REVIEW ARTICLE

Subclinical Hypothyroidism in Children

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Need and purpose of review: Subclinical hypothyroidism is a biochemical diagnosis characterized by raised thyroid stimulating hormone and normal free T4, without clinical features of hypothyroidism. This review analyzes the current evidence to arrive at a consensus and algorithm to manage this condition.

Methods: We searched Pubmed, Cochrane and Embase for articles published between 1990 to 2014, and identified 13 relevant articles dealing with pediatric subclinical hypothyroidism which were suitable to include in our review.

Conclusions: Subclinical hypothyroidism is often a benign problem which requires expectant management with periodic monitoring of thyroid function tests and natural progression to overt hypothyroidism occur lot less frequently than expected. There is a paucity of robust randomized intervention studies, especially studies focusing on clinical outcomes. Thyroid replacement therapy is not justified in children with subclinical hypothyroidism when Thyroid stimulating hormone is <10 mIU/L. The main risk factors for progression to overt hypothyroidism are female sex, goiter, family history of thyroid disorder, strongly positive thyroid peroxidase antibodies and symptoms suggesting hypothyroidism. An algorithm for managing this condition is suggested.

Keywords: *Hypothyroidism, Goiter, Thyroid function tests.*

Subclinical hypothyroidism (SCH) is a biochemical condition characterized by serum levels of Thyroid Stimulating Hormone (TSH) above the statistically defined upper limit of reference range, with normal concentration of thyroid hormones, and without clinical features of hypothyroidism [1]. SCH is a common disorder with a prevalence of 1-10% in adults and about 2% in children; epidemiological studies concerning childhood and adolescence are scarce [2-4]. SCH is mostly detected incidentally as patients exhibit few or no signs of thyroid dysfunction. The abnormalities most frequently associated in the pediatric population are goiter, poor school performance, weight gain, increased cholesterol levels, impaired growth velocity, anemia, excessive sleepiness, weakness, and impaired psychomotor and cognitive development [4,5].

NORMAL TSH LEVEL

TSH is secreted in a pulsatile manner and shows diurnal variation. The levels may vary based on the time of sampling as well as its relation to food [6]. Most of the commercially available kits use third generation TSH assays like radioimmunoassay, chemiluminescence or electrochemiluminescence method. There is no biological reference range derived from these kits based on studies in pediatric population in India. The reference range given in the kit by the manufacturers of these assays vary. TSH above the laboratory reference ranges are considered abnormal by most pediatricians. These factors add to the difficulty in interpreting the TSH values and in decision-making for the clinician [7]. Two large population studies from India by Marwaha, *et al*. [8,9] reported normograms for TSH in Indian children. In study amongst children 5-16 yrs, the mean and 97th percentile for TSH (radioimmunoassay method) was, 3.17 and 7.5, respectively. This gives us a range of 1.33-5.01 mIU/L as normal values for our population. Almost 12% of the reference population had TSH values above the normal range provided by the test kit manufacturer. Such patients need long-term follow up for development of overt hypothyroidism.

ETIOLOGY

SCH is most commonly (50-80% of cases) caused by chronic autoimmune thryoiditis, which is typically characterized by high titers of thyroid peroxidase antibodies, thyroglobulin antibodies and rarely TSH-receptor blocking antibodies [10]. There are many causes of potentially reversible/irreversible subclinical hypothyroidism [11] (***Box* I**). Non-thyroidal causes include diabetes mellitus, cystic fibrosis, celiac disease, and chronic renal failure [12].

