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Original Article

Multifaceted delineation of atrophic thyroiditis among pediatric population: An extensive literature survey

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Highlights

- Atrophic thyroiditis in children is characterized by profound hypothyroidism.
- Children with atrophic thyroiditis had notably small thyroid glands.
- Pediatric atrophic and Hashimoto thyroiditis may be distinct entities.

Abstract. Autoimmune hypothyroidism is categorized into Hashimoto thyroiditis (HT) and atrophic thyroiditis (AT). Although a consensus exists among Japanese endocrinologists that pediatric AT is associated with severe hypothyroidism, the question remains whether AT and HT are separate conditions. To investigate the clinical characteristics of pediatric AT, we conducted a comprehensive literature review using PubMed and ICHUSHI, a local database. We identified 54 patients (43 females), diagnosed ≤ 18 yr of age, based on 19 English- and 28 Japanese-language publications; 45 patients were Japanese. The onset of the disease typically occurs before puberty. The patients exhibited severe hypothyroidism, with median TSH level of 518.8 μIU/mL (interquartile range [IQR]: 333.0–808.6) and median Free T4 level of 0.16 ng/dL (IQR: 0.08–0.40). Common findings included a low height SD score (median –2.54 SD), low height-velocity SD score (median –3.60 SD), body mass index +1 SD (40%), delayed bone age (64%), pericardial effusion (70%), and an enlarged pituitary gland (78%). Abnormal blood test results were frequently observed, including Hb (82%), CPK (83%), AST (94%), ALT (82%), and total cholesterol (95%). Ultrasound 3D volumetry, conducted for 14 thyroid lobes, revealed 13 lobes below the 25th percentile. In conclusion, our study underscores the clinical presentation of pediatric AT, marked by severe hypothyroidism and a small thyroid gland. Nevertheless, the paucity of data on non-Japanese patients suggests a need for further research to determine if AT and HT are indeed distinct entities.

Key words: atrophic thyroiditis, autoimmune hypothyroidism, autoimmune thyroiditis, idiopathic myxedema, juvenile myxedema

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Introduction

Autoimmune hypothyroidism is typically divided into Hashimoto thyroiditis (HT), characterized by the presence of a goiter, and atrophic thyroiditis (AT) without a goiter, also known as Ord's disease or idiopathic myxedema (1–5). However, whether these conditions have distinct pathophysiological foundations remains unclear. In a study of 139 Danish adults with autoimmune hypothyroidism, thyroid volumes displayed an unimodal distribution, suggesting no qualitative differences between HT and AT (6). In children, the absence of anti-TSH receptor-blocking antibodies (TSBAB) was once believed to be unique to AT (7), but recent findings contradict this, demonstrating that 6/18 Japanese pediatric patients with AT tested positive for TSBAB (8).

Japanese specialists strongly agree that pediatric AT leads to profound hypothyroidism, often accompanied by severe growth failure (7–17). However, this perspective is infrequently discussed in English-language textbooks and reviews (1–5). This study seeks to clarify the clinical characteristics of children with AT and reevaluate the relevance of classifying autoimmune hypothyroidism into HT and AT.

Methods

An extensive literature search was conducted to detail the clinical symptoms, as well as the laboratory and imaging characteristics, of pediatric patients with AT. The search included English-language literature on PubMed with the terms "atrophic thyroiditis OR idiopathic myxedema OR juvenile myxedema OR Ord's disease" and Japanese literature via ICHUSHI, a database by the Japan Medical Abstracts Society (https://www.jamas.or.jp/about/english.html). The inclusion criteria specified patients diagnosed with AT who were 18 yr old or younger. Exclusion criteria were patients with inconsistent descriptions, including increased thyroid volume on ultrasonography (US), or those lacking sufficient data, like Conference Abstracts. For each qualifying patient and our patient, we gathered background information, estimated age at onset, clinical features, treatment course, and results from laboratory and imaging studies.

For children of Japanese ancestry, height SD score (Ht-SDS), height velocity SDS (ΔHt-SDS), %-overweight, and body mass index (BMI) SDS (BMI-SDS) were assessed using the latest national standards and a calculator provided by the Japanese Society for Pediatric Endocrinology: http://jspe.umin.jp/medical/chart_dl.html. To calculate ΔHt-SDS, height value was inspected from the figure of growth chart in most cases. For non-Japanese patients, Ht-SDS and BMI-SDS were calculated using WHO AnthroPlus software: https://www.who.int/tools/growth-reference-data-for-5to19-yr/application-tools.

