# Autoimmune Thyroiditis

16

Filippo De Luca, Tommaso Aversa, Giuseppina Salzano, Giuseppina Zirilli, Concetta Sferlazzas, and Malgorzata Wasniewska

## Abbreviations

| | |
|---|---|
| DS | Down's syndrome |
| HT | Hashimoto's thyroiditis |
| US | Ultrasonographic |
| FNAC | fine-needle-aspiration cytology |
| GD | Graves' disease |
| TS | Turner syndrome |
| Htx | Hashitoxicosis |
| TG | Thyroglobulin |
| TSH | Thyrotropin |
| TGAb | TG-autoantibodies |
| TRAb | TSH receptor autoantibodies |
| L-T4 | Levothyroxine |
| TPOAb | Thyroid peroxidase autoantibodies |
| SH | Subclinical hypothyroidism |

## 16.1 Definition

Thyroiditis is characterized by inflammation of thyroid gland and can present as acute, subacute, or chronic diseases. Chronic autoimmune lymphocytic thyroiditis or Hashimoto's thyroiditis (HT) is by far the most common inflammatory thyroid

F. De Luca, MD (✉) • T. Aversa, MD, PhD • G. Salzano, MD, PhD
G. Zirilli, MD, PhD • C. Sferlazzas, MD • M. Wasniewska, MD, PhD
Department of Pediatric, Gynecological, Microbiological and Biomedical Sciences, University of Messina, Via Consolare Valeria, Messina 98125, Italy
e-mail: filippo.deluca@unime.it; taversa@unime.it; gsalzano@unime.it; zirillig@gmail.com; concetta.sferlazzas@unime.it; mwasniewska@unime.it



G. Bona et al. (eds.), *Thyroid Diseases in Childhood: Recent Advances from Basic Science to Clinical Practice*, DOI 10.1007/978-3-319-19213-0_16

disorder in childhood, whereas the other forms of thyroiditis are very rare [1]. Furthermore, HT is the most frequent pediatric thyroid disease and the most common cause of goiter and acquired hypothyroidism in children and adolescents from iodine-replete areas in the world [2]. HT is being increasingly detected during the last years because of the higher awareness among pediatricians, the availability of better autoantibody assays and ultrasonographic (US) machines, and the more diffuse access to fine-needle aspiration cytology (FNAC) [3].

HT diagnosis in children is usually suspected in the presence of goiter, even in the absence of thyroid dysfunction signs and symptoms, and may also be established incidentally, during medical checkups, or in the evaluation of children with other autoimmune diseases [4].

HT was described for the first time in 1912 by the Japanese physician Hakaru Hashimoto in four middle-aged women, who presented with chronic thyroid disease and a histopathological picture characterized by lymphocyte infiltration, fibrosis, parenchymal atrophy, and eosinophilic changes of some acinar cells. Although it is known from over a century ago, HT may still sometimes present with surprisingly different clinical entities and frequently astonishes many physicians with one of its many faces [5].

The aim of this survey is to report the most recent views on epidemiology, pathophysiology, presentation, evolution over time, and long-term prognosis of HT in childhood and adolescence.

## 16.2 Epidemiology and Risk Factors

HT is a relatively common disease, whose prevalence in pediatric age has been reported to range from 0.3 to 3.3 %, achieving its peak during adolescence, whereas it is only infrequently diagnosed during the first 3 years of life [6]. Its prevalence between genders is markedly different, with five- to ten-fold excesses in girls [7]. HT prevalence is also significantly conditioned by environmental iodine status with lower prevalence rates in the pediatric populations with low urinary iodine levels [8].

An epidemiological peculiarity of HT is the significant clustering within families, with 31.6 % of children exhibiting a family history of thyroid autoimmune disorders in first-degree relatives [9]. A further epidemiological peculiarity of HT in childhood is the relatively frequent association with other autoimmune extrathyroidal diseases (17.6 %) [9]. Among the associated autoimmune diseases, the ones that are most frequently encountered in pediatric age are celiac disease, type 1 diabetes, vitiligo, and Addison's disease [9]. In adulthood, the autoimmune extrathyroidal diseases which are most frequently associated with HT are rheumatoid arthritis, pernicious anemia, vitiligo, Addison's disease, and celiac disease [10]. In the light of the above data and the results of other studies, it is largely accepted that HT segregates within families and that both children and adults with HT are more exposed to other autoimmune diseases [10–12].

**Table 16.1** Constitutional, environmental, and clinical factors that may condition an increased susceptibility to Hashimoto's thyroiditis in pediatric age

| Constitutional and environmental factors | Clinical factors |
|---|---|
| Female sex | Antecedents of Graves' disease |
| Adolescent age | Association with extra-thyroidal autoimmune diseases |
| Familiarity for thyroid diseases | |
| Iodine status alterations | Association with Turner syndrome |
| Selenium deficiency | Association with Down's syndrome |

Another relevant risk factor for HT in childhood is the association with either Down syndrome (DS) or Turner syndrome (TS), i.e., two chromosomopathies which have been shown to be linked with increased prevalence rates of both Graves' disease (GD) [13, 14] and HT [15, 16]. According to a very recent study on children' HT, 9 % of young patients with HT are affected by either DS or TS [9]. In particular, the prevalence of HT in TS is generally reported to fluctuate from 10 [17] to either 17 [18] or 21 % [19], and also in DS, HT is by far the most common autoimmune disease [20].

