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Review Article

Subclinical Hypothyroidism in Children: Normal Variation or Sign of a Failing Thyroid Gland?

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Subclinical hypothyroidism (SCH), defined by a normal total or free T4 level and a mildly elevated TSH (typically 5–10 mU/L), is common in children, but there is currently no consensus on management. Several recent pediatric studies indicate that progression of SCH to overt hypothyroidism (OH) is uncommon and that over a period of several years, elevated TSH usually either normalizes or persists but does not increase. The etiology appears to be multifactorial, with some cases representing minor developmental abnormalities, some related to obesity, some to mild autoimmune thyroiditis, and some associated with mutations in the gene for the TSH-receptor. There are no pediatric studies showing clinical benefit of treating these children with thyroid hormone, but additional studies in this area are needed. Since few cases of pediatric SCH progress to OH, treatment can be deferred, and periodic follow-up testing may be the preferred strategy, with elevated thyroid antibodies or a goiter being considered risk factors for eventual OH.

1. Introduction

Primary care physicians and pediatric endocrinologists frequently face the decision of what to do about the child who has a normal total or free T4 level and a slightly elevated TSH (typically 5–10 mU/L), a situation usually referred to as subclinical hypothyroidism (SCH) [1]. The reasons for ordering the tests in the first place vary, but many primary care physicians believe that prompt evaluation and treatment are essential. The response of pediatric endocrinologists may range from a decision to start thyroid hormone immediately after confirmation of the elevated TSH, to recommending frequent monitoring of TSH for prolonged periods, to the suggestion that unless a follow-up test shows a further significant rise in TSH or a subnormal free T4, no action should be taken.

There are several reasons for this lack of consensus among pediatric endocrinologists. First, there have been until recently a scarcity of studies reporting on the natural history of SCH in children; thus there has been concern that if untreated, SCH will frequently progress to overt hypothyroidism (OH). OH will be defined here as a low total or free T4 with a TSH of >20 mU/L, which all clinicians would agree requires treatment, though occasionally one encounters a clearly low free T4 with a TSH in the 10–20 mU/L range. There are no controlled pediatric studies (as there are in adults) looking at outcomes of children with SCH treated with l-thyroxine versus those given placebo. Furthermore, there is a high risk of developmental delay in infants who have untreated severe congenital hypothyroidism (low T4 and TSH usually >100). Since many children with SCH are identified during newborn screening or during the first year of life, physicians may be concerned that failing to treat SCH will expose the child to the risk of developmental delay if OH develops later or that treatment is needed to prevent growth retardation [1].

The cost implications of the decision to treat or not to treat an individual child with thyroid hormone may seem small, considering that thyroid hormone costs only $100–$200 per year depending on whether one uses generic l-thyroxine or a brand. However, the decision to treat a child with SCH long term may involve a lifetime of thyroid hormone replacement and frequent monitoring of total or free T4 and TSH levels. At a widely used commercial lab, the

cost of a free T4 is $144, and the TSH test costs $170; during the first years of life, it is typical for tests to be repeated every few months, with less frequent but at least annual testing as the child gets older.

This paper will summarize what we know about the natural history of SCH in children and will explore some of the etiologies for both transient and persistent mild elevation of TSH. While brief reference will be made to adult studies on SCH, it is important to point out why one cannot simply extrapolate adult data to children. Many children with SCH are identified at a young age, so the elevated TSH is often not an acquired condition due to mild autoimmune thyroiditis, as is typically the case in adults, but likely a mild, compensated congenital condition.

2. Why Are Thyroid Tests Ordered So Frequently?

One key reason SCH appears to be so common in children is that an increasing number of children undergo thyroid testing. Thyroid tests are most helpful in the child with a newly detected goiter or when there are more than one of the classic symptoms of hypothyroidism or hyperthyroidism. In practice, thyroid tests are often ordered in situations where OH is unlikely to be found, including (1) as part of a lab evaluation for obesity, (2) in the work-up of fatigue with no goiter and no other symptoms of hypothyroidism, (3) in children with a family history of hypothyroidism, (4) in short healthy children with normal growth rates, (5) in patients about to start or patients taking psychoactive medications, (6) in children with precocious or delayed puberty, and (7) in girls with irregular menses. One study from Germany looked at thyroid tests in over 1400 patients evaluated for obesity and reported hypothyroidism in only 0.3%, indicating the low yield in screening this population [2]. A recent study from one insurance company in Israel found that 24% of 12–16 year old children had at least one TSH ordered over a 5-year period, a very high proportion [3].

3. Natural History Studies of SCH in Children (Summarized in Table 1)

Many cases of SCH in children are identified in the newborn period due to screening for congenital hypothyroidism. A longitudinal study from Italy followed a group of 44 infants identified with elevated TSH on newborn screening, whose follow-up TSH at a mean of 22 days of life was either normal (<5 mU/L; 23 infants) or mildly elevated (5–12 mU/L; 21 infants) [4]. All of the 16 children who had TSH levels <4.0 mU/L at 16–44 months continued to have normal TSH at 4.1–6.6 years and at 7.2–9.5 years. Of the 28 whose TSH levels were in the 4–11 mU/L range at 16–44 months, 1/3 had their TSH normalized during prolonged follow-up, but 2/3 had persistent TSH elevation. Twenty of 28 were treated with l-thyroxine and then withdrawn from treatment 2 months before retesting; none had a TSH >10 mU/L off treatment. Thyroid ultrasound revealed hypoplasia of one lobe or thyroid hemiagenesis or goiter in half the subjects. The authors concluded that mild TSH elevation in the newborn period may be a marker for significant congenital anatomic or thyroid function abnormalities and that such children are at high risk for persistent TSH elevation. However, since none of their subjects developed OH during follow-up of up to 9.5 years, the practical significance of these congenital abnormalities is not clear.

A novel approach to studying the outcome of mild TSH elevation was taken by an Israeli group, who used a database of 121,000 children followed by a single organization who had a TSH done in 2002 [3]. Patients who had both a low free T4 and TSH >10 mU/L at the initial screening or during follow-up (only 0.4%) were treated. There were 2.9% whose initial TSH was >5.5 to 10 mU/L, and over the subsequent 5 years 73.6% had the TSH normalize, in 1/4 it remained borderline, and it rarely increased to >10 during subsequent testing. For patients with a normal free T4 and TSH >10 mU/L who were not treated, the second TSH was normal in 40%, decreased to the mildly elevated range in 33%, and remained >10 mU/L in only 25%.

In a recent prospective follow-up study of 92 Italian children ages 5–15 with "idiopathic" SCH (no goiter and negative thyroid antibodies) [5], 38 patients had normalization of TSH (none in the first 6 months, 16 between 6 and 12 months and 22 between 12 and 24 months). There were 54 patients (59%) whose TSH remained elevated in the 5–10 range, and only 11 patients had TSH increase to >10 mU/ml; in all cases it was between 10.5–15 mU/L. Free T4 levels remained normal in all patients. No lab test done at baseline was predictive of either normalization or a further increase in TSH.

The most common cause of acquired OH in both children and adults is autoimmune or Hashimoto's thyroiditis (AIT). Moore [6] reported on 18 children (mostly age 10–19) who had mild to significant TSH elevation (as high as 60 mU/L), normal T4, positive thyroid antibodies, and in some cases a goiter. Eleven were monitored off treatment and 7 were treated for 5–10 years and then retested after at least 1 year off treatment. In 7 patients, TSH normalized, in 10 patients it remained mildly to moderately elevated but with a normal T4, and only a single patient had both a low T4 and elevated TSH. Three patients in the treated group with initial TSH in the 50–64 range had normal T4 and TSH in the 3–10 range off therapy. This small study shows that SCH due to AIT can persist for years without progression to OH and that patients with moderate TSH elevation may have a recovery of thyroid function over time.

