

REVIEW ARTICLE

Subclinical Hypothyroidism in Children: A Review

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Abstract

Subclinical hypothyroidism is defined as serum levels of TSH above the upper limit of the reference range in the presence of normal concentrations of total T4 or free T4. This biochemical profile might be an indication of mild hypothyroidism, with a potential increased risk of metabolic abnormalities and cardiovascular disease among adults. Whether subclinical hypothyroidism results in adverse health outcomes among children is a matter of debate and so management of this condition remains challenging. Mild forms of untreated subclinical hypothyroidism do not seem to be associated with impairments in growth, bone health or neurocognitive outcome. However, ongoing scientific investigations have highlighted the presence of subtle proatherogenic abnormalities among children with modest elevations in their TSH levels. Although current findings are insufficient to recommend levothyroxine treatment for all children with mild asymptomatic forms of subclinical hypothyroidism, they highlight the potential need for assessment of cardiovascular risk among children with this condition. Increased understanding of the early metabolic risk factors associated with subclinical hypothyroidism in childhood will help to improve the management of affected individuals.

Keywords: *Subclinical hypothyroidism, children.*

Introduction

From the biochemical point of view, subclinical hypothyroidism (SCH) is characterized by mildly elevated serum TSH concentrations, with normal concentrations of serum free and total triiodothyronine (T3) and thyroxine (T4), without the typical symptoms of thyroid disease. SCH prevalence in adults ranges from 4 to 10%.¹ In the pediatric population, the prevalence of this thyroid disorder is estimated to be less than 10%.² According to Biondi et al¹, children with SCH can present some minimal or nonspecific signs and symptoms. There is a paucity of long-term prospective research studying the natural history of subclinical hypothyroidism and its consequences in childhood.^{3,4} A preliminary SCH diagnosis is confirmed by laboratory tests when TSH concentration is above the statistically defined upper limit of the reference range.⁵

In the adult population with subclinical thyroid disease, SCH is associated with a risk of progression to overt thyroid disease, lipid disorders, increased risk of atherosclerosis, and mortality due to

cardiovascular diseases.⁶ The published data regarding the clinical manifestation of SCH in children and adolescents are inconsistent as most papers indicate SCH to be asymptomatic.⁷ Accordingly, the aim of this paper is to analyze studies reporting signs and symptoms presented by children and adolescents diagnosed with subclinical hypothyroidism.

Natural progression of SCH and effects of intervention

There are very few prospective studies evaluating the natural progression of SCH in pediatric age group (Table I). In a study from India, a cohort of 32 children with SCH and autoimmune thyroiditis (AIT) and goiter were followed.⁸ Development of overt hypothyroidism (12.5% in this cohort) was insidious and was not accompanied by symptoms and signs. In a larger study on 323 children with either Hashimoto or idiopathic SCH followed up for 3 years, 13.5% of SCH developed overt hypothyroidism.⁹ The study could not detect predictive factors for

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progression of SCH to overt hypothyroidism in idiopathic SCH. Wasniewska et al¹⁰ followed up 92 patients with idiopathic SCH over 2 years, and none of them developed overt hypothyroidism. Lazar et al¹¹ studied 3510 patients with SCH over 5 years and showed that 73.6% of them normalized TSH. Elevated antibodies [thyroid peroxidase (TPOab) and thyroglobulin antibodies (TGAb)] may predict future overt hypothyroidism and TPOab>TGAb may predict impending thyroid failure in AIT.^{12,13}

Leonardi et al¹⁴ studied 44 Italian children “false positive” to neonatal screening for congenital

hypothyroidism; 28 of them had SCH on retesting at 2 to 3 years of age. Twenty of these 28 children were treated with replacement therapy and then withdrawn from therapy 2 to 3 months prior to re-evaluation. Out of the 28 children with SCH, TSH was normal in 9 children (32%) and persistently elevated in the remaining 19 (62%) at 4.1 to 6.6 years of age. At 7.2 to 9.5 years of age, TSH remained normal in 9 children who previously normalized their thyroid function, returned to normal in 5 out of 19 of the children with previous elevated TSH and persisted above normal in remaining 14 children.

