Five-year prospective evaluation of thyroid function in girls with subclinical mild hypothyroidism of different etiology

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Abstract

Aim: To follow-up for 5 years thyroid status evolution in 127 girls with mild (TSH 5–10 mU/I) subclinical hypothyroidism (SH) of different etiologies.

Patients: The population was divided into two age-matched groups of 42 and 85 girls with either idiopathic (group A) or Hashimoto’s thyroiditis (HT)-related SH (group B). Group B was in turn divided into three subgroups, according to whether SH was either isolated or associated with Turner syndrome (TS) or Down syndrome (DS).

Results: At the end of follow-up the rate of girls who became euthyroid was higher in group A (61.9% vs 10.6%), whereas the rates of patients who remained SH (55.3% vs 26.2%), became overtly hypothyroid (30.6% vs 11.9%) or required levothyroxine (L-T4) therapy (63.5% vs 23.8%) were higher in group B. Among the girls of group B, the risk of remaining SH or developing overt hypothyroidism was higher in the subgroups with TS or DS than in those with isolated HT.

Conclusions: Long-term prognosis of mild and idiopathic SH is frequently benign, even though a L-T₄ treatment may be needed throughout follow-up in almost a quarter of cases; long-term prognosis is different in the girls with either idiopathic or HT-related SH; and the association with either TS or DS impairs the outcome of HT-related SH.

Introduction

Subclinical hypothyroidism (SH) is a biochemical condition characterized by serum thyrotropin (TSH) concentrations above the upper limit of the reference range and serum free thyroxine (FT₄) levels within the reference range (1). In pediatric age, SH is detected with increasing frequency, as thyroid function tests are routinely performed in children with very different clinical problems (2, 3). SH may be possibly caused by the same thyroid disorders that result in overt thyroid function impairment, in particular, Hashimoto’s thyroiditis (HT) (4). In many cases, however, no definite etiology can be found (idiopathic SH).

The main clinical problem in the patients with SH is whether they should be treated or not, a problem that is still controversial due to the lack, even in adulthood, of randomized trials revealing significant benefits of levothyroxine (L-T₄) treatment on hypothyroid symptoms, life quality, serum lipid levels, and/or heart function (5).

In childhood, this is an even more controversial issue (6, 7, 8, 9, 10) and the only available study comparing the effects of L-T₄ treatment vs no therapy in idiopathic SH suggests that therapy is unable to modify post-therapy outcome of hyperthyrotropinemia and to prevent the risks
of a subsequent TSH increase after treatment withdrawal (11). In the children with HT-related mild SH, it has been just recently reported that the evolution of thyroid function tests seems to be frequently characterized by a deterioration over time, whereas such risk is very low in the children with idiopathic SH (12). However, the available prospective studies on the natural history and prognosis of SH in children are very few and based on 2–3 years follow-up investigations (12, 13, 14, 15, 16), which hampers the ability of drawing firm conclusions about the relevance of those findings.

In the present study, we have prospectively investigated the evolution of thyroid hormonal status, throughout a 5-year period, in a selected population consisting of only girls with either idiopathic or HT-related mild SH. In a limited number of cases, HT was associated with either Turner syndrome (TS) or Down syndrome (DS), i.e., two chromosomopathies that are known to be linked with an increased risk of autoimmune diseases (17, 18, 19, 20, 21, 22, 23, 24, 25) and especially thyroid diseases (26, 27, 28, 29, 30, 31).

The aims of our study were to establish, through a prolonged follow-up, whether long-term thyroid status prognosis may differ in the girls with either idiopathic or HT-related mild SH and whether the association with either TS or DS may modify the outcome of HT-related SH.

**Patients and methods**

**Study population**

The study population consisted, overall, of 127 girls aged between 2.5 and 18.0 years at the time of SH diagnosis (median 9.7 years), who were identified in our clinics, during the period 2000–2008, as having a mild and either idiopathic or HT-related SH and fulfilled the following inclusion criteria: age ≤18.0 years at the time of SH diagnosis; TSH serum levels ranging between 5 and 10 mU/l; and no concomitant chronic treatment with pharmacological agents that might interfere with SH progression, such as antiepileptics, glucocorticoids, or iodinated drugs.