Mutations in several proteins involved in TSH action have been demonstrated. Loss of function mutations in the

BOX I DIFFERENTIAL DIAGNOSIS OF ELEVATED TSH AFTER INFANCY

Reversible
- Autoimmune thyroiditis
- Recovering from acute illness
- Recovering from subacute thyroiditis
- Antithyroid drugs
- Simple obesity
- Cortisol deficiency
- Laboratory error

Irreversible
- Autoimmune thyroiditis
- Thyroid dysgenesis
- Subtotal/hemi thyroidectomy
- Neck radiotherapy,
- Reidel's thyroiditis

TSH receptor gene have been demonstrated [13,14]. Dual oxidase 2 (DUOX2), phosphodiesterase 8B and thyroidperoxidase mutations have also been reported as causes of mild elevations of TSH [15-17]. Congenital conditions are commonly associated with SCH. SCH is also associated with Down syndrome; present in up to 32% of these patients. Anti-thyroid antibodies were not more likely to be found in this group than in patients with a normal TSH [18]. Almost one-third patients with William syndrome also have SCH with negative anti-thyroid antibodies [19].

Abnormal sialylation of the carbohydrate moiety of TSH with resultant reduced metabolic clearance may also contribute to elevated TSH in occasional cases of hypothyroidism [20].

EPIDEMIOLOGY

Large scale population studies focussing on the prevalence of SCH among children, especially from India are limited. With the difficulty in defining normal TSH, the prevalence reported in different studies may vary depending on the cut-off value. The sample selection in many of the studies is strictly not representative of the general pediatric population. In some follow-up studies, a mildly elevated TSH has been documented to normalize after few months [21]. Persistently elevated TSH over a period of time may be the best indicator to assess the true prevalence of SCH in the pediatric population.

Marwaha, *et al*. [22] conducted a large nationwide survey on the thyroid status after 2 decades of salt iodization in India. The prevalence of subclinical and overt hypothyroidism was 6.1% and 0.4%, respectively among the study population (total population of 38961 children). TSH elevation was found more common among children with goiter. The prevalence of goitre among the studied population was 15.5%, much above 5% prescribed by WHO. Further, thyroid autoimmunity, as defined by positive thyroperoxidase antibody titers, was observed in 3.6% of the study population and was more common among girls. In another study from Chandigarh, India, goiter prevalence was 15.1% and that of SCH was 2.6%. The population studied was iodine sufficient in that study with prevalence of autoimmunity not significantly different from the controls [23]. A study from USA, done primarily to assess cognitive parameters among adolescents with thyroid disorders, the prevalence of SCH was 1.7% [4]. Lazar, *et al*.[21], in a retrospective analysis from an insurance-based large database of children between 6 months to 16 years of age, reported a prevalence of elevated TSH (5.5-10.0 mIU/6) to be 2.9% [21]. Transiently elevated TSH may occasionally be diagnosed as part of newborn screening program. In a large series from China**,** the incidence was 1 in 8809 neonates [24]. The TSH elevation was treated with thyroxine replacement, considering its critical role in neurocognitive development, with a favourable outcome at 2-3 years follow up. Long term follow-up of these children was not available to know whether the TSH rise was transient or persisted beyond 3 years of age. SCH is observed more commonly in obese children when compared with normal weight controls; excess adipose tissue is hypothesized to signal elevation in TSH [25].

Children with Down syndrome are at increased risk – upto 28 times the normal population – for hypothyroidism. Autoimmune predisposition or dysgenesis may contribute to thyroid dysfunction among children with this chromosomal anomaly [26]. In this setting, SCH may warrant treatment as the progression to overt hypothyroidism is more likely.

Type 1 diabetes predisposes children to thyroid dysfunction. In a study by Soliman, *et al.* [27], the prevalence of SCH in children (mean age 10 yrs) with type I diabetes was 11.2%. Other conditions which may be associated with elevated risk for SCH include antiepileptic drug usage and celiac disease.

CLINICAL ISSUES

Most patients with SCH exhibit few or no signs or symptoms of hypothyroidism. It has been suggested that some patients have functional, clinical, or biochemical manifestations of hypothyroidism that are more common than age-matched controls [28]. Goiter is the most common manifestation [12]. The abnormalities found

most commonly in the pediatric population include weight gain, increased cholesterol levels, impaired growth velocity, anemia, sleepiness, weakness, and impaired psychomotor and cognitive development [5].