Table I
Natural history and progression of SCH in Paediatric case series

Authors	Number of patients	Level of evidence/ Type of study	Period of follow-up	Key results	Comments
Gopalakrishnan et al ⁸	98 of which 32 had SCH	Longitudinal study	24 months	4/32 patients with SCH developed OH	Important to monitor TFT. Development of OH is insidious and may not be accompanied by symptoms and clinical signs.
Radetti et al ⁹	323	Retrospective cross-sectional	3 years	13.5% of SCH developed OH	There were no predictors in pts of SCH.
Wasniewska et al ¹⁰	92 with SCH	Prospective observational	2 years	38 normalized TSH 54 remained SCH 11 had increase of TSH more than 10miu/mL	None developed OH. Natural progression in idiopathic SCH is a progressive decrease over time of TSH in majority.
Lazar et al ¹¹	121052 of which 2.9% had SCH	Prospective observational	5 years	In SCH group 73.6% normalized TSH, 2% increase >10miu/mL, and 0.03% had OH	Female patients with >7.5miu/mL of TSH are at greater risk of sustained raise. OH
Radetti et al ¹²	160 of which 55 were SCH Rest euthyroid	Prospective observational	5 years	16/55 SCH normalized TFT. 16 remained SCH 23 had twofold rise above the normal limit	Presence of goitre and elevated TGAb, together with increase in TPOab and TSH may predict future OH. At 5 yrs 50% of all participants remained euthyroid.
Zois et al ¹³	29 with AIT of which 7 had SCH	Prospective observational	5 years	All 7 continued to be in SCH None of the 29 developed OH	TPOab>TGAb increase predicted impending thyroid failure in AIT. Thyroid hypoechogenicity seem to predict the same
Leonardi et al ¹⁴	44	Prospective observational	8 years	14 had SCH at end of the study. None developed OH	Newborn false positive TSH have an increased risk of developing SCH

SCH- Subclinical Hypothyroidism, TFT- Thyroid function tests, TPOab- thyroid peroxidase antibodies, TGAb- thyroglobulin antibodies, TSH- Thyroid stimulating hormone, OH- Overt hypothyroidism, AIT- autoimmune thyroiditis.

Table II
Studies reporting effect of replacement therapy in childhood SCH

Authors	Patients	Type of study	Follow-up	Results	Comments
Wasniewska et al ¹⁵	69 treated SCH vs 92 untreated SCH	Case control	2 y	Significant difference was not found	TSH value changes between treated and untreated groups were similar. therapy is unable to prevent the risk of further TSH increase after treatment withdrawal
Cetinkaya et al ¹⁶	2067 total, 39 SCH	Interventional	12 mo	Showed improvement in growth velocity; no hyperthyroidism noted after replacement.	Short stature can be associated with SCH. Thyroid hormone replacement improves the height in such patients
Chase et al ¹⁷	25 diabetic children with SCH	Case control	2 y	Prepubertal diabetics showed increased growth velocity than postpubertal diabetics	Higher the initial TSH value showed increased growth velocity
Aijaz et al ¹⁸	11 SCH children	Interventional	91 d	Short term thyroxine therapy showed no neuropsychological benefits as compared to normal population	Thyroxine therapy showed no positive effect on neuro-psychological function in children with SCH
Moore et al ¹⁹	18 with SCH and AIT	Prospective observational	5.8 yrs	7/18 were euthyroid10 remained SCH1 became OH	Expectant management is recommended in majority of SCH with minimally elevated TSH

SCH- Subclinical hypothyroidism, TFT- Thyroid function tests, TSH- Thyroid stimulating hormone, OH- Overt hypothyroidism, AIT- autoimmune thyroiditis, TRH- thyrotrophin releasing hormone.

Effects of treating children with SCH

This aspect has been even less investigated, and a summary of the evidence is presented in Table II. Wasniewska et al¹⁵ compared thyroxine treated and thyroxine untreated SCH over 2 years and found no significant changes in TSH values in both groups. Cetinkaya et al¹⁶ treated 39 children with short stature and SCH; an improvement in height was significant in prepubertal as compared to pubertal age group, with no progression to overt hypothyroidism in any in the cohort. Chase et al¹⁷ noted a similar significant height increase in the prepubertal age group as compared to the pubertal age group when children with SCH and type 1 diabetes were given thyroxine replacement therapy. Aijaz et al¹⁸ studied short-term thyroxine replacement therapy and its effects in neuropsychological outcome and concluded no significant change. Moore et al¹⁹ recommended

expectant management is in majority of SCH with minimally elevated TSH. Chase et al¹⁷ found that prepubertal diabetics had increased growth velocity than postpubertal diabetics.

Diagnosis and management

The management of subclinical hypothyroidism in childhood is a controversial issue. The first step in managing a child with a modest increase in TSH levels should be the differentiation between persistent and transient forms of subclinical hypothyroidism (Fig 1).²⁰ Persistent subclinical hypothyroidism should be confirmed by re-evaluation of the TSH levels at 4-12 weeks after the first test to rule out abnormal values caused by laboratory problems, diurnal variation in TSH concentration and transient causes of subclinical hypothyroidism (recovery phase from non-thyroidal illness or subacute thyroiditis).

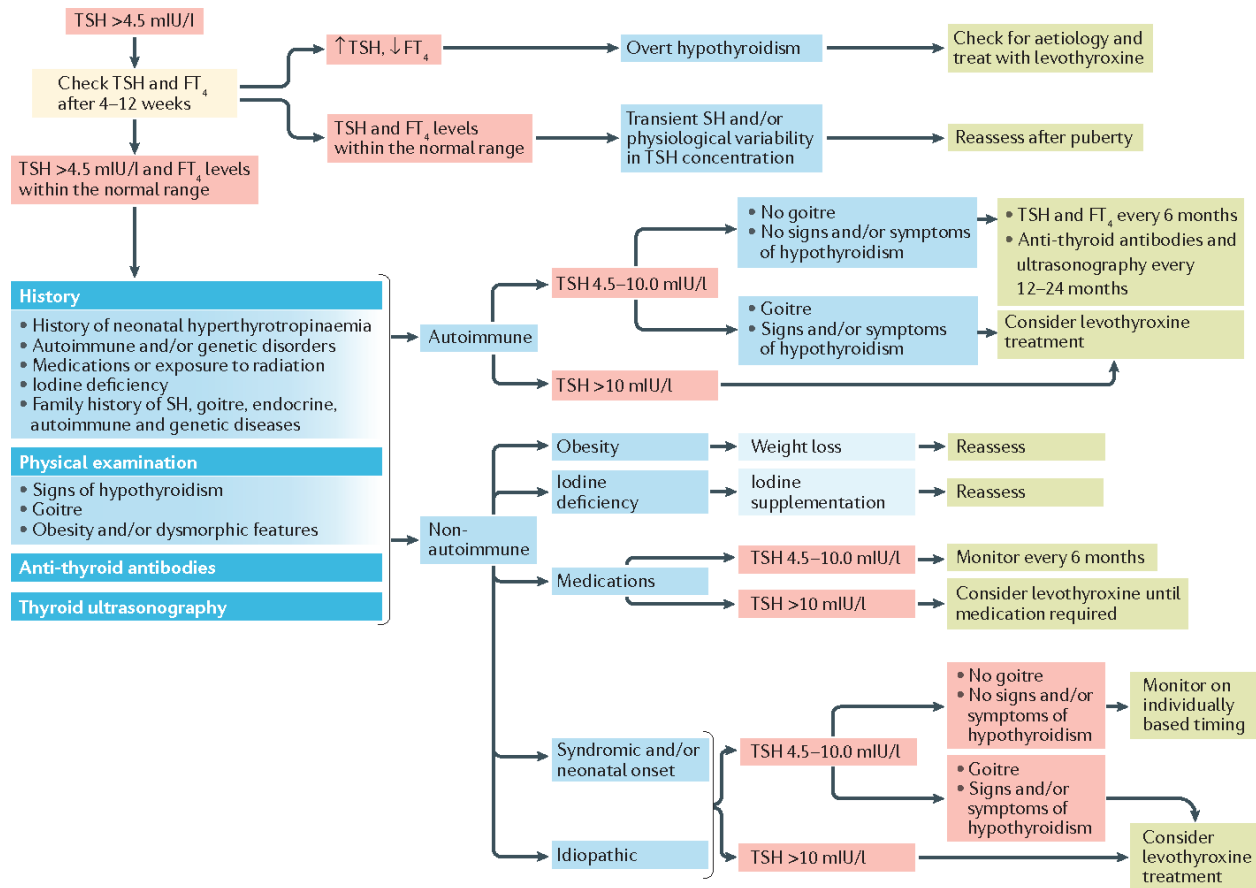


Fig 1 Proposed management of children with subclinical hypothyroidism. The initial step in the management of a child with a mild increase in TSH concentration should be confirmation of hyperthyrotropinaemia by re-evaluation of TSH levels 4-12 weeks after the first test. If an elevated TSH concentration persists, the diagnostic process should first include careful assessment of the child's history and a clinical evaluation focused on the detection of signs and symptoms suggestive of thyroid dysfunction. Thereafter, evaluation of anti-thyroid antibodies and thyroid ultrasonography will enable differentiation between autoimmune and nonautoimmune forms of subclinical hypothyroidism (SCH). The subsequent management and follow-up will depend both on the aetiology and the degree of TSH elevation. The final decision on treatment should be based on the assessment of clinical symptoms or signs of mild thyroid impairment and on the risk of progression to overt hypothyroidism. FT₄, free T₄.

