

In children with Hashimoto's thyroiditis the evolution over time of thyroid status may differ according to the different presentation patterns

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Summary. *Aim:* to report the salient literature news concerning the relationships between thyroid function presenting patterns and subsequent biochemical evolution of Hashimoto's thyroiditis (HT) in pediatric age. *Design:* the most recent reports from pediatric literature concerning biochemical thyroid function patterns at HT presentation and their spontaneous changes over time were analyzed and shortly commented. *Results:* from the analysis of pediatric literature on this theme, it emerges that HT in children may present with a very heterogeneous biochemical picture ranging from overt hypothyroidism to overt hyperthyroidism. The presenting biochemical pattern may also condition its subsequent evolution over time. *Conclusions:* a) the most common biochemical pattern at HT diagnosis in children is euthyroidism, followed by overt hypothyroidism, subclinical hypothyroidism (SH) and hyperthyroidism; b) the association with HT negatively affects the evolution over time of SH; c) in the cases with either Turner syndrome or Down syndrome the evolution over time of SH is more severe than in those without these chromosomopathies. (www.actabiomedica.it)

Key words: autoimmune thyroid diseases, Down syndrome, euthyroidism, hyperthyroidism, overt hypothyroidism, subclinical hypothyroidism, Turner syndrome, thyroid function patterns

List of abbreviations

HT: Hashimoto's thyroiditis; SH: subclinical hypothyroidism;
TS: Turner syndrome; DS: Down syndrome; GD: Graves' disease.

Background

Hashimoto's thyroiditis (HT) is by far the most common form of thyroiditis in childhood, with a relative prevalence that has been reported to fluctuate around 98% (1). Moreover, HT is one of the most common children's autoimmune disorders and the most frequent cause of pediatric thyroid diseases in iodine-replete areas of the world.

At the time of diagnosis, HT children may be asymptomatic and the main reasons for referral are thyromegaly and findings which occur while working on unrelated problems for high-risk groups (2). Thyroid function at HT presentation may be extremely variable, ranging from euthyroidism to overt hypothyroidism or, occasionally, hyperthyroidism (3). Also its evolution over time may be as much variable, at least according to the most recent reports on HT natural course in children and adolescents(4-11).

The aim of the present review is to report the salient literature news concerning the relationships between thyroid function presenting patterns and subsequent biochemical evolution of HT in pediatric age.

Biochemical thyroid function patterns at HT presentation

According to a very recent study (12), that was based on the largest number of children and adolescents so far reported in the literature, the most common biochemical pattern at HT diagnosis seems to be euthyroidism (52.1% of cases), followed by overt hypothyroidism, subclinical hypothyroidism (SH) and either overt or subclinical hyperthyroidism (Table 1). These data are not very far from those reported by other authors (8,13). According to other pediatric epidemiological studies (4-6,9), in contrast, the prevalence of euthyroidism at HT presentation seems to be distinctly lower and the most frequent biochemical patterns recorded at HT diagnosis are overt hypothyroidism and SH (Table 1).

In the series by Wasniewska et al (12), biochemical and clinical involvement was mainly conditioned by patients' age, resulting particularly severe in the children with early and prepubertal HT presentation, a finding that had been previously recorded also in another study population (13).

Other variables which may be involved in conditioning the risk of thyroid dysfunctions at HT diagnosis are environmental factors (14) and the association with other autoimmune diseases or chromosomopathies, such as Turner syndrome (TS) or Down syndrome (DS) (12).

The association with TS is known to be able to significantly affect the biochemical HT presentation, by conditioning a less severe thyroid function initial involvement. In the majority of TS girls, in fact, HT presents with a euthyroid biochemical pattern (73.3%

of cases), whereas the prevalence of overt hypothyroidism (3.3%) is negligible and significantly lower than in HT girls without TS (15). The less severe biochemical pattern exhibited by TS girls at HT presentation is not necessarily linked with a specific karyotype (15).

In contrast, in DS children biochemical presentation of HT has been just recently reported to be characterized by a more severe initial picture, as substantiated by the high prevalence of SH (63.0%) and the low prevalence of euthyroidism (13.7%) (16). Thyroid dysfunctions at HT diagnosis are, on overall, significantly more common in children with DS than in those without DS (16).

Evolution over time of thyroid function picture

It may change according to the different presentation patterns of HT (17). In the cases presenting with euthyroidism natural course of thyroid function seems to be characterized by a progressive deterioration over time in around 50% of HT children (10). The initial presence of thyromegaly and/or elevated thyroglobulin autoantibodies have been considered as predictive factors for the future development of hypothyroidism (10).

Also in the cases presenting with SH the natural history of thyroid function in children' HT has been reported to be characterized by a spontaneous deterioration over time (11). Such trend has been demonstrated to be irrespective of other concomitant risk factors, with a low probability of spontaneous TSH normalization (21.9%) (18). Furthermore, the risk of

Table 1. Prevalences (%) of the different thyroid function patterns at Hashimoto's thyroiditis presentation, according to different pediatric epidemiological studies

| Authors (reference) * | Euthyroidism | Subclinical hypothyroidism | Overt hypothyroidism | Overt hyperthyroidism | Subclinical hyperthyroidism |
|--------------------------|--------------|----------------------------|----------------------|-----------------------|-----------------------------|
| Demirbilek et al (5) | 44.2 | 22.5 | 23.2 | 10.1 | — |
| Fava et al (9) | 30.4 | 60.8 | 8.8 | — | — |
| Gopalakrishnan et al (4) | 24.6 | 32.6 | 42.8 | — | — |
| Ozen et al (6) | 36.7 | 32.7 | 16.8 | 5.9 | 7.9 |
| Skarpa et al (13) | 57.0 | 32.9 | 8.3 | 1.8 | — |
| Wang et al (8) | 53.2 | 31.9 | 14.9 | — | — |
| Wasniewska et al (12) | 52.1 | 19.2 | 22.2 | 3.5 | 3.0 |

*according to the reference list of the present study

developing over time a biochemical picture of overt hypothyroidism seems to be significantly higher in the children with HT-related SH than in those with idiopathic SH (18). Moreover, HT-related SH may also be associated with an increased probability of developing over time a pathological increase of thyroid volume (18).