Pubertal development at the time of AT diagnosis was assessed according to Tanner stages. For Japanese patients, precocious and delayed puberty was defined by domestic recommendations: breast development < 7.5 yr, genital bleeding < 10.5 yr, and testicular enlargement < 9 yr were considered as 'early', whereas no pubertal sign >12 yr (girl) or >14 yr (boy) was considered 'delayed'. Patients who did not meet these criteria were categorized as 'appropriate'. For non-Japanese patients, puberty assessment was based on the descriptions provided by the authors.

Pre-treatment levels of TSH, Free T3, Free T4, T3, and T4 were measured as indicators of thyroid function. Given the wide methodological diversity in hormone measurement and the lack of detailed disclosure regarding exact methods, the reported values were accepted as presented. When a normal range for each hormone was provided, cases were classified as either normal or abnormal. Due to historical variations in methods for measuring autoantibodies including anti-thyroid peroxidase antibody (TPO-Ab), microsome hemagglutination test (MT), anti-thyroglobulin antibody (TG-Ab), thyroglobulin hemagglutination test (TT), anti-TSH receptor antibody (TRAb), TSH binding inhibitory immunoglobulin (TBII), TSBAB, and thyroid stimulating antibody (TSAB), specific cut-off values could not be established. Therefore, a dichotomous approach of positive or negative was employed to assess the titers and levels of these autoantibodies. For analytical purposes, TPO-Ab and MT, TG-Ab and TT, and TRAb and TBII were grouped to evaluate positivity. IGF-1 levels were assessed according to national standards (18). Laboratory data, including hemoglobin (Hb), creatine phosphokinase (CPK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine (Cre), total cholesterol (TC), LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C), and triglycerides (TG), were evaluated using age- and sex-specific national standards in Japanese.

Thyroid volume was calculated using the formula: width × thickness × height × π/6, based on values reported from the thyroid US. The resulting thyroid volumes were compared with age- and sex-specific references developed by Japanese researchers (19). The authors' descriptions were used for assessing thyroid echogenicity and blood flow.

Statistics

Collected data were reported as either the median with interquartile range (IQR) and/or total range, or as counts with percentages, depending on the nature of the data. The Wilcoxon rank-sum test was employed for comparisons between the two groups. Differences were considered statistically significant at a two-sided P value of less than 0.05. All statistical analyses were conducted using Microsoft® Excel® 2019 (Microsoft Corporation) and JMP® Pro 17 (JMP Statistical Discovery, LLC).

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Results

Overall, our study identified 43 female patients (including our own) and 11 male patients across 19 English-language and 28 Japanese-language studies (**Fig. 1**). The referenced literature is detailed in Supplementary Tables 1 and 2. Among these 54 patients, 45 were of Japanese ancestry. The age at diagnosis ranged from 0.6 to 18 yr, with a median age of 11.8 yr (IQR: 9.0–13.5), while the estimated age of disease onset, available for 43 patients, had a median of 8.0 yr (IQR: 5.5–9.8) (**Fig. 2**). The chief complaints and associated comorbidities varied widely and are listed in **Tables 1 and 2**, respectively. The most common chief complaint was poor growth and/or short stature (n = 24, 44%), followed by edema and chronic fatigue/malaise in eight patients (15%). Down syndrome was noted in five patients (9%). Graves' disease (GD) was observed in three patients; two developed GD during L-thyroxine (L-T4) treatment for AT, while the third experienced rapid thyroid destruction after GD remission (20).

Family history

Autoimmune thyroiditis was reported in relatives of only three patients; two had mothers with HT, and one had an affected cousin. Accordingly, no familial recurrence of AT was identified. Hypothyroidism of unknown etiology was documented in two patients, in the proband's mother and father, respectively. Furthermore, hyperthyroidism in relatives was noted in four patients: a grandfather, grandmother, aunt, and uncle. Overall, nine patients (17%) had a thyroid-related family history.

