

Subclinical Hypothyroidism In Childhood, Treatment Or Only Follow-Up?

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Abstract

Background: Subclinical hypothyroidism is defined as serum levels of thyroid-stimulating hormone (TSH) above the upper limit with normal concentrations of free T4 (fT4). Its management remains challenging. The aim of the study was to evaluate clinical and laboratory findings as well as clinical course of children with SH followed in a third level hospital. 65 patients aged between 2 and 18 years were retrospectively studied.

Methods: The patients were followed for a median period of 9 months (range 6 months to 24 months). Those who normalized TSH levels were discharged (Group 1). If TSH persisted mild elevated (5-10 μ UI/mL) with normal fT4 and negative TPOAb/TgAb were classified as Group 2 and followed semiannually without treatment. In those patients who's TSH raised \geq 10 μ UI/mL or maintained TSH 5-10 μ UI/mL and positive TPOAb/TgAb were considered suitable for thyroxin therapy (Group 3, G3).

Results: By ROC curves analysis we tested which initial TSH concentration best discriminated between patients who reverted to normality (Group 1) from those who finally required treatment (Group 3), the best cut-off being a TSH concentration $>$ 8.1 μ UI/mL (93.18% E, 57.14% S, AUC 0.765 \pm 0.107, p= 0.01). In 89% of our patients, TSH concentrations spontaneously reverted to normality or remained stable without treatment, whereas less than 11% progressed to clinical hypothyroidism.

Conclusion: patients with initial TSH concentrations above 8.1 μ UI/mL have an increased risk of progression to hypothyroidism.

Background

Subclinical hypothyroidism (SH), also known as isolated hyperthyrotropinemia, is defined as serum thyroid-stimulating hormone (TSH) concentrations above the upper limit of the reference range and normal concentrations of free T4 (fT4). This situation occurs in less than 3% of children and adolescents (1,2), but is a cause of concern for parents and primary care physicians and represents a frequent cause of referral to a pediatric endocrinologist.

TSH normal range (0.4–0.5 μ UI/mL to 4.0–5.0 μ UI/mL) depends on the method used with large variations found between different TSH assays. Idiopathic SH is characterized by mild elevations of TSH concentrations levels (5–10 μ UI/mL) with peripheral hormones, fT4 and triiodothyronine within normal ranges, absence of thyroid autoimmunity or other conditions that may account for the increase in TSH, such as certain medications or genetic disorders (Down syndrome, Pseudohypoparathyroidism and others), and without clinical signs or symptoms of thyroid failure.

The natural course of idiopathic SH is unclear. Most patients normalize TSH values and a small percentage progress to overt hypothyroidism (3–7). The risk of progression to overt hypothyroidism depends on the cause of SH with high risk in autoimmune forms. There is a lack of conclusive studies that determine whether these children with SH might benefit from levothyroxine treatment (7–9).

On the other hand, adverse health outcomes of SH in childhood remain controversial.

Although it might not produce adverse effects on growing and development processes (5, 8, 10), it has been recently associated with overweight/obesity and metabolic abnormalities (11,12). Nevertheless, prospective studies that determine those deleterious effects are lacking.

This study aimed to analyze the characteristics and natural evolution of a cohort of children with SH referred to a third level hospital. We also aimed to establish a TSH cut-off point that allowed us to predict the likelihood of progressing to hypothyroidism at the early stages.

Methods

We analyzed retrospectively patients who were diagnosed with SH and referred to the Endocrinology Unit of our hospital between 2014 and 2018. SH was defined as TSH concentration mildly elevated (5–10 μ UI/mL) with fT4 within the normal reference range (0.7–1.48 ng/dL). Patients were assessed at the time of diagnosis, at month 3 and every 6 months during follow-up if necessary.

Patients

Inclusion criteria were as follows: Patients referred for SH aged 2 to 18 with at least two analytical records: one at the time of diagnosis and another one during the follow-up. Patients under 1-year-old and who receive pharmacological treatment that could alter the TSH concentrations (anticonvulsants, antipsychotics, glucocorticoids, iodine or iodine-rich diet) were excluded. We also excluded patients with genetic syndromes or under an acute disease. All patients reside in an area by the Mediterranean Sea with an iodine-sufficient population.