The mechanism responsible for the increased risk of autoimmune thyroid disorders and other autoimmune diseases in TS has been recently postulated to be associated with haploinsufficiency for X-chromosome-related genes [21], which may play an important role in the pathogenesis of autoimmune conditions [22]. Whereas some investigators reported that autoimmune thyroid disorders are especially common in TS girls with X-isochromosome karyotype, according to other authors HT is not associated with any specific karyotype [17, 18, 23].

Also in DS children, the mechanisms responsible for the strong association with HT have not been clearly elucidated [20].

The main epidemiological risk factors for HT are summarized in Table 16.1.

## 16.3 Pathophysiology

The current dogma is that HT develops in genetically predisposed individuals, in conjunction with exposure to environmental triggers [24].

The strongest evidence for a genetic contribution to the etiology of HT lies in twin studies, which demonstrated a higher concordance rate in monozygotic than in dizygotic twins: 30–40 % vs 0–7 % [25]. Thus, the twin data corroborate the presence of a substantial inherited susceptibility to HT [24].

The HT susceptibility genes can be divided into immunomodulating genes and thyroid-specific genes. The first group includes the cytotoxic T lymphocyte antigen-4 (CTLA-4) and the protein tyrosine phosphatase nonreceptor-22 (PTPN22) genes and especially some HLA haplotypes (DQA1, DQ2, and DRB1-1401) [26]. The second group includes thyroglobulin (TG) and thyrotropin (TSH) receptor genes [24, 26]. All these genes seem to participate in the immunological synapse

and/or the signaling pathways activated by the immunological synapse. This provides a potential molecular explanation for interactions between these HT susceptibility genes [24].

Among the environmental triggers, an important role is played by iodine status alterations [27] and selenium deficiency [28]. In particular, iodine deficiency is seen more frequently in the HT cases with hypothyroidism, while iodine excess is observed more frequently in those with hyperthyroidism [29]. However, it is well known that iodine supplementation is associated with an increasing risk of HT in people from iodine-deficient areas [30, 31] and that patients with HT are prone to develop hypothyroidism following iodine administration. The mechanism underlying the proimmunogenic effect of iodine in humans remains to be explained [7], but in mice the incorporation of iodine increases the immunogenicity of TG [32].

Another environmental factor which might be able to affect an increased susceptibility to HT is selenium deficiency, probably due to the effects of this mineral on immune systems [28]. Experimental studies demonstrated a significant reduction in TG-autoantibodies (TGAbs) following selenium supplementation in mice with iodine-induced autoimmune thyroiditis [33]. Nevertheless, clinical studies on the beneficial effects of this treatment in patients with HT are very few [28].

In the individuals who are genetically predisposed to HT and exposed to environmental risk factors, humoral autoimmunity is triggered by the abnormal stimulation of T lymphocytes, with consequent destruction of thyroid cells by chemotaxis, autoantibodies, and inflammatory cascade. The degradation of thyroid cells may be possibly compensated by increased TSH secretion, with consequent hyperplasia of epithelial cells and gland enlargement. However, increased TSH serum levels and goiter are not always detected in patients with HT.

In addition to the usual form of HT, other variants such as the fibrous type are also known. The most recently recognized variant is immunoglobulin G4 HT, which may occur as isolated thyroid limited disease or as a part of a generalized immunoglobulin G4-related sclerosing disease [34–36].

## 16.4 Interrelations with GD

Although HT and GD have different phenotypes and the mechanisms leading to their dichotomy are unknown, they are generally believed to share a number of common etiological factors. In fact, there have been reports on monozygotic twins in whom one twin had HT and the other had GD [37]. Moreover, both diseases may aggregate in the same families [38] or may even coexist in the same gland [39], and some patients may progress over time from one form to the other.

The metamorphosis of clinical phenotype from GD to HT or vice versa has been, in recent years, the theme of several reports, which raised interesting questions about the mechanisms of these fluctuations and concluded that, in the general population, there exists a continuum between HT and GD within the spectrum of

autoimmune thyroid diseases [40–44]. A mechanism that has been postulated to account for the switching from HT to GD is the alteration in the biological activity of TSH receptor autoantibodies (TRAbs), from predominantly thyroid-blocking antibodies during the HT phase to thyroid-stimulating antibodies when GD manifests itself [40]. According to this hypothesis, the emergence of thyroid-stimulating antibodies after levothyroxine (L-T4) therapy might be sufficient to counteract thyroid-blocking antibody inhibition [45]. However, although the pathophysiological bases of these conversion phenomena have not been clearly elucidated as of yet, it is well assessed, in the clinical practice, that GD presentation may be preceded in 3.7 % of cases by HT antecedents [41] and that this metamorphosis is by far more frequent (25.7 % of cases) in the patients with DS or TS [46]. It has been suggested, on the basis of these findings, that these chromosomal abnormalities might favor metamorphosis from HT to GD and that children with these chromosomopathies and coexisting HT might be at higher risk of progressing to GD [46]. However, the pathophysiological bases of this predisposition need to be elucidated.