The entire series was divided into two groups, according to whether SH in the different cases was idiopathic (group A) or HT-related (group B). Patients of group A fulfilled the following criteria: negativity for both thyroglobulin and thyroid peroxidase serum autoantibodies (TGAbs and TPOAbs respectively) and no thyroid enlargement and no hypoechogenic gland pattern at ultrasonography. Patients of group B fulfilled the following criteria for diagnosis of HT: positivity for serum TGAbs or TPOAbs and a hypoechogenic thyroid pattern, consistent with autoimmune thyroid disease.

In both groups the patients were in good clinical status and clinically euthyroid at the time of recruitment. All of them had been referred to our pediatric endocrine centers by their pediatricians, due to the incidental finding of high TSH levels at their annual check-up, based on a diagnostic protocol that also included TSH measurement.

Group A consisted of 42 girls who were younger than 15 years at recruitment. Of these, 27 were prepubertal and 15 pubertal. Group B consisted of 85 girls, who were not older than 18 years at recruitment. Of these, 57 were prepubertal and 28 pubertal (Table 1).

### Table 1

Ages (years) and prevalences (%) of pubertal patients, TSH (mIU/l), FT₄ (pmol/l), thyroid peroxidase and thyroglobulin autoantibody (TPOAbs and TgAbs) serum levels (mIU/l) at the start of follow-up in the two groups with either idiopathic subclinical hypothyroidism (SH; group A) or Hashimoto’s thyroiditis (HT)-related SH and in three subgroups of patients with HT-related SH.

<table>
<thead>
<tr>
<th>Age</th>
<th>Pubertal patients</th>
<th>TSH</th>
<th>FT₄</th>
<th>TPOAbs</th>
<th>TGAb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A (n=42)</td>
<td>7.4 (2.5–14.0)</td>
<td>35.7</td>
<td>6.0 (5.0–9.9)</td>
<td>14.3 ±3.4</td>
<td>–</td>
</tr>
<tr>
<td>Group B (n=85)</td>
<td>9.0 (2.5–18)</td>
<td>32.9</td>
<td>6.4 (5.0–9.9)</td>
<td>13.3 ±3.0</td>
<td>100 (34–6400)</td>
</tr>
<tr>
<td>P</td>
<td>0.2000</td>
<td>0.7550</td>
<td>0.0420</td>
<td>0.1160</td>
<td>–</td>
</tr>
<tr>
<td>Subgroup B1a (n=22)</td>
<td>10.5 (4.0–15.9)</td>
<td>50.0</td>
<td>5.6 (5.0–7.8)</td>
<td>14.3 ±3.4</td>
<td>305.5 (40–2042)</td>
</tr>
<tr>
<td>Subgroup B2b (n=21)</td>
<td>13.3 (6.3–18.0)</td>
<td>42.9</td>
<td>7.3 (5.0–9.4)</td>
<td>13.9 ±2.5</td>
<td>347.0 (40–6400)</td>
</tr>
<tr>
<td>Subgroup B3c (n=42)</td>
<td>4.5 (2.5–18.0)</td>
<td>19.0</td>
<td>7.0 (5.0–9.9)</td>
<td>12.1 ±3.5</td>
<td>66.4 (34–2400)</td>
</tr>
<tr>
<td>P B1 vs B2</td>
<td>0.0070</td>
<td>0.6400</td>
<td>0.0008</td>
<td>0.6440</td>
<td>0.0420</td>
</tr>
<tr>
<td>P B1 vs B3</td>
<td>0.0004</td>
<td>0.0100</td>
<td>0.0020</td>
<td>0.0240</td>
<td>0.4420</td>
</tr>
<tr>
<td>P B2 vs B3</td>
<td>0.0001</td>
<td>0.0450</td>
<td>0.7970</td>
<td>0.0530</td>
<td>0.0030</td>
</tr>
</tbody>
</table>

*No association with either Turner or Down syndrome.

*Association with Turner syndrome.