All patients had a complete clinical record, physical examination including anthropometric characteristics (height, weight), and thyroid exploration at the time of diagnosis and during follow-up visits. We calculated body mass index (BMI) and represented the results as standard deviation (SD) according to age and sex. Obesity was considered if the BMI-SD was above 2 for the reference population.

Thyroid function test consisted of TSH, fT4 and thyroid autoantibodies (anti-peroxidase (TPOAb) and antithyroglobulin (TgAb)). If necessary, a thyroid ultrasound was made to assess thyroid size and echogenicity.

All patients had an initial TSH concentration mildly elevated (5–10 μ UI/mL) with fT4 within the normal reference range. The patients were followed for a median period of 24 months. Those patients who normalized TSH levels at the follow-up were discharged (Group 1, G1) whereas those who persisted with elevated TSH were followed.

If TSH persisted mild elevated (5–10 μ UI/mL) with normal fT4 and negative TPOAb/TgAb were classified as Group 2 (G2) and followed semiannually without treatment. In those patients who's TSH raised \geq

10 μ UI/mL or maintained TSH 5–10 μ UI/mL and positive TPOAb/TgAb were considered suitable for thyroxin replacement therapy due to hypothyroidism/thyroiditis (Group 3, G3).

Biochemical and hormonal determinations

Blood samples were drawn at 8 a.m. after an overnight fast. Samples were centrifuged and sera kept frozen at -20 °C until analysis. Analysis of serum TSH was performed with CLIA with the aid of an Abbott ARCHITECT instrument (Abbott Diagnostics Division). Total coefficient of variation (CV) was < 3.3%, functional sensitivity was 0.0038 μ UI/mL; reference range [99% confidence interval (CI)]: 0.35–4.94 μ UI/mL; fT4 was measured by Abbott ARCHITECT instrument (Abbott Diagnostics Division; total CV was < 7%, sensitivity of the assay was < 0.4 ng/dL; reference range (99% CI): 0.70–1.48 ng/dL (conversion factor ng/dL *12.87 = pmol/L). TPOAb were measured by an Abbott ARCHITECT instrument (Abbott Diagnostics Division). Total CV was < 7.6%, sensitivity of the assay was 0.16 IU/mL; reference range: <5.61 IU/mL

Statistical analyses

The normality of the evaluated variables was established using the Kolmogorov-Smirnov test. Quantitative variables are presented as mean \pm SD whereas qualitative variables were expressed as percentages. Differences among groups were assessed by the One Way ANOVA and a post hoc Sheffé's test. Receiver Operating Characteristic (ROC) analysis was used to determine the value of baseline TSH that would best discriminate between patients who had a normal TSH on a second test from those who develop hypothyroidism. All tests were two-tailed and a p value < 0.05 was considered statistically significant. Statistical analyses were performed using the SPSS package 12.0 and MedCalc Software 12.7.0 (Acacialaan 22, B-8400 Ostend, Belgium).

The study was approved by the Ethics Committee. All patients or legal surrogates gave informed consent prior to participation.

Results

The study included 65 patients diagnosed with SH (51% female). The mean age at diagnosis was 7.3 \pm 3.39 years. Clinical and laboratory findings at the time of diagnosis are shown in Table 1. The main reason for the study of thyroid function was routine analytical (43%, n: 28), short stature or low weight (15.3%, n: 10), obesity (12.3%, n: 8), asthenia (10.7%, n: 7) or others (18.4%, n: 12).

There was a family history of thyroid disease in eight cases (12.3%). At the time of diagnosis, all patients were asymptomatic of thyroid dysfunction, and these patients were observed without treatment.