## 16.5 Criteria for Diagnosis

HT diagnosis is based on the combination of clinical features, positivity of thyroid peroxidase autoantibodies (TPOAbs) and TGAbs, and specific US alterations, while thyroid function tests, radioiodine uptake, and FNAC are less relevant for diagnostic purposes.

TPOAbs are generally considered as the most specific serological marker of HT, since they are detected in around 95 % of HT patients, whereas they are rare in healthy individuals. TPOAb titers, moreover, are closely associated with the degree of US hypoechogenicity. TGAbs are positive in only 60–80 % of HT patients, which demonstrates a low degree of sensitivity. Moreover, they are also less specific since they are positive in a greater proportion of healthy controls. Nevertheless, also TGAbs have their own usefulness [47]. In fact, TGAbs and TPOAbs may represent two different aspects of the autoimmune response against thyroid gland, with TGAbs reflecting a more initial type of immune response and TPOAbs reflecting a later adaptive immune response [7].

US criteria for diagnosis of HT are based on the finding of a reduced echogenicity of thyroid gland, which reflects the histological changes occurring in the parenchyma as consequences of the inflammatory destruction of thyroid follicles. These are replaced by small lymphocytes, so that gland echogenicity progressively decreases, becoming similar to that of the surrounding strap muscles [7]. Thyroid echogenicity may be scored, in the clinical practice, according to the standards assessed many years ago by Sostre and Reyes [48]. These US scores maintain over the years a satisfactory clinical reliability and may be still employed, even nowadays, in the clinical practice, since they are able to depict the severity of inflammatory gland injury. In fact, they may also correlate with gland size and/or thyroid

**Table 16.2** Echographic scores vs goiter size, thyroid function clinical and biochemical status and antimicrosomal autoantibodies (MCHAbs) in adults with Hashimoto's thyroiditis

| Scores | Goiter size | Euthyroidism | Overt hypothyroidism | MCHAbs positive |
|---|---|---|---|---|
| | (grams) | (%) | (%) | >1:1,600 (%) |
| G1 | 27 | 100 | 0 | 0 |
| G2 | 37 | 50 | 0 | 62.5 |
| G3 | 33 | 25 | 50 | 83.3 |
| G4 | 52 | 9 | 83 | 75.0 |

According to the study of Sostre and Reyes [48]

function status and/or severity of autoimmune process, as found by Sostre and Reyes [48]. According to that study, the gradual decrease of thyroid echogenicity from G1 to G4 patterns is accompanied by a progressive increase in goiter size, hypothyroidism prevalence, and autoantibody positivity, as well as by a concomitant decrease of euthyroidism prevalence (Table 16.2).

## 16.6 Thyroid Function Tests at Presentation

At the time of diagnosis, children and adolescents with HT may be asymptomatic, and the main reasons for referral are goiter, hypothyroid symptoms, and findings which occur while working on unrelated problems or for high-risk groups [49].

Thyroid function at presentation may significantly vary in the different pediatric reports [3], ranging from euthyroidism to overt hypothyroidism or, occasionally, overt hyperthyroidism [50]. Further complaints of thyroid function reported in children and adolescents at HT presentation include either subclinical hypothyroidism (SH) [3, 51, 52] or more rarely, subclinical hyperthyroidism [53].

In a very recent study, we retrospectively evaluated clinical and laboratory characteristics at HT diagnosis in 608 children and adolescents from three pediatric endocrinology centers in Northern and Southern Italy [9]. Our test results at presentation showed euthyroidism in 52.1 % of patients, overt or SH in 41.4 %, and overt or subclinical hyperthyroidism in 6.5 %. The mean age of patients with thyroid dysfunctions was significantly lower than that found in euthyroid children. Other variables related to thyroid function patterns were prepubertal status and association with either DS or TS, which correlated with increased risk of thyroid dysfunctions [9]. Overall, thyroid function patterns at HT presentation seem to be mainly conditioned by children's age, with an increased risk of severe gland dysfunctions in the cases with early HT presentation [9]. Other factors that may also be involved in the biochemical presentation pattern of HT are the association with either chromosomopathies or other autoimmune diseases [9, 54] and environmental factors [55].

The different presentation modes of HT have been recently summarized and commented in a commentary of our study group [56].

## 16.7 Clinical Features

The most frequent clinical manifestation of juvenile variant of HT is goiter, but most children may also be asymptomatic at the time of diagnosis.

The prevalence of goiter is generally higher in hypothyroid children [52]. By contrast, other authors have reported an increased prevalence of goiter in euthyroid patients [49]. Finally, according to others, the prevalence of goiter is comparable in euthyroid, hypothyroid, and SH patients [57].

Other less frequent manifestations are those originating from compression of the cervical structures that are anatomically contiguous to thyroid gland and include hoarseness, cough, dysphonia, dysphagia, or, more rarely, dyspnea.

In the cases with more severe impairment of thyroid function, systemic manifestations may also be observed and include signs of hypothyroidism or even hyperthyroidism in the cases presenting with hashitoxicosis (Htx).