Growth parameters

At diagnosis, Ht-SDS was available for 51 patients (94%), with a median of –2.54 SD [IQR: –3.7– –1.9]. Of these, 37 patients (72%) were classified as having short stature, defined as < –2 SD. ΔHt-SDS at diagnosis could be assessed only in Japanese patients (n = 35), with a median of –3.60 SD [IQR: –5.3– –1.1]. For 43 Japanese patients, %-overweight was calculated, with a median of 18.8% [IQR: 4.7–43.6]. Of these, 21 patients (49%) were classified as obese, including nine with morbid obesity (> 50% overweight), six with moderate obesity (30–50% overweight), and six with mild obesity (20–30% overweight). The BMI-SDS was assessed in 47 patients, with a median of +0.52 SD [IQR: –0.4–1.7]. Forty percent of these patients (19/47) had a BMI > +1 SD. Bone age (BA) was reported in 36 patients. When assessed relative to chronological age (CA), the median BA/CA was 0.75 [IQR: 0.61–0.84], with 23 patients (64%) demonstrating delayed skeletal maturation, as indicated by a BA/CA < 0.8. Information on final height was available for five Japanese female patients, with a median height of 152.0 cm [IQR: 147.2–154.1], corresponding to –1.2 SD of the Japanese population. These patients were typically diagnosed late: three at 14 yr, one at 12 yr, and one at 9 yr. One male patient of African descent was reported to reach a height of 160 cm (21).

Sexual development

Assessment of pubertal development at diagnosis was possible in 33 patients, of whom 28 (85%) were deemed "appropriate" for their age. Three patients

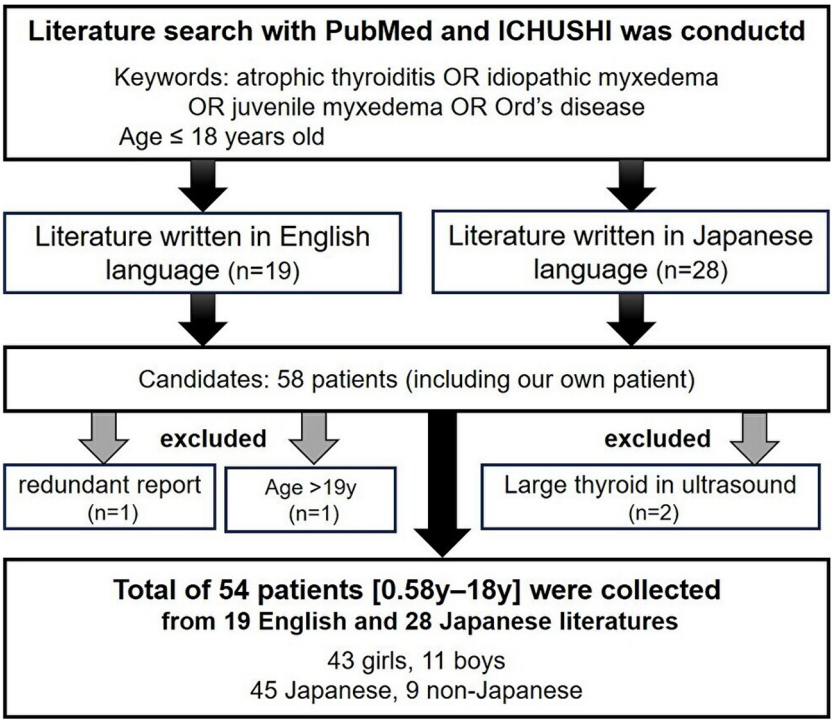

Fig. 1. Study flowchart.

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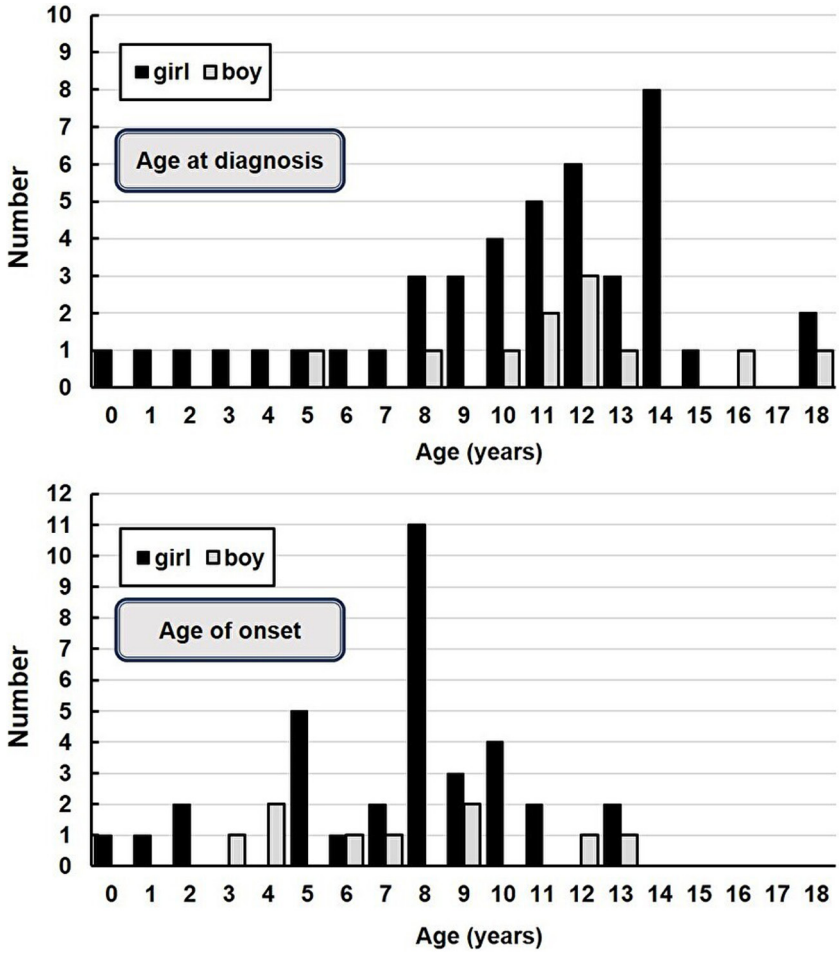

