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Approach to Subclinical Hypothyroidism in Children

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<http://dx.doi.org/10.5772/55134>

1. Introduction

1.1. Definition of SCH

SCH is defined when serum TSH concentration is above the statistically upper limit of the reference range while serum free T_4 (FT_4) concentration is within its reference range (Biondi & Cooper, 2008; Surks et al., 2005). Other names for SCH include compensated, early, latent, mild, minimally symptomatic, preclinical hypothyroidism and euthyroid hyperthyrotropinemia (Chu & Crapo, 2001). It suggests a compensated early state of primary thyroid failure whereby an increased level of TSH is required to maintain normal levels of thyroid hormones. The reference TSH levels in a normal population aged 12 and older (excluding individuals with medications or diseases that might influence thyroid function) were assessed at 0.45 to 4.12 mIU/l (2.5th–97.5th percentile) (Hollowell et al., 2002). Although there were age, gender, and ethnic group differences, they were small and it was therefore not considered necessary to adjust the reference for these parameters. Additional studies assessing the normal TSH reference in children have shown broad differences between adult and children that were dependent on the patient's age (Elmlinger et al., 2001; Hübner et al., 2002; Kapelari et al., 2008; Soldin et al., 2009; Strich et al., 2012; Zurakowski et al., 1999), indicating that the definition of SCH is age-dependent. A panel of experts divided patients with SCH into two groups: patients with mildly increased serum TSH levels (4.5–10 mIU/l) and patients with more severely increased serum TSH levels (>10 mIU/l) (Surks et al., 2004).

2. Prevalence of SCH

The prevalence of SCH is about 4% to 10% in the adult population (Biondi & Cooper, 2008; Hollowell et al., 2002; Surks et al., 2004), with a higher prevalence in women and the elderly.

The prevalence of congenital hypothyroidism (CH) has increased in the last two decades from 1 in 4000 births (Grüters et al., 1993) to as high as 1 in 2000 births in the Hispanic population in the United States (Harris & Pass, 2007). Explanations for the increase in prevalence of CH in the United States include lower TSH cut-off levels, increasing numbers of preterm or very low weight babies who can be affected by a transient rise in TSH levels and reflect more benign or transient cases (Grüters & Krude, 2011) and higher numbers of neonates with Hispanic background in the tested population. The precise incidence of SCH in children is not well defined; however, a prevalence of about 1 in 8260 births was found in Europe for transient CH and SCH (Klett & Schönberg, 1981).

3. Etiology of SCH

The different causes of SCH in children are summarized in Table 1. The most common cause in children, as well as in adults, is AITD. In the newborn, hyperthyrotropinemia can reflect a physiological condition, as well as maternal AITD and perinatal exposure to iodine. Loss-of-function mutations of genes that are involved in thyroid development and thyroid hormone synthesis may also present as euthyroid hyperthyrotropinemias at birth or later on in life. Additional etiologies are acquired thyroid infiltration diseases, thyroid injury, and secondary effects of medication that influences thyroid hormone synthesis or clearance of thyroid hormones. Mild hyperthyrotropinemia may be a consequence of obesity. Laboratory interference in the assay process is not a rare cause for elevated TSH. Many of these causes result in overt hypothyroidism with time, or even at presentation.

AITD	Risk factors: family history of AITD-associated autoimmune disorders (diabetes mellitus type 1, celiac disease, pernicious anemia, viteligo, atrophic gastritis, etc.) as part of autoimmune polyglandular syndrome type 1 & 2. In Down syndrome and Turner’s syndrome
Congenital hyperthyrotropinemia	Iodine exposure or endemic iodine deficiency, maternal AITD, maternal drug treatment like propylthiouracil and metimazole
Persistent TSH after subacute thyroiditis or painless thyroiditis	
Thyroid injury	Partial thyroidectomy, radioactive iodine therapy, external radiotherapy of head and neck, chemotherapy
Drugs	Iodine and iodine-containing medications (amiodorone, radiographic contrast agents), lithium, interferon α , sulfonamides
Inadequate replacement therapy of hypothyroidism	Inadequate dosage, noncompliance, drug interactions (iron, calcium carbonate, dietary soy), increased T_4

	clearance (phenytoin, carbamazepine, phenobarbital), malabsorption
β-thalassemia major	Due to hemosiderosis
After bone marrow transplantation	
Thyroid infiltration	Amyloidosis, sarcoidosis, hemochromatosis, cystinosis, primary thyroid lymphoma
Obesity	
Genetic	Loss-of-function mutations in <i>TSHR</i> , <i>GNAS</i> , <i>PAX8</i> , <i>TTF-1</i> , <i>DUOX2</i>
Laboratory interferences	Macro-TSH, heterophilic antibodies, thyroid autoantibodies, RF

Table 1. Causes of SCH in children

3.1. Transient hyperthyrotropinemia in newborns

Hyperthyrotropinemia in newborns is mainly a physiological condition reflecting the TSH surge which occurs immediately after birth. Additional etiologies for this condition include iodine deficiency that is common in areas of endemic goiter or secondary to iatrogenic iodine overload during fetal and postnatal life. Significant exposure to iodine may be caused by transplacental crossing of iodine to the fetus or secretion of iodine into the breast milk consumed by the newborn. In addition, the newborn, and especially premature newborns, can be exposed to iodine overload through contrast medium in imaging studies or to iodine in topical agents. Rare causes of neonatal hyperthyrotropinemia are transplacental passage of thyroid-blocking antibodies and antithyroid drugs from mother to fetus in maternal autoimmune diseases. Genetic etiologies include TSH resistance (RTSH), mainly due to mutations in *TSHR*. Additional inherited defects include mutations in *DUOX2*, *PAX8*, *TTF-1* and *GNAS1*. Long-term follow-up and laboratory and imaging evaluation are needed to define the specific etiology and to select the appropriate clinical approach in each case. Sakka et al. (2009) reported significant elevations in TSH levels in children born after in-vitro fertilization. The authors hypothesized that this might represent an epigenetic developmental abnormality related to preimplantation manipulation of the embryo.

3.2. Maturation of thyroid hormone metabolism

Fetal thyroid develops under the influence of increasing TSH levels during the last half of gestation. Serum TSH increases from low levels at 18 weeks to a peak of 7–10 mU/l at term. Fetal hypothalamic–pituitary feedback matures during the second trimester (Fiser & Klein, 1981; Fisher & Polk, 1989; Rakover et al., 1999). More recent studies sampling fetal cord blood have shown measurable TSH levels at as early as 15 weeks gestation which peak in the second trimester and then plateau at that level until term (Hume et al., 2004; Thorpe-Beeston et al., 1991). At birth, in response to extrauterine exposure, there is acute release of TSH (TSH surge) that peaks at a concentration of about 70 mU/l at 30 min and remains elevated for 3 to 5 days

after birth. The increase in FT₄ levels at birth is TSH-dependent. Increased FT₄ secretion continues for 1 to 2 months after birth. Normal pediatric age-dependent references for thyroid hormones have shown TSH concentrations as high as 9.64 mIU/l in the first months after birth, suggesting that hyperthyrotropinemia in the first year of life reflects normal phenomena and does not necessarily require further evaluation or therapy (Hübner et al., 2002).

3.3. Maternal Autoimmune Thyroid Diseases (AITDs)

Transplacental transfer of thyroid-stimulating antibodies (TSAbs) and TSH binding inhibitor antibodies (TBIAbs) from mother to fetus has been described in the presence of maternal AITDs. In maternal Graves' disease, the infant is at risk for congenital hyperthyroidism (Ogilvy-Stuart et al., 2002), CH and euthyroid hyperthyrotropinemia (Fu et al., 2005). Fu et al. (2005) reported on 78 mothers with AITDs; about half of their babies had transient hyperthyrotropinemia, seven had overt hypothyroidism and one had hyperthyroidism (Fu et al., 2005). The severity of the clinical presentation correlated with the levels of maternal autoantibodies. Congenital hyperthyroidism resulted from maternal transfer of TSBabs. Transient CH or hyperthyrotropinemia resulted from the mother consuming anti-thyroid drugs such as metimazole and propylthiouracil, which have a short half life of a few days (Cheron et al., 1981), and from transplacental transfer of TBIAbs, which are eliminated from the infant's serum after a few months in parallel to the elimination of maternal immunoglobulins. Papendieck et al. (2009) described 28 newborns of mothers with Graves' disease diagnosed with neonatal hyperthyroidism (9 newborns), primary hypothyroidism (14) and central hypothyroidism (5). Spontaneous remission was shown in all of the affected babies between 16 days and 8 months apart from 2 babies who had permanent hypothyroidism. The authors concluded that infants born to mothers with Graves' disease should be assessed by a pediatric endocrinologist to better identify thyroid diseases in the offspring. In maternal Hashimoto's thyroiditis, the infant is at risk for transient CH or hyperthyrotropinemia due to transplacental transfer of TBIAbs. To determine the incidence of transient CH due to TRAbs, all dried neonatal blood specimens from the neonatal screening in North America were screened for TRAbs (Brown et al., 1996) and only 2% of babies diagnosed with CH were positive for TRAbs, suggesting that maternal AITD is a rare etiology of CH. The occurrence of transient hypothyroidism due to maternal Hashimoto's thyroiditis was reported mainly as a case report (Matsuura et al., 1980; Zakarija et al., 1990; Wada et al., 2000). We described transient CH in three siblings born to a mother with well-controlled Hashimoto's thyroiditis with extremely high levels of TBIAbs (Rakover et al., 1990). The baby had high TBIAbs concentrations and as reflected by sequential serum measurements, these antibodies disappeared after 4 months. In one sibling, the thyroid gland was absent in a ^{99m}Tc scan performed on the first days of life but repeated scan after the age of 2 years, revealed a gland of normal size and position. Absence of distal femoral epiphysis at birth was shown. Interestingly, the three siblings had minor abnormal neurological signs in late childhood such as dyslexia, attention deficit disorder and coordination disorders. These neurological findings, along with the lack of distal femoral epiphysis at birth, suggested *in-utero* fetal hypothyroidism. A less favorable intellectual outcome was reported in babies with transient CH born to mothers positive for TBIAbs compared to babies with permanent hypothyroidism of other etiologies, especially if unrec-

ognized maternal hypothyroidism was present *in utero* (Matsuura et al., 1990; Wada et al., 2000). Our findings as well as other reports raised the dilemma of whether prenatal follow-up, after umbilical cord blood sampling and intra-amnionic L-T₄ injections, if indicated, is required to prevent late neurological sequels in these cases (Abalovich et al., 2007; De Groot et al., 2012; Wada et al., 2000). It is recommended that all babies born to mothers with AITDs be reviewed in the first 3 days of life and a thyroid function test be taken to identify those babies with transient CH that require L-T₄ therapy, or babies with congenital hyperthyroidism requiring anti-thyroid drugs (Ogilvy-Stuart et al., 2002). The approach for *in-utero* treatment of fetal thyroid disease is still a matter of debate (De Groot et al., 2012).

3.4. Exposure to iodine

Abnormal thyroid function due to either iodine deficiency or iodine overload has been described in prenatal and postnatal periods. In cases of iodine overload, the Wolff-Chaikoff mechanism blocks the uptake of iodine by the thyroid gland resulting in reduced T₄ production and in turn increased TSH secretion via a negative feedback mechanism. Sava et al. (1984) showed that newborns from areas of iodine deficiency in Sicily were at higher risk for hyperthyrotropinemia; the increase in risk was related to the degree of iodine deficiency as reflected by iodine cord blood measurements. On recall, only two patients were diagnosed with CH which required L-T₄ therapy for as long as 1 year. The authors suggested the need for maternal iodine prophylaxis therapy in areas of endemic iodine deficiency. Transient thyroid function abnormalities have also been observed in neonates born to mothers with excessive iodine intake. Maternal iodine exposure was reported accompanying excess iodine in the diet (Nishiyama et al., 2004), use of iodine compounds such as povidone iodine in topical applications, exposure to contrast medium during pregnancy and the use of antiseptic agents in obstetric departments (Grüters et al., 1983). Prenatally, maternal iodine crosses the placenta and concentrates in the fetal thyroid gland, whereas postnatally, the newborn is exposed to iodine through the breast milk (Chanoine et al., 1988; Koga et al., 1995). Premature babies are particularly susceptible to iodine-induced hypothyroidism due to immaturity of the thyroid-pituitary negative feedback mechanism and to higher exposure to iodine-containing agents in intensive care (Delange et al., 1984). Uses of iodine in Cesarean sections and in neonatal intensive care units are additional causes for newborn iodine overload and therefore it is recommended to avoid iodine compounds in deliveries and in the neonate intensive care units. In newborns, exposure to iodine may be attributed to umbilical iodine application as well. Iodine overload may cause either transient hyperthyroidism with symptoms of tachycardia and failure to gain weight (Rakover & Adar, 1989) or may present as CH or persistent hyperthyrotropinemia. Nishiyama et al. (2004) described 15 babies with transient CH or persistent hyperthyrotropinemia born to mothers in Japan who consumed a high iodine diet during their pregnancies; among them, 12 babies were treated with L-T₄. The authors recommended that food be labeled with their precise amount of iodine to avoid high intake of iodine by pregnant women. CH and hyperthyrotropinemia in cases of iodine overload or deficiency are transitory; however, whether transient hypothyroidism or hyperthyrotropinemia can result in permanent neurological sequels in these cases is not clear, and it is therefore recommended that short-term L-T₄ therapy be considered on an individual basis.

4. Genetic etiology of SCH

4.1. TSH Resistance syndrome (RTSH)

RTSH is a condition in which thyroid cells show reduced sensitivity to TSH. This condition is characterized by elevated serum TSH concentration, a normal or hypoplastic thyroid gland and normal to very low levels of thyroid hormones (Refetoff, 2003). The diagnosis of RTSH defect is based on the absence of thyroid antibodies, a lack of goiter, measurable serum thyroglobulin, and familial occurrence of hyperthyrotropinemia or hypothyroidism. Most of the cases of RTSH are attributed to mutations in the *TSHR* but in many cases, no such mutations were found, suggesting that additional genes are associated with RTSH syndrome (Xie et al., 1997). The diagnostic work-up of RTSH should exclude *PAX8* mutations, which are characterized by thyroid dysgenesis associated with kidney abnormalities (Grüters et al., 2003; Park & Chatterjee, 2005) and mutations in *GNAS1*, which encodes $G\alpha$ subunit, causing pseudo-hypoparathyroidism (PHP). Another form of RTSH is an autosomal dominantly inherited disease characterized by euthyroid hyperthyrotropinemia, for which the specific gene has not yet been identified. This condition has been linked to a locus on chromosome 15q25.3-26.1 (Grasberger et al., 2005). Loss-of-function mutations of *DUOX* genes are an additional cause for transient hyperthyrotropinemia.

4.2. TSH Receptor (*TSHR*)

Loss-of-function mutations in *TSHR* manifest with a variable clinical spectrum of phenotypes ranging from severe uncompensated RTSH presenting with CH, or partially compensated RTSH presenting with SCH or even with normal thyroid function (for review see Tenenbaum-Rakover, 2012). CH is commonly detected by TSH-based neonatal screening but may be missed by total T_4 (TT_4)-based screening since, in many cases, TT_4 levels are within the normal range at birth. The degree of CH is variable and depends on the genotype. Severe forms manifest as overt CH; moderate forms manifest as hypothyroidism identified by neonatal screening without clinical symptoms of hypothyroidism and mild forms present with hyperthyrotropinemia and normal thyroid hormone levels. Most of the described cases of CH are detected by neonatal screening with elevated TSH and normal TT_4 levels, but without any clinical symptoms or signs of hypothyroidism (de Roux et al., 1996; Tenenbaum-Rakover et al., 2009). Nevertheless, L- T_4 therapy is initiated in most cases to prevent future consequences of untreated CH. At the age of 2 to 3 years, when L- T_4 is withdrawn, thyroid hormones remain low in the severe mutations; however in milder mutations, despite extremely elevated TSH levels, thyroid hormone levels are normal, indicating compensated hypothyroidism (Tenenbaum-Rakover et al., 2009). ^{99m}TC scan commonly reveals a normal or hypoplastic gland but in some cases, an absence of thyroid gland has been demonstrated, suggesting thyroid agenesis. On the other hand, the presence of detectable thyroglobulin as well as the demonstration of a thyroid gland in the normal position in ultrasonographic imaging exclude thyroid agenesis and indicate a diagnosis of RTSH. The affected patients who are not identified by neonatal screening are commonly identified by routine laboratory tests in childhood or even as adults and are commonly asymptomatic. Most of the described cases are heterozygous for

TSHR mutations, but biallelic mutations have been reported as well. To date, about 50 different *TSHR* mutations have been reported, presenting with a spectrum of phenotypes ranging from overt CH to mild euthyroid hyperthyrotropinemia. Subjects with euthyroid hyperthyrotropinemia commonly have stable TSH levels and do not develop overt hypothyroidism with time. The phenotype correlates with the genotype as the latter is reflected in the severity of hyperthyrotropinemia and the decrease in FT₄ levels. Screening for *TSHR* mutations should be considered in individuals with apparent nonautoimmune SCH. In view of the variability in phenotypes and outcomes among individuals with this condition, careful long-term follow-up is recommended and replacement therapy should be considered on an individual basis according to thyroid hormone levels in the clinical context. In cases with loss-of-function mutations in *TSHR* presenting with CH, early initiation of L-T₄ therapy is recommended to prevent late-effect consequences of hypothyroidism as in other etiologies of CH. However, withdrawal of L-T₄ at the age of 2 to 3 years revealed transient hypothyroidism in some cases, putting the need for lifelong replacement therapy into question (Alberti et al., 2002; Tenenbaum-Rakover et al., 2009). SCH caused by *TSHR* mutations with mild to moderate loss of function maintains stable compensated RTSH and may not necessitate thyroid hormone replacement. Moreover, most patients with RTSH do not present with symptoms of hypothyroidism or with biochemical parameters of uncompensated hypothyroidism, such as elevated creatinine phosphokinase (CPK) and liver enzymes and hyperlipidemia (Tenenbaum-Rakover et al., 2009). The presence of normal FT₄ levels argues against the need for replacement treatment, especially when inadvertent overtreatment, producing subclinical hyperthyroidism, can have undesirable effects (Samuels et al., 2008). Contrasting with this approach, it has been shown that some subjects with RTSH have a slight decrease in FT₄ levels compared to controls, although remaining within the normal range, which may point to a condition of compensated hypothyroidism in these affected patients. In addition, the possibility of secondary pituitary enlargement in patients with extreme hyperthyrotropinemia may support L-T₄ replacement therapy. In view of the variability in phenotypes for the different types of mutations, as well as between individuals with the same genotypes, it is recommended that careful follow-up and cautious administration of L-T₄ be considered based on individual thyroid hormone levels in the clinical context.

4.3. Pseudohypoparathyroidism (PHP)

Loss-of-function mutations in *GNAS1*, which encodes Gs α subunit, cause PHP and lead to a syndrome of resistance to multiple G-coupled receptor hormones. Resistance to parathyroid hormone (PTH) is the main feature of PHP (Mantovani, 2011; Mantovani et al., 2002). RTSH is commonly clinically manifested during childhood or adulthood but may present at birth as CH identified by neonatal screening. In most cases, hypothyroidism is mild and may present with hyperthyrotropinemia for long durations without any clinical symptoms of hypothyroidism. ^{99m}Tc scan generally demonstrates a hypoplastic gland in a normal position but absence of a thyroid gland, demonstrated by ultrasonographic imaging, has been reported as well. SCH is the presenting laboratory finding of PHP in many cases. RTSH is commonly found in PHP-Ia but is also reported in PHP-Ib. The phenotype of patients with PHP-Ia includes Albright osteodystrophy presenting with brachydactyly, round face, short stature, central

obesity, subcutaneous ossifications and variable degree of mental retardation. Clinicians should be aware of this rare syndrome; in those cases of SCH occurring in obese subjects or with Albright osteodystrophy phenotype, PHP should be suspected and further hormonal and molecular evaluations should be considered.

4.4. Dual Oxidase maturation factor (*DUOX*)

Loss-of-function mutations in *DUOX* have been reported in children with CH and in transient hyperthyrotropinemia of the newborn (De Marco et al., 2011; Hoste et al., 2010; Maruo et al., 2008; Moreno et al., 2002). Hydrogen peroxide (H_2O_2) is an essential co-substrate for oxidation of iodine and iodination of thyroglobulin by the thyroid peroxidase (TPO) enzyme. *DUOX1* and *DUOX2* proteins have a crucial role in H_2O_2 generation and therefore in thyroid hormone synthesis. The structure of these proteins includes seven putative transmembrane domains. Moreno et al. (2002) showed that biallelic mutations of *DUOX2* result in organification defect presenting with permanent CH, whereas monoallelic mutations result in transient CH or hyperthyrotropinemia (OMIM#606758) (Moreno et al., 2002). In contrast, sequencing of *DUOX2* in Japanese children diagnosed with transient congenital hyperthyrotropinemia revealed eight novel mutations of the *DUOX2* gene, all with biallelic mutations (Maruo et al., 2008). The authors concluded that even complete inactivation of *DUOX2* causes transient, but not permanent CH, due to the presence of *DUOX1*, which maintains the supply of H_2O_2 required for oxidation after the neonatal period. However, late onset of hypothyroidism or SCH may appear in adulthood during periods of increased requirement for thyroid hormones, such as in pregnancy (Ohye et al., 2008). The organification defect is characterized by normal position and location of the thyroid gland in a ^{99m}TC scan, high iodine uptake with partial positive perchlorate discharge test. Goiter may be present or develop over time (Moreno et al., 2002; Ohye et al., 2008).

4.5. Thyroid dysgenesis

Three transcription factors have been identified as involved in thyroid development: *TTF-1*, *TTF-2* and *PAX8*. The discovery of these transcription factors in a knockout mouse model was followed by descriptions of the phenotypes in humans. Human mutations in *TTF-2* are very rare and present with CH, cleft palate and spiky hair (OMIM#602617). Patients with *TTF-1* and *PAX8* mutations present with either CH or persistent congenital hyperthyrotropinemia; the former are associated with lung and neurological involvement while the latter are associated with kidney abnormalities.

4.5.1. *TTF-1* mutations

TTF-1, also known as *NKX2.1*, is a transcription factor involved in thyroid development. *Ttf1*-null mice were born dead, lacking a thyroid gland, lung parenchyma and pituitary gland, and with severe defects in the ventral forebrain. Heterozygous mice presented a euthyroid phenotype with reduced motor-coordination skills (Park & Chatterjee, 2005). In humans, *TTF-1* mutations have been reported in children presenting with SCH, lung involvement presenting with neonatal respiratory distress and neurological involvement presenting with hypotonia,

persistent ataxia, dysarthria, microcephaly, choreathetosis and developmental delay (OMIM #600635). *TTF-1* mutations are inherited in an autosomal dominant manner. Patients present with variable thyroid phenotypes ranging from permanent severe CH to persistent congenital hyperthyrotropinemia resembling RTSH (Devriendt et al., 1998; Krude et al., 2002; Pohlenz et al., 2002) with hypoplasticity or agenesis of the thyroid gland or the gland in a normal position (Krude et al., 2002). *TTF-1* mutations may also present with isolated benign hereditary chorea without thyroid phenotype (Breedveld et al., 2002).

