Free elemental iodine also sublimates into the atmosphere directly from soils and rocks due to its high volatility. When rain falls, iodine precipitates on the surface of the earth and runs off into soils and rocks, where it can then be taken up by plants.

Vegetables do not provide adequate dietary iodine, and vegans are susceptible to iodine deficiency even in areas with sufficient iodine [15]. Meat, milk, eggs, fish and other animal products are the most important dietary sources of iodine in human nutrition. The estimated mean iodine concentration in animal tissues other than the thyroid gland (i.e. skeletal muscle) is approximately 0.1 mg/kg [16]. However, the iodine content of animal tissues depends on the addition of iodine to background animal feed [16]. Seafood and marine fish are the most important sources of iodine, since marine fauna and flora accumulate large amounts of soluble iodine from seawater. Fresh and farmed fish contain less iodine than seawater products. Thus, fish from rivers or lakes usually have lower levels of this element [17,18]. Iodine intake varies between geographic areas, but also among individuals in a given geographic region, and, indeed, individual intakes vary from day to day. Iodine intake also depends largely on age [19,20,21,22]. In Germany, milk and dairy products provide about 35% of the daily iodine requirement. The remaining two thirds are supplied by meat and meat products, bread and cereals, and fish [19]. In Denmark, milk provides more than 30% of the daily iodine intake [20], and a similar percentage has been reported in Swiss children [21]. In Dutch schoolchildren, seafood is a minor source of iodine, as it is consumed only about once a month [22].

As a result of nutrition policies allowing the addition of iodine to foods, processed foods containing significantly higher levels of iodine have become available in the last few decades and have been used to provide iodine prophylaxis to counteract the clinical consequences of iodine deficiency in national programs. Iodization of salt for human consumption is a worldwide strategy recommended for this purpose. Iodine can be ingested through chronic consumption or exposure to certain medications, such as amiodarone, povidone-iodine, iodine-based radiocontrast media, and multivitamin preparations. For example, 200 mg of amiodarone (the average daily maintenance dose) contains 75 mg of iodine, five hundred times the recommended daily requirement for the element. Iodine-based radiocontrast media contain grams of iodine.

Recommended Intake

Daily iodine intake varies from less than ten micrograms in areas with extreme iodine deficiency to several hundred milligrams in patients taking iodine supplements. Generally, the recommended daily intake for adults and the elderly is 150 mcg of iodine. In pregnant or lactating women, the iodine requirement increases to at least 200–250 mcg per day [23]. The iodine requirement per kilogram of body weight is higher in neonates and children than in adults, corresponding to an absolute iodine intake requirement of 70–120 mcg in children and 40 mcg in neonates [24]. These guidelines consider the daily turnover of thyroid hormones in healthy individuals, with average iodine intake associated with the lowest TSH values in the normal range, smallest thyroid volumes, and lowest incidence of transient hypothyroidism at neonatal screening, and average levothyroxine requirements to restore euthyroidism in patients with thyroid agenesis or after thyroidectomy [23].

Iodine deficiency

A healthy diet in areas with historical iodine deficiency provides about 50% of the daily iodine requirement in adults, which is

insufficient to ensure adequate supplies of the micronutrient. This problem is particularly acute in certain settings, such as pregnancy and lactation, where iodine requirements are nearly double.
Several biomarkers have been used to estimate daily iodine intake in the population. For example, urinary iodine excretion rate is a reliable indicator of daily iodine intake, since 90% of circulating iodine is excreted in urine [2]. The most useful laboratory markers of iodine exposure in a community screening program are 24-hour urine iodine concentration and urine iodine to creatinine ratio. However, spot urine iodine concentrations are preferred over 24-hour samples for population-based surveys, as the former are impractical [25]. In iodine-sufficient areas, the median 24-hour iodine concentration is equal to or greater than 100 μg/L, corresponding to a daily intake of at least 130 μg.

According to WHO, iodine deficiency disorders (IDD), including goiter, hypothyroidism, intellectual disabilities, reproductive disorders, decreased child survival, and varying degrees of growth and developmental abnormalities, affect more than a billion people worldwide [26].