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. Development of overt hypothyroidism (12.5% in this cohort) was insidious, and was not accompanied by symptoms and signs [29]. 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. The study could not detect predictive factors for progression of SCH to overt hypothyroidism in idiopathic SCH **[**30**]**. Wasniewska, *et al*. [31] followed up 92 patients with idiopathic SCH over 2 years, and none of them developed overt hypothyroidism. Lazar, *et al*. [21] studied 3510 patients with SCH over 5 years and showed that 73.6% of them normalized TSH. Elevated antibodies (thyroid peroxidise (TPOab) and thryoglobulin antibodies (TGab)) may predict future overt hypothyroidism and TPOab>TGab may predict impending thyroid failure in AIT [32,33]. Leonardi, *et al*. [35] studied 44 Italian children "false positive" to neonatal screening for congenital hypothyroidism; 28 of them had SCH on re-testing at 2-3 years of age. Twenty of these 28 children were treated with replacement therapy and then withdrawn from therapy 2-3 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 4.1-6.6 yrs of age. At 7.2-9.5 yrs 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 fourteen childrens.

Effect 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 al*. [37] compared thyroxine treated and untreated SCH over 2 years and found no significant changes in TSH values in both groups. Cetinkaya, *et al*. [38] treated 39 children with short stature and SCH; improvement in height was significant in pre-pubertal as compared to pubertal age group, with no progression to overt hypothyroidism in any in the cohort. Chase, *et al*. [39] noted a similar significant height increase in the pre-pubertal age group as compared to the pubertal age group when children with SCH and type 1 diabetes were given