4.5.2. *PAX8* mutations

PAX8 is thyroid transcription factor which is a key gene in mammalian embryonic development. Homozygous Pax8-null mice die shortly after weaning and their survival is dependent on thyroxine replacement therapy. Mutations in the *PAX8* gene in humans are characterized by thyroid dysgenesis associated with kidney abnormalities (Damante 1998; Grüters et al., 2003; Narumi et al., 2011; Park & Chatterjee, 2005; Vilain et al., 2001) inherited in an autosomal dominant manner (OMIM#167415). The thyroid gland is hypoplastic (Vilain et al., 2001) or in an ectopic location. Partial organification defect and partial iodide transport defect have been reported (Jo et al., 2010). To date, 31 mutations have been described in the *PAX8* gene, presenting as permanent CH or as mild SCH (Narumi et al., 2011; Narumi et al., 2012). Screening for *PAX8* gene mutations in 300 Chinese patients with CH revealed only two subjects with heterozygous *PAX8* mutations, suggesting that *PAX8* mutation is a very rare etiology for CH (Liu et al., 2012).

5. Outcome of neonatal hyperthyrotropinemia

Neonatal hyperthyrotropinemia may be transitory or permanent. Transient congenital hyperthyrotropinemia has been shown in iodine deficiency or due to iodine overload and in both of these cases, full recovery is expected within days to a month after the cause has been removed. In maternal AITD, TRAbs disappear within 4 to 8 months. A less favorable intellectual outcome was reported in these cases, probably due to *in-utero* fetal hypothyroidism (Matsuura et al., 1990; Wada et al., 2000). In cases of persistent congenital hyperthyrotropinemia, minor thyroid abnormalities (Calaciura et al., 2002; Daliva et al., 2000; Leonardi et al., 2008; Miki et al., 1989; Zung et al., 2010) have been reported in late childhood. Longitudinal studies assessing the outcome of subjects with neonatal hyperthyrotropinemia have shown a prevalence of 50% SCH with morphological alterations of the thyroid in early childhood (3 years) (Calaciura et al., 2002), which decreases in follow-up to 30% in late childhood (8 years), suggesting that persistent hyperthyrotropinemia represents minor congenital thyroid abnormalities (Leonardi et al., 2008). In about 50% of the subjects morphological, immunological or genetic abnormalities were found. A high rate of thyroid autoantibodies was identified at the age of 2 to 3 years in about 25% of the subjects (Calaciura et al., 2002); morphological changes such as enlarged or hypoplastic thyroid gland or its hemiagenesis were shown in 10% of the cases. Zung et al. (2010) showed that subjects with persistent vs. transient hyperthyrotropinemia had a higher rate of abnormal thyroid imaging and therefore thyroid imaging was

recommended to distinguish between the persistent and transient forms. Moreover, genetic analysis revealed heterozygous mutations of *TPO* and *TSHR* (Calaciura et al., 2002) in about 5% of the children with SCH following transient neonatal hyperthyrotropinemia. These findings indicate that hyperthyrotropinemia at birth may represent an inherited thyroid disease that interferes with thyroid hormone synthesis or thyroid genesis. In contrast to these studies, Köhler et al. (1996) showed no increase in the risk of thyroid abnormalities and normal neurological development as well as normal growth in children with hyperthyrotropinemia at birth; they therefore recommended avoiding longitudinal surveys of these children to prevent parents' anxiety (Köhler et al., 1996). In summary, neonatal hyperthyrotropinemia may be persistently associated with either autoimmune disease, inherited thyroid hormone synthesis defects or morphological changes, and therefore long-term follow-up throughout childhood is recommended in cases where TSH levels are persistently above the normal range during the first year of life.

6. Pediatric-age-dependent thyroid hormone reference

The commonly available normal reference range provided by commercial companies for thyroid hormone levels in routine laboratories is for adults. Using this may result in an erroneous interpretation of the results of thyroid function in children. Moreover, great variability exists between the pediatric references published in the literature (Elmlinger et al., 2001; Hübner et al., 2002; Kapelari et al., 2008; Soldin et al., 2009; Strich et al., 2012; Zurakowski et al., 1999). The variability in the normal reference range is attributed to different types of assays, different ethnic and age groups and different sample sizes. Even in the same assay, different laboratories can provide different normal ranges (Hübner et al., 2002; Kapelari et al., 2008; Strich et al., 2012). The variability between assays results from the different standards, antibodies and methods used [two-site immunoassay commonly gives lower results than radioimmunoassays (RIAs)]. Furthermore, the references established for children in different age groups make use of different populations; for example, hospitalized children (Hübner et al., 2002; Kapelari et al., 2008) have lower FT₃ concentration due to non-thyroidal illness, whereas references using routine laboratory samples (Strich et al., 2012) may include samples from children bearing unidentified thyroid diseases, which may cause an upward bias in the TSH levels. Despite these limitations, it is still clear that childhood references are very different from adult references. Strich et al. (2012) showed that in 11,000 samples of children aged 0 to 18 years taken from a routine laboratory database, the upper limit of TSH was 1 mIU/ml above the provided reference and the lower normal range of FT₃ was 0.5 to 2 pmol/l higher than the reference. Hübner et al. (2002) analyzed thyroid hormone levels in children with the ADVIA® Centaur™ analyzer. They showed elevated TSH levels in the first year of life with an upper limit of 9.64 mIU/l, which decreased gradually to 4.9 mIU/l at the age of 18 years. The same trend was shown with FT₄, decreasing from 17.2 to 14.7 pmol/l from 1 to 18 years of age. The upper limit of FT₃ levels showed the same, albeit less pronounced trend, from 8.2 to 6.63 pmol/l. The authors suggested using continuous-age-dependent reference ranges in children who show better agreement with biological reality, as these are more reliable than discontinuous

reference ranges. No significant sex-specific effects on age-adjusted hormone levels were shown (Hübner et al., 2002; Kapelari et al., 2008). In recent years, there has been some controversy regarding the normal TSH range for adult populations following the laboratory guidelines from the National Academy of Clinical Biochemistry, indicating that 85% of normal adult individuals have TSH levels below 2.5 mIU/l. These findings raised a debate over whether subjects with TSH levels above 2.5 mIU/l have SCH and should be further followed-up by repeated TSH measurements (Surks et al., 2004; Wartofsky & Dickey, 2005). In summary, age-dependent references should be used to interpretate thyroid functions in childhood. Hyperthyrotropinemia as high as 6.0 mIU/l (Hübner et al., 2002) with normal thyroid hormone levels and without clinical symptoms, during the first months of life can be considered within the upper normal limit for age and therefore not requiring L-T₄ therapy. Follow-up with repeated thyroid function tests is recommended in cases of persistent hyperthyrotropinemia to identify those infants which may develop late onset overt hypothyroidism.

