MANAGEMENT OF ENDOCRINE DISEASE

Subclinical hypothyroidism in children

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Abstract

Subclinical hypothyroidism (SH) is biochemically defined as serum TSH levels above the upper limit of the reference range in the presence of normal free T4 (FT4) concentrations. While there is a general agreement to treat subjects with serum TSH levels above 10 mU/L, the management of mild form (TSH concentrations between 4.5 and 10 mU/L) is still a matter of debate. In children, mild SH is often a benign and remitting condition and the risk of progression to overt thyroid dysfunction depends on the underlying condition, being higher in the autoimmune forms. The major concern is to establish whether SH in children should always be considered an expression of mild thyroid dysfunction and may deserve treatment. Current data indicate that children with mild SH have normal linear growth, bone health and intellectual outcome. However, slight metabolic abnormalities and subtle deficits in specific cognitive domains have been reported in children with modest elevation of TSH concentration. Although these findings are not sufficient to recommend levothyroxine treatment for all children with mild SH, they indicate the need for regular monitoring to ensure early identification of children who may benefit from treatment. In the meanwhile, the decision to initiate therapy in children with mild SH should be based on individual factors.

European Journal of
Endocrinology
(2020) 183, R13–R28

Introduction

Subclinical hypothyroidism (SH), also known as isolated hyperthyrotropinemia or mild hypothyroidism, is a biochemical condition characterized by serum TSH concentrations above the upper limit of the reference range, but normal concentrations of free T4 (FT4) (1).

The upper limit of the normal range for TSH lays between 4.0–5 mU/L, but considerable differences exist in childhood

across and within age ranges and laboratory assays (2). Therefore, it is advisable to diagnose SH after at least two independent measurements of TSH concentrations.

SH has been recently categorized as grade 1, or mild, when TSH level is between the upper limit of the reference range and 9.9 mU/L, and grade 2, or severe, when TSH is 10 mU/L or higher (3).

Invited Author's profile

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In adults SH is a common finding with a prevalence up to 10% of the population (3). The vast majority of studies do not provide sufficient evidences to routinely recommend levothyroxine (L-T4) replacement in all adults with SH (4, 5). International guidelines from American Thyroid Association and European Thyroid Association (6, 7) recommend treatment at TSH levels >10 mU/L, while for patients with a lower TSH threshold treatment decision should be based on symptoms and individual factors (3, 8).

Data regarding the prevalence of mild SH in children and adolescents are scanty. The results of the National Health and Nutrition Examination Survey (NHANES III), involving 1327 adolescents aged 13–16 years, revealed a prevalence of SH of 1.7% (9). Another study evaluating thyroid function tests performed during routine assessment in 121,052 children aged 0.5–16.0 years showed a prevalence of mild SH of 2.9% (10).

In children, SH is often a benign and remitting condition and the long-term clinical consequences of increased TSH are still debated (11). Therefore, in children the need for L-T4 supplementation remains controversial, particularly in mild SH (12, 13, 14).

In this review we summarize current knowledge on mild and persistent SH in children and provide suggestions for the management of this condition in childhood.

Methods

We searched the PubMed database from the National Library of Medicine by using the following keywords: 'Hashimoto thyroiditis', 'genetic syndromes', 'obesity', 'iodine deficiency', 'linear growth', 'cardiac morphology', 'cardiac function', 'neurocognitive outcome', 'bone health', 'cardio-metabolic risk', 'lipids', 'blood pressure', 'glucose metabolism', in combination with 'mild hypothyroidism' or 'mild thyroid dysfunction' or 'subclinical hypothyroidism' or 'hyperthyrotropinemia'. The limits were set to only English-language articles and those involving human subjects. We included all case-control studies, case series and meta-analysis that were published in English from 1990 to date. This search allowed us to identify several publications that were selected on the basis of research methodology and scientific relevance.

Evolution of SH according to the etiology

SH in children is often a benign and remitting condition and the risk of progression to overt thyroid dysfunction

depends on the underlying condition. The main causes of SH in children are reported in Table 1.

Hashimoto thyroiditis

As for adults, the most frequent cause of SH in children is chronic Hashimoto thyroiditis (HT).

Data regarding the evolution of SH in children with HT are rather heterogeneous, depending on the variability in the number of patients enrolled, the years of follow-up and the severity of SH (3).

Recent studies on large cohorts of children and adolescents with HT indicate that up to 53% of children with mild elevation in serum TSH show progressive deterioration of thyroid function to overt hypothyroidism over a period of 1–5 years (15, 16, 17, 18, 19); in contrast, the rate of progression is only 10–15% in euthyroid subjects (15, 16, 18, 20). However, approximately 30–45% of children with mild HT-related SH normalize thyroid function tests during follow-up (15, 16, 18, 19, 20, 21).

Several factors have been associated with an increased risk of evolution into overt hypothyroidism, including age at presentation (22), the presence of goiter (21), higher TSH and thyroperoxidase autoantibodies (TPO Ab) levels at diagnosis (16) and/or progressive increase in both TPO Ab and TSH concentrations over time (16, 21). Finally, the presence of other autoimmune conditions (i.e. celiac disease) or genetic syndromes (i.e. Down and Turner), in children with HT-related SH, is associated with an increased risk of developing overt thyroid dysfunction (16, 23, 24).

Genetic syndromes

As shown in Table 1 SH may be associated with many genetic syndromes and is particularly frequent and best studied in Turner and Down syndrome.

Table 1 Etiology of subclinical hypothyroidism in children.

- Hashimoto thyroiditis
- Persistent neonatal hyperthyrotropinemia
- Thyroid gene defects and gland dysgenesis
- Nutritional iodine deficiency or excess
- Drugs
- Exposure to ionizing radiations
- Syndromes (i.e. Down, Turner, Williams, Pseudohypoparathyroidism)
- Obesity
- Macro-TSH
- Idiopathic

In patients with Turner syndrome (TS), SH is a frequent finding and is mainly related to the presence of HT (25). The natural history of HT-related SH in TS is characterized by increased rate of deterioration of thyroid function (23, 26). One of the largest studies, involving 90 TS patients with HT, reported a progression to overt hypothyroidism in up to 67.7% of subjects, regardless of the karyotype, over a median period of 4.9 years (27).

In children with Down syndrome (DS) SH is also frequent, with a prevalence ranging between 25.3 and 60% (28) and can be diagnosed already in the neonatal period, regardless of prematurity, low birth weight or perinatal risk factors (29).

One of the most common cause of SH in DS patients is autoimmune thyroid disease, especially after the first decade of life (30) and HT is more likely to present with SH in DS, compared to the general population (24).

Other causes of non-autoimmune mild TSH elevation include increased gene dosage for superoxide dismutase-1, resistance to TSH action (31), Zn deficiency (32) or specific TSH setting (33). Thyroid hypoplasia (34), and mild primary thyroid dysfunction peculiar to the syndrome (35) have also been reported.

Several follow-up studies (30, 31, 36, 37, 38) indicate a high rate of spontaneous resolution in patients negative for anti-thyroid antibodies (up to 89.7%) (36), whereas risk factors for progression to overt hypothyroidism include increasing age (30), goiter (36), positive TPO Ab (30, 38), and higher baseline TSH concentrations (38).

Obesity

SH is a common finding in overweight and obese children with a prevalence of 7–23% (39, 40), most often without any other signs of thyroid disease. A few children with obesity and elevated TSH levels have hypoechogenic thyroid gland pattern at ultrasound (41, 42), which could represent a feature of thyroid derangement due to obesity itself or an early marker of a seronegative autoimmune thyroiditis. However, autoimmune thyroiditis has seldom been reported as a cause of mild TSH increase in childhood obesity (40). It has been hypothesized that an increase in TSH concentrations may represent an adaptive mechanism aiming to increase energy expenditure (43). In this respect, the presence of an adipose tissue-hypothalamic-pituitary-thyroid axis has been proposed. In this model, leptin secreted by adipocytes might be involved in the cross-talk between adipocytes and hypothalamus, with the aim of increasing the release of TRH and TSH,

and the peripheral conversion of T4 into T3 (44). Several other hypothesis have been proposed, including low-grade inflammation of the thyroid parenchyma (which could also explain common finding of non-autoimmune thyroid hypoechogenicity at ultrasound), a partial failure of the negative pituitary feedback due to thyroid hormone resistance at the pituitary level, loss of function of the TSH-R or iodine deficiency (40, 43).

Despite uncertainty regarding the underlying mechanism, the findings that abnormalities in thyroid function mostly normalize after weight loss support the hypothesis that the TSH increase in patients who are obese is reversible and seems to be a consequence rather than a cause of obesity (44, 45, 46, 47). Weight loss may also induce a normalization of parenchymal alterations at thyroid ultrasound in obese patients with no anti-thyroid antibodies (48).

L-T4 treatment in addition to weight management interventions has no beneficial effect on BMI reduction (49, 50). Therefore, in the absence of clinical and laboratory evidence of hypothyroidism, therapy with thyroid hormone seems unnecessary.

Neonatal hyperthyrotropinemia and thyroid genetic defects

In the last two decades, the lowering of cut-off values for TSH in the neonatal screening has resulted in an increased rate of detection of mild, potentially transient, neonatal TSH increase (51, 52, 53). The cause of neonatal hyperthyrotropinemia and the effects on health outcomes are still unclear.

Isolated hypertropinemia may be associated with maternal and neonatal iodine deficiency or excess, drugs, and prematurity (54). Genetic mutations like heterozygous mutation in the gene encoding the TSH receptor (*TSHR*) or in the gene encoding dual oxidase 2 (*DUOX2*) have also been associated with SH (54). Simple or compound *TSHR* heterozygous mutation were detected in up to 30% of subjects with SH, half of them having neonatal hyperthyrotropinemia, with a high prevalence of first-degree family history for SH (55). In up to 20% of the cases neonatal hyperthyrotropinemia can be associated with subtle abnormalities of thyroid gland morphology or volume (56).

Finally, neonatal hyperthyrotropinemia may also be found in the context of complex syndromes, like pseudohypoparathyroidism (57) or brain-lung-thyroid syndrome (58).

Data on long-term evolution of neonatal SH are scanty; one study reported that most neonates with mildly elevated TSH levels show progressive normalization of thyroid function, even though in up to 32% mild TSH increase may persist (59).

In children with SH due to heterozygous loss-of-function *TSHR* mutations, data on long-term follow-up suggest that this is a stable compensated condition with an appropriately adjusted set-point for pituitary-thyroid feedback, not requiring replacement therapy (55, 60, 61).

Drugs, exposure to ionizing radiations and iodine deficiency/excess

Several drugs such as interferon-alfa (62), amiodarone (63), and antiretrovirals (64) may impair thyroid function. SH is also frequently observed in children taking antiepileptic drugs (phenobarbital, phenytoin, carbamazepine, and valproic acid) (62, 65). Even though the underlying mechanisms are not completely understood, these changes in thyroid function are generally reversible on discontinuation of therapy (61).

Moreover, a transient mild elevation of TSH may also be observed in children treated with thyroid hormone who are undertreated or non-compliant to the treatment or in cases of interaction with other substances (i.e. iron, calcium) (1).

Environmental as well as therapeutic exposure to ionizing radiation during childhood can also cause mild thyroid dysfunction. Although primary hypothyroidism in childhood cancer survivors is a well-known effect, the prevalence of SH compared with overt hypothyroidism is not yet well defined (66). Noteworthy, both internal (radioactive iodine ^{131}I) and external irradiation are also associated with an increased risk to develop thyroid cancer. Given the trophic effect exerted by TSH on thyroid epithelial cells, post-radiation SH may further increase the risk of thyroid cancer, with relevant implications for treatment decision in these patients (66).

Finally, chronic low iodine intake may result in mild-to-severe SH as well as in goiter and overt hypothyroidism (67). Interestingly, population studies indicate that SH may also occur in subjects with high iodine intake (68).

Idiopathic SH

In children with no definite underlying cause SH is labeled as idiopathic. The natural course of idiopathic SH is generally benign with a low risk of progression into overt

hypothyroidism. In a large retrospective study, 73.6% of children with mild SH normalized TSH concentrations in a second measurement within a period of 5 years. Only 8.5% of subjects exhibited a deterioration of thyroid function requiring levothyroxine treatment and the main predictors of evolution were initial TSH >7.5 mIU/L and female gender (10).

In two prospective studies idiopathic SH was associated with a low rate of evolution into overt hypothyroidism (12%), and the rate of TSH normalization was 41.3 and 61.9% after 2- (69) and 5-year follow-up (23), respectively.

Children with idiopathic SH had a lower risk of deterioration in thyroid status over time (11.1 vs 53.1%) and higher probability of spontaneous TSH normalization (41.1 vs 21.9%) with respect to children with mild HT-related SH after 2 years of follow-up (17). Similarly, in another study thyroid function remained stable over 3-year observation in the majority of children with idiopathic SH (47.5%) as compared to children with HT-related SH (19.9%) (16).

Transient or falsely elevated TSH

A condition of transient increase in serum TSH should always be suspected in cases of isolated SH.

Transient increases in TSH levels can be due to intra-individual or between-laboratory variations.

TSH secretion has a circadian rhythm with a maximum during night and a minimum in the afternoon. Sleep has a suppressive effect on TSH, so that sleep deprivation can lead to higher levels of TSH (70). In females, transient rise in TSH concentrations can also occur in the peri-ovulatory phase (71). In addition to physiological variation, several other factors may affect the assessment of TSH, as macro-TSH or interferences with the specific assay (i.e. anti-Ru, heterophilic, and human anti-animal antibodies) (72).

Macro-TSH is characterized by high-molecular-weight complexes of TSH (mainly bound to IgG) with low bioactivity, that accumulate in the circulation because of slow clearance, and can be recognized by available immunoassays as hyperthyrotropinemia (73). This has been reported in 0.79% of subjects with subclinical hypothyroidism (73). The presence of macro-TSH can be screened with the polyethylene glycol (PEG) precipitation method (showing TSH precipitation ratios $>70\%$) or dilution tests, and better characterized by gel filtration chromatography (73).