Iodized salt has significantly reduced the prevalence of iodine deficiency in many iodine-deficient countries worldwide [23,27]. However, nearly one-third of the world's population still lives in geographic areas where iodine deficiency and related disorders are endemic [28].
Diffuse or nodular enlargement of the thyroid gland is the first and most common pathophysiological consequence of iodine deficiency. As mentioned above, iodine deficiency reduces intrathyroidal T4 synthesis with a subsequent adaptive increase in serum TSH concentration. If undiagnosed, TSH elevation over months to years is sufficient to stimulate hyperplasia and enlargement of the thyroid gland. This adaptive response is usually sufficient to maintain euthyroidism for several years when subclinical iodine deficiency occurs. "Endemic" goiter refers to an epidemiological condition in which more than 5% of school-aged children are diagnosed with an enlarged thyroid gland in a population [29]. Moderate to severe iodine deficiency can lead to primary hypothyroidism because TSH stimulation and thyroid enlargement are insufficient to ensure euthyroidism. In addition to iodine deficiency, other agents have been identified as goitrogenic in humans and can precipitate thyroid dysfunction if they occur concomitantly with iodine deficiency. These agents include thiocyanate, isothiocyanates, polyphenols, phthalate esters, polychlorinated and polybrominated biphenyls, organochlorines, polycyclic aromatic hydrocarbons, and lithium [30,31,32]. Meanwhile, thiocyanate, isothiocyanate, perchlorate, and lithium, as a few examples, inhibit iodide transport by NIS. Phenolic compounds and phthalates interfere with iodine oxidation and organification, and lithium interferes with the enzymatic proteolysis of Tg and blunts T4 release. Polybrominated biphenyls increase the rate of thyroid hormone metabolism glands [33]. Iodine supplementation is a therapeutic strategy to prevent thyroid enlargement in patients chronically exposed to goitrogens, particularly when iodine uptake and metabolism are affected (e.g., perchlorate, lithium, and thiocyanate) [30]. Iodine deficiency early in life can significantly affect brain development. Thyroid hormones are essential for myelination of the central nervous system, which occurs before and shortly after birth. Primary hypothyroidism associated with iodine deficiency has been found to adversely affect cognitive function with potentially irreversible intellectual consequences [34,35]. Adequate maternal iodine exposure early in pregnancy is essential for proper intellectual development of the child, regardless of hypothyroidism. In a longitudinal study from the UK, verbal IQ, reading accuracy and comprehension were significantly lower in children of women with an iodine to creatinine ratio of less than 150 μg/g than in women with a ratio equal to or greater than 150 μg/g [36]. Iodine deficiency is also associated with increased rates of miscarriage and stillbirth, as well as congenital disorders including congenital hypothyroidism in the offspring [37,38]. Congenital hypothyroidism comprises two classic clinical features with specific phenotypes: neurologic and myxedematous. The former is characterized by intellectual impairment and developmental delays, and various neurologic defects including cochlear malformation leading to deafness, cortical defects with intellectual impairment, and striatal malformation with motor impairment [39].

Patients do not exhibit features of hypothyroidism and the prevalence of goiter is similar to that seen in the general population. The hypothyroid phenotype includes dwarfism with delayed bone and sexual maturation, intellectual disability, and overt hypothyroidism. Thyroid development is critically affected and patients typically have low thyroid volume or thyroid atrophy [40].

Neurologic cretinism is due to thyroid hormone deficiency early in embryonic development, resulting from severe maternal iodine deficiency during the phase when thyroid development is not yet complete [41]. Myxedema cretinism is due to thyroid failure late in pregnancy or early infancy [42]. Pure forms of myxedematous cretinism predominate in Central Africa, while in other endemic regions such as New Guinea and parts of South America, only neurological cretinism has been described. Mixed forms have been observed in India [43]. The specific geographic distribution of these different phenotypes suggests that factors other than iodine deficiency may be involved, including hereditary factors, a diet high in thiocyanate [44], and low levels of selenium, zinc, copper, manganese, iron, and antioxidants (e.g. vitamin A) [45,46]. The prevalence of endemic goiter and other IDDs is extremely low in most European countries, while subclinical iodine deficiency remains a widespread health problem in Western and Central Europe [47].
However, iodine deficiency remains a
public health problem even in Europe. First, iodine intake is expected to be quite low in certain subgroups of the population, such as people following a vegan diet without consuming iodised salt or using supplements containing iodine and other micronutrients (such as selenium and zinc) [48] and those who poorly comply with dietary recommendations or have an increased need for iodine (e.g. during pregnancy and lactation) [49]. A recent systematic review of national surveys and subnational studies confirmed that in Europe some subjects have iodine intakes below recommended levels, particularly among girls and women [50].

Iodine Excess

In most regions, common diets provide low levels of normal iodine supply and are more likely to cause iodine deficiency than iodine excess [52]. However, individuals living in some regions may be exposed to extreme iodine overload due to their diet. Chronic iodine overload is generally well tolerated, as most individuals exposed to large amounts of iodine do not show any thyroid complaints [53]. However, chronic overexposure may increase the risk of subclinical hypothyroidism and possibly goiter due to persistent overstimulation of TSH [54].
Acute iodine poisoning is a rare emergency that occurs after ingestion of grams of iodide. Common clinical manifestations include burning mouth, sore throat, fever, nausea, vomiting, diarrhea, and, in severe cases, coma [23]. Acute iodine excess dramatically suppresses thyroid hormone synthesis due to the described Wolff-Chaikoff effect. This is usually temporary and reversible, but it can be permanent in certain conditions such as chronic autoimmune thyroiditis [23].
The acceptable daily intake of iodine is about 200 mcg for infants up to 3 years old, 250 mcg for children aged 4–6 years, 300 mcg for children aged 7–10 years, 450 mcg for children aged 11–14 years, 500 mcg for children aged 15–17 years, and 600 mcg for adults, including pregnant or lactating women [26].

