Mini Review

Subclinical hypothyroidism in children

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ABSTRACT

The prevalence of SH in the pediatric population is < 2%, the caveat being the limited number of studies addressing SCH in the pediatric population. Despite the limited data available, SCH in children and adolescents appears to be a benign and remitting disease with a low risk of evolution to OH. It appears that thyroid hormones appear to be functioning well despite elevated TSH. Predictors of progression include, goiter, celiac disease, and positive anti TPO.

Key words: Subclinical hypothyroidism in children, congenital developmental anomalies

DEFINITION

Subclinical hypothyroidism (SCH) is bio chemically defined as a serum thyrotropin thyroid stimulating hormone (TSH) is above the upper-limit of the statistically defined reference range while the serum free thyroxine (FT4) is within its reference range.[1] The prevalence of subclinical hypothyroidism (SH) in the pediatric population is <2%, the caveat being the limited number of studies addressing SCH in the pediatric population.[2]

MANIFESTATIONS

Most patients with SH 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.[3] A goiter is the most common manifestation.[4] 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]

CAUSES [TABLE 1]

A number of patients with SCH are identified during screening for congenital hypothyroidism in new borns. Mild TSH elevations (4-11 mU/mL) identified during neonatal screening often persist after withdrawal of thyroxine but seldom progress to overt hypothyroidism. Many of the TSH elevations seen in these children are the consequence of congenital developmental anomalies. For instance, half of the patients in one series with persistent mild TSH elevations had hemiagenesis or hypoplasia of one lobe or goiter.[6]

Newborns classified as false positive at congenital hypothyroidism screening are risk of SCH in infancy and childhood. In a series of patients who had transient neonatal hyperthyrotropinemia which remitted after a few

| Causes                                      | Ref     |
|---------------------------------------------|---------|
| Developmental anomalies (hypoplasia, hemiagagenesis) | [6]     |
| Mutations in TSH receptor, dual oxidase 2, phosphodiesterase 8B, thyroid peroxidase | [8-12]  |
| Short for gestational age                    | [13]    |
| Down’s syndrome, William’ syndrome          | [14,15] |
| Autoimmune thyroiditis                      | [21]    |

TSH: Thyroid stimulating hormone

Table 1: Causes and associations of subclinical hypothyroidism in children

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weeks up to 70% of patients had persistent TSH elevation.[7] Mutations in the several proteins involved in TSH action have been demonstrated. Loss of function mutations in the TSH receptor gene have been demonstrated.[8,9] Dual oxidase 2 (DUOX2), phosphodiesterase 8B and thyroid peroxidase mutations have also been reported as causes of mild TSH elevations.[10-12] Up to 50% of children born small for gestational age were reported to have an exaggerated TSH response to thyrotropin releasing hormone (TRH); this group had a baseline TSH of 6.2 as opposed to 3.2 in the “normal” group.[13]

Other congenital conditions are commonly associated with SCH. SCH is also associated with Down’s syndrome being found in up to 32% of patients with these conditions. Anti-thyroid antibodies were not more likely to be found in this group than in the patients with a normal TSH.[14] Up to 31.5% of 92 patients with William’s syndrome had SCH with negative anti-thyroid antibodies.[15]

Thyroid functions tests (TFTs) are frequently ordered in children. In a study from Israel looking at children between 12 and 16 years of age covered by one insurance company, 24% of children had a TSH ordered in a 5 year period.[16] Obesity is a frequent cause for ordering a TFT; TSH abnormalities are distinctly uncommon when screening for thyroid dysfunction in obesity. In a study of over 1400 children with obesity only 0.3% had abnormal TFTs.[17] Other reasons for ordering thyroid function tests include fatigue, psychoactive illness, delayed or precocious puberty.

**Natural History and Progression**

A study from India evaluated the natural history of SCH; Of 32 children with goitrous autoimmune thyroid disease, followed up for 2 years, TSH normalized in 21.9%, 12.5% developed hypothyroidism while 65.6% remained stable as SCH.[18] In a retrospective multicenter trial, of the 55 Italian children followed, 29.1% normalized their TSH; of the remaining, 29.1% had values between one and two times above normal while 41.5% had values between greater than two times above normal. Presence of goiter, thyroglobulin antibody, TSH levels and progressive increase in anti-thyroid peroxidase (TPO) antibodies were predictive of progression to hypothyroidism in the whole group but not in individual patients.[19] In a prospective cohort of 92 Italian children followed for 2 years with other causes of SCH excluded and labeled “idiopathic,” 41.3% normalized their TSH and 12% increased their TSH to >10 mIU/L; however, none of these patients proceeded to overt hypothyroidism.[20] In the large Israeli cohort vide above, progression over 5 years depended on the level of TSH. In children with TSH between 5 mIU and 10 mIU, TSH normalized in 73.6%, increased in 2% with only 0.03% developing overt hypothyroidism (OH) requiring treatment. If the initial TSH was >10 mIU/L, 40% normalized their TSH, 33% reduced their value to between 5.5 and 10 mIU/L and 0.2% progressed to OH. An initial TSH of >7.5 and female genders were predictive of sustained TSH of >10.[20]

In a retrospective follow-up of 87 children with autoimmune thyroiditis and 59 children with an isolated increase in TSH, over a 3 year period, only 13.5% of children developed OH. Predictors for progression in children with autoimmune thyroiditis (AIT) included presence of celiac disease (4-fold), elevated TSH (3.4-fold) and increased anti TPO antibodies (3.5-fold); there were no predictors identifiable in patients with increased TSH.[21]

**Effects of Therapy or Clinical Follow-Up**

In a longitudinal study that included prepubertal and pubertal patients from Turkey with idiopathic short stature and SCH, replacement with 2 mcg/kg of levothyroxine (LT4) resulted in increases in growth velocity and growth velocity SDS.[22] Similar results were seen in 25 type 1 diabetic patients given 2-4 mg/kg over 2 years. Improvement was better in patients with higher TSH at entry.[23] In a longitudinal study from Italy, patients 69 patients with mild TSH elevation (5-10 mIU/L) were treated with a starting dose of 2 mcg/kg; no effects on BMI SDS was found; height velocity was not reported.[24] In a cross-sectional study of a longitudinal cohort of 36 children with SCH followed between 3 and 9 years, there was no negative impact on height, BMI, maturation or neurocognitive function seen.[25] There are no studies that have examined the impact of therapy or clinical follow-up on cardiovascular function, lipid profile or bone mass.

**Conclusions and Implications for Practice**

SCH is common in children for protean reasons. Persistent TSH elevation after a “false positive” neonatal screen is notable since it warrants follow up. Certain diseases are associated with a higher incidence of SCH and warrant screening. Obesity is a common cause of TSH measurement in children but has a low yield. AIT is the commonest cause.

Despite the limited data available, SCH in children and adolescents appears to be a benign and remitting disease with a low risk of evolution to OH. It appears that thyroid hormones appear to be functioning well despite elevated
TSH. Predictors of progression include, goiter, celiac disease, and positive anti-TPO. These are 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.

There is no consensus on therapy of SCH in children. It appears to be prudent to treat children with clinical signs or symptoms, goiter or a TSH >10 mIU/mL and withhold it in patients with no symptoms, goiter or a TSH between 5 mIU/mL and 10 mIU/mL until further research clarifies these issues.

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