7. Laboratory pitfalls

In about 0.5 to 5% of patient samples, hyperthyrotropinemia with normal thyroid hormone levels results from laboratory interference (Ismail et al., 2002). Such interference includes the presence of heterophilic antibodies, rheumatic factor (RF), autoimmune antithyroid hormone antibodies and the presence of macro-TSH.

7.1. Heterophilic antibodies

Heterophilic antibodies are antibodies produced against poorly defined antigens of various animal immunoglobulins. The best known heterophilic antibodies are human antimouse antibodies (HAMAs). Since immunometric assays use animal antihuman antibodies, the presence of human antimouse immunoglobulins in an individual's serum could interfere with the antigen-antibody binding reaction, resulting in falsely high or low hormonal levels. This interference is very rare in competitive RIAs but well recognized in the two-site sandwich immunometric assays (Després & Grant, 1988; Halsall et al., 2009; Kaplan & Levinson, 1999). High false-positive results are commonly reported in the latter, whereas false low levels are reported in competitive RIAs. High levels of α -fetoprotein, human chorionogonadotropin, follicle-stimulating hormone, luteinizing hormone, ferritin and tumor markers were described in TSH measurements secondary to the presence of heterophilic antibodies. Since TSH is commonly measured in routine evaluations for various medical complaints, elevated TSH level due to the presence of heterophilic antibodies is not a rare finding. Transient neonatal hyperthyrotropinemia identified by neonatal screening was reported by Czernichow et al. (1981), attributed to maternal heterophilic antibodies. The antibodies disappeared from the circulation within 2 months in the infants and within 4 to 6 months in the mothers (Czernichow et al., 1981). When heterophilic interference is suspected, further evaluation is indicated. The first step is to assess the sample using other immunoassays with different antibodies. The sample should be remeasured after dilution (Ross et al., 2008). Nonlinearity in sample dilution indicates the presence of laboratory interference. Preincubation of a patient's sample with

antiheterophilic tube or mouse serum confirms the diagnosis of heterophilic antibodies. The clinician should be aware that hyperthyrotropinemia with normal thyroid hormone levels and without clinical symptoms of hypothyroidism in the newborn or in childhood may be the result of interference by heterophilic antibodies. The diagnosis of hyperthyrotropinemia due to heterophilic antibodies cancels the need for further expensive laboratory and imaging investigations and avoids unnecessary L-T₄ therapy.

7.2. Thyroid hormone autoantibodies

Thyroid hormone autoantibodies are present in about 1 to 7% of patients with autoimmune thyroid diseases, mainly Graves' disease. Antibodies against thyroglobulin and thyroid peroxidase are very common in Hashimoto's thyroiditis and Graves' disease; however, antibodies against thyroid hormones T₃ and T₄ are less common and anti-TSH autoantibodies are even rarer. The presence of thyroid hormone autoantibodies interferes with the assay procedure, giving higher hormonal levels (Després & Grant, 1998). We had one case of a 16-year-old girl with Graves' disease (unpublished data) who presented with severe symptoms of hypothyroidism, 4 months after 8 mCi of I-131 therapy, with bradycardia and excessive weight gain. Thyroid function was confusing, with extremely high TSH 136 mIU/dl (0.35–5.5 mIU/dl), extremely high FT₄ > 6 (0.88–12.76 ng/ml); low FT₃ 30 ng/dl (60–180 ng/dl) and extremely high thyroid stimulating immunoglobulin (TSI) 164 IU/l, anti-TPO > 1000 U/ml and antithyroglobulin > 3000 U/ml. Measuring FT₄ in another assay using different antibodies revealed low FT₄, confirming the clinical diagnosis of hypothyroidism post-radioactive iodine therapy. The increase in FT₄ and TSI concentrations was associated with the autoimmune overreaction post-I-131 therapy with production of anti-FT₄ autoantibodies. This case demonstrates the importance of being aware of the existence laboratory interferences for making correct clinical decisions.

7.3. Macro-TSH

Macro-TSH is a macromolecule that is formed when anti-TSH IgG combines with a TSH molecule. Due to their large size, these macromolecules are less efficiently cleared from the circulation by the kidneys, and therefore accumulate in the serum. Since they are nonfunctioning, they have no clinical significance and therefore may lead to unnecessary therapy. This condition is commonly described in patients with asymptomatic hyperprolactinemia caused by macroprolactinemia (Batista et al., 2012). Macro-TSH is rarer than macroprolactinemia with only about 13 cases described to date (Halsall et al., 2006; Loh et al., 2012; Mendoza, 2009; Newman et al., 2006; Rix et al., 2011; Sakai et al., 2009). The presence of macro-TSH should be suspected when the patient is asymptomatic and has elevated TSH level which does not correlate with additional thyroid function. Nonlinearity when the subject's serum is diluted indicates the presence of interfering antibodies. The presence of macro-TSH is proven by adding polyethylene glycol (PEG) to the patient's serum. Recovery results less than 50 to 30% of the pre-PEG results indicate the presence of macro-TSH. The diagnosis of macro-TSH is confirmed by gel-filtration chromatography but this technique is not routinely available. The presence of macro-TSH is not part of AITD or autoimmunity. Misdiagnosis of CH identified

by TSH-based neonatal screening was described in newborns which were later found to have macro-TSH of maternal origin (Halsall et al., 2006; Newman et al., 2006; Rix et al., 2011). It is suggested that maternal TSH levels be measured in cases of euthyroid neonates with elevated serum TSH and normal thyroid hormone. When maternal TSH is persistently elevated, the presence of macro-TSH should be considered. Further analysis, including recovery with PEG, is indicated to avoid unnecessary L-T₄ treatment. Macro-TSH spontaneously disappears from the infant's serum at the age of 6 to 8 months in parallel with the elimination of maternal immunoglobulins.