Fig. 2. Distribution of patient age at diagnosis (upper panel, n = 54) and estimated age at onset (lower panel, n = 43). Forty patients (74%) were diagnosed between 8 and 14 yr of age, whereas 32 patients (74%) were estimated to develop atrophic thyroiditis between 4 and 10 yr of age.

were considered "delayed" due to the absence of pubertal signs at ages 12 (female), 13 (female), and 18 (male) yr. Two female patients, both with Down syndrome, were categorized as "early" at diagnosis after developing genital bleeding at 8 yr of age along with subtle breast development (Tanner B2). One of these patients was diagnosed with LHRH-dependent precocious puberty due to elevated gonadotropin levels, while the other lacked gonadotropin data. Additionally, one female patient entered puberty at 9 yr of age, 1 yr following the initiation of L-T4 supplementation.

Thyroid function, autoantibodies, and IGF-1

The distributions of TSH, Free T3, and Free T4 levels are displayed in **Fig. 3**. The median and IQR for each value were as follows: TSH 518.8 [333.0–808.6, n = 52] μIU/mL, Free T3 1.00 [0.42–1.23, n = 34] pg/mL, and Free T4 0.16 [0.08–0.40, n = 45] ng/dL. Forty-eight patients (92%) exhibited TSH levels > 100 μIU/mL. Median T3 was 33 ng/dL [30–50, n = 19], and median T4 was 1.0 μg/dL [0.90–1.79, n = 22], with less frequent reliable data. When compared with the reference ranges provided by each author, TSH levels were consistently above normal in all 19 cases, whereas Free T3 and Free T4 levels were below normal in 11/12 and 13/14 cases, respectively. The positivity rates for thyroidal autoantibodies are illustrated in **Fig. 3**. High positivity rates were observed for TPO-Ab/MT (92%) and TG-Ab/TT (82%), with 38 patients testing positive for both. Positivity rates for TSBAB stood at 63%, while those for TRAb/TBII and TSAB were similar at 53% and 50%, respectively. IGF-1 levels, reported exclusively in Japanese patients (n = 16), were all below –2 SD when compared with age-specific national standards.

General laboratory examinations

The results for Hb, CPK, AST, ALT, Cre, TC, LDL-C, HDL-C, and TG are presented in **Fig. 4** and Supplementary Table 3. The tests in which more than 80% of patients exhibited abnormal values included low Hb (82%), high CPK (83%), high AST (94%), high ALT (82%), high TC (95%), and high LDL-C (100%).

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Table 1. Total number of chief complaints (duplicates)

Physique	declined growth rate/short stature	24
	obesity/excessive weight gain	2
	poor weight gain	2
Physical symptoms	edema	8
	chronic fatigue/malaise	8
	abdominal pain	4
	constipation	3
	coxalgia	2
	developmental delay	2
	abdominal distension	1
	headache	1
	anorexia	1
Gonadal dysfunction	genital bleeding	3
	amenorrhea/delayed sexual development	2
	excessive menstruation	1
Blood test	anemia	4
	liver dysfunction	2
	renal dysfunction	1
	hyperlipidemia	1
Medical checkup	low voltage in electrocardiogram	1
	heart murmur	1

Table 2. Accompanying complications (duplicates)

Congenital		**(Auto)immune/Allergy**	
Down syndrome	**5**	Bronchial asthma	**1**
Musculoskeletal		Systemic lupus erythematosus	**1**
Slipped capital femoral epiphysis	**2**	GAD antibody-related neuropathy	**1**
Endocrine		Idiopathic thrombocytopenic purpura	**1**
Graves' disease	**3**	Myasthenia gravis	**1**
Precocious puberty	**1**	Purpuric nephritis	**1**
Hypoadrenalism	**1**	Recurrent candida stomatitis	**1**
Ovarian hyperstimulation	**1**	**Miscellaneous**	
Giant testicle	**1**	Pervasive developmental disorder	**1**
Cardiovascular		Leukemia	**1**
Pulmonary artery stenosis	**1**	Scalp epithelioid	**1**
Patent ductus arteriosus	**1**	Retinitis pigmentosa	**1**
Ventricular septal defect	**1**		

GAD: Glutamic acid decarboxylase.

Imaging study of the thyroid gland

Thyroid gland size was assessed by US in 38 patients. For the remaining 16 patients who did not undergo US, the absence of goiter was confirmed by scintigraphy (n = 6), autopsy following a sepsis-like condition (n = 1), and palpation only (n = 9). Additionally, US 3D volumetry (see Methods) was performed on 14 thyroid lobes from seven patients, with 13 lobes falling below the 25th percentile and five below the 2.5th percentile for the reference range. Information on thyroidal blood flow was available for 10 patients, with seven exhibiting decreased flow. Thyroid echogenicity was described in 17 patients: 12 had decreased echogenicity, three had normal, and two had increased echogenicity. The 24-h radioactive iodine uptake was reported in 13 patients, with a median uptake of 3.3% [IQR: 0.95–8.1].

Cardiac US and pituitary imaging

Cardiac US results were documented for 23 patients, 16 of whom (70%) exhibited pericardial effusion. Imaging studies of the pituitary gland were performed in 27 patients (skull radiograph in two, CT scan in two, and MR imaging in 23), revealing enlarged pituitaries and/or ballooned sellae in 21 patients (78%).

Initial treatment

Information on the initial dose of L-T4 was available for 23 patients, with a median dose of 0.8 μg/kg/d [IQR: 0.5–1.6]. A clear schedule for increasing the L-T4 dose was stated for 15 of the 23 patients. The time required for TSH normalization, which was arbitrarily defined as <10 μIU/mL, was 2 mo [IQR: 1–3] (n = 27).

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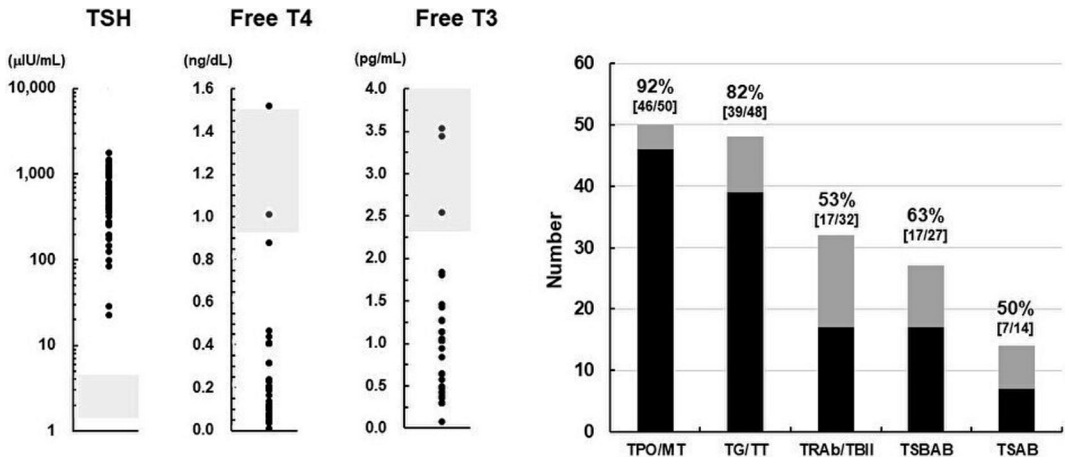

Fig. 3. Left panel: Distribution of the thyroid function tests. The shaded area represents the reference range. Note that a logarithmic scale is used for TSH. Right panel: Results of the thyroidal autoantibodies. Black bars indicate the patients' number of positive results, whereas gray bars indicate those of negative results. A positive rate is demonstrated above each bar. TPO, anti-thyroid peroxidase antibody; MT, microsome hemagglutination test; TG, anti-thyroglobulin antibody; TT, thyroglobulin hemagglutination test; TRAb, anti-TSH receptor antibody; TBII, TSH binding inhibitory immunoglobulin; TSBAB, anti-TSH receptor-blocