

COMMENTARY

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Thyroid function test evolution in children with Hashimoto's thyroiditis is closely conditioned by the biochemical picture at diagnosis

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Abstract

Aim of this commentary is to summarize the salient literature views on the relationships between presentation and evolution patterns of thyroid function in children with Hashimoto's thyroiditis (HT).

According to the most recent reports, children with HT and subclinical hypothyroidism (SH) are more prone to the risk of developing severe thyroid dysfunctions over time, if compared to those presenting with euthyroidism. In contrast, children presenting with HT and either overt or subclinical hyperthyroidism are inclined to exhibit a definitive resolution of the hyperthyroid phase within some months, although there is a wide variability between the different individuals.

The natural history of frank hypothyroidism in the children with HT has never been investigated so far, since in these cases an immediate onset of replacement treatment is mandatory.

Conclusions: 1) a deterioration of thyroid status over time may be observed especially in the children presenting with SH, but also in those presenting with euthyroidism; 2) a definitive resolution of the hyperthyroid phase is generally observed in those presenting with either overt or subclinical hyperthyroidism.

Keywords: Hashitoxicosis, Overt hyperthyroidism, Overt hypothyroidism, Subclinical hyperthyroidism, Subclinical hypothyroidism, Thyroid status natural course

Background

Hashimoto's thyroiditis (HT) is a relatively common disease, whose prevalence in childhood has been reported to range around 3% and to achieve its peak during adolescence [1]. It is the commonest form of thyroiditis in pediatric age [2] and the most frequent cause of pediatric thyroid disease in iodine – replete areas of the world [3].

At the time of diagnosis, children with HT are frequently asymptomatic, with a thyroid function picture ranging from euthyroidism (52.1% of cases) to either overt hypothyroidism (in 22.2% of cases) or, more rarely, subclinical hypothyroidism (SH) (in 19.2% of cases) [4]. Other complaints of thyroid function, which may be

sometimes (6.5% of cases) encountered in pediatric age at HT presentation, include either subclinical or overt hyperthyroidism [4–6]. It has been also reported that, in at least 3–4% of the children with Graves' disease (GD), the onset of hyperthyroidism may be preceded by HT antecedents [7], which suggests the existence of a continuum between HT and GD, within the broad spectrum of autoimmune thyroid disorders (AITDs) [8–10].

According to the available pediatric epidemiological studies, the prevalence rates of thyroid function patterns, at HT diagnosis, may significantly vary in the different series [4, 11–17], as summarized in Table 1.

Although the recent literature includes many reports on the biochemical presentation of HT in pediatric age [4–6, 11–17], only few studies have specifically addressed whether the hormonal pattern at HT presentation may in

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Table 1 Prevalence rates (%) of the main thyroid function patterns, at Hashimoto's thyroiditis presentation, in pediatric cohorts, according to different epidemiological studies

Authors	Nos. patients	Euthyroidism	Subclinical hypothyroidism	Overt hypothyroidism	Hyperthyroidism
Zak et al. (2005) [11]	100	63	26	—	11
Svensson et al. (2006) [12]	90	39	47	14	—
Demirbilek et al. (2007) [13]	162	43.2	24.1	21	not stated
Gopalakrishnan et al. (2007) [14]	98	24.5	32.6	42.9	—
de Vries et al. (2009) [15]	114	21	42	37	—
Ozen et al. (2011) [16]	101	36.7	32.7	16.8	13.8
Skarpa et al. (2011) [17]	228	57	32.9	8.3	1.8
Wasniewska et al. (2012) [4]	608	52.1	19.2	22.2	6.5

any way condition the subsequent course of thyroid function tests over time [5, 18–20].

The aim of the present review is to analyze the available studies on this topic, i.e. the possible relationships between presentation and evolution patterns of thyroid function in children with HT.

Long-term prognosis of thyroid function in the cases presenting with euthyroidism

Euthyroidism is the commonest presentation pattern of HT in pediatric age [4–6].

Whereas in adults it is often observed a progressive shift from euthyroidism toward SH or frank hypothyroidism [21], in childhood and adolescence the natural long-term evolution of thyroid tests may be quite variable. In fact, in the 4-year follow-up study by Radetti et al. [18], a large majority of initially euthyroid patients remained euthyroid. In contrast, according to the more recent study by Aversa et al. [20], only 57.1% of initially euthyroid children remained euthyroid even five years after HT diagnosis. The remaining 42.9% deteriorated their thyroid status over time, thus developing a SH in 30.6% of cases and an overt biochemical hypothyroidism in 12.3% [20]. The presence of goiter and elevated thyroglobulin autoantibodies at HT diagnosis might be considered as predictor for the future development of hypothyroidism [18].