Excess iodine increases physiological responses

The thyroid gland is a highly sensitive organ, capable of responding to variable dietary iodine intake and, when stimulated,

accumulating iodine over a concentration gradient of up to 80 times. Most individuals with normal thyroiditis can consume up to 2 g iodine per day without clinical response, unless they have underlying thyroiditis and live in iodine-sufficient areas. With high iodine intake, only minor changes in TG concentrations are observed: serum T4 and T3 concentrations may decrease by 25% and 15%, respectively, with a corresponding increase in TSH of 12 mIU/L, although these values remain within the reference interval in most individuals.
Although thyroid volume may increase slightly on ultrasound imaging, goiter or thyroid dysfunction are not clinically evident. Most of these mild side effects are reversible.

Iodine prophylaxis

A thousand years have passed since the first medical descriptions of significant reductions in goiter size in patients consuming large quantities of seaweed and sea sponges, typical foods of Asian coastal regions. However, iodine was discovered accidentally in 1811 by Courtois, and two years later it was characterized and described as a new element by Gay-Lussac [55]. Jean- François Coindet, a Swiss physician born and working in Geneva, was the first to suggest that the historically reported reduction in goiter size after ingestion of seaweed was due to its high iodine content [56]. He thus created the first "therapeutic" iodine solution by dissolving 48 grains (3.1 g) of iodine in a volume ounce (about 28 ml) of distilled alcohol. Based on empirical and anecdotal case series, Koynde provided the first evidence for the effectiveness of iodine fortification in reducing goiter size in patients with goiter. News of Koynde's experience quickly spread throughout Europe, causing criticism, particularly due to safety concerns regarding overexposure to iodine. This delayed the widespread use of fortification as a primary treatment for multinodular goiter. Years later, more detailed studies were conducted by David Marin, who conducted a clinical trial of an iodine prophylaxis program for schoolgirls in 1917 [56]. He found that iodine prophylaxis prevented the development of goiter in children with initially normal thyroid size and caused a significant reduction in thyroid size in about two-thirds of schoolgirls with initially enlarged thyroid glands [56]. In the United States, iodine prophylaxis began in 1924 in Michigan, which belongs to the so-called goiter belt, a group of states in which endemic goiter was widespread. Fortified (iodized) salt was first used for iodine prophylaxis; the iodine concentration was 100 mg per kg of salt, resulting in an estimated average intake of 500 μg of iodine per day, since the average recommended salt intake at that time was approximately 6.5 g per day.
Consumption of iodized salt has increased significantly since the 1950s. Since then, consumption of iodized salt as the primary salt for household use has remained stable at about 50% [57]. The US FDA recommends fortifying iodized salt in the range of 46–76 mg iodide/kg [58]. Iodine

prophylaxis programs in Europe began in areas recognized as endemic for iodine deficiency since the 1920s, such as Switzerland (1922), Austria (1923, discontinued after several years and steadily resumed in 1963), and the Netherlands (1928). Over the years, iodine prophylaxis was introduced in other countries, including Poland (1935), Finland (1940), Portugal (1971), Italy (1972), Germany (1980), and Spain (1982). Consumption of iodized salt was initially voluntary, and the iodine content of fortified salt was generally insufficient to prevent or treat endemic goiter, especially in moderately endemic areas. The iodine content of fortified salt varies considerably across Europe, from 10 mg iodine/kg in Austria to 60 mg iodine/kg in Spain. The variation is based on the severity of iodine deficiency, dietary policies and information campaigns promoting iodine prophylaxis [59]. The production of iodized salt was officially authorized by law in 1972 in Italy. Thereafter, iodine prophylaxis began selectively in endemic regions and was extended to the whole country five years later. The iodine content of fortified salt was 15 mg/kg and the consumption of iodized salt was voluntary. Epidemiological data for 1994 were collected and analyzed in Pescopagano, a small village in Basilicata. An analysis of about 1400 citizens living with subclinical iodine deficiency who had never received iodine prophylaxis showed that iodine deficiency (mean urinary iodine excretion of 55 μg/L) was associated with a progressive increase in the prevalence of goiter with age, a high incidence of autonomously functioning thyroid nodules and other forms of hyperthyroidism, and thyroid autoimmunity [60]. Other epidemiological reports have confirmed a direct relationship between the severity of iodine deficiency and the prevalence of anatomical and functional thyroid disorders and intellectual disabilities. Results of 10-year iodine prophylaxis for correction of iodine deficiency showed that it reduced the risk of endemic goiter in schoolchildren, suggesting that widespread use of iodized foods would be desirable to reduce IDD. At that time, a new ministerial decree (1991) established that the iodine content of fortified salt should be increased to 30 mg/kg, but iodine fortification was still voluntary. Law 55, promulgated at the end of March 2005, reorganized and regulated iodine prophylaxis to reduce the risks associated with iodine deficiency. Strict monitoring of the effectiveness of iodine prophylaxis and information campaigns to promote iodine consumption were then carried out. In 2009, the Ministry of Health set up the National Observatory for Monitoring Iodine Prophylaxis at the National Institute of Health to collect and analyze the effect of iodine prophylaxis over time. Salt market reports before the law showed that iodized salt consumption was well below 50% of salt intake. Iodine sufficiency was found in only three regions of Italy (Liguria, Tuscany and Sicily). However, six of the nine regions (Liguria, Emilia-Romagna, Marche, Tuscany, Calabria and Sicily) were areas with endemic goiter. In collaboration with the regional observatories, post-legislative surveillance data were collected by the National Observatory for the Monitoring of Iodine Prevention and analyzed from 2015 to 2019. Salt market reports showed a significant increase in the consumption of iodized salt (65% of all commercial salt). National household consumption of iodized salt rose to 63%, ranging from 50% (Sicily) to over 75% (Veneto and Tuscany), while the national percentage of school canteens using iodized salt was 78%, with regional differences ranging from 65% in Sardinia to 97% in Sicily.