In summary, clinicians should be aware of false laboratory results attributed to interference in the immunoassay methods, mainly in evaluating euthyroid hyperthyrotropinemia. In cases in which there are discrepancies between the clinical presentation and the laboratory results, antibody interference should be suspected. This may be followed up by further laboratory evaluation. Accurate diagnosis leads to a better clinical approach and may allow avoiding unnecessary treatment.

8. Obesity and hyperthyrotropinemia

Obesity in children has become a great medical concern in the last two decades. Thyroid function tests are part of the diagnostic work-up in children who are overweight or obese. Moderate elevation in TSH levels in up to 20% of obese children has been demonstrated in many studies (Eliakim et al., 2006; Grandone et al., 2010; Reinehr, 2011; Reinehr et al., 2006; Shalitin et al., 2009). Among them, only 7 to 20% showed positive thyroid autoantibodies (Eliakim et al., 2006; Grandone et al., 2010). It has been speculated that hyperthyrotropinemia in obesity is a result of elevated leptin which stimulates the hypothalamic–pituitary–thyroid axis (Reinehr, 2011). The question is whether the elevation in TSH is the cause for or a consequence of obesity and whether it merits treatment with L-T₄. Reiter et al. (2006) did not find any association between hyperthyrotropinemia and lipid profile, whereas Shalitin et al. (2009) showed a positive correlation between hyperthyrotropinemia and waist circumference and triglyceride levels, supporting the need to treat those children. The fact that hyperthyrotropinemia was accompanied by normal FT₄ and elevated FT₃ levels (Reinehr et al., 2006) disagrees with the hypothesis of SCH as the cause for obesity in these children. Moreover, weight loss led to a significant reduction in TSH levels (Eliakim et al., 2006; Grandone et al., 2010; Reinehr et al., 2006) and L-T₄ therapy had no significant influence on body weight or lipid profile (Eliakim et al., 2006). Most of the studies agree that hyperthyrotropinemia in obesity is a consequence rather than a cause, and therefore L-T₄ therapy is unnecessary in obese children (Eliakim et al., 2006; Grandone et al., 2010; Reinehr, 2011; Reinehr et al., 2006).

9. Autoimmune Thyroid Disease (AITD) — Hashimoto's thyroiditis

Hashimoto's thyroiditis is characterized by the presence of thyroid autoantibodies [anti-thyroid peroxidase (TPO) and anti-thyroglobulin (TG)], with or without goiter. This condition

is characterized by hypoechogenicity of the thyroid gland in ultasonographic imaging and lymphocytic infiltration of the gland in fine-needle aspiration. The disease commonly appears in adolescence, with predominantly females affected. Among children with acquired hypothyroidism, 66% had AITD (Hunter et al., 2000), and about 30% to 50% had a family history of thyroid diseases (de Vries et al., 2009). The risk of overt hypothyroidism in adults with thyroid autoantibodies is estimated at 4.3% per year (Vanderpump & Tunbridge, 2002); however, there are only a few pieces of data on the natural history of Hashimoto's thyroiditis in children (Gopalakrishnan et al., 2008; Jaruratanasirikul et al., 2001; Moore, 1996; Radetti et al., 2006; Rallison et al., 1991). Hypoechogenicity of the thyroid gland in ultrasound imaging is a useful tool for the diagnosis of AITD (Marcocci et al., 1991; Pedersen et al., 2000; Wolfgang et al., 2002), showing higher sensitivity than the thyroid autoantibody tests (100 vs. 63.3%) (Rago et al., 2001). Marwaha et al. (2008) showed that among children with hypoechogenic appearance of the gland, 41.4% were positive for FNA, 30.6% were positive for TPO antibodies and 46.8% showed abnormal thyroid function. They concluded that ultrasound echogenicity is useful tool for the diagnosis of AITD in children but less sensitive compared to adults (Marwaha et al., 2008). Moreover, the occurrence of hypoechogenicity has been found to predict evolution toward hypothyroidism over time in euthyroid subjects (Marcocci et al., 1991; Rago et al., 2001). Disagreement also exists with regard to the criteria for L-T₄ therapy in childhood SCH (de Vries et al., 2009; Padberg et al., 2001; Radetti et al., 2006; Svensson et al., 2006). Thyroid function in Hashimoto's thyroiditis in children at presentation is variable. Özen et al. (2011) found that 36.7% of children were euthyroid, 32.7% had SCH, 16.6% were hypothyroid, 7.9% had subclinical hyperthyroidism and 5.9% presented with hyperthyroidism (Hashitoxicosis) (Özen et al., 2011). The main complaint was goiter presenting in 57.85% of patients, most of which were female (5.7:1, F:M). Similar findings were found by others showing that about 70% of children are either euthyroid or have SCH (Demirbilek et al., 2007; de Vries et al., 2009; Skarpa et al., 2011). Moore (1996) showed a benign course of SCH in children and adolescents with AITD and therefore suggested careful follow-up rather than treating them empirically. Gopalakrishnan et al. (2008) found that only 12.5% of children with either goiterous euthyroid or SCH develop overt hypothyroidism within 2 years. In contrast, Jaruratanasirikul et al. (2001) showed that 50% of subjects with SCH develop overt hypothyroidism within 5 years, supporting the need for long-term monitoring of thyroid function in patients with thyroid autoantibodies. de Vries et al. (2009) suggested that L-T₄ therapy of euthyroid children with AITD, if appropriately monitored, is not harmful and may even be beneficial. Further benefit consisted of reducing thyroid volume in those patients with goiter with or without overt hypothyroidism (Svensson et al., 2006). Padberg et al. (2001) demonstrated that prophylactic L-T₄ therapy of patients with euthyroid AITD reduces both serological and cellular markers of autoimmune thyroiditis, indicating that L-T₄ therapy might be useful for stopping progression of the disease. In contrast, the findings in an adult population that unnecessary long-term thyroxine therapy or overdose is associated with increase risk for osteopenia, cardiac disease and other harmful effects (Samuels et al., 2008) argues against regular therapy in children with AITD-associated SCH.

10. Natural history

The annual rate of progression of SCH to overt hypothyroidism (elevated TSH with low thyroid hormones) in an adult population was 4.3% in women with positive thyroid autoantibodies and only 2% when antibodies were negative (Biondi & Cooper, 2008). Huber et al. (2002), in a prospective study, found that 28% of women with SCH developed overt hypothyroidism after 10 years of follow-up. In children, the risk for progression to overt hypothyroidism is less common and recovery is more frequent. About 25% of subjects with goiterous thyroiditis had spontaneous remission and 33% developed hypothyroidism over 20 years of follow-up (Rallison et al., 1991). Radetti et al. (2006) showed, retrospectively, in 160 children with AITD in an over 5-year follow-up that abnormal thyroid functions occur in 34.3% at presentation whereas 47.55% had abnormal thyroid function at last visit. However, 10% of patients with SCH became euthyroid. TSH concentrations showed large fluctuations over time. The presence of goiter and elevated thyroid autoantibodies at presentation together with an increase in thyroid autoantibodies and TSH levels in the course of the follow-up were predictive factors for development of overt hypothyroidism. After 5 years, more than 50% became or remained euthyroid, and therefore a poor predictive outcome could be shown in individual patients. The authors suggested that medical therapy should be considered only when significant deterioration of thyroid function appears (Radetti et al., 2006).

11. Treatment

The dilemma of whether to treat children with SCH is a matter of debate. The risk of developing overt hypothyroidism in an adult population with SCH was estimated at between 2 to 4.3% per year, with higher occurrence in patients with positive thyroid autoantibodies and increased TSH at presentation (Vanderpump & Tunbridge, 2002). In adults, despite extensive studies and discussion, two different approaches still exist; one expert panel reviewed the available evidence and concluded that patients with TSH above 10 mIU/l with normal FT₄ levels may be treated, whereas subjects with TSH between 4.5 and 10 mIU/l should be followed-up without treatment considering the adverse effects of L-T₄ on mineral health and heart and the lack of evidence to support the benefits of the treatment (Surks et al., 2004). On the other hand, a joint statement of experts from three endocrine societies (American Association of Clinical Endocrinologists, American Thyroid Association, Endocrine Society) recommended treatment of subjects with TSH between 4.5 and 10 mIU/l, arguing that lack of evidence does not necessarily mean lack of benefit (Gharib et al., 2004). Moreover, in view of the recent suggestion to revise the reference range for adult TSH from 0.3 to 3 mIU/l by the National Health and Nutrition Examination Survey in United States, indicating that values above this range can be considered early thyroid failure, additional subjects will be included in the range of TSH within which thyroxine therapy is justified (Hollowell et al., 2002). In children, most of the subjects with SCH remain euthyroid over time, and therefore careful follow-up rather than treating them empirically was suggested (Moore, 1996; Radetti et al., 2006). It is commonly accepted that children with TSH above 10 mIU/l should be treated even if the FT₄ is within a normal

range while those with TSH between 4.5 and 10 mIU/l with thyroid autoantibodies should be followed up with repeated thyroid function tests but without treatment (Gopalakrishnan & Marwaha, 2007). Still, the benefit of L-T₄ therapy has been questioned and some studies have shown no difference in metabolic parameters or neurocognitive function between treated and untreated subjects (Aijaz et al., 2006; Biondi & Cooper, 2008). On the other hand, it has been shown that L-T₄ therapy of patients with euthyroid AITD reduces both serological and cellular markers of autoimmune thyroiditis, indicating that L-T₄ therapy might be useful in stopping disease progression (Padberg et al., 2001) and reducing thyroid volume in those patients with goiter (Svensson et al., 2006). Stable euthyroid hyperthyrotropinemia is a common condition that usually does not present with clinical symptoms or signs. Furthermore, biochemical parameters such as increased liver enzyme, hypercholesterolemia or elevated CPK are negative, indicating a euthyroid state. It is therefore recommended not to treat children without evidence of clinical hypothyroidism. However, those children with TSH above 10 mIU/l or with a trend toward increasing TSH and decreasing FT₄ over time might benefit from L-T₄ therapy. Side effects of L-T₄ therapy on the heart with such as resting tachycardia and on individuals' behavior, such as restlessness and sleep disturbances, should be considered in the clinical decisions for initiation of therapy. In euthyroid hyperthyrotropinemia caused by heterozygous loss-of-function mutation of *TSHR*, TSH levels tend to be stable over the years and therefore no therapy is indicated (Tenenbaum-Rakover, 2012). In newborns, a different approach should be taken since delay in therapy may result in permanent intellectual damage. In the case of TSH levels above 10 mIU/l, early initiation of therapy should be considered, even if thyroid hormones are within the normal range. In view of the controversy that still exists around L-T₄ therapy in SCH, it is recommended that the decision to initiate therapy be considered on an individual basis taking into account the benefits and possible side effects. In pregnant women and in newborns, initiation of therapy should be more urgent, whereas in other cases, sequential thyroid function tests along with clinical follow-up and further investigation, including laboratory, imaging and molecular analyses, might be a more reasonable approach prior to initiation of therapy.

12. Conclusion

The variable causes of SCH in children of different age groups were reviewed. The outcome of SCH in infancy and during childhood was shown to be dependent on etiology. Long-term follow-up is recommended since SCH may develop into overt hypothyroidism. Initiation of L-T₄ therapy in children, similar to adults, is still a matter of debate. In newborns, early initiation of therapy should be considered even if thyroid hormones are within the normal range to prevent possible late neurological sequelae; in older children, on the other hand, it is recommended that the decision to initiate therapy be considered on an individual basis, taking into account its benefits and possible side effects.

Acknowledgements

Thanks to Camille Vainstein for professional language editing.

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