Table 2 shows the clinical and laboratory characteristics of patients classified into 3 different groups according to evolution. TSH concentrations returned to normal ranges in 44 patients (67.6%) (G1), 14 patients (21.5%) maintained slightly elevated TSH concentrations with negative thyroid antibodies (G2)

and 7 patients (10.7%) had TSH $\geq 10\mu\text{UI/mL}$ or TSH 5– $10\mu\text{UI/mL}$ and positive TPOAb/TgAb (6 patients) (G3).

Thyroid autoimmunity was observed in 85% of patients of G3 and none of G1 and G2 ($p > 0.001$).

The prevalence of females was higher in the G3 (71%), but in the other two groups, the distribution was similar (50% in G1 and 57% G2), which concurs with a female sex preponderance in thyroid autoimmune diseases. Regarding the age, no differences were found among the 3 groups.

Mean baseline TSH concentrations differed among the 3 groups ($p = 0.012$). By Scheffé contrasts, significant differences were found in TSH values between G1 and G3 ($F = 4.768$; $p = 0.016$) whereas no differences were found between G1 and G2 or between G2 and G3. No differences were found in fT4 concentrations at baseline among the 3 groups ($F = 3.083$; $p = 0.053$) (Fig. 1).

By ROC curves analysis we tested the ability of baseline TSH to discriminate patients of G1 from G3. The optimal cut-off point for baseline TSH for discriminating between patients who reverted to normality (G1) from those who displayed overt hypothyroidism (G3) was $> 8.1\mu\text{UI/mL}$ (sensitivity: 57.14%; specificity of 93.18%) with an Area Under Curve (AUC) 0.765 ± 0.107 ; 95% CI: 0.625–0.872; $p = 0.01$ (Fig. 2).

BMI evolution was evaluated during the study and no significant difference was found in obesity (BMI-SD > 2) prevalence during follow-up in all patients (12.3–10.7%). Contrary to what one would expect, none of the patients with obesity belong to the G3.

Of all the patients, 36.9% underwent a thyroid ultrasound, being goiter or nodule finding on the physical examination the main indication as well as prior to the start of levothyroxine treatment. Ultrasound structure suggestive of thyroiditis was found in 6 patients, all in the G3. There were 2 patients with nodules on ultrasound without other significant findings.

Discussion

In general terms, SH seems to affect less than 3% of the child population and usually displays a natural course towards the maintenance or spontaneous resolution in variable time in most cases (68–88%) and only a few cases progress to overt hypothyroidism or autoimmune thyroiditis. There are few studies to date that evaluate SH and its evolution in childhood (5,10,13,14). In our study, most of the patients either normalized their TSH levels or maintained their TSH levels under subclinical range values (89%). Only a small percentage presented overt hypothyroidism or autoimmune thyroiditis and needed treatment (11%). These data are similar to those of a 2-year prospective study presented by Wasniewska et al., in which 88% of patients normalized or preserved their TSH levels and 12% developed hypothyroidism (5).

In an attempt to anticipate events, Lazar et al. found that predictive factors for sustained abnormal TSH levels were initial TSH $> 7.5\mu\text{UI/mL}$ and female gender (1). Recently, Gammons et al. concluded that a TSH $> 8\mu\text{UI/mL}$ would be the cut-off point to refer to pediatric endocrinologist for evaluation and management (15). In our study, baseline TSH was the best predictor of the evolution to SH over time, as

already postulated by these other authors. Patients with an initial TSH > 8.1 μ UI/mL had an increased risk of developing hypothyroidism and therefore deserved more studies and a longer follow-up. We are aware that it has low sensitivity, but high specificity and an AUC of 0.765 \pm 0.107, which means that it is a reliable diagnostic test.

Regarding the weight, in our study, no significant changes were detected between obesity prevalence at baseline and during follow-up in all the patients, and the BMI-SD did not worsen during follow-up in any patient. However, in the G2 group, those who persisted with a TSH 5–10 μ UI/mL had a higher prevalence of obesity (data not shown), which would suggest that it may have a role in increasing TSH levels. It is thought that the mildly elevated TSH is the consequence of obesity rather than the cause, as an attempt to increase energy expenditure, with an improvement of the thyroid function parameters when lowering the BMI, as has been mentioned on multiples studies (16–21). Contrary to what one would expect, none of the patients with obesity belong to the G3 with overt hypothyroidism.

It is known that autoimmunity is a key factor that determines the major progression to hypothyroidism. In our study, almost all patients in G3 met this condition and 71.4% were women, which is a distribution that already occurs in most autoimmune diseases. Nevertheless and in spite of being the commonest cause of hypothyroidism, pediatric patients not always reach that condition. Lazarus et al. analyzed the results of 7 observational studies and showed that elevated TgAb and TPOAb at diagnosis were associated with an increased risk of progression in some but not all studies (7).

Treatment with levothyroxine was initiated in all patients who presented TSH \geq 10 μ UI/mL or TSH 5–10 μ UI/mL and positive TPOAb/TgAb (G3). The dilemma arises in deciding whether patients with maintained mildly elevated TSH (G2) should be treated or not with levothyroxine and what benefits it can bring against possible consequences of SH, since good-quality studies examining the effect of treatment of SH in children are lacking (9,22,23). In our case, no patients were treated since none presented associated symptoms or alterations that could be related to it.

The current study has its limitations. For instance, it is a retrospective study with a small number of patients and genetic causes such as alterations in the TSH receptor that could explain mildly elevated TSH have not been investigated. On the other hand, the possible impact on growth and intellectual development has not been assessed in this study.

Conclusion

Although SH in childhood is a frequent issue and a matter of concern between primary care pediatrics, it seems to be a benign and remitting condition; based on our results and in comparison with the literature, expectant behavior is the best option, always individualizing each patient. Perhaps by making a virtual consultation with the specialist, many cases could be resolved and, therefore, save time and resources.

However, in the case of pediatric SH, prospective studies are lacking to determine a sensitive and specific level of TSH to predict the progression to hypothyroidism. It is important to find out if it is a process with

negative or positive autoimmunity, since on this latter case, the probability of progression to hypothyroidism is greater. As seen in the current study, we propose a TSH level of $> 8.1 \mu\text{UI/mL}$ as a predictive value for progression to hypothyroidism, and therefore these patients deserve more studies and follow-up and perhaps treatment as well.

Abbreviations

TPOAb

Anti-peroxidase thyroid autoantibody

TgAb

Antithyroglobulin thyroid autoantibody

AUC

Area Under Curve

BMI

Body mass index

CI

Confidence interval

fT4

Free T4

G1

Group 1

G2

Group 2

G3

Group 3

ROC

Receiver Operating Characteristic

SD

Standard deviation

SH

Subclinical hypothyroidism

TSH

Thyroid-stimulating hormone

CV

Total coefficient of variation

Declarations

Ethics approval and consent to participate: This article was approved by the ethics committee Centre de comitè d'ètica de la Investigació Clínica Hospital Universitari Germans Tries i Pujol (CEI-HUGTiP) as it

contains human data. Informed verbal consent was obtained from all individual participants or legal surrogates included in the study to use their data. The ethics committee agrees as it is a prospective study without intervention and with anonymous data.

Consent for publication: Not applicable.

Availability of data and materials: The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests

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Author contribution:

MM conceptualized and designed the study, proposed the new terminology, controlled the analyses, drafted the first and final manuscript.

SM organized the data collection, carried out the initial analyses, and drafted the initial manuscript.

CA organized the data collection, carried out the initial analyses and submitted the manuscript.

MG performed the statistical analysis.

JB reviewed the manuscript and approved the final manuscript.

MG reviewed the statistical analysis, Reviewed the final manuscript.

All authors were involved in writing the manuscript and approved the final version.

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Tables

Table 1. Clinical and laboratory characteristics at baseline.