The mean urinary iodine concentration was 124 μg/L, indicating adequate iodine intake, with no differences between rural and urban areas. Sufficient iodine intake was achieved in Veneto, Emilia-Romagna, Umbria, Marche, Lazio and Calabria, while iodine deficiency was eliminated in Tuscany, Liguria and Sicily. In seven of the nine regions surveyed (Liguria, Sicily, Tuscany, Emilia-Romagna, Umbria, Marche and Lazio), the prevalence of goitre diagnosed in schoolchildren was below 5%, indicating a significant reduction in the number of goitre endemic areas. The incidence of neonatal TSH > 5 mIU/L, an indicator of insufficient iodine exposure during pregnancy, decreased from 6.1% in 2010 to 4.9% in 2018. Despite these improvements, the safe threshold of 3% is still far from being reached, indicating the need for additional supplements from healthcare providers, including obstetricians, gynecologists, and pediatricians. The number of prescriptions for antithyroid drugs, a surrogate for hyperthyroidism incidence, has decreased by 7.4% over time in Italy (reference years: 2001 vs. 2018). Prescription rates have decreased significantly (by more than 10%) in seven regions, namely the province of Trento (−16.5%), Basilicata (−13.9%), the province of Bolzano (−12.7%), Tuscany (−12.5%), Sardinia (−11.8%), Liguria (−11.3%), and Friuli- Venezia Giulia (−10.5%). Since 1990, universal iodine fortification programmes have made significant progress worldwide, with an increasing number of countries adhering to mandatory salt iodization levels of 15–40 mg/kg. The number of countries achieving adequate (median urinary iodine concentration 100–199 μg/L) and more than adequate (median urinary iodine concentration 200–299 μg/L) iodine intake has increased significantly in the following decades. It was estimated that 88% of the world's population used iodized salt in 2018, with the highest consumption in East Asia and the Pacific (92%) and the lowest coverage in West and Central Africa (78%). According to the 2021 Global Iodine Scorecard, among school-age children, 146 countries have achieved adequate iodine exposure (defined as median urinary iodine concentration of 100–300 μg/L), while 26 still have endemic mild or moderate iodine deficiency.

Case Report

A healthy 6-year-old girl with a goiter is described. Her thyroid function tests showed normal TSH, low free T4, and elevated free T3 and T3, mimicking a biochemical picture of thyroid hormone (TH) alpha resistance.

A 6-year-old girl was referred to a pediatric endocrinologist because of abnormal thyroid lab results that were done as part of an evaluation for an acquired goiter at 1½ years of age. She had no symptoms of hypothyroidism or hyperthyroidism. Her past medical history showed a normal neonatal thyroid screen. She was evaluated for macrocephaly at one year of age with a cranial ultrasound, which was normal. She had normal growth and development. She was a strict vegan and did not take any dietary supplements. The family used non-iodized salt. Most of the vegetables consumed by the family were from their own farm, including cruciferous vegetables and soybeans. Family history revealed a benign thyroid nodule in the maternal grandmother. On examination, she had stable vital signs, height 124.6 cm (z-score = 1.60), weight 25.5 kg (z-score
= 1.23), and body mass index 16.45 kg/m2 (z-score = 0.71). She had a diffuse, painless, smooth, soft thyroid enlargement with both lobes measuring 6–7 cm vertically (Figures 1 and 2). Initial laboratory tests performed externally revealed TSH 5.04 μIU/mL (0.35–5.5 μIU/mL), free T4 (FT4)
0.3 ng/dL (0.8–1.8 ng/dL), total T4 2.4 μg/dL (4.5–12 μg/dL), reverse T3 <5 ng/dL (8.3–22.9), total T3 258 ng/dL (94–241 ng/dL), and negative thyroid peroxidase antibodies (<28 IU/mL) and thyroglobulin antibodies (17.9 IU/mL). Thyroid ultrasound showed a markedly enlarged thyroid gland with heterogeneous echotexture, microcystic changes, and fibrous septa. Serum thyroglobulin was 1098 μg/L (normal <13 μg/L) and urine iodine was 15.8 μg/L (median urine iodine <20 μg/L—severe iodine deficiency [6]), confirming the diagnosis of IDH. The patient was started on 150 μg iodine per day, and the family began consuming iodized salt. Thyroid function tests performed after 3 months of iodine supplementation showed TSH 2.72 μIU/mL, total T3 182 ng/dL, total T4 9.3 μg/dL, and reverse T3 17.2 ng/dL. She remained clinically and biochemically euthyroid for a year after her initial presentation, with no change in goiter size. We describe a 6- year-old healthy child raised on a vegan diet with IDG with normal TSH, low T4 and free T4, elevated T3 and free T3, and low reverse T3. Hypothyroxinemia, a biochemical disorder characterized by low T4 and normal TSH together with elevated T3 (low serum T4/T3), as seen in our patient, is characteristic of TH alpha resistance. A similar biochemical picture can also be seen in individuals with disorders of decreased TH synthesis - congenital hypothyroidism due to dyshormonogenesis and acquired hypothyroidism due to iodine deficiency, as well as in individuals with Allan-Herndon-Dudley syndrome due to a mutation in the TH transmembrane transporter MCT8. Patients with Allan-Herndon-Dudley syndrome have severe psychomotor retardation, congenital hypotonia, and progressive spastic paralysis, and have an X-linked inheritance pattern, making it easily distinguishable from the other conditions mentioned above. Thyroid dyshormonogenesis is typically characterized by elevated TSH with low T4, but patients with partial iodide organification defects and defects in the Pendrin gene or apical iodide transporter may have normal TSH with low/low normal T4. Patients with TH alpha resistance may exhibit a wide range of phenotypes, ranging from mild phenotypes with minimal symptoms to severe phenotypes with growth and psychomotor retardation, skeletal dysplasia, macrocephaly, facial dysmorphism, and symptoms of hypothyroidism. They may also have normocytic or macrocytic anemia or mildly elevated creatine kinase. Our patient was evaluated at one year of age for macrocephaly and had a normal cranial ultrasound. She had normal hemoglobin (13.6 g/ dL) on presentation. We considered referring her to a genetics clinic while awaiting the results of a urine iodine and thyroglobulin test. Low urinary iodine and elevated thyroglobulin confirmed the diagnosis of IDG in our patient.

TH levels are maintained by a feedback mechanism involving the hypothalamus, pituitary gland, and thyroid gland. Local TH signaling is mediated by intrathyroidal and extrathyroidal mechanisms, and systemic TH signaling is mediated by the hypothalamic-pituitary-thyroid (HPT) axis. Once in the target tissues, TH enters the cells via transmembrane TH transporters such as MCT 8 and MCT 10. Once inside the cells, iodothyronine deiodinase (Dio) enzymes metabolize the thyroid hormones into active (T4 to T3 via Dio 1 and 2) or inactive (T4 to rT3 and T3 to T2 via Dio 3) forms. Combined action Dio enzymes, together with differences in the expression of thyroid hormone transmembrane transporters, allow different tissues to control intracellular thyroid hormone levels, maintaining clinical euthyroidism in most tissues, regardless of the levels present in the general circulation. The active thyroid hormone T3 mediates its actions through the TH receptors alpha and beta.

Iodine deficiency stimulates intra- and extrathyroidal autoregulatory mechanisms. Initially, there will be an increase in vascularization and iodine uptake. As iodide availability continues to be reduced, intrathyroidal autoregulatory changes result in preferential synthesis of T3 over T4, resulting in low serum T4, normal to slightly elevated T3, and normal TSH resulting in normal T3. The proportion of fully iodinated thyroglobulin decreases and the proportion of poorly iodinated thyroglobulin increases, resulting in leakage into the circulation. Increases in serum T3/T4 ratios and thyroglobulin levels are markers of these TSH-independent autoregulatory mechanisms. As a result of these autoregulatory changes, there will be an increase in thyroid weight and volume, which does not mean that TSH is or was elevated. At the level of target tissues, the integral action of thyroid hormone transmembrane transporters and deiodinase enzymes plays a key role in maintaining normal intracellular T3 levels and clinical euthyroidism for as long as possible. In all but infants, both intrathyroidal and extrathyroidal mechanisms responding to iodine deficiency are fully functional even in mild iodine deficiency. Thus, patients remain clinically and biochemically euthyroid until intrathyroidal and extrathyroidal mechanisms fail to maintain normal T3 levels at the tissue level in severe and chronic iodine deficiency. This TSH-independent autoregulation explains the characteristic biochemical abnormality observed in our patient with IDH.

The most common cause of acquired goiter among children and adolescents in developed countries is chronic autoimmune thyroiditis, while iodine deficiency remains the most common cause of goiter worldwide. The best sources of iodine are seafood, dairy products, and eggs. Vegans or people with multiple food allergies, lactose intolerance, or restrictive diets are at risk of developing iodine deficiency. Goitrogens also contribute to iodine deficiency in vulnerable populations with borderline iodine status. Concomitant iron, vitamin A, and selenium deficiencies further worsen iodine status in people with limited iodine stores [4]. There have been case reports of IDG recurring in people on a restrictive diet in the United States.

Our patient was a strict vegan, making her vulnerable to iodine deficiency. Her diet included cabbage, broccoli, and cauliflower. She also had a strong taste for soy, consuming it daily. Cruciferous vegetables and soy contain goitrogens that interfere with iodine absorption, which may have further contributed to our patient's iodine deficiency. The patient's thyroid function tests mimicked alpha thyroid hormone resistance with high T3/T4, low reverse T3, and normal TSH. This diagnosis was also initially considered in our patient, as patients with TH resistance may have a milder presentation with minimal symptoms. Even after an extensive search, we could not find a case report of children with IDH presenting with a biochemical picture mimicking alpha TH resistance. A study examining the TH profile of fifty children with goitre, aged 6–11 years, living in an area endemic for iodine deficiency, showed normal T4 and TSH levels in all but three subjects. Two patients had low T4 with elevated TSH, and one had elevated T4 with normal TSH. Twenty- four percent of the patients had elevated T3. The patient responded well to iodine supplementation with normalization

of thyroid function tests after 3 months and continued to be clinically and biochemically euthyroid on follow-up. The diagnosis of IDH should be considered in those on a restricted diet when acquired goiter is present and, although uncommon, those with IDH may have thyroid function tests that mimic alpha thyroid hormone resistance.

Case Report: Thyroid Tuberculosis in a Woman

A 60-year-old retired Ethiopian female teacher presented to the University of Gondar College of Medicine and Health Sciences, Gondar, Ethiopia, with a complaint of anterior neck swelling of 6 years duration, with a recent increase in size 3 months prior to her current presentation. She had visited a nearby health center with this complaint and had taken unspecified antibiotics without improvement. She had a history of low grade intermittent fever, unspecified weight loss, and night sweats, but no cough, loss of appetite, pressure effects, or bowel, bladder, joint, or nervous system involvement. She had no family history (first-degree relatives) of diabetes, hypertension, or any other significant noncommunicable diseases including cancer. Her past medical history was unremarkable. She had no history of hospitalization. She had no history of any surgical procedures. Physical examination revealed a soft to firm multinodular anterior cervical mass measuring 2 x 3 cm on the left lobe of the thyroid gland. She had no axillary, cervical, or intra- abdominal lymphadenopathy. Based on the above findings, a preliminary clinical diagnosis was multinodular goiter, excluding follicular tumor. The liver was not palpable below the costal margin. There was no splenomegaly. Other clinical findings were within normal limits. Laboratory studies performed on the same day of admission, including complete blood count (CBC), erythrocyte sedimentation rate (ESR), and electrocardiogram (ECG), were unremarkable. In the complete blood count, the total white blood cell (WBC) count was 4000 µL with 54% granulocytes, 42% lymphocytes, 2% eosinophils, and 2% monocytes. The platelet count was 350,000 µL. The hemoglobin was 14.5 g/dL with a mean corpuscular volume (MCV) of 85 fL. The ESR was 75 mm/ hr. GeneXpert for the detection of Mycobacterium tuberculosis in pus samples was positive. Renal function testing revealed a blood urea nitrogen (BUN) level of 14 mg/dL and a serum creatinine level of 0.7 mg/dL. Liver function tests showed total bilirubin 0.6 mg/dL, serum albumin 4.2 g/dL, and serum aspartate transaminase (AST/SGOT) and serum alanine transaminase (ALT/SGPT) 32 and 34 IU/L, respectively. Urinalysis was also done and was normal. She was screened for RVI and was nonreactive. Serum TSH, total T4, and total T3 were 3 µIU/mL, 7 µg/dL, and 1.5 ng/mL, respectively. Neck ultrasound was performed and revealed abscess-like collections in the left lobe of the thyroid gland in the setting of a multinodular goiter. Chest radiography was done and revealed normal-appearing lung parenchyma and a thyroid mass. Abdominal and pelvic ultrasound was done and was normal. Due to limited number of pathologists and long waiting list of patients, she underwent fine needle aspiration cytology (FNAC) 2 weeks after initial presentation. Repeat FNAC smears showed extensive caseous necrosis on a dirty background.
Given the above cytopathology results and positive GeneXpert result of pus sample, thyroid tuberculosis was diagnosed and the patient was started on 2 tablets RHZE/4 RH 3 orally daily, which is defined as the preferred first-line treatment regimen for tuberculosis in Ethiopia, and pyridoxine 50 mg orally daily for 6 months. Thereafter, she underwent regular liver function tests. The patient had an uneventful course without significant adverse effects. Currently, the patient has completed her TB treatment and is doing well. After completion of TB treatment, the patient underwent neck ultrasound, which revealed multinodular goiter without abscesses.