A larger study of the natural history of children with AIT from Italy examined 160 children with positive thyroid antibodies, ultrasonography of the thyroid compatible with AIT, and TSH either normal or 100–200% of the upper limit of normal (ULN) [7]. Patients were treated if their TSH increased to >200% ULN or followed for at least 5 years. In the 55 patients with TSH 100–200% of the ULN at the first visit, TSH normalized in 29%, remained mildly elevated in 29%, and became elevated to >200% of the ULN in 42%. Since treatment was started as soon as TSH exceeded 200% of the ULN, it was not clear what proportion actually would have developed OH with a low free T4. Although larger

Table 1: Natural history studies of subclinical hypothyroidism in children.

Patient population	N with SCH	Years of f/u	Outcomes	Ref
Abnormal newborn screening TSH	28	7.2–9.5 years	9 with normal TSH 19 with TSH 4–10 0 with TSH >10	[4]
Children in a single health care system screened in 2002; no known thyroid disease	3,475	Up to 5 years	73.6% with normal TSH ≈25% with TSH 5.5–10 ≈2% with TSH >10	[3]
Idiopathic SCH—no antibodies, no goiter	92	2 years	38 with normal TSH 43 with TSH 5–10 11 with TSH >10 (10.5–15)	[5]
Autoimmune thyroiditis: nl T4 and TSH 5–64 mU/L	18	Mean of 5.8 years	7 with normal TSH 10 with normal T4, ↑ TSH 1 with low T4, ↑ TSH	[6]
Autoimmune thyroiditis	55	At least 5 years	16 with normal TSH 16 with TSH 1-2x ULN 23 with TSH > 2x ULN	[7]
Patients with SCH maintained on low doses of l-thyroxine	30	Mean of 3.5 years on l-thyroxine then stopped	14 with TSH <5 12 with TSH 5–9.9 4 with TSH 10–15	[9]
Down syndrome: mean age 16.4 ± 10 years	70	2–7 years	19 with normal TSH 46 with SCH 3 with overt hypothyroidism 2 with hyperthyroidism	[10]

thyroid volume and increased thyroglobulin antibodies were somewhat predictive of deterioration of thyroid function for the group as a whole, no parameters predicted the course in individual patients.

In a series of 23 children with AIT based on one positive thyroid antibody and the typical ultrasonographic pattern (usually a heterogeneous and hypoechogenic pattern) [8], there were 7 euthyroid patients, 14 with SCH and 2 with OH. Euthyroid patients had persistently normal TSH during a median of 4.7 years of follow-up. Patients with SCH and OH were treated with l-thyroxine for a median of 6.4 years. After withdrawal from therapy, 10/14 children with SCH had TSH levels very close to initial levels, 3 patients with initial TSH 13.7 ± 3 had normalization of TSH (2.7 ± 0.7), and only one of 14 had worsening thyroid function.

The author recently analyzed a group of 30 children started on l-thyroxine when they had normal total or free T4 but a mildly to moderately elevated TSH (range of 5–40 mU/L). These selected children did not require increases in l-thyroxine dose over time (in some cases it was decreased), and TSH remained normal on 25–50 mcg/day [9]. Seventeen of the 30 were started on treatment in the first year of life (10 in the first 2 months), and 6 had Down syndrome. They were treated for a mean of 3.5 years (range 0.5–8.5 years). After at least one month off treatment, most children had slightly lower but still normal free T4 levels; 14/30 had TSH <5 mU/L, 12/30 had TSH 5.0–9.9 mU/L, and 4 had TSH 10–15 mU/L. None had a TSH higher than the initial level which prompted initiation of therapy, and none developed typical hypothyroid symptoms. This study, like the ones cited above, suggests that most children with normal free T4 and mildly elevated TSH, many identified in the first year of life, do not have a clinical course of progressive thyroid failure.