When approaching a child with SH, clinicians should be aware of the possible interferences and suspect them in

cases with marked difference in comparison to previous results for the same test or discrepancies with other clinical or biochemical parameters. A low threshold of suspicion should be kept in specific categories of patients (e.g. recent immunization, transfusion, autoimmune disease, monoclonal therapy) who are more prone to develop interfering factors.

Moreover, in order to rule out laboratory problems and transient variations, elevations in TSH concentrations should always be confirmed at least two times, with a second determination in 4 to 12 weeks' time.

To date there is no enough evidence to provide indications on the specific management of children with transient elevation of TSH.

Health consequences of SH and effects of thyroid hormone treatment

In children, well-designed randomized clinical trials and large prospective observational studies have not been performed, and thus, the potential effects of persistent SH on health outcomes as well as the need for L-T4 treatment are still a matter of debate. The main recent studies on the effects of persistent SH (both mild or severe) on growth and cardio-metabolic outcomes in cohorts of at least 20 children are summarized in [Table 2](#).

Linear growth and bone health

Thyroid hormones play a key role in promoting linear growth, by acting directly on bones or by influencing the growth hormone–insulin-like growth factor 1 axis (GH-IGF-1). So far, only a few studies have evaluated the effects of SH and/or L-T4 treatment on linear growth.

Normal height and growth velocity were documented in a prospective study on a large cohort of 92 children with untreated mild idiopathic SH lasting from 2 years (69). However, in a series of 88 children and adolescents with mild or severe non-autoimmune SH, short stature was detected in 19.3% of the subjects, with no association with the degree of the increase in TSH levels or the presence of morphological abnormalities at thyroid ultrasound. It has to be outlined that this study also included children referred for growth impairment (42). In another cohort of children with untreated mild idiopathic SH lasting from 2 to 9 years, linear growth, bone maturation and IGF-1 concentrations were normal and comparable to healthy matched controls. In this series, 22% of subjects presented at study entry with familial short stature, but growth and

bone maturation progressed normally during follow-up (74). Finally, in prepubertal children with heterozygous *TSHR* mutation no differences in height and bone maturation were detected between treated severe and untreated mild subjects (55).

Accordingly, recent data from two prospective studies did not show any significant change in height and linear growth after 2-year L-T4 treatment in children with mild idiopathic SH (75, 76).

Even in children with autoimmune SH, normal height and growth velocity were documented over a follow-up of 5 years in those who did not progress to overt hypothyroidism (21).

In another study evaluating HT-related SH associated with other autoimmune diseases such as type 1 diabetes mellitus (77), short stature was observed only in patients with severe SH (TSH >50 mU/L and T4 levels at the low end of the reference range). In these patients, 1-year L-T4 treatment was effective in improving growth rate (77).

Data on skeletal health in children and adolescents with SH are scanty, and do not show abnormalities in biochemical markers of bone metabolism, lumbar bone mineral density (BMD) and ultrasound parameters of bone quality (55, 78, 79). Untreated children with mild SH due to heterozygous *TSHR* mutations showed normal BMD, comparable to severe SH children receiving L-T4 treatment (55). Moreover, no appreciable effects after L-T4 therapy on BMD were detected among children with autoimmune SH (78).

Neurocognitive outcome

Thyroid hormones influence fetal and postnatal brain development and function, by regulating neuronal migration, differentiation, myelination and synaptogenesis (80). Untreated overt hypothyroidism before the age of 3 years, when thyroid hormone play a pivotal role, is well-known to cause mental retardation. Whether neonates with a mild TSH increase (TSH concentrations between 6–20 mU/L) but normal FT4 concentration may have subtle brain damage is still unclear. In a large cohort study, Lain *et al.* (81) found a worse neurocognitive outcome in school-age children whose neonatal screening TSH concentrations were between the 99.5th and 99.9th percentiles (about 9 and 14 mU/L in whole blood). Conversely, in a Belgian cohort, mild elevation of neonatal TSH was not associated with neurodevelopment impairment at preschool age (82, 83).

Concern exists regarding long-term health effects of SH particularly in growing children in whom subtle

Table 2 Summary of main recent studies assessing the effects of persistent SH on linear growth and cardio-metabolic outcomes in children.

Study	Number of patients	Age (years)	SH aetiology	Study design	Outcomes evaluated	Baseline or follow-up results	Duration of follow-up or treatment	Effects of treatment
Radetti <i>et al.</i> (21)	55	8.9 ± 3.6	Autoimmune	Longitudinal, retrospective	Linear growth	Normal baseline height No changes in height Vs baseline	5 years	na
Rapa <i>et al.</i> (42)	88	1–18	Unselected	Cross-sectional	Linear growth	Normal baseline height and weight ↑ prevalence of idiopathic short stature Vs normal population	na	na
Wasniewska <i>et al.</i> (69)	92	8.1 ± 3.0	Idiopathic	Longitudinal prospective	Linear growth	Normal baseline height and BMI No changes in height and BMI SDS Vs baseline	2 years	na
Cerbone <i>et al.</i> (74)	36	9.7 ± 0.6	Idiopathic	Cross-sectional	Linear growth	Normal height, bone age and IGF-1	na	na
Wasniewska <i>et al.</i> (75)	69 treated SH 92 untreated SH	9.4 ± 4.0	Idiopathic	Case-control prospective	Linear growth	Normal baseline height and BMI in both groups	2 years	No changes in height and BMI SDS Vs baseline in both groups
Cerbone <i>et al.</i> (90)	49	8.5 ± 0.5	Idiopathic	Case-control longitudinal prospective	Lipids, glucose metabolism, BP, BMI, WC, WHtR, Hcy, CRP, fibrinogen, adiponectin	Glucose metabolism, BP, CRP, fibrinogen, and adiponectin comparable to controls ↓ HDL C Vs controls ↑ TG/HDL C, AI and Hcy Vs controls; ↑ WC and WHtR Vs controls Lipids and Hcy correlated with SH duration WHtR correlated with SH degree	na	na
Cerbone <i>et al.</i> (76)	39	9.2 ± 3.5	Idiopathic	Case-control prospective	Linear growth, Lipids, Glucose metabolism, BP, Hcy, ADMA	Height, BMI, BP and glucose metabolism normal and comparable to controls ↑ WHtR Vs controls ↓ HDL C Vs controls ↑ TG/HDL C ratio, AI, Hcy, and ADMA Vs controls	2 years	No changes in height and BMI SDS Vs baseline ↓ WHtR Vs baseline ↑ HDL C Vs baseline ↓ ADMA, AI, Hcy, TG/ HDL C Vs baseline

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Vigone <i>et al.</i> (55)	14 untreated SH 20 treated SH	9.4 ± 1.2 7.9 ± 1.3	Heterozygous mutations in TSH receptor	Retrospective	Linear growth, Lipids	Normal height, BMI and metabolic parameters Height, BMI, Lipids comparable between the two groups	1–15 years na
Marwaha <i>et al.</i> (92)	315	12.8 ± 2.8	Unselected	Cross-sectional prospective	Lipids	↓ HDL C Vs controls only for TSH > 10 mU/L No differences for TSH < 10 mU/L Vs controls TSH levels correlated with TC, LDL C, HDL C	na
Catli <i>et al.</i> (99)	27	10 (median)	Autoimmune and idiopathic	Case-control prospective	Lipids	Lipid profile comparable to controls	6 months after normalizing thyroid profile
Zhang <i>et al.</i> (97)	29	11–16	Unselected	Case-control Cross- sectional prospective	Lipids, glucose metabolism, BP, WC	Lipid profile, glucose metabolism and BP comparable to controls ↑ prevalence of obesity Vs controls ↑ WC Vs controls TSH levels correlated with TC, LDL C, TG, WC, BP	na
Jin <i>et al.</i> (93)	154	14.4 ± 3.0	na	Cross-sectional retrospective	Auxology, lipids, glucose metabolism	Height, WC, BMI and glucose metabolism comparable to controls ↑ TC, TG Vs controls TSH levels correlated with TC and TG	na
Lee <i>et al.</i> (101)	143	14.2 ± 2.5	Unselected	Case-control	Lipids, BP, prevalence of metabolic syndrome components	↑ TC and BP Vs controls ↑ prevalence of obesity and increased abdominal adiposity Vs controls Systolic BP higher in non- obese SH compared to non-obese euthyroid subjects TSH levels correlated with systolic BP and TG	na
Chen <i>et al.</i> (103)	124	11.1 ± 2.3	na	Cross-sectional prospective	BP	↑ BP Vs controls TSH levels correlated with BP	na
Catli <i>et al.</i> (104)	31	10.3 ± 3.4	Autoimmune and idiopathic	Case-control prospective	Cardiac morphology and function	↑ IVS thickness and LVMI Vs controls ↓ E'm; ↑ E/E'm in lateral mitral localisation Vs controls ↑ IVRTm, IVCTm and MPI in lateral mitral and IVS localization Vs controls	6 months after normalizing thyroid profile ↑ LVESD and LVEDD Vs baseline ↓ IVCTm, MPI Vs baseline

(Continued)

Table 2 Continued.