In the cases presenting with overt hyperthyroidism, i.e. hashitoxicosis, a definitive resolution of hyperthyroidism has to be generally expected after an average period of eight months from the time of diagnosis (19), although there may be a wide variability between subjects (20). However, the hyperthyroid phase, that may be observed in only few HT children (21), is always followed by definitive resolution with persistent euthyroidism or hypothyroidism and no hyperthyroid relapses (19,20). Pharmacological therapies are very infrequently required and non-pharmacological therapies are never needed (19,20).

In the children presenting with HT-related subclinical hyperthyroidism a spontaneous normalization of TSH serum levels occurs within the first 24 months following HT diagnosis (22), as well as in those with hashitoxicosis (19). According to the results of the only available study on the longitudinal course of HT-related subclinical hyperthyroidism in childhood, the frequency with which this condition risks progressing to clinically overt hyperthyroidism has to be considered very low, irrespective of both TSH and FT4 baseline serum concentrations (22).

The natural history of HT in the cases presenting with overt hypothyroidism is not well known, since these children are generally treated with replacement therapy from the time of diagnosis.

Finally, another possible evolutive pattern of thyroid function in HT children is the switching towards a picture of hyperthyroidism in the context of a Graves' disease (GD). This finding has raised in the last years interesting questions about the metamorphosis of phenotype in thyroid autoimmunity and has confirmed the existence of a continuum between HT and GD within the spectrum of autoimmune thyroid diseases (23-29). Such a conversion process from HT to GD is not very common in the pediatric general population (3.7% of cases) (25), whereas it is significantly more frequent (25.7% of cases) in the children with either TS or DS (30).

Table 2 summarizes the prevalences of the different thyroid function patterns at the end of follow-up in untreated children with HT, according to different epidemiological studies. From the analysis of these reports it emerges that natural evolution over time of thyroid function picture may be extremely variable in HT children, probably due to the different nature of these studies (either retrospective or prospective) and the different duration of follow-up periods.

Discussion

From the analysis of pediatric literature, it is confirmed that HT in children may present with a very heterogeneous biochemical picture, which may also condition its subsequent evolution.

A question which has been largely debated during the last years is whether the children presenting with HT-related SH and mild elevations of serum TSH should be treated since the time of diagnosis or only in

Table 2. Prevalences (%) of the different thyroid function patterns at the end of follow-up in untreated children with Hashimoto's thyroiditis, according to different epidemiological studies

| Authors (reference) * | Euthyroidism | Subclinical hypothyroidism | Overt hypothyroidism | Hyperthyroidism |
|--------------------------|--------------|----------------------------|----------------------|-----------------|
| Aversa et al (18) | 21.9 | 21.9 | 53.1 | 3.1 |
| Demirbilek et al (5) | 57.4 | 13.9 | 27.9 | 0.8 |
| Fava et al (9) | 43.5 | 43.5 | 13.0 | — |
| Gopalakrishnan et al (4) | 28.6 | 21.4 | 50.0 | — |
| Ozen et al (6) | 57.2 | 42.8 | — | — |

*according to the reference list of the present study

light of the subsequent course. According to the very recent report by Aversa et al (18), it may be argued that the association with HT exerts, per se, a negative influence on the evolution of SH, by conditioning an increased risk of both thyroid status deterioration and gland enlargement. Therefore, it may be concluded, on the basis of that comparative and prospective study (18), that SH may have a different outcome in the idiopathic cases and in those with an underlying HT. Whereas in the children with an idiopathic form SH is frequently characterized by a mild biochemical course (31-35), in those with an underlying HT its evolution over time is generally more severe (18,36,37).

Consequently it might be reasonable to consider the possibility of a different management approach to the children with HT-related SH vs those with an idiopathic form. A strict monitoring of thyroid status changes would be especially suitable for the children with DS or TS, who are particularly inclined to deteriorate over time thyroid function picture (15,16). However, thyroid function tests should be periodically repeated in all the patients with HT, in order to detect progression to hypothyroidism in initially euthyroid or SH patients as well as reversibility of SH (5).

Another interesting point which emerges from the analysis of pediatric literature is that HT in children may not infrequently present with a hyperthyroid biochemical picture (5,6,12,19-22) and may evolve towards hyperthyroidism, even though this evolutive pattern is very uncommon, at least in the pediatric general population (5,8,25). Nevertheless, in the HT children with either DS or TS the switching from HT to GD has been just recently demonstrated to be significantly more frequent than in HT children without these chromosomopathies, thus suggesting that children with either TS or DS are more likely to progress from HT to GD (30). A mechanism which has been guessed to account for the evolution from HT to GD is the alteration in the biological activity of TSH receptor autoantibodies, from predominantly thyroid-blocking antibodies during the HT phase to thyroid-stimulating antibodies when GD manifests itself (23). However, the pathophysiological bases of these findings have not been completely elucidated to date (30).

Conclusions: a) the most common biochemical pattern at HT diagnosis in children is euthyroidism,

followed by overt hypothyroidism, SH and hyperthyroidism; b) the association with HT negatively affects the evolution over time of SH; c) in the cases with either TS or DS the evolution over time of SH is more severe than in those without these chromosomopathies.

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