On overall, from the analysis of the available longitudinal studies concerning the long-term prognosis of thyroid function in patients with HT, it may be argued that even the children who are initially euthyroid, at the time of HT diagnosis, should undergo a biochemical follow-up of thyroid function. A periodical monitoring of thyroid tests over time is even more indicated in adults, who are more incline than young patients to the risk of deteriorating their thyroid status [21].

Long-term prognosis of thyroid function in the cases presenting with SH

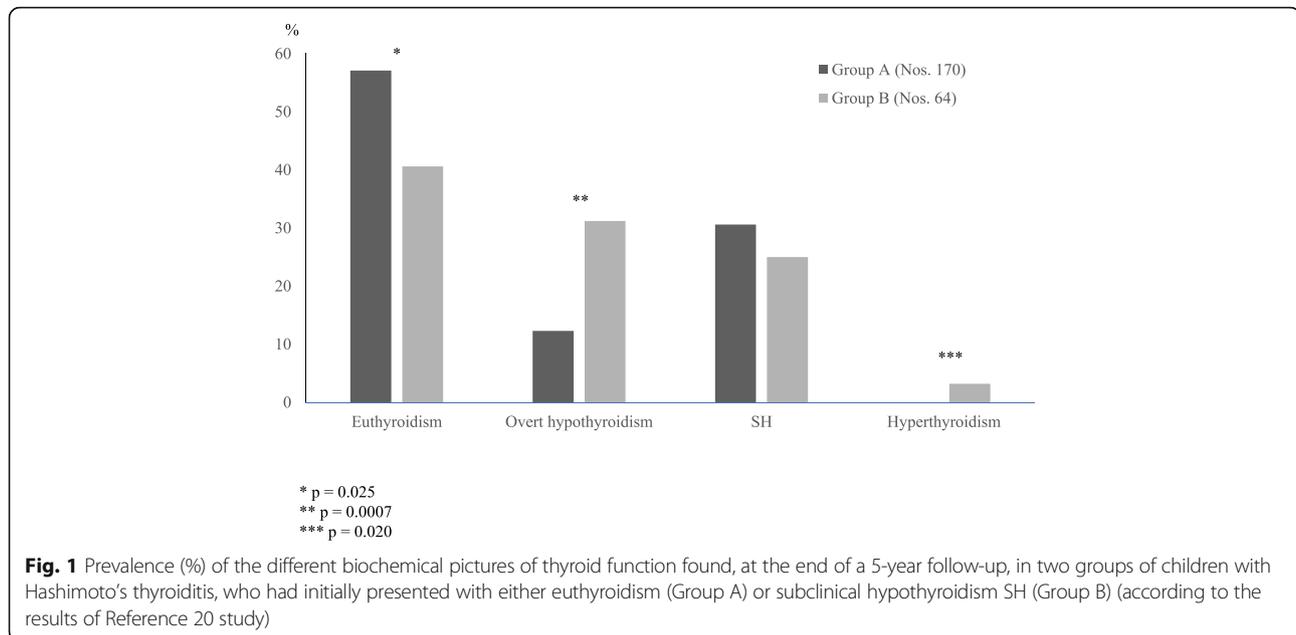
The natural evolution of thyroid status, in HT children who presented with SH, has been just recently reported

to be more severe than in those who presented with euthyroidism [20]. In fact, at the end of a 5-year follow-up, the prevalence of patients with overt hypothyroidism was significantly higher in the cohort with initial SH, whereas the prevalence of those with euthyroidism was significantly higher in the other group (Fig. 1). Furthermore, in the same study [20], a 0.8% of the children who had presented with SH developed over time a picture of GD (Fig. 1), a sequence of events which has been reported to occur more often in young patients with either Turner syndrome (TS) or Down syndrome (DS) [22–27], but may also be observed in the general pediatric population [7–10].

It has to be underlined that the long-term prognosis of thyroid status in children with HT-related SH is not necessarily unfavorable, since 40.6% of the SH patients included in the study by Aversa et al. [20] spontaneously normalized TSH values at the end of follow-up (Fig. 1), as also observed by other authors [28–30].

Thyroid function prognosis, however, is on overall significantly more severe in children with HT-related SH than in those with idiopathic SH and underlying AITDs [31]. In fact, the percentage of SH children who, during a 2-year follow-up, increase TSH values to > 10 mU/l and require L-T4 therapy is known to be significantly higher in the subgroup with HT-related SH than in those with idiopathic SH [31]. Therefore, it may be inferred that the association with HT is able to exert a negative impact on the course of SH in pediatric age.

It has to be emphasized that the process of spontaneous deterioration of thyroid function, that may occur over time in the children with HT-related SH, may be very slow and not predictable in the single case [19]. Therefore, although surveillance is mandatory in all these cases, it might be necessary a long time to infer whether L-T4 treatment should be implemented or not [20]. The coexistence of additional risk factors, such as celiac disease or elevated TSH and thyroid peroxidase autoantibodies, at HT diagnosis, seems to augment the probabilities that SH children with HT may develop a



frank hypothyroidism 3 years later [19]. Thus, an elevated TSH at HT diagnosis could be considered as the best predictor for a thyroid function deterioration from SH to overt hypothyroidism, as already suggested by other studies concerning patients with SH and no underlying AITDs [32, 33].

Finally, another factor which might exert a negative impact on the long-term evolution of SH is the association with either TS or DS, two chromosomopathies that may be linked with an increased risk of thyroid status deterioration over time [25, 26, 34]. In fact, the prevalence of euthyroidism in two cohorts of children with HT-related SH and either DS or TS was found to be significantly lower, at the end of a 5-year follow-up, than that detected in children with HT-related SH but without DS or TS (Fig. 2).

Long-term prognosis of thyroid function in the cases presenting with overt hyperthyroidism

Such a presentation pattern of HT, that is also called Hashitoxicosis (Htx), is not very common in the pediatric age, although Htx is generally reported as the second commonest cause of hyperthyroidism in childhood, after GD [35]. This condition is believed to result from unregulated release of stored thyroid hormones, during inflammatory-mediated destruction of thyroid [36]. Presenting symptoms are very similar to those of GD and differential diagnosis between these two conditions may be challenging, if only based on clinical and biochemical findings [36, 37]. Nevertheless, thyrotropin receptor autoantibodies, which are accepted to be one of GD hallmarks [36], are generally absent in the children with Htx [37].

According to the few available reports on the natural history of Htx in pediatric age [36, 37], the hyperthyroid phase is always followed by definitive resolution, with persistent euthyroidism and no hyperthyroid relapses [37]. Management of children with Htx requires only a prolonged clinical and biochemical follow-up, but pharmacological treatment may be occasionally needed only in few selected cases; non-pharmacological therapies are never required [37]. A spontaneous and definitive resolution of hyperthyroidism generally occurs on average five months after Htx presentation, although there is a wide variability between the different individuals (Table 2). The children with a more severe Htx course and a longer duration of the hyperthyroid phase have been reported to exhibit higher thyroid autoantibodies at Htx diagnosis [37]. Nevertheless, such a finding needs to be confirmed by further reports.

Long-term prognosis of thyroid function in the cases presenting with subclinical hyperthyroidism

Subclinical hyperthyroidism is defined as a serum TSH concentration below the lower limit of the reference range, when FT4 levels are within their reference ranges [38]. Such a biochemical condition may be detected in 3% of the children at HT presentation, a prevalence that is very close to the one of Htx, i.e. 3.5% [4].

The natural history of HT-related subclinical hyperthyroidism has been so far investigated in only few children [39]. According to the results of that prospective study, HT-related subclinical hyperthyroidism may spontaneously resolve in all cases within the first 1–24 months after HT presentation (Table 2).

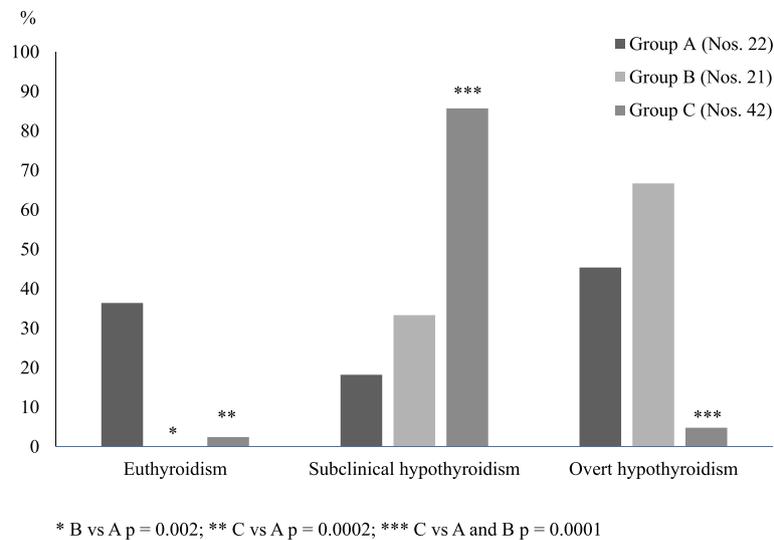


Fig. 2 Prevalence (%) of the main biochemical pictures of thyroid function found, at the end of a 5-year follow-up, in three groups of children with Hashimoto's thyroiditis (HT)-related subclinical hypothyroidism (SH) and no chromosomopathies (Group A) or HT-related SH and Turner syndrome (Group B) or HT-related SH and Down's syndrome (Group C) (according to the results of Reference 26 study)

On the basis of those findings, it was argued that, at least in childhood, the frequency with which HT-related subclinical hyperthyroidism risks progressing to overt hyperthyroidism should be considered very low, irrespectively of both TSH and FT4 serum concentrations at HT diagnosis [39]. According to other reports, the risk of progression to frank hyperthyroidism in the patients with this biochemical condition is distinctly higher, particularly in the cases with undetectable TSH levels at entry [40–42]. However, it has to be considered that, in those reports, natural history of subclinical hyperthyroidism was investigated in elderly patients [40–42], as against as in the study by Aversa et al. [39], which included only children and adolescents.

According to the results of the only available pediatric study on the natural history of subclinical

hyperthyroidism, the evolution of this condition over time does not seem to differ from that observed in the children with Htx, at least in terms of duration of TSH suppression periods. These findings suggest that Htx and HT-related subclinical hyperthyroidism might be simply different stages along the same continuum [39].

Long-term prognosis of thyroid function in the cases presenting with overt hypothyroidism

A picture of overt hypothyroidism may be observed, at diagnosis of HT, in 22.2% of the children, which represents the 2nd most frequent thyroid function pattern at HT presentation in pediatric age, after euthyroidism [4].

Nevertheless, the natural history of frank hypothyroidism in the children with HT has never been investigated to now, since in these cases a replacement treatment is always initiated immediately after diagnosis [15]. Treatment of overt thyroid failure, in fact, is always mandatory and urgent, especially in very young infants, who are also exposed to the risk of a permanent impairment of neuropsychological development, if not treated early [43].

However, the long-term evolution of thyroid function in the children with HT and overt hypothyroidism might be postulated to be not very far from the one historically reported by Rallison et al. in a large series of children with HT [44].

Finally, when we consider the very different biochemical patterns of thyroid function which may characterize HT presentation in children and adolescents, we should take into account a possible role of environmental factors, such as iodine status. In fact, a hypothyroid

Table 2 Spontaneous duration of TSH suppression and follow-up periods after TSH normalization (months) in two groups of untreated children with Hashimoto's thyroiditis who initially presented with either overt (Group A) or subclinical hyperthyroidism (Group B) (according to the results of Reference [37] and [39] studies)

	Group A (Nos. 10)	Group B (Nos. 11)	p
TSH suppression duration			
Mean ± SD	4.8 ± 2.0	7.8 ± 7.1	0.203
Range	3–23	1–24	
Follow-up periods			
Mean ± SD	21.5 ± 11.0	33.6 ± 19.5	0.094
Range	12–39	12–69	

presentation pattern may be observed more frequently in iodine deficient areas, whilst a hyperthyroid presentation picture may be found more often in areas where iodine intake is elevated [45, 46]. It has to be clarified, however, that all the patients of our cohort with either overt or subclinical hyperthyroidism at HT presentation exhibited an optimal iodine intake [37, 39].

Conclusions

a) The long-term evolution of thyroid function in children and adolescents with HT is significantly different according to whether HT has initially presented with either euthyroidism or SH or overt hyperthyroidism or subclinical hyperthyroidism; b) a progressive deterioration of thyroid status over time occurs especially in the children presenting with SH, but may also be observed in those presenting with euthyroidism; c) however, many children with either euthyroidism or SH at entry may be found to be euthyroid even five years after HT presentation; d) a definitive resolution of hyperthyroidism is generally observed within 24 months after HT diagnosis in both the groups of patients with either Htx or subclinical hyperthyroidism at entry.

Abbreviations

AITDs: Autoimmune thyroid disorders; DS: Down syndrome; GD: Graves' disease; HT: Hashimoto's thyroiditis; Htx: Hashitoxicosis; SH: Subclinical hypothyroidism; TS: Turner syndrome

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Authors' contributions

FDL wrote the paper; GC and RG have been involved in revising the manuscript for important intellectual outcome; GS and GZ have given substantial contributions to conception and design; MV has given substantial contribution to acquisition, analysis and interpretation of data; TA and MW have been involved in drafting the manuscript and looking for the most suitable references. All authors read and approved the final manuscript. Each Author listed on the manuscript has seen and approved the submission of the present version of the manuscript and takes full responsibility for the manuscript.

Ethics approval and consent to participate

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Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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