Study	Number of patients	Age (years)	SH aetiology	Study design	Outcomes evaluated	Baseline or follow-up results	Duration of follow-up or treatment	Effects of treatment
Arslan <i>et al.</i> (105)	41	9.6 ± 4.7	Unselected	Case-control	BP Cardiac morphology and function	BP comparable to controls ↑ mitral and tricuspid IVCT and IVRT ↓ mitral and tricuspid Ea, Aa	na	na

Only studies including at least 20 patients have been included in the table.

Aa, peak late diastolic annular velocity; ADMA, asymmetric dimethylarginine; AI, atherogenic index; BP, blood pressure; CRP, C-reactive protein; E' m, early diastolic wave; E, early transmitral flow velocity; Ea, peak early diastolic annular velocity; HDL, high-density lipoproteins; HOMA, Homeostasis Model Assessment; IVCTm, isovolumic contraction time; IVRTm, isovolumic relaxation time; IVS, interventricular septum; LDL, low-density lipoproteins; LVEDD, left ventricle end-diastolic diameter; LVESD, left ventricle end-systolic diameter; LVIDd, left ventricular internal diameter end diastole; LVMI, left ventricle mass index; LVPWd, left ventricular posterior wall end diastole; MPI, myocardial performance index; n.a., not available/not applicable; SDS, standard deviation score; SH, subclinical hypothyroidism; TAPSE, tricuspid annular plane systolic excursion; TC, total cholesterol; TG, triglycerides; VM, verbal memory; VR, visual recall; WC, waist circumference; WHtR, waist-to-height ratio.

abnormalities may easily affect neurocognitive development (11).

In the NHANES III study cognitive functions have been found to be normal in mild SH adolescents, with even better performances than euthyroid subjects in block design and reading (9). However, other studies reported an association between mild increases in TSH concentrations and subtle alterations in verbal comprehension, immediate and long-term recall (84) and attention problems (85, 86).

In addition, subtle changes in auditory event-related potentials evaluated through auditory stimuli applied during the electroencephalography recordings, reflecting memory tasks and attentional process, were detected in a small cohort of children with SH despite normal cognitive functions (87). Whether these early neuro-electrical variances may result, over time, in clinical neurocognitive alterations need to be further evaluated.

Moreover, in one study 6 months of L-T4 treatment were associated with an improvement in visual and verbal memory as well as in verbal recall scores in children with mild SH (88).

Conversely, in a prospective case-control study evaluating neuropsychological outcome among children with mild SH, no differences were detected in verbal, performance and full-scale intellectual quotient (IQ) scores, as well as in degree of depression and behavioral problems, in comparison to healthy controls matched for socioeconomic status (74). These data were further confirmed by a recent study on children with mild TSH resistance. Indeed, IQ scores in untreated children with mild SH due to heterozygous *TSHR* mutation were normal and comparable to children with severe SH treated with L-T4 (55).

Accordingly, a recent prospective study in children with mild and long-lasting idiopathic SH documented normal global, verbal and performance IQ scores, in comparison to matched controls and no changes on neurocognitive function after 2-year L-T4 treatment (89).

Cardio-metabolic outcomes

Although the majority of the studies do not show overt dyslipidemia, there is evidence that children with SH may develop subtle pro-atherogenic abnormalities in lipid profile (90, 91, 92). In fact, unfavorable levels in HDL cholesterol (HDL C) have been demonstrated in both severe (TSH >10 mU/L) (92) and mild (TSH <10 mU/L) untreated SH (90, 91). Moreover, the results of a recent large national survey revealed higher concentrations of total cholesterol and triglycerides in SH, compared to

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euthyroid subjects (93). Similarly, in a large observational study, children and adolescents with mild SH ($n=228$), showed higher total cholesterol and non-HDL C levels than euthyroid controls ($n=1215$) with a positive association with TSH levels (94). A significant correlation between TSH concentrations, triglycerides (93, 95, 96), total cholesterol (93, 96) and non-HDL C (97, 98) has also been reported in other studies.

Conversely, in a study including 27 children with mild or severe SH, lipid profile was comparable to controls at baseline and did not change after achievement of euthyroidism with L-T4 treatment (99). However, in a longitudinal study on 49 children with mild untreated SH, we found decreased HDL C and increased triglycerides/HDL C (which estimates small dense low-density lipoproteins and is predictor of increased arterial stiffness) and total/HDL C (also known as atherogenic index), in comparison to healthy controls, even after correction for indexes of adiposity (90). In this study lipid parameters correlated with duration of SH (90). In a subsequent study, 39 out of these 49 children were treated with L-T4 for 2 years and a significant increase in HDL C, and decrease in triglycerides/HDL C ratio and atherogenic index was observed (76). In this regard, it is worth to mention that a recent meta-analysis of 12 randomized controlled trials involving a total 940 adult patients with SH suggested that L-T4 treatment has a beneficial effect on lipid profile even in patients with mild SH (100).