If an elevated TSH level persists after retesting, a diagnostic evaluation is recommended. The child's history should focus on the presence of neonatal hyperthyrotropinaemia; autoimmune and/or genetic conditions, use of medications known to interfere with thyroid function; previous exposure to ionizing radiation; and endemic iodine deficiency. Attention should be given to the presence of subclinical hypothyroidism, goitre, endocrine diseases, autoimmune diseases or genetic conditions in other members of the patient's family. Physical examination should focus on signs of hypothyroidism, goitre, weight gain and clinical features suggestive of specific genetic conditions.¹

Given that Hashimoto thyroiditis is the condition most often responsible for the onset of subclinical hypothyroidism in childhood, all patients with the persistent form should be screened for the presence of anti-thyroid antibodies and undergo ultrasonography of the thyroid gland. Moreover, based on the history and physical examination, further investigations can be considered for some children. These are *TSHR* genotype for cases arising in familial settings, urinary iodine excretion for those living in endemically deficient areas or screening for resistance to parathyroid hormone, follicle stimulating hormone or luteinizing hormone if pseudohypoparathyroidism type 1a is suspected.

The subsequent management and follow-up of persistent forms of subclinical hypothyroidism should depend both on the aetiology and degree of TSH elevation. The final decision on treatment should be made according to the assessment of clinical symptoms or signs of mild thyroid impairment and the risk of progression to overt hypothyroidism.⁸

In the most common clinical scenario of autoimmune subclinical hypothyroidism, treatment with levothyroxine should be considered for all children affected by severe forms (TSH level >10 mIU/l) or among those with mild subclinical hypothyroidism in the presence of goitre or the signs or symptoms of hypothyroidism.

Untreated children should be monitored every 6 months (thyroid function tests) and every 1-2 years (anti-thyroid antibodies and ultrasonography). Careful monitoring is particularly recommended in the presence of chromosomal abnormalities (Turner syndrome and Down syndrome)²¹ or other autoimmune conditions to assess increased risk of progressive thyroid dysfunction.

Management of children with reversible causes of subclinical hypothyroidism should focus on modifiable factors. Diet and lifestyle changes are advisable for children who are overweight or obese; thyroid function should be checked after weight loss.²² Iodine supplementation is recommended among children living in areas with endemic iodine deficiency and/or with documented reduced iodine excretion. Thyroid function in such cases should be re-evaluated after iodine normalization.¹³

The use of some medications, such as antiepileptic drugs and IFN- α , might interfere with thyroid function. Treatment with levothyroxine should be considered for children with a TSH level >10 mIU/l until medications are discontinued. Children with mild forms of subclinical hypothyroidism should be monitored every 6 months.¹⁸

The management of children with genetic conditions and neonatal hyperthyrotropinaemia should be evaluated on an individual basis.¹⁵ Intervention should depend on the child's age, the degree of TSH elevation and the underlying genetic condition. However, as for other aetiologies, levothyroxine is recommended for severe forms of subclinical hypothyroidism and for symptomatic children, whereas careful monitoring is suggested for the mild and asymptomatic forms.

The management of idiopathic subclinical hypothyroidism is particularly challenging. Children with severe forms (TSH level >10 mIU/l), goitre or symptoms suggestive of hypothyroidism should receive treatment. For children with mild forms (TSH level <10 mIU/l), a trial of levothyroxine can be considered if there is a clinical suspicion of hypothyroidism. In the absence of signs and symptoms, regular clinical evaluation of TSH and free T4 levels, along with periodic re-evaluation of anti-thyroid antibodies, is advisable and should be tailored on the basis on the duration and degree of TSH elevation.⁵

Repeated TSH monitoring can be avoided for children with stable but mild increases of TSH concentration after 2 years of follow-up, unless indicated by the onset of goitre or signs and symptoms suggestive of hypothyroidism.

Finally, it must be highlighted that all forms of subclinical hypothyroidism that resolve at any point during follow-up should be considered for re-evaluation of thyroid function later in life, particularly during adolescence and pregnancy.

Conclusion

The decision about treatment of SCH in children and adolescents is still a matter of debate. None of the consensus statements published about the management of SCH addressed the issue of SCH in the pediatric population. However, according to the available limited evidence in children, SCH seems to be a self-limiting condition with a low rate of progression to overt hypothyroidism. Therefore, treatment of SCH in children should be considered only when TSH values are higher than 10 mIU/L, when clinical signs or symptoms of impaired thyroid function or goiter are detected, or when SCH is associated with other chronic diseases. On the other hand, in children with SCH having no goiter, negative anti-thyroid antibodies or a TSH level of 5-10 mIU/L, replacement therapy is not justified because of the low risk to develop overt hypothyroidism.

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