4. SCH in Down Syndrome and Other Syndromes

It has been long known that SCH is particularly common in children with Down syndrome. Rubello et al. reported that 32.5% of a group of 344 Italian Down syndrome children had SCH and that thyroid antibodies were not much more likely to be found in this group (18.7%) than in Down syndrome patients with normal TSH (15.7%) [10]. During a mean of 3 years of follow-up of 70 patients, TSH normalized in 27% and remained mildly elevated in 66%; overt hypothyroidism developed in 7% and hyperthyroidism in 4%, but only in the subset of patients who were antibody positive (Table 1). Another study of 137 children with Down syndrome found 4 cases of congenital hypothyroidism (3%), 8 cases (6%) of acquired OH, and 4 cases (3%) of hyperthyroidism [11]. All of the acquired OH children and the hyperthyroid children had positive thyroid peroxidase antibodies. There were an additional 53 cases (39%) with normal T4 and mildly elevated TSH (5–13 mU/L), of whom 24% had positive antibodies, compared with 13% positive antibodies in children with TSH <5 mU/L. No improvement in growth velocity was found in the 9 patients with mild TSH elevation who were treated with l-thyroxine. The etiology of the high frequency of SCH in Down syndrome is unknown. Tonacchera et al. did not find inactivating mutations of the TSH-receptor in 12 Down syndrome children with elevated TSH [12], and Konings et al. found no evidence for a TSH

with reduced biological activity in serum from children with Down syndrome compared to normal children [13].

In a study of 92 children with William syndrome between the ages of 0.2 and 17 years, none were found to have OH, but 31.5% had SCH, with negative thyroid antibodies and stable thyroid function over time [14]. Thyroid function has also been evaluated in detail in a large group of 120 subjects from infancy to age 32 with the chromosome 18 q-syndrome. There were 12% with primary hypothyroidism and several patients were found who fit the definition of SCH, but the frequency of SCH in this population was not defined [15].

5. Does SCH Cause Symptoms and Is Treatment Beneficial?

There is an almost complete lack of pediatric randomized controlled trial data on this subject so one is obligated to refer to adult studies. The debate over treatment of adult SCH has persisted for years, and review articles have been published. In 2001, the Journal of Clinical Endocrinology aired both sides of the debate, with one article taking the position "Subclinical hypothyroidism is mild thyroid failure and should be treated" [16] and the other article stating "The treatment of subclinical hypothyroidism is seldom necessary" [17]. In the latter article, studies were reviewed which examined the effect of treatment of SCH on improved quality of life, blood lipid levels, or resolution of hypothyroid symptoms. While some studies do appear to show slight improvement in lipid levels with treatment, a rigorous analysis indicates that for studies which included only subjects with TSH in the 4.5–10 mU/L range, no benefit was seen. In 2005, a consensus statement was published jointly by the American Association of Clinical Endocrinologists, the American Thyroid Association, and The Endocrine Society which concluded after review of the evidence and an opinion survey of thyroid specialists that treatment of patients with SCH with TSH levels of 4.5–10 mU/L was appropriate [18]. However, in the same issue, the chairman of the panel appointed by the 3 societies voiced disagreement with the consensus statement [19], concluding that the only adverse outcome of not treating adults with SCH was development of OH at a rate of 2.6% per year in patients without thyroid peroxidase antibodies and 4.3% per year in the presence of thyroid antibodies, based on data from the Wickham survey of thyroid disease in the community [20].

Since thyroid hormone is important for brain development in young children, the effect of SCH and its treatment on cognitive development would be of interest. One report used data from the Third National Health and Nutrition Examination Survey (NHANES III) which included 1327 adolescents ages 13–16, of whom 1.7% ($n = 22$) had SCH [21]. Curiously, the mean reading and block design scores in the SCH children were *higher* than for the 1275 euthyroid subjects, though the clinical significance is not clear. One treatment study looked at 11 children (8 with congenital SCH and 3 with acquired SCH) who had a battery of tests off and on thyroid hormone replacement for an average of 91 days and no differences in neuropsychological test scores were found [21].