*Association with Down syndrome.
Patients of group B were in their turn divided into three subgroups, according to whether HT-related SH was either isolated (subgroup B1), associated with TS (subgroup B2), or DS (subgroup B3). These subgroups consisted, respectively, of 22, 21, and 42 girls.

Median ages (and ranges) at the start of follow-up and prevalences of the girls who had entered puberty at that time, in the different groups and subgroups, are detailed in Table 1.

Study design

All of the girls who were diagnosed in our clinics, during the period 2000–2008, as having a mild and either idiopathic or HT-related SH and fulfilled the above reported inclusion criteria were consecutively recruited for this prospective study.

From the time of recruitment all of them were followed-up as outpatients every 12 months for a pre-established period of 5 years and only those who completed the entire follow-up period were considered for this study.

At each examination TSH, FT4, TPOAb, and TGAb serum levels were investigated. In the patients who exhibited, at the annual investigations, a further increase in TSH levels to >10 mIU/l and/or a pathological decrease of FT4 levels to <10.3 pmol/l, l-T4 treatment was begun immediately, according to our guidelines (4) and other recommendations (32, 33). In the patients who, during follow-up, exhibited a dramatic fall in TSH serum levels to <0.3 mIU/l and/or a concomitant increase of FT4 to >24.4 pmol/l, methimazole treatment was begun immediately.

With regard to thyroid function at the end of the 5-year observation period, patients of both groups were evaluated according to FT4 and TSH serum levels and classified into the following biochemical patterns: euthyroidism (both TSH and FT4 within normal limits); SH (normal FT4, as opposed to elevated TSH); overt hypothyroidism (elevated TSH with low FT4); and hyperthyroidism (suppressed TSH, as opposed to either normal or elevated FT4).

The prevalence rates of the patients who, in the two groups, either normalized or maintained TSH within the initial limits, exhibited an overt hypothyroidism biochemical picture at the end of follow-up or required l-T4 therapy during the 5-year follow-up period were compared between them. The same comparisons were performed, in the context of group B patients, among those belonging to the subgroups B1, B2, and B3.

The girls who were under l-T4 therapy at the end of 5-year follow-up were analyzed 6 weeks after treatment withdrawal. Those who were under methimazole treatment at the end of observation period were considered as patients who shifted over time from HT to Graves’ disease (GD), provided that TSH receptor autoantibodies (TRABs) were positive.

Methods

Serum levels of TSH (normal range 0.3–4.5 mIU/l) and FT4 (normal range 10.3–24.4 pmol/l) were measured by RIA methods. TPOAbs (reference range 0–20 IU/ml) and TGAbs (reference range 0–30 IU/ml) were measured by chemiluminescent immunometric assays (34).

TRAB serum levels were measured by a second generation radioreceptor assay using the human recombinant TSH receptor only in the patients who, during follow-up, developed a hyperthyroid biochemical picture and underwent methimazole therapy. According to this method, values above 1.5 IU/ml are considered as positive (35).

Statistical analysis

Results are expressed as mean±S.D. or median and range values, as appropriate. Comparisons between groups were performed by Student’s unpaired and paired t-test (normally distributed data) or Mann–Whitney and Wilcoxon test (non-normally distributed data), as appropriate. Frequency rates were compared by the χ2 test. Correlations between quantitative variables were assessed using Pearson’s correlation analysis. The level of significance was set at 0.05 for all of the statistical analyses. The study design was approved by the ethical committees of the hospitals participating in our study and the children’ parents gave informed consent. Appropriate consent was also obtained earlier from the study group for thyroid diseases of the Italian Society for Pediatric Endocrinology and Diabetology.

Results

Main data at the start of follow-up

Median age at follow-up onset was not significantly different in the girls of group A than in those of group B (Table 1). Even though expressed as mean±S.D., patients’ age at entry was similar in these two groups (7.5±3.8 years vs 8.9±4.9 years, P=0.200). Furthermore, the prevalence rates of patients who had entered puberty at follow-up initiation did not significantly differ in these two groups.
Among the girls of group B, the oldest ones belonged to subgroup B2, while the youngest ones belonged to subgroup B3. Consequently, the prevalence of girls who had entered puberty at the time of SH diagnosis was significantly lower in subgroup B3 than in the other two subgroups.

TSH values were initially slightly higher in group B than in group A, whereas no differences were detected between these groups in terms of FT4 values.

In the context of girls with HT-related SH, those with DS (subgroup B3) exhibited both higher TSH and lower FT4 values with respect to those of subgroup B1, whereas the girls with TS (subgroup B2) exhibited higher TSH but very similar FT4 levels when compared with subgroup B1 patients. Both TSH and FT4 values were not different in subgroups B2 and B3.

The lowest autoantibody serum levels were initially found in the subgroup of girls with DS, whereas no differences were detected between subgroups B1 and B2.

**Main data at the end of follow-up**

Median age at the end of follow-up was very similar in the girls of groups A and B and no significant differences between these cohorts were detected even though age was expressed as mean ± s.d. (12.3 ± 4.0 years vs 13.8 ± 4.9 years, P = 0.0941; Table 2). Furthermore, the prevalence rates of patients who had entered puberty at the time of study withdrawal did not significantly differ in these groups.

Among the girls of group B, the oldest ones belonged to subgroup B2, whereas the youngest ones belonged to subgroup B3. Consequently, the prevalence of girls who had entered puberty at the end of follow-up period was significantly lower in subgroup B3 than in the other two subgroups.

During follow-up median TSH serum levels significantly decreased in the patients of group A, while they significantly increased in group B girls. Therefore, at the end of follow-up, median TSH values became significantly higher in group B patients than in those of group A. By contrast, during the same observation period, mean FT4 serum levels significantly decreased in group B girls, whereas they remained unchanged in those of group A. Nevertheless, mean FT4 levels, at the end of follow-up, did not significantly differ in these two groups.

In the context of patients with HT-related SH, during follow-up, those with TS (subgroup B2) as well as the girls with no chromosomopathies (subgroup B1) exhibited both a significant increase of TSH values and a significant decrease of FT4 values. By contrast, during the follow-up period, the girls of subgroup B3 maintained substantially unchanged baseline TSH and FT4 serum levels.

As a consequence of these time-related changes, at the end of follow-up, the girls of subgroup B2 showed the highest TSH values and the lowest FT4 values, with respect to the patients of the other two subgroups. By contrast, at the end of follow-up, the girls with DS exhibited TSH and FT4 serum levels that were not significantly different than those detected in subgroup B1 patients.

**Thyroid function patterns at the end of 5-year follow-up**

At the end of follow-up, the majority of girls with idiopathic SH (26/42) became biochemically euthyroid.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Age (years) and prevalence (%) of pubertal patients and TSH (mIU/l) and FT4 (pmol/l) serum levels at the end of follow-up in the two groups with either idiopathic subclinical hypothyroidism (SH; group A) or Hashimoto’s thyroiditis (HT)-related SH and in three subgroups of patients with HT-related SH.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A (n = 42)</td>
<td>Age (7.5–19.0)</td>
</tr>
<tr>
<td>Group B (n = 85)</td>
<td>Age (7.5–23.0)</td>
</tr>
<tr>
<td>Subgroup B1** (n = 21)</td>
<td>Age (9.0–20.9)</td>
</tr>
<tr>
<td>Subgroup B2** (n = 21)</td>
<td>Age (13.1–23.0)</td>
</tr>
<tr>
<td>Subgroup B3** (n = 42)</td>
<td>Age (7.5–23.0)</td>
</tr>
<tr>
<td>P B1 vs B2</td>
<td>P 0.0092</td>
</tr>
<tr>
<td>P B1 vs B3</td>
<td>P 0.0004</td>
</tr>
<tr>
<td>P B2 vs B3</td>
<td>P 0.0001</td>
</tr>
</tbody>
</table>

*Vs the corresponding levels measured at the start of follow-up.

**No association with either Turner or Down syndrome.

**Association with Turner syndrome.

**Association with Down syndrome.
whereas such an evolutive pattern was observed in a very low number of girls with HT-related SH (9/85) (Table 3).

Among the 16 patients of group A who did not become over time biochemically euthyroid, 10 (62.5%) required L-T4 treatment during follow-up. Over time, five of them had developed an overt hypothyroidism and the remaining five had increased their TSH values to >10 mU/l.