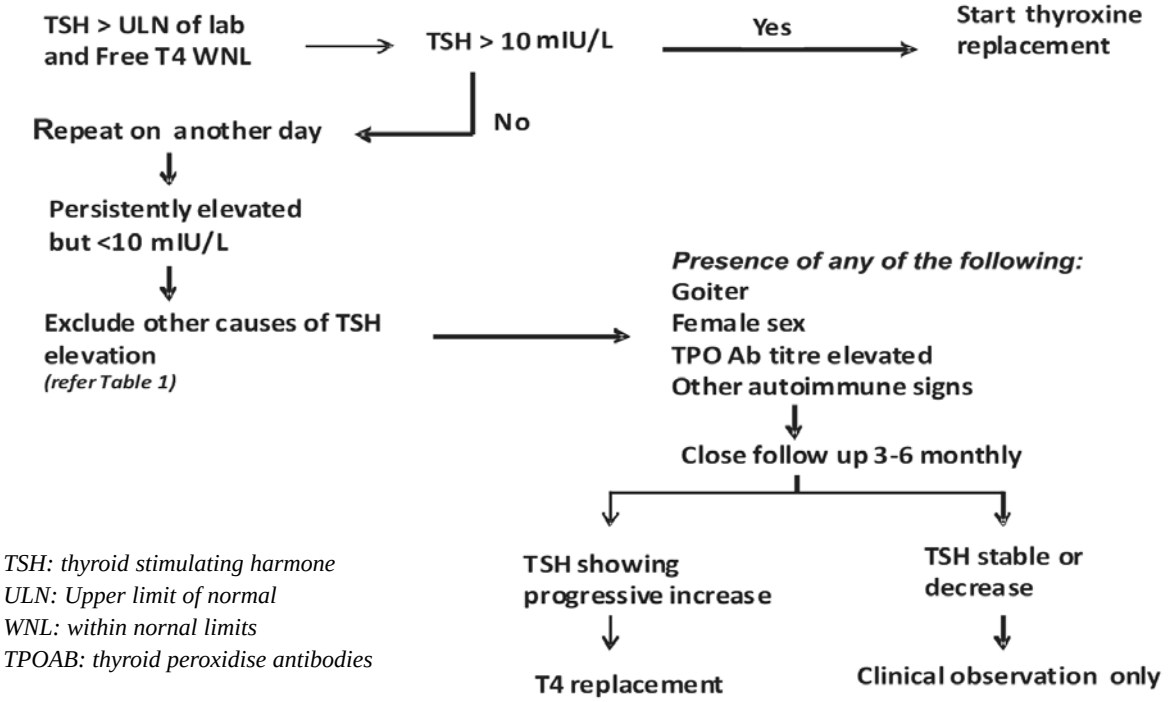

FIG.1 *Approach to subclinical hypothyroidism (SCH) in children.*

TABLE I NATURAL HISTORY AND PROGRESSION OF SCH IN PEDIATRIC CASE SERIES

Authors Year; Place	*Number of patients*	*Level of evidence/ Type of study*	*Period of follow-up*	*Key results*	*Comments*
Radetti, *et al.* [32] 2012; Italy	323	Retrospective cross-sectional	3 years	13.5% of SCH developed OH	There were no predictors in pts of SCH.
Wasniewska, *et al*. [31] 2009; Italy	92 with SCH	Prospective observational	2 years	38 normalized TSH54 remained SCH11 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.* [21] 2009; Israel	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.
Gopalakrishanan, *et al*. [29]2008; India	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.
Leonardi, *et al*. [35] 2008; Italy	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
Radetti, *et al.* [30] 2006; Italy	160 of which 55 were SCH Rest euthyroid	Prospective observational	5 years	16/55 SCH normlaized 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*. [33] 2006; Greece	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
Jaruatanasirikul, *et al*. [34]2001; Thailand	46 of which 8 had SCH	Prospective observational	6 years	4/8 SCH normalized TSH4/8 developed OH	No clinical or biochemical marker at baseline predicted course of SCH
Moore, *et al.* [36] 1996; UK	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, TPOab- thyroid peroxidise 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.* [37]	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
Aijaz, *et al*. [5]	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
Cetinkaya, *et al.* [38]	2067 total, 39 SCH	Interventional	12 mo	Showed improvement in growth velocity; no hyper-thyroidism noted after replacement.	Short stature can be associated with SCH. Thyroid hormone replacement improves the height in such patients
Chase, *et al*. [39]	25 diabetic children with SCH	Case control	2 y	Pre-pubertal diabetics showed increased growth velocity than postpubertal diabetics	Higher the initial TSH value showed increased growth velocity

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

thyroxine replacement therapy. Aijaz, *et al*. [5] studied short term thyroxine replacement therapy and its effects in neuropsychological outcome and concluded no significant change .

MANAGEMENT OF SCH

Based on available literature, SCH seems to be a benign condition which requires periodic follow-up and monitoring of thyroid function tests. Expectant management is the norm for this condition. Natural progression to OH does occur but lot less frequently than expected. There appeared to be no long-term effects of untreated SCH on growth, puberty or neuro-cognitive function; however, there is a lack of high-quality evidence.

We propose an algorithm (***Fig.* 1)** for management of subclinical hypothyroidism in pediatric age group. The first step in our setting on patients with elevated TSH, especially below 10mIU/L, is to repeat the test on another day, preferably from another laboratory with a different kit. SCH in adults is associated with dyslipidemia and subtle cardiac dysfunction, with reasonable benefit of treatment of SCH on those parameters. However, pediatric studies focussing on the same are scarce and more research is needed on these issues in this age group.

Girls, goiter, family history of thyroid disorder, other autoimmune problems, markedly elevated TPO titers (at least 3 times the upper limit of normal and symptoms which may correlate with hypothyroidism are risk factors; a clinical decision to start on thyroxine may be taken if any or combination of above is present.

SUMMARY

SCH is a biochemical entity commonly faced by practising pediatricians. Several factors including clinical condition of the child and laboratory factors influencing TSH levels should be considered while interpreting the results. Clinical decision to treat marginal elevation in TSH should be made keeping in mind that more often TSH normalizes without treatment if followed up over a period of time. Even if the decision to treat the slightly elevated TSH is made, a clear plan should be made to stop treatment and reassess after 1-2 years to see if the treatment is required lifelong.

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