Severe acquired hypothyroidism can result in slow growth and short stature. A recent study from Brazil looked at thyroid tests in 367 short children (average age 10.9 years) with no defined cause. SCH was found in 46 patients or 12.5%, but there was no difference in total T4 level or height SD score between the short children with SCH and those with normal TSH [22]. The authors treated 20 of the 46 SCH children SCH with l-thyroxine for 12 months; there was no significant difference in growth velocity between the treated and untreated SCH children, and the control short children with normal TSH [23].

In the absence of any evidence that treatment of SCH in children is beneficial, some clinicians take the view that since severe untreated OH can cause developmental delay in newborns and slowing of growth in older children, one should err on the side of caution. This view is summarized in a 2007 commentary [24], proposing that thyroid antibodies and ultrasound can be performed in all children with SCH and that "because the potential harm of early treatment appears to be so minor and limited, it seems prudent to err on the side of provisional diagnosis and early treatment rather than wait until sufficient information is available to determine the issue of whether to treat or not."

6. Etiology of Subclinical Hypothyroidism

Since most recent longitudinal studies show that at about 1/3 of patients with SCH have normalization of TSH over time whereas most of the remainder have persistent mild TSH elevation, causes of SCH will be considered in these 2 distinct subgroups.

6.1. Transient SCH

(1) Random TSH Variation. TSH levels in healthy individuals tend to fluctuate during the day as well as over time. One study compared early morning fasting and late morning TSH levels in 100 patients. In 97, TSH declined during the morning, by a mean of 26% [25]. If we define a TSH of >5.0 mU/L as abnormal, a child could have a TSH of 6.0 mU/L on one occasion and 4.0 mU/L when repeated later (particularly if done at a different time of day) with no real change in thyroid status. Although one might conclude that SCH had "resolved", the TSH remains in the range which may be normal for that child but mildly elevated for the general population.

(2) Non-Thyroidal Illness. A child with an active or recent acute illness may have a transient drop in thyroid hormone production. During the recovery phase, a transient increase in TSH is the normal mechanism for restoring normal free T4 levels, and TSH will return to normal within a short period of time.

(3) Mild AIT Which Recovers or Improves. As noted above [6, 8], pediatric AIT does not inevitably destroy

the thyroid but may go into remission, allowing the thyroid gland to recover and TSH to normalize, even in cases where enlargement of the thyroid gland persists.

6.2. Persistent SCH

(1) The normal TSH range is defined as range in which 95% of values in healthy people fall; thus about 2.5% of normal individuals will have and maintain a TSH at or slightly above the upper end of the normal range.

(2) Mild Developmental Thyroid Abnormalities. The study which followed children with mild TSH elevation found on newborn screening [4] identified 8 of 19 children with hypoplasia of one lobe or hemiagenesis of the thyroid. If these minor developmental abnormalities are functionally related to the TSH elevation, there appears to be a sufficient amount of thyroid tissue to sustain normal thyroid hormone production for many years. Whether TSH levels would increase in such patients after the pubertal growth spurt, when there is often an increase in thyroid hormone requirement, is not known.

(3) Children Born Small for Gestational Age. A recent study from Argentina of 53 children born SGA, with mean age 5.6 ± 3.2 years, impaired catch-up growth, and negative thyroid antibodies, found that 1/2 had an exaggerated TSH response to thyrotropin releasing hormone (TRH) compared to control children. Both groups had identical mean free T4 levels but the group with exaggerated TRH response had a mean TSH of 6.2 (4.2–14.6) versus 3.2 (1.6–7) in the normal TRH response group. The authors speculate that children with intrauterine growth retardation may develop abnormal TSH regulatory circuitry characterized by an abnormal TSH set point without alteration in thyroid function [26].