In the context of group B, most girls maintained, over time, a condition of SH or deteriorated their thyroid function picture to overt hypothyroidism. The prevalence of patients who needed L-T4 therapy during follow-up was, therefore, significantly higher in the patients of group B than in those of group A.

In group B, the poorest scores in terms of TSH normalization during follow-up were observed in both the subgroups with chromosomopathies. Nevertheless, while most girls with TS worsened their initial thyroid function pattern from SH to overt hypothyroidism over time, the majority of those with DS remained SH.

If subgroup B1 girls were compared with those of group A, the risk of developing an overt hypothyroidism over time was significantly higher (45.4% vs 11.9%, P=0.003). Furthermore, the percentage of subgroup B1 girls who required L-T4 therapy during follow-up was significantly higher (63.6% vs 23.8%, P=0.002).

A shifting from HT to GD (with increased FT4, suppressed TSH and positive TRABs) was recorded during follow-up in 3/85 girls of group B (but in none of group A). All of these girls belonged to the subgroup B3.

### Discussion

To the best of our knowledge, this is the first prospective study aiming to compare the outcome of thyroid function tests, after a 5-year follow-up, in two sex- and age-matched pediatric populations with either idiopathic or HT-related mild SH.

The first consideration, which emerges from the analysis of the results of our longitudinal study, is that the natural history of idiopathic SH in pediatric age seems to be characterized by a benign long-term evolution. In fact, the majority of these patients (61.9%) spontaneously normalized over time their TSH values, and only a small minority (11.9%) became overtly hypothyroid. Nevertheless, it has to be pointed out that almost a quarter of group A girls required L-T4 treatment during the observation period, which underlines the importance of a biochemical follow-up, even in the children with idiopathic and mild SH (33, 36). According to the recent guidelines of the European Thyroid Association, in these children monitoring can be performed every 12 months due to the low risk of progression (33).

Furthermore, the results of the present study confirm, on the basis of a more prolonged prospective evaluation, the recent inference that underlying HT negatively affects the natural course of SH in children, irrespective of other concomitant risk factors (12). In fact, when compared with group A girls, those belonging to group B exhibited both decreased probabilities of TSH normalization and an increased risk of thyroid function deterioration over time, irrespectively of whether HT-related SH was or was not

### Table 3

Prevalences (%) of the different biochemical patterns of thyroid function detected, at the end of a 5-year follow-up, in the two groups with either idiopathic subclinical hypothyroidism (SH; group A) or Hashimoto’s thyroiditis (HT)-related SH (group B) and in three subgroups of patients with HT-related SH and a percentage of those who, in the different groups and subgroups, required L-T4 treatment during follow-up.

<table>
<thead>
<tr>
<th></th>
<th>Euthyroidism</th>
<th>SH</th>
<th>Overt hypothyroidism</th>
<th>Hyperthyroidism</th>
<th>Overall dysfunctions</th>
<th>L-T4 therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A (n=42)</td>
<td>61.9</td>
<td>26.2</td>
<td>11.9</td>
<td>0</td>
<td>38.1</td>
<td>23.8</td>
</tr>
<tr>
<td>Group B (n=85)</td>
<td>10.6</td>
<td>55.3</td>
<td>30.6</td>
<td>3.5</td>
<td>89.4</td>
<td>63.5</td>
</tr>
<tr>
<td>P</td>
<td>0.0001</td>
<td>0.020</td>
<td>0.0200</td>
<td>0.2180</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Subgroup B1 (n=22)a</td>
<td>36.4</td>
<td>18.2</td>
<td>45.4</td>
<td>0</td>
<td>63.6</td>
<td>63.6</td>
</tr>
<tr>
<td>Subgroup B2 (n=21)b</td>
<td>0</td>
<td>33.3</td>
<td>66.7</td>
<td>0</td>
<td>100</td>
<td>80.9</td>
</tr>
<tr>
<td>Subgroup B3 (n=42)c</td>
<td>2.4</td>
<td>85.7</td>
<td>4.8</td>
<td>7.1</td>
<td>97.6</td>
<td>54.8</td>
</tr>
<tr>
<td>P A vs B1</td>
<td>0.0520</td>
<td>0.4730</td>
<td>0.0030</td>
<td>–</td>
<td>0.0520</td>
<td>0.0020</td>
</tr>
<tr>
<td>P B1 vs B2</td>
<td>0.0020</td>
<td>0.2550</td>
<td>0.1610</td>
<td>–</td>
<td>0.0020</td>
<td>0.2060</td>
</tr>
<tr>
<td>P B1 vs B3</td>
<td>0.0002</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.1990</td>
<td>0.0002</td>
<td>0.4950</td>
</tr>
<tr>
<td>P B2 vs B3</td>
<td>0.4760</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.2090</td>
<td>0.4760</td>
<td>0.0420</td>
</tr>
</tbody>
</table>