The most frequent symptoms of hypothyroidism at HT presentation are constipation, bradycardia, and changes of skin and appendages (dry, cold, yellowish, and thickened skin, coarse hairs, and thin nails). Less frequent presenting manifestations of hypothyroidism involve hematopoietic system (hypochromic and microcytic anemia), skeletal muscles (increased transaminase serum levels), and neuropsychiatric system (memory and attention loss, with inability to concentrate and impaired scholastic performances). Clinical pictures of hypothyroidism may be associated with a strong positivity of TPOAbs and TGAbs [52] and a more severe degree of hypoechogenicity [48].

In a limited number of cases (3.5 %), HT may present with a transient hyperthyroid picture, and this presentation pattern is known as Htx, which is believed to result from unregulated release of stored thyroid hormones during inflammatory-mediated destruction of thyroid gland. It is the second commonest cause of hyperthyroidism in childhood [58], and its presenting clinical picture is not very different from that observed in GD [59]. However, in the majority of cases, the differential diagnosis with GD is straightforward, considering the milder clinical and biochemical phenotype, the absence of TRABs, and the spontaneous resolution of hyperthyroidism that is frequently observed. Nevertheless, in some cases with clinical and biochemical features overlapping between Htx and GD, differential diagnosis between these two disorders may be very complicated [58, 59], and duration of biochemical hyperthyroidism may be abnormally extended (Fig. 16.1). In these few cases, a prolonged treatment with antithyroid drugs (1–2 years) may be also needed, whereas a nonpharmacological treatment is never needed [60].

## 16.8 HT and Nodular Disease

The literature contains only few specific studies about children with nodular HT, and the available data on the occurrence of thyroid cancer in HT refer almost exclusively to adults.

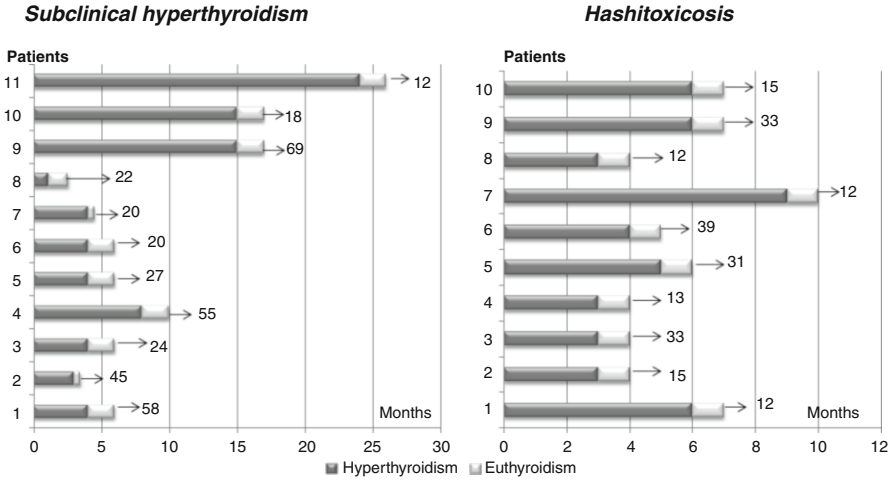


**Fig. 16.1** Duration of biochemical hyperthyroidism in two groups of children with either subclinical hyperthyroidism or hashitoxicosis (Refs. [60, 71], respectively). *Grey bars* refer to the periods during which they were hyperthyroid, whilst white bars indicate the development of persistent euthyroidism. The *arrow* and number at the end of each bar refer to the overall duration of follow-up (months) after resolution of hyperthyroidism

The only available study aiming to analyze the relationships among HT, thyroid nodules, and cancer in a large population of pediatric patients has recently demonstrated that nodular disease occurs in 31.5 % of young patients with HT, while cancer occurs in 3 % of cases and in 9.6 % of the subset with nodules, with papillary carcinoma being the most common histological type [55]. This cancer prevalence in HT patients is equal to or higher than that reported in other pediatric studies [61, 62] and much lower than that found in other study populations consisting primarily of adults [63].

Among the children of that series [55], the diagnostic accuracy of FNAC in differentiating benign from malignant lesions was 94.4 %, with a sensitivity of 88.9 and a specificity of 100 %. Other two factors that were significantly associated with cancer risk were the clinical finding of locoregional lymphadenopathy and the US evidence of nodular growth under L-T4 therapy. No other clinical, biochemical, or US factors were significantly predictive of cancer risk (Table 16.3).

Overall, the most recent findings on the links between HT, nodular disease, and thyroid cancer do not support the hypothesis [64] that the lymphocytic infiltration of thyroid gland, which is typical of HT, may play any protective role against proliferation of cancerous cells.

## 16.9 Natural Evolution Over Time and Long-Term Prognosis

The evolution over time of biochemical pictures is conditioned by presentation patterns and may significantly vary according to them.