(4) Mild Stable Autoimmune Thyroiditis. Although it seems more likely that AIT would over time either resolve or cause thyroid failure, there may be a variant form of AIT in which the gland's minimally impaired ability to produce thyroid hormone remains stable over a long period of time.

(5) Obesity. There have been several reports linking obesity to increased TSH. The best of these, a study of 86 patients at the Cleveland Clinic who underwent weight reduction surgery, found that prior to surgery, 10.5% had thyroid tests consistent with SCH and there was a strong correlation between BMI and TSH [27]. Following weight loss surgery with a mean decrease in BMI from 49 to 32 kg/m^2, mean TSH decreased from 4.5 to 1.9 mU/L with no change in free T4 levels. A pediatric study which looked at multiple factors involved in SCH reported that 28.4% of 88 patients with SCH and negative thyroid antibodies were obese or overweight [28]. While the mechanism for obesity-related elevation of TSH has not been elucidated, it is not surprising that when screening obese children for thyroid disease, SCH is found far more often than OH.

(6) Mutations in the TSH-Receptor (TSH-R). A breakthrough in understanding SCH has come from studies showing that some children with SCH have defined mutations in the TSH-receptor (TSH-R) gene. A recent study from Japan examined 102 children with permanent TSH elevation found on newborn screening; 3/70 with TSH >10 mU/L had mutations in each of the 2 TSH-R genes, and 3/32 with TSH 5–10 mU/L had single mutations in the TSH-R gene [29]. In the study from Italy cited above [25], of their 88 pediatric SCH subjects, 10 had mutations where an effect on TSH-receptor signaling had been found in previous studies; most of the TSH-R mutations is this study were found in one allele. In the most recent report on the subject, TSH-R mutations were found in 11 of 39 or 28% of a group of 39 children with nonautoimmune SCH. Three of the subjects had hypoplastic glands on ultrasound [30]. These observations provide a logical explanation as to why many of children with SCH are identified in the newborn period and why their TSH remains so stable over many years of follow-up. If the TSH-receptor has a reduced ability to bind or be activated by TSH, it may take 2–4 times the normal amount of TSH to optimally activate the TSH-receptors (i.e., mild TSH resistance).

7. Conclusions from Literature Review

The weight of evidence from the above studies points to most cases of persistent SCH representing stable alterations of the child's pituitary-thyroid axis such that normal free T4 levels are maintained over a period of many years in the presence of slightly elevated TSH levels. It is notable how infrequently SCH progress to OH over time, even in those children with features suggestive of AIT where such progression should be common. While only a minority of SCH patients may have mutations of the TSH-R, that situation provides the clearest example for what may prove to be the underlying physiology of most cases of persistent pediatric SCH: euthyroidism with (for a variety of reasons both congenital and acquired) a mild elevation of TSH.

8. Suggestions for Management of SCH

While there is a need for placebo-controlled treatment trials in SCH children looking at neurocognitive functioning and lipid levels, given the negative or inconclusive outcomes of such studies in adults, where it is far easier to study large numbers of patients, it does not seem likely that such studies in children would provide strong evidence in favor of treatment. Thus with the information currently available, the following suggestions for how SCH could be managed are proposed.

(1) When screening for thyroid disease, primary care physicians should be advised to only order a free T4 and TSH. T3 uptake, T3, and free T3 add cost and are often abnormal in the absence of thyroid disease. There is controversy as to how helpful thyroid antibodies are as a screening test, since they are often positive in normal children, though less often than in adults. For example, in the NHANES III study in the US, 13% of the total population had thyroid peroxidase, and 11.5% had thyroglobulin antibodies; for the subset of 12–19 year olds (children under 12 were not included), the figures were 4.8% and 6.3%, with higher rates of positivity in females than in males [31].