Some additions

Tuberculosis is an infectious disease that is a major cause of ill health and a leading cause of death worldwide. Before the coronavirus disease (COVID-19) pandemic, TB was the leading cause of death from a single infectious agent, surpassing HIV/AIDS. Estimating the burden of TB disease during the COVID-19 pandemic is difficult and relies heavily on country- and region- specific dynamic models for low- and middle-income countries. New national TB incidence surveys and up-to-date cause-of-death data from national vital registration systems of high quality and coverage are needed to provide more accurate estimates after the pandemic. TB can affect almost any organ or tissue in the body. Extrapulmonary lesions tend to be more common in children and immunocompromised individuals. To establish the diagnosis of extrapulmonary TB, appropriate specimens including pleural fluid; pericardial or peritoneal fluid; biopsy specimens of the pleura, pericardium, and peritoneum; lymph node tissue; and bone marrow, bone, blood, urine, brain, or cerebrospinal fluid should be obtained for acid-fast bacilli (AFB) staining, mycobacterial culture, and drug susceptibility testing. Tissue specimens should also be examined microscopically after routine and AFB staining, but the absence of AFB and granulomas or even the absence of culture of M. tuberculosis does not exclude the diagnosis of tuberculosis.

Bacteriologic assessment of the response to treatment in extrapulmonary tuberculosis is often limited by the difficulty in obtaining follow-up specimens. Thus, response must often be assessed on the basis of clinical and radiographic findings. Primary tuberculosis (TB) of the thyroid is extremely uncommon and can have a number of different clinical presentations. It commonly mimics more common conditions such as thyroid adenoma or carcinoma, lymphoma, infective or granulomatous thyroiditis, Graves' disease, multinodular goiter, or bacterial abscess. This delays the diagnosis, especially when there is no evidence of involvement of other organs. Thyroid tuberculosis is a rare disease, and primary thyroid involvement is even rarer. It is a rare disease even in countries where tuberculosis is endemic. Diagnosis is often difficult because the clinical picture has no clear characteristics. The clinical course of the disease may resemble toxic goiter or acute thyroiditis, or it may follow a subacute or chronic growth pattern without specific symptoms. Histologically, the presence of necrotizing epithelioid cell granulomas together with Langhans-type giant cells is the hallmark of thyroid tuberculosis. The demonstration of acid-fast bacilli on Ziehl-Neelsen staining confirms the diagnosis, but this stain is often negative in tissue sections. In our case, the patient presented with low-grade intermittent fever, unspecified weight loss, and night sweats, but she did not have a cough. Repeat smears from the thyroid abscess showed extensive caseous necrosis on a dirty background, and GeneXpert of the pus sample was positive. In general, first-line treatment for TB consists of combination therapy with isoniazid, rifampin (rifapentine and rifabutin in certain situations), pyrazinamide, and ethambutol. In the presence of drug resistance or intolerance to first-line drugs, second-line drugs may be used.
Adults with pulmonary or extrapulmonary TB are eligible for a 6-month 2HRZE/4HR regimen, except for patients with central nervous system, bone, or joint TB, for whom some expert groups suggest longer therapy (ie, 9–12 months). Our patient was also started on a 2HRZE/4HR regimen.

The decision to initiate combination antituberculous chemotherapy should be based on epidemiologic information; clinical, pathologic, and radiographic data; and the results of microscopic examination of sputum (smears) stained for acid-fast bacilli (and other appropriately collected diagnostic specimens) and cultures for mycobacteria. A purified protein derivative (PPD)-tuberculin skin test may be done during the initial evaluation, but a negative PPD-tuberculin skin test does not exclude the diagnosis of active tuberculosis. However, a positive PPD- tuberculin skin test confirms the diagnosis of culture-negative pulmonary tuberculosis and of latent tuberculosis infection in individuals with stable abnormal chest radiographs consistent with inactive tuberculosis. If suspicion for tuberculosis is high or the patient is seriously ill with disease, pulmonary or extrapulmonary, that is thought to be tuberculosis, combination chemotherapy using one of the recommended regimens should be started promptly, often before the AFB smear results are known and usually before the mycobacterial culture results are available. A positive AFB smear

provides strong evidence for the diagnosis of tuberculosis. If the diagnosis is confirmed by isolation of M. tuberculosis or a positive nucleic acid amplification test, treatment can be continued until completion of the standard course of therapy. When initial AFB smears and cultures are negative, a diagnosis other than tuberculosis should be considered and appropriate investigations performed. If no other diagnosis is established and the tuberculin PPD skin test is positive (in which case an induration of 5 mm or more is considered positive), empirical combination chemotherapy should be started. If there is a clinical or radiographic response within 2 months of starting therapy and no other diagnosis is established, a diagnosis of culture-negative pulmonary tuberculosis can be made and treatment can be continued with an additional 2 months of INH and RIF to complete a total of 4 months of treatment, an adequate regimen for culture- negative pulmonary tuberculosis. If there is no clinical or radiographic response within 2 months, treatment can be stopped and other diagnoses, including inactive tuberculosis, can be considered.

If AFB smears are negative and suspicion for active tuberculosis is low, treatment can be deferred until mycobacterial culture results are known and a comparative chest radiograph is available (usually within 2 months). In initially untreated patients with low suspicion, if cultures are negative, the PPD-TB skin test is positive (induration 5 mm or greater), and the chest radiograph is unchanged at 2 months, one of the three regimens recommended for the treatment of latent TB infection can be used. These include (1) INH for 9 months, (2) RIF with or without INH for 4 months, or (3) RIF and PZA for 2 months. Because of reports of increased hepatotoxicity with the RIF–PZA regimen, it should be reserved for patients who are unlikely to complete a longer course of treatment, can be closely monitored, and have no contraindications to the use of this regimen. Patients suspected of having TB should have appropriate specimens collected for microscopic examination and mycobacterial culture. If the site of disease is the lung, three sputum specimens should be obtained. Sputum induction with hypertonic saline may be required to obtain specimens, and bronchoscopy (both performed with appropriate infection control measures) may be considered for patients who are unable to produce sputum, depending on the clinical circumstances. Susceptibility testing to INH, RIF, and EMB should be performed on a positive initial culture, regardless of the source of the specimen. Susceptibility testing to second-line drugs should be performed only in reference laboratories and should be limited to specimens from patients who have previously received therapy, have had contact with patients with drug-resistant tuberculosis, have demonstrated resistance to rifampin or other first-line drugs, or have positive cultures after more than 3 months of treatment. It is recommended that all patients with tuberculosis receive counseling and testing for HIV infection at least at the time of treatment initiation, if not sooner. CD4+ lymphocyte counts should be obtained for patients with HIV infection. Patients with risk factors for hepatitis B or C virus (eg, injection drug use, birth abroad in

Asia or Africa, or HIV infection) should have serologic testing for these viruses. For all adult patients, baseline measurements of serum aminotransferases (aspartate aminotransferase [AST], alanine aminotransferase [ALT]), bilirubin, alkaline phosphatase, serum creatinine, and platelet count should be obtained. Visual acuity and red-green disc imaging should be obtained when EMB is to be used. In our case, her RVI status was nonreactive and all baseline studies were normal. Second-line anti-TB drugs are classified as such because of the relative lack of clinical data, unfavorable or poorly characterized pharmacokinetic profile, and/or increased incidence and severity of adverse effects. Experience with some of these drugs is increasing due to the need for alternative treatments for drug-resistant TB. WHO suggests using a 6-month regimen consisting of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPalm) rather than a 9-month or longer (18-month) regimen in patients with MDR/RR-TB.

The significance of anterior neck swelling is that most cases remain asymptomatic, so patients do not seek medical care until much later. Thus, they remain undiagnosed and serve as a potential source of morbidity and mortality in the community. On the other hand, the diagnosis is often missed due to other common causes of anterior neck swelling, such as multinodular colloid goiter or thyroid neoplasms. In our patient, who reported from a TB-endemic area, anterior neck swelling, in the absence of other relevant clinical and laboratory data, initially misled the physician. The lack of suspicion of tuberculosis resulted in a long period of suffering for the patient. The patient was very pleased with the intervention and the care provided.

Conclusion of this case report

We present a case of a 60-year-old Ethiopian female patient who was diagnosed with thyroid tuberculosis mimicking multinodular goiter by cytopathology and GeneXpert and was started on 2 tablets of RHZE/4 RH 3 PO daily and pyridoxine 50 mg PO daily for 6 months after she presented with multinodular anterior neck swelling. Anterior neck swelling due to Mycobacterium tuberculosis infection needs to be included in the spectrum of unusual manifestations of tuberculosis infections and tuberculosis as a differential diagnosis needs to be kept in mind when a patient with anterior neck swelling is encountered in a tuberculosis endemic area. We believe that with further accumulation of cases and experience in the future, our understanding of primary thyroid tuberculosis will improve and the diagnosis and treatment of this disease will be improved.

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