aNo association with either Turner or Down syndrome.
bAssociation with Turner syndrome.
cAssociation with Down syndrome.
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associated with TS or DS. In fact, even in the subgroup with HT and no chromosomopathies, \( \text{\texttt{L-T_4}} \) therapy was needed more often than in the group with idiopathic SH.

The different SH outcome in groups A and B cannot be explained by a different age or a different distribution of prepubertal and pubertal patients, because such parameters were very similar in the two groups.

Another peculiar aspect of the present study is that the patient series with HT-related SH was in turn divided in three subcohorts of girls with or without chromosomopathies. This study design gave us the opportunity to evaluate whether the association with either TS or DS may modify the natural history of mild SH in the girls with HT.

Our results confirm, throughout a prospective 5-year study, the sporadic reports that the association with either TS (26, 37) or DS (38) seems to be able to affect the course of HT by increasing the risk of a thyroid function deterioration over time. In particular, it is noteworthy that the almost totality of our patients with HT-related SH and associated TS or DS exhibited, at the end of the observation period, a biochemical picture of thyroid dysfunction: either SH, overt hypothyroidism or hyperthyroidism.

In the present study, both TGAb and TPOAb serum levels were distinctly lower in DS girls than in those with TS, which seems to support the hypothesis that, in the pathogenesis of HT-related SH, other factors apart from autoimmunity might be involved in DS patients (39, 40, 41). However, it has to be emphasized that, in the present study, all the DS girls with SH exhibited an underlying HT.

A further finding that deserves to be emphasized in this study is that, in 7.1% of DS girls, HT switched over time toward GD. This is not surprising considering that such a conversion is known to be detectable in the natural history of patients with HT (42, 43, 44, 45, 46) and has also been specifically described in children with either TS (29, 30, 31) or DS (38, 47). Moreover, the shifting HT→GD has been, just recently, found to be more common in GD children with these chromosomal aberrations than in those without them (48).

Finally, from a methodological point of view, it is known that age-specific reference ranges should be used when measuring TSH and FT\(_4\) in children. During very early life, in fact, the values of these hormones may range widely, making it challenging to interpret measurements in infants and, especially, newborns (49). In the present study, however, median ages of the girls included in the two study groups with either idiopathic or HT-related SH were very similar and no patients <2.5 or >18 years were initially included in the overall study population.

Nevertheless, we are well aware of the fact that, in the context of group B, median ages were significantly different in the subgroups, particularly between subgroups B2 and B3. Therefore, TSH and FT\(_4\) values in these subgroups might be hard to compare among them. In fact, it is known that TSH values are greatest during the first months of life and subsequently tend to decrease with age (50).

Surprisingly, in the present study, the highest TSH values were detected, both at entry and at the end of follow-up, in the subgroup of TS patients, i.e., those with the most advanced median age. These findings suggest that, if compared with the other patient subgroups, the TS girls with HT-related SH are per se more inclined to deteriorate their thyroid status over time, irrespective of age.

**Conclusion**

Long-term prognosis of mild and idiopathic SH is frequently benign, even though a \( \text{\texttt{L-T_4}} \) treatment may be needed throughout follow-up in almost a quarter of cases. Long-term prognosis is different in the girls with either idiopathic or HT-related SH. The association with either TS or DS impairs the outcome of HT-related SH.

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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