(2) A normal total or free T4 with a TSH of 5–10 mU/L is generally not the cause of whatever symptoms prompted the ordering of the thyroid tests in the first place, since it is the decrease in free T4 not increased TSH, which results in hypothyroid symptoms. Different patients have different set points for free T4, so that a child with a free T4 of 1.1 ng/dL (0.9–1.5) and TSH 2.0 mU/L is euthyroid, while another patient with free T4 1.1 ng/dL and TSH 30 mU/L presumably once had a higher free T4, now has a failing thyroid gland and needs treatment. Nonetheless, few patients experience classic symptoms of hypothyroidism until their free T4 falls below the population normal range.

(3) If there is a goiter or the TSH is >10 mU/L, treatment is more likely to be indicated, as the odds of underlying thyroid disease are greater. While there are no pediatric studies which make this point clear, one study of adults older than age 55 calculated the progression of SCH to OH as 1.76 cases per 100 patient yearly with an initial TSH of 5.0–9.9, 19.67 for an initial TSH 10–14.9, and 73.47 for an initial TSH 15.0–19.9 [32]. In the same study, having a goiter increased the odds of progression to OH by a factor of 2.47.

(4) If there is no goiter and TSH is <10, repeat free T4 and TSH is suggested in 6–12 months. Repeating the tests within a month, as is often done, usually results in a TSH similar to the initial one and provides no new information. By waiting 6–12 months, one allows time for either normalization of TSH or progression to OH. It may be more helpful to measure thyroid antibodies with the second free T4 and TSH than as a screening test. If they are negative, it would provide reassurance that one is likely not dealing with AIT and would decrease the need for subsequent testing, while strongly positive antibody levels would signal the need for closer monitoring of thyroid tests.

(5) Further studies are needed to answer the question of how long one needs to monitor TSH in a child with SCH to make sure he or she has not progressed to OH. It is proposed that TSH be rechecked periodically for 2 years (longer if there is a goiter or strongly positive antibodies). If the TSH remains in the 5–10 mU/L range, the child could be considered to have a stable mild TSH elevation and not require repeat testing unless a goiter appears, or there are new symptoms suggestive of OH.

(6) Since a child with TSH 5–10 mU/L, no goiter, and negative antibodies is unlikely to progress to OH, it is difficult to justify treatment. Even though an occasional child in this group will develop symptomatic OH during follow-up, long-term outcome is not improved by "catching it early." In the less common situation when free T4 is normal but TSH is 10–15, progression to OH is more likely, particularly if there is evidence of AIT. Treating such patients seems reasonable, but periodic monitoring off therapy should also be an option.

(7) For children in the first 2 years of life with a clearly normal free T4 but mild persistent TSH elevation, the risk of developmental delay by withholding treatment should be very small, as AIT and progression to OH at this age appear to be rare. If a decision is made to treat and the TSH remains <5 mU/L, a one-month trial off l-thyroxine for reevaluation of thyroid status around the age of 3 years is suggested.

9. Conclusion

SCH is a very common finding in children, and several etiologies have been identified. Natural history studies indicate that over time, the majority of elevated TSH levels either revert to normal or remain mildly elevated. Children with persistent TSH elevation may be viewed as normal variants in which there is a stable equilibrium allowing normal thyroid hormone production in the presence of mild TSH elevation. The number of cases in which progression to OH has been small in all studies was reviewed, so occasional monitoring rather than immediate treatment may be the preferred strategy. Studies on children with mutations of the TSH-receptor suggest that some SCH patients without features of AIT may have increased TSH due to thyroid resistance to the effect of TSH. Preliminary studies suggest that treatment of SCH has no beneficial effect on growth, but additional studies are needed to determine if there are any measurable benefits (aside from the lowering of TSH) to treating such children with l-thyroxine.

Abbreviations

SCH: Subclinical hypothyroidism
OT: Overt hypothyroidism
AIT: Autoimmune thyroiditis
TSH: Thyroid stimulating hormone
TSH-R: TSH-receptor.

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