**Table 16.3** Analysis of the factors with or without predictive value for cancer in children with Hashimoto's thyroiditis and nodular disease

| Predictive factors | Non-predictive factors |
|---|---|
| Male sex | Age |
| Suspicious cytology | Thyroid function tests |
| Locoregional lymphadenopathy | Uninodularity vs multinodularity |
| Echographic evidence of nodular growth under L-T4 therapy | Nodule echogenicity |

According to the study by Corrias et al. [55]

Among the HT children presenting with biochemical euthyroidism, 42 % remain persistently euthyroid after a 5-year follow-up, and 52 % develop over time an SH condition, whereas only 6 % become overtly hypothyroid [4]. The presence of goiter and elevated TGAbs at presentation, together with progressive increase in both TPOAb and TSH serum levels, may be predictive factors for a future deterioration of thyroid function [4].

Among the children presenting with HT-related SH, the risk of deterioration over time of thyroid function is even higher, even though the process is very slow and not predictable in the single case [65]. The coexistence of additional risk factors such as celiac disease, elevated baseline TSH, and TPOAb serum levels further increases such a risk 3.4–4.0 fold [65]. Therefore, it can be argued that HT children with SH and additional risk factors should be followed up with periodical TSH measurements [65], since the risk of worsening thyroid function over time is higher in the SH children with an underlying HT than in those with no underlying thyroid disease [9, 66, 67]. This inference is supported by the most recent reviews on SH [68–70].

In the children presenting with HTx, a definitive resolution of hyperthyroidism is generally observed on average 8 months after Htx diagnosis, even though there is a wide variability between subjects [60]. Hyperthyroid phase in children with Htx is always followed by definitive resolution (Fig. 16.1) and evolves to permanent euthyroidism or hypothyroidism, with no relapses [60].

Finally, in the cases presenting with HT-related subclinical hyperthyroidism, this biochemical picture may spontaneously resolve in the majority of cases within the first 24 months after HT diagnosis (Fig. 16.1), and the risk of a progression toward clinically overt hyperthyroidism has to be considered very low, irrespectively of both TSH and FT4 baseline serum levels [71].

Long-term prognosis is variable, with remission, recurrence, and evolution into permanent hypothyroidism all being described [7]. However, according to the historical study by Rallison et al. [72] based on 61 children and adolescents between 11 and 18 years, the long-term evolution of HT after a 20-year follow-up is characterized by a permanent remission in 33 % of cases, while in the remaining 67 % of patients the thyroid injury persists over time. This evolutive trend does not seem to be conditioned by L-T4 therapy [72].

**Table 16.4** Main risk factors and etiological factors for subclinical hypothyroidism in children and adolescents

| Risk factors | Etiological factors |
|---|---|
| Familial antecedents of thyroid diseases | Hashimoto's thyroiditis |
| Obesity | Non-compliance with levothyroixine treatment in primary hypothyroidism |
| Antecedents of radiation to head and neck | |
| False positivity at congenital hypothyroidism screening | Chronic treatment with iodine containing medications |
| TSH receptor gene alterations | Overtreatment with anti-thyroid drugs in |
| Down's syndrome | Graves' disease |
| Turner syndrome | Chronic non-thyroidal diseases |

## 16.10 HT and SH

SH is a common clinical problem that is caused by the same thyroid disorders that cause overt thyroid failure and especially HT (Table 16.4). Its average worldwide prevalence has been reported to be in the range 4–10 % in large general population screening surveys [73], 7–26 % in the elderly [74], and <2 % in childhood and adolescence [75].

In the last years, SH has been discussed in a number of editorials, commentaries, controversies, and letters to editors concerning this topic [76]. Discussions are mainly focused on whether SH should be treated or not. In children with the idiopathic form, current views are not in favor of a systematic treatment of SH, considering the low risk of a spontaneous deterioration over time of thyroid function [66]. By contrast, in the children with HT-related SH, the risk of a worsening over time of thyroid function tests seems to be more elevated [66, 77]. Therefore, considering that an underlying HT may negatively affect the evolution over time of children' SH and that L-T4 therapy may have some beneficial effects on the clinical course of HT-related SH and on antibody titers [53], a different treatment policy might be hypothesized for the children with HT vs those with idiopathic SH. Nevertheless, such hypotheses should be verified through comparative investigations based on very large study populations.

## 16.11 Treatment

Synthetic L-T4 remains the only effective drug available to patients with HT, many decades after the start on its production on a large scale (in 1960). This treatment is mandatory in the cases with overt hypothyroidism or progressively worsening SH, whereas it is controversial in the cases with mild SH or euthyroid goiter. If thyroid enlargement is severe, it may be efficaciously counteracted by L-T4 treatment [57].

Therapy is given daily at doses of 2 mcg/kg body weight, but this initial dose needs to be periodically monitored.

Although this is a symptomatic treatment, which addresses the symptoms rather than the etiology and the pathogenesis of this disorder, nevertheless it is effective in most patients, and economic and therefore pharmaceutical companies have not been stimulated, over the years, to develop new drugs [7].

This treatment is not always lifelong, considering that in a 33 % of cases HT may have a positive long-term prognosis, with complete remission of the autoimmune process and consequent normalization of biochemical and clinical picture [72].

Thyroidectomy is indicated only in the cases with a clinical picture of severe cervical compression or, more frequently, in the children with a thyroid nodule that, at cytology, is suspicious for malignancy [78]. When advisable, avoiding thyroidectomy is particularly relevant in HT patients [7], since the surgical complications are more numerous in this disorder than in other thyroid diseases [79].

## References

1. Wasniewska M, Vigone MC, Cappa M et al (2007) Acute suppurative thyroiditis in childhood: relative frequency among thyroid inflammatory diseases. J Endocrinol Invest 30:346–347
2. Brown RS (2013) Autoimmune thyroiditis in childhood. J Clin Res Pediatr Endocrinol 5(Suppl 1):45–49
3. Gopalakrishnan S, Chugh PK, Chhillar M et al (2008) Goitrous autoimmune thyroiditis in a pediatric population: a longitudinal study. Pediatrics 122:e670–e674
4. Radetti G, Gottardi E, Bona G et al (2006) The natural history of euthyroid Hashimoto's thyroiditis in children. J Pediatr 149:827–832
5. Baretić M (2011) 100 years of Hashimoto thyroiditis, still an intriguing disease. Acta Med Croatica 65:453–457
6. Foley TP Jr, Abbassi V, Copeland KC, Draznin MB (1994) Brief report: hypothyroidism caused by chronic autoimmune thyroiditis in very young infants. N Engl J Med 330:466–468
7. Caturegli P, De Remigis A, Rose NR (2014) Hashimoto thyroiditis: clinical and diagnostic criteria. Autoimmun Rev 13:391–397
8. Doğan M, Acikgoz E, Acikgoz M et al (2011) The frequency of Hashimoto thyroiditis in children and the relationship between urinary iodine level and Hashimoto thyroiditis. J Pediatr Endocrinol Metab 24:75–80
9. Wasniewska M, Corrias A, Salerno M et al (2012) Thyroid function patterns at Hashimoto's thyroiditis presentation in childhood and adolescence are mainly conditioned by patients' age. Horm Res Paediatr 78:232–236
10. Boelaert K, Newby PR, Simmonds MJ et al (2010) Prevalence and relative risk of other autoimmune diseases in subjects with autoimmune thyroid disease. Am J Med 123:183.e1–189.e1
11. Knapp PE (2010) Risk of other autoimmune diseases increased in people with Graves' disease or Hashimoto's thyroiditis relative to the general UK population. Evid Based Med 15:158–159
12. Jenkins RC, Weetman AP (2002) Disease associations with autoimmune thyroid disease. Thyroid 12:977–988
13. Goday-Arno A, Cerda-Esteva M, Flores-Le-Roux JA et al (2009) Hyperthyroidism in a population with Down syndrome. Clin Endocrinol 71:110–114
14. Valenzise M, Aversa T, Corrias A et al (2014) Epidemiology, presentation and long-term evolution of Graves' disease in children, adolescents and young adults with Turner syndrome. Horm Res Paediatr 81:245–250
15. Goldacre MJ, Seminog OO (2014) Turner syndrome and autoimmune diseases: record-linkage study. Arch Dis Child 99:71–73
16. Aversa T, Lombardo F, Valenzise M et al (2015) Peculiarities of autoimmune thyroid diseases in children with Turner or Down syndrome: an overview. Ital J Pediatr 41:39

17. Radetti G, Mazzanti L, Paganini C et al (1995) Frequency, clinical and laboratory features of thyroiditis in girls with Turner's syndrome. Acta Paediatr 84:909–912
18. Gawlik A, Gawlik T, Januszek-Trzciakowska A et al (2011) Incidence and dynamics of thyroid dysfunction and thyroid autoimmunity in girls with Turner's syndrome: a long-term follow-up study. Horm Res Paediatr 76:314–320
19. Livadas S, Xekouki P, Fouka F et al (2005) Prevalence of thyroid dysfunction in Turner's syndrome: a long-term follow-up study and brief literature review. Thyroid 15:1061–1066
20. Popova G, Paterson WF, Brown A, Donaldson MD (2008) Hashimoto's thyroiditis in Down's syndrome: clinical presentation and evolution. Horm Res 70:278–284
21. Bakalov VK, Gutin L, Cheng CM et al (2012) Autoimmune disorders in women with turner syndrome and women with karyotypically normal primary ovarian insufficiency. J Autoimmun 38:315–321
22. Invernizzi P, Miozzo M, Selmi C et al (2005) X chromosome monosomy: a common mechanism for autoimmune diseases. J Immunol 175:575–578
23. El-Mansoury M, Bryman I, Berntorp K et al (2005) Hypothyroidism is common in Turner syndrome: results of a five-year follow-up. J Clin Endocrinol Metab 90:2131–2135
24. Jacobson EM, Tomer Y (2007) The genetic basis of thyroid autoimmunity. Thyroid 17:949–961
25. Brix TH, Kyvik KO, Hegedüs L (2000) A population-based study of chronic autoimmune hypothyroidism in Danish twins. J Clin Endocrinol Metab 85:536–539
26. Tomer Y (2010) Genetic susceptibility to autoimmune thyroid disease: past, present, and future. Thyroid 20:715–725
27. Laurberg P, Cerqueira C, Ovesen L et al (2010) Iodine intake as a determinant of thyroid disorders in populations. Best Pract Res Clin Endocrinol Metab 24:13–27
28. Drutel A, Archambeaud F, Caron P (2013) Selenium and the thyroid gland: more good news for clinicians. Clin Endocrinol 78:155–164
29. Ergür AT, Evliyaoğlu O, Şıklar Z et al (2011) Evaluation of thyroid functions with respect to iodine status and TRH test in chronic autoimmune thyroiditis. J Clin Res Pediatr Endocrinol 3:18–21
30. Reinhardt W, Luster M, Rudorff KH et al (1998) Effect of small doses of iodine on thyroid function in patients with Hashimoto's thyroiditis residing in an area of mild iodine deficiency. Eur J Endocrinol 139:23–28
31. Yoon SJ, Choi SR, Kim DM et al (2003) The effect of iodine restriction on thyroid function in patients with hypothyroidism due to Hashimoto's thyroiditis. Yonsei Med J 44:227–235
32. Barin JG, Talor MV, Sharma RB et al (2005) Iodination of murine thyroglobulin enhances autoimmune reactivity in the NOD.H2 mouse. Clin Exp Immunol 142:251–259
33. Xue H, Wang W, Li Y et al (2010) Selenium upregulates CD4(+)CD25(+) regulatory T cells in iodine-induced autoimmune thyroiditis model of NOD. H-2(h4) mice. Endocr J 57:595–601
34. Li Y, Bai Y, Liu Z et al (2009) Immunohistochemistry of IgG4 can help subclassify Hashimoto's autoimmune thyroiditis. Pathol Int 59:636–641
35. Li Y, Nishihara E, Hirokawa M et al (2010) Distinct clinical, serological, and sonographic characteristics of hashimoto's thyroiditis based with and without IgG4-positive plasma cells. J Clin Endocrinol Metab 95:1309–1317
36. Li Y, Zhou G, Ozaki T et al (2012) Distinct histopathological features of Hashimoto's thyroiditis with respect to IgG4-related disease. Mod Pathol 25:1086–1097
37. Aust G, Krohn K, Morgenthaler NG et al (2006) Graves' disease and Hashimoto's thyroiditis in monozygotic twins: case study as well as transcriptomic and immunohistological analysis of thyroid tissues. Eur J Endocrinol 154:13–20
38. Desai MP, Karandikar S (1999) Autoimmune thyroid disease in childhood: a study of children and their families. Indian Pediatr 36:659–668
39. Doniach D (1975) Humoral and genetic aspects of thyroid autoimmunity. Clin Endocrinol Metab 4:267–285
40. Ludgate M, Emerson CH (2008) Metamorphic thyroid autoimmunity. Thyroid 18:1035–1037

41. Wasniewska M, Corrias A, Arrigo T et al (2010) Frequency of Hashimoto's thyroiditis antecedents in the history of children and adolescents with graves' disease. Horm Res Paediatr 73:473–476
42. Kamath C, Young S, Kabelis K et al (2012) Thyrotrophin receptor antibody characteristics in a woman with long-standing Hashimoto's who developed Graves' disease and pretibial myxoedema. Clin Endocrinol 77:465–470
43. Troisi A, Novati P, Sali L et al (2013) Graves' thyrotoxicosis following Hashimoto's thyroiditis. Res Rep Endocr Disord 3:13–15
44. Champion B, Gopinath B, Ma G et al (2008) Conversion to Graves' hyperthyroidism in a patient with hypothyroidism due to Hashimoto's thyroiditis documented by real-time thyroid ultrasonography. Thyroid 18:1135–1137
45. McLachlan SM, Rapoport B (2013) Thyrotropin-blocking autoantibodies and thyroid-stimulating autoantibodies: potential mechanisms involved in the pendulum swinging from hypothyroidism to hyperthyroidism or vice versa. Thyroid 23:14–24
46. Aversa T, Lombardo F, Corrias A et al (2014) In young patients with Turner or Down syndrome, Graves' disease presentation is often preceded by Hashimoto's thyroiditis. Thyroid 24:744–747
47. McLachlan SM, Rapoport B (2004) Why measure thyroglobulin autoantibodies rather than thyroid peroxidase autoantibodies? Thyroid 14:510–520
48. Sostre S, Reyes MM (1991) Sonographic diagnosis and grading of Hashimoto's thyroiditis. J Endocrinol Invest 14:115–121
49. de Vries L, Bulvik S, Phillip M (2009) Chronic autoimmune thyroiditis in children and adolescents: at presentation and during long-term follow-up. Arch Dis Child 94:33–37
50. Zak T, Noczyńska A, Wasikowa R et al (2005) Chronic autoimmune thyroid disease in children and adolescents in the years 1999–2004 in Lower Silesia, Poland. Hormones 4:45–48
51. Demirbilek H, Kandemir N, Gonc EN et al (2009) Assessment of thyroid function during the long course of Hashimoto's thyroiditis in children and adolescents. Clin Endocrinol 71:451–454
52. Skarpa V, Kappaousta E, Tertipi A et al (2011) Epidemiological characteristics of children with autoimmune thyroid disease. Hormones 10:207–214
53. Özen S, Berk Ö, Şimşek DG, Darcan S (2011) Clinical course of Hashimoto's thyroiditis and effects of levothyroxine therapy on the clinical course of the disease in children and adolescents. J Clin Res Pediatr Endocrinol 3:192–197
54. Aversa T, Messina MF, Mazzanti L et al (2014) The association with Turner syndrome significantly affects the course of Hashimoto's thyroiditis in children, irrespective of karyotype. Endocrine [Epub ahead of print] doi:10.1007/s12020-014-0513-6
55. Corrias A, Cassio A, Weber G et al (2008) Thyroid nodules and cancer in children and adolescents affected by autoimmune thyroiditis. Arch Pediatr Adolesc Med 162:526–531
56. De Luca F, Santucci S, Corica D et al (2013) Hashimoto's thyroiditis in childhood: presentation modes and evolution over time. Ital J Pediatr 39:8
57. Svensson J, Ericsson UB, Nilsson P et al (2006) Levothyroxine treatment reduces thyroid size in children and adolescents with chronic autoimmune thyroiditis. J Clin Endocrinol Metab 91:1729–1734
58. Williamson S, Greene SA (2010) Incidence of thyrotoxicosis in childhood: a national population based study in the UK and Ireland. Clin Endocrinol 72:358–363
59. Nabhan ZM, Kreher NC, Eugster EA (2005) Hashitoxicosis in children: clinical features and natural history. J Pediatr 146:533–536
60. Wasniewska M, Corrias A, Salerno M et al (2012) Outcomes of children with hashitoxicosis. Horm Res Paediatr 77:36–40
61. Carson HJ, Castelli MJ, Gattuso P (1996) Incidence of neoplasia in Hashimoto's thyroiditis: a fine-needle aspiration study. Diagn Cytopathol 14:38–42
62. Nguyen GK, Ginsberg J, Crockford PM, Villanueva RR (1997) Hashimoto's thyroiditis: cytodiagnostic accuracy and pitfalls. Diagn Cytopathol 16:531–536

63. Neuhold N, Kaiser H, Kaserer K (2001) Latent carcinoma of the thyroid in Austria: a systematic autopsy study. Endocr Pathol 12:23–31
64. Loh KC, Greenspan FS, Dong F et al (1999) Influence of lymphocytic thyroiditis on the prognostic outcome of patients with papillary thyroid carcinoma. J Clin Endocrinol Metab 84:458–463
65. Radetti G, Maselli M, Buzi F et al (2012) The natural history of the normal/mild elevated TSH serum levels in children and adolescents with Hashimoto's thyroiditis and isolated hyperthyrotropinaemia: a 3-year follow-up. Clin Endocrinol 76:394–398
66. Wasniewska M, Salerno M, Cassio A et al (2009) Prospective evaluation of the natural course of idiopathic subclinical hypothyroidism in childhood and adolescence. Eur J Endocrinol 160:417–421
67. Cerbone M, Bravaccio C, Capalbo D et al (2011) Linear growth and intellectual outcome in children with long-term idiopathic subclinical hypothyroidism. Eur J Endocrinol 164:591–597
68. De Luca F, Wasniewska M, Zirilli G et al (2010) At the end of a two year follow-up elevated TSH levels normalize or remain unchanged in most the children with subclinical hypothyroidism. Ital J Pediatr 36:11
69. Monzani A, Prodam F, Rapa A et al (2012) Natural history of subclinical hypothyroidism in children and adolescents and potential effects of replacement therapy: a review. Eur J Endocrinol 168:R1–R11
70. Bona G, Prodam F, Monzani A (2013) Subclinical hypothyroidism in children: natural history and when to treat. J Clin Res Pediatr Endocrinol 5(Suppl 1):23–28
71. Aversa T, Valenzise M, Corrias A et al (2014) Subclinical hyperthyroidism when presenting as initial manifestation of juvenile Hashimoto's thyroiditis: first report on its natural history. J Endocrinol Invest 37:303–308
72. Rallison ML, Dobyns BM, Meikle AW et al (1991) Natural history of thyroid abnormalities: prevalence, incidence, and regression of thyroid diseases in adolescents and young adults. Am J Med 91:363–370
73. Chu JW, Crapo LM (2001) The treatment of subclinical hypothyroidism is seldom necessary. J Clin Endocrinol Metab 86:4591–4599
74. McDermott MT, Ridgway EC (2001) Subclinical hypothyroidism is mild thyroid failure and should be treated. J Clin Endocrinol Metab 86:4585–4590
75. Wu T, Flowers JW, Tudiver F et al (2006) Subclinical thyroid disorders and cognitive performance among adolescents in the United States. BMC Pediatr 6:12
76. Arrigo T, Wasniewska M, Crisafulli G et al (2008) Subclinical hypothyroidism: the state of the art. J Endocrinol Invest 31:79–84
77. Aversa T, Valenzise M, Corrias A et al (2015) Underlying Hashimoto's thyroiditis negatively affects the evolution of subclinical hypothyroidism in children irrespective of other concomitant risk factors. Thyroid 25:183–7
78. Caturegli P, De Remigis A, Chuang K et al (2013) Hashimoto's thyroiditis: celebrating the centennial through the lens of the Johns Hopkins hospital surgical pathology records. Thyroid 23:142–150
79. McManus C, Luo J, Sippel R, Chen H (2012) Is thyroidectomy in patients with Hashimoto thyroiditis more risky? J Surg Res 178:529–532