	N: 65
Female (%)	33 (51.6%)
Age years	7.3± 3.39
BMI-SD	0.01 ±1.41
Referral diagnosis	
Short stature/low weight	10 (15.3%)
Overweight/Obesity	8 (12.3%)
Asthenia	7 (10.7%)
Routine	28 (43%)
Others	12 (18.4%)
Familiar History (Autoimmune disease)	8 (12.3%)
TSH (μUI/mL)	6.98±1.15
Free thyroxin (ng/dL)	1.13±0.18

Table 2. Clinical and laboratory characteristics among groups.

N.S.: non significant

^a : p<0.016 group 1 vs group 3

^b: p<0.001 group 1 vs group 2

^c p<0.001 group 1 vs group 3

^d: p<0.001 group 2 vs group 3

	Group 1	Group 2	Group 3	Significance
N (%)	44 (67,6%)	14 (21,5%)	7 (10,7%)	
Female (%)	51.2%	42.9%	71.4%	N.S.
Age years at baseline	6.98±3.74	7.8±3.0	8.25±1.0	N.S.
BMI-SD at baseline	-0.18±1.38	0.6±1.64	0.06±0.9	N.S.
TSH (μUI/mL) at baseline	6.74±0.99 ^a	7.2±1.14	8.06±1.53	0.012
Free thyroxin (ng/dL) at baseline	1.16±0.17	1.11±0.20	0.99±0.13	N.S.
TSH (μUI/mL) at follow-up	3.64±1.18 ^{b, c}	6.66±1.52 ^d	11.96±4.11	0.001
Free thyroxin (ng/dL) at follow-up	1.09±0.16	1.03±0.18	0.98±0.27	N.S.
TPO positivity (%)	0%	0%	85%	0.001

Figures

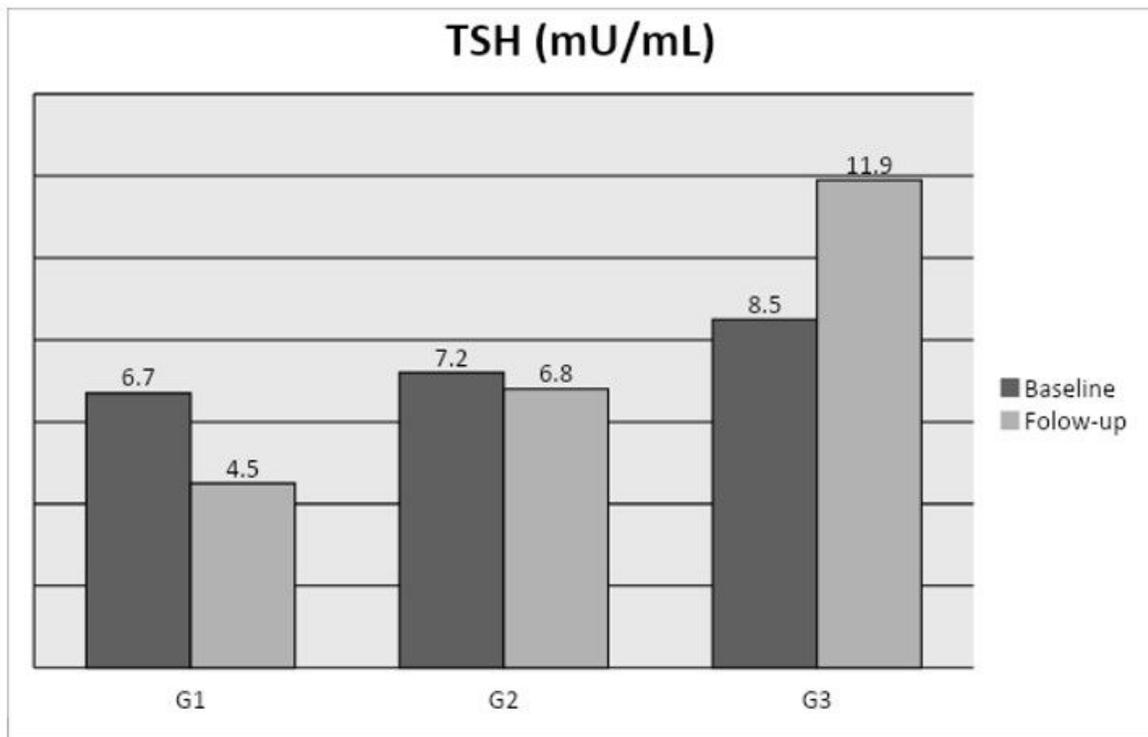


Figure 1

TSH values at baseline. Patients were classified into three groups according TSH levels at the end of the follow up. Group 1 (G1): TSH $\leq 5\mu\text{UI/mL}$ (n: 44); Group 2 (G2): TSH 5-10 $\mu\text{UI/mL}$, normal fT4 and negative TPOAb/TgAb (n: 14); Group 3 (G3): suitable for thyroxin therapy due to TSH $\geq 10\mu\text{UI/mL}$ or TSH 5-10 $\mu\text{UI/mL}$ and positive TPOAb/TgAb (n: 7).

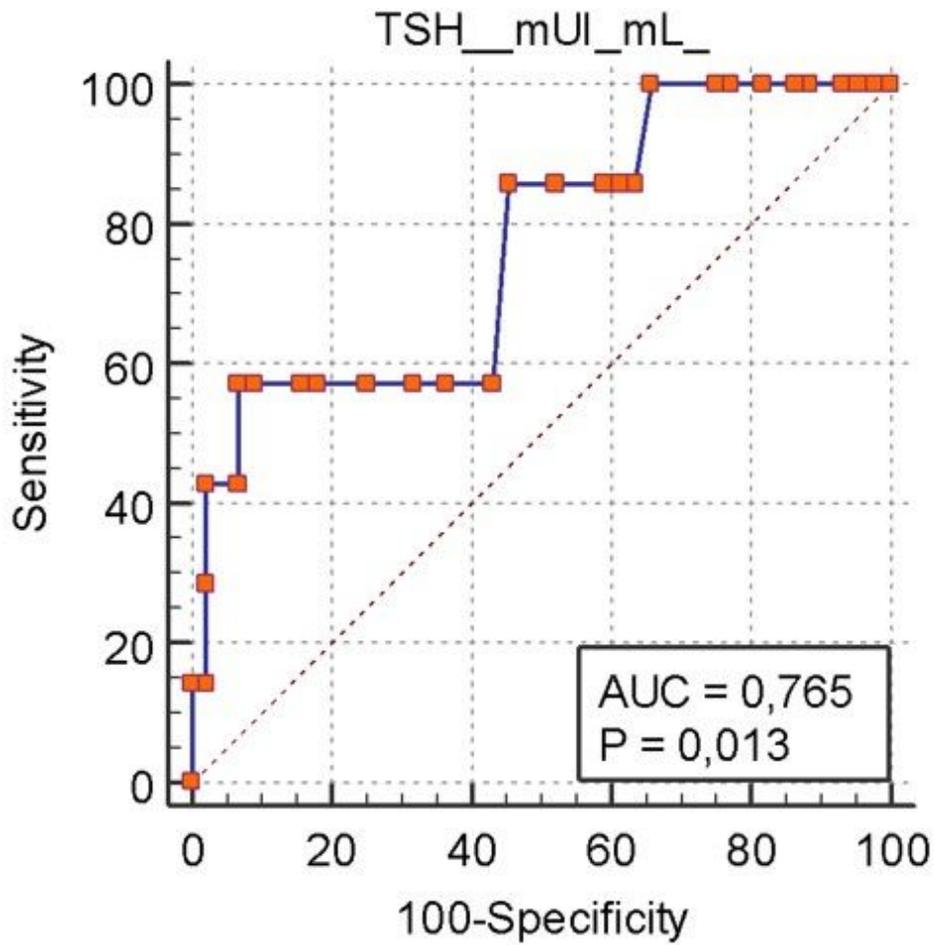


Figure 2

ROC curve showing the sensitivity and specificity of a TSH >8.1mUI/mL to discriminate between G1 and G3.