As discussed above, an isolated mild increase in TSH levels is a common finding in overweight and obese children and weight reduction is generally associated with a decrease in TSH concentrations, suggesting that obesity represents a cause more than a consequence of increased TSH concentrations (43, 47). Noteworthy, in normal weight children with persistent SH, higher indexes of visceral adiposity (i.e. increase in waist circumference and waist-to-height ratio) have been documented with respect to euthyroid controls (90, 97, 101), despite not being associated with increased BMI (55, 69, 74, 90). Furthermore, L-T4 treatment exerts beneficial effects on visceral adiposity as documented by a significant decrease in waist-to-height ratio after 2 years of treatment (76) with no changes in BMI (75, 76).

A few studies reported an association between TSH concentrations and blood pressure values (101, 102, 103) and a tendency to develop systolic and diastolic hypertension in children with SH compared to euthyroid subjects (103). Conversely, other studies (76, 104, 105) did not show any difference in blood pressure between mild or severe SH and euthyroid subjects. Moreover, 2 years of

L-T4 treatment were not associated with changes in both systolic and diastolic blood pressure (76).

TSH levels have been associated with subtle alterations in fasting glucose and insulin levels and Homeostasis Model Assessment (HOMA) index (95). However, in the few pediatric studies available, no relationship has been reported between SH and altered glucose metabolism (76, 90, 93, 106).

Higher homocysteine levels, which are thought to be an independent risk factor for CV disease (107), have been reported in children with mild SH, with respect to euthyroid controls, in some (76, 90) but not all studies (108). In addition, higher levels of asymmetric dimethylarginine (ADMA), acting as a competitive inhibitor of endothelial nitric oxide synthase, were found in mild SH patients compared to controls (76), despite no differences in other early markers of endothelial dysfunction and atherosclerotic changes such as flow mediated dilation and carotid intima-media thickness (76, 109). Two years of L-T4 treatment were associated with an improvement in ADMA concentrations, and with a trend towards a reduction in homocysteine levels (76).

Finally, TSH and thyroid hormones influence cardiac contractility, myocardial oxygen consumption, cardiac output, thus contributing to the maintenance of cardiovascular homeostasis. So far only few studies evaluated cardiac consequences of SH in children. Compared to euthyroid controls, children with mild or severe SH showed an increase in interventricular septum thickness and left ventricular mass index (104) and subclinical ventricular diastolic dysfunction (104, 105), which are reverted by L-T4 treatment (104).

In summary, available data suggest that children with long-standing SH may develop a cluster of subtle pro-atherogenic risk factors, such as unfavorable changes in lipid profile, increase in visceral adiposity and in early markers of atherosclerotic changes, which might predispose them to develop cardiovascular disease in the future. However, further long-term controlled studies are needed to clarify whether persistent SH is associated with CV abnormalities and whether a trial of L-T4 therapy will be effective in preventing CV morbidity.

Management of children with SH

In childhood and adolescence the management of SH is controversial due to the lack of high-quality data on long-term outcomes. A proposal of management is illustrated in Fig. 1.

Figure 1

Management of subclinical hypothyroidism in children.

When approaching a child with SH the first step is to re-evaluate TSH concentrations after 4–12 weeks depending on the degree of TSH elevation. In the same confirmatory blood test, it is advisable to check for the presence of anti-thyroid antibodies. Thyroid ultrasound plays a role in evaluating possible gland morphological or structural abnormalities and thus it represents an important tool in the work-up of persistent forms of SH, especially when no clear causes are identified. Indeed, thyroid ultrasound could be avoided in the initial work-up of those cases with a clear-cut etiology that does not require morpho-structural assessment of the thyroid gland (i.e. obesity, drugs, macro-TSH and familial non-goitrous conditions).

Family and personal history, as well as clinical examination are of paramount importance for establishing further diagnostic work-up. Family history should focus on the presence of SH, goiter, and endocrine, genetic, or autoimmune conditions in other family members. Personal history should investigate the presence of neonatal SH, autoimmune and/or genetic conditions, use

of drugs/substances interfering with thyroid function, iodine intake or exposure to ionizing radiation.

Physical examination should be aimed at recognizing signs of hypothyroidism, goiter and dysmorphic features suggesting genetic conditions.

Specific genetic analysis should be deserved to familial cases of SH and/or syndromic conditions. Urinary iodine excretion is a good marker for population iodine status, with values between 100 and 299 µg/L suggesting optimal iodine nutrition in school-aged children; however, it is not useful for individual assessment (67). Indeed, spot urinary iodine concentration may vary widely from day to day and it only estimates iodine intake over the past few days (67). Therefore, careful questions on dietary intake are required to establish iodine deficient status.

Once the diagnostic work-up has been completed, the following management strictly depends on the underlying cause of SH. Despite the lack of strong evidence on the beneficial effects of replacement therapy, similar to what recommended for adults L-T4 treatment should be considered for autoimmune or non-autoimmune forms of

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SH when TSH concentrations are above 10 mIU/L. In mild forms, current data in general justify to advice against treatment. However, a trial with L-T4 can be considered in selected cases of persistent SH experiencing relevant signs or symptoms of hypothyroidism. It remained to be defined whether a trial with L-T4 might be also considered in cases of persistent SH experiencing CV risk factors (dyslipidemia and or cardiovascular dysfunction), in order to reduce CV morbidity.

In HT a treatment with L-T4 should also be considered in case of thyroid gland enlargement (110, 111) or nodular goiter (7). Benefits and possible effects of L-T4 treatment must be always discussed with the family and treatment should be continued only if it results in clear beneficial effects.

Furthermore, treatment with L-T4 may be justified in patients with SH and a history of neck irradiation, in order to reduce the theoretical increased risk of thyroid cancer due to the trophic effect of TSH on thyroid epithelial cells (66), in particular in those children with evidence of thyroid nodule (112) or with other risk factors such as young age at radiation exposure, high dose of radiations, personal and familial susceptibility (113).

In particular cases, euthyroidism can be achieved after reverting the cause of SH like weight loss in overweight/obese subjects, iodine supplementation in cases with iodine deficiency or discontinuation of a specific drug when possible.

In subjects with mild SH and no signs or symptoms of hypothyroidism regular evaluation of thyroid function is indicated. Careful monitoring is particularly recommended in subjects with chromosomal abnormalities (TS and DS) or autoimmune conditions, due to the increased risk of progression into overt thyroid dysfunction. The timing of clinical and laboratory monitoring will depend on the underlying cause and should be tailored on individual patient's factors.

Although the effects of SH on neurocognitive function are still not completely defined, in view of the important role played by thyroid hormone in brain development, infants and children below two years of age deserve careful monitoring. In neonates, the European Society for Pediatric Endocrinology (ESPE) guidelines (114) recommend to start L-T4 treatment if venous TSH concentration is persistently above 20 mIU/L, even if serum FT4 concentration is normal. For TSH concentration between 6 and 20 mIU/L, but normal FT4 levels, the decision to start treatment should be individualized as there are insufficient evidence to recommend for or against treatment. In healthy babies with mild SH lasting

more than 3–4 weeks, clinicians should discuss with the family whether to repeat thyroid profile after additional 1–2 weeks, especially for values around 10 mIU/L or to start treatment and retest off treatment after the age of 3 years, or even earlier (114).

The decision to start treatment with L-T4 depends on multiple factors, such as the age of the patient, the duration of the thyroid dysfunction, the trend of TSH values, the etiology, the presence of syndromes and/or other pathologies, and the parents' choice and reliability (54).

Finally, in cases with known genetic etiology, the management of SH is also controversial. In patients heterozygous for *TSHR* mutations, SH is generally considered a compensated thyroid dysfunction with an appropriately adjusted set point for pituitary-thyroid feedback and does not require treatment. Nevertheless, if heterozygous mutations of *TSHR* are detected in patients belonging to special categories (preterm infants, small for gestational age neonates, infants born after multiple pregnancies and/or conceived by assisted reproduction techniques), L-T4 supplementation might be considered (55). In contrast, in carriers of biallelic mutations, a trend towards an increase in TSH levels with a concomitant decline in FT4 concentrations has been observed, suggesting the need for long-term follow-up and/or L-T4 therapy (54).

Conclusions and future perspectives

The best management of mild SH in children is still not clear. So far, there is no evidence that mild untreated SH is associated with alterations in health outcomes. However, subtle abnormalities in early CV risk factors and deficits in specific cognitive domains have been documented, and a beneficial effect of L-T4 treatment on these abnormalities has been reported. Nevertheless, these findings are not sufficient to recommend L-T4 treatment in all children with mild SH and need to be further confirmed by adequately powered controlled studies.

In the meantime, the decision to initiate therapy should be based on individual factors, and the evaluation of early CV risk biomarkers and neurocognitive assessment in selected children with SH may help in the decision regarding treatment. In subjects who do not meet criteria for treatment, regular clinical evaluation and thyroid function monitoring is advisable to early identify those children who may benefit from therapy.

Improving our knowledge on health consequences of untreated SH in childhood will help to better understand the management of this condition and to develop specific monitoring or treatment strategies.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Received 18 January 2020

Revised version received 28 March 2020

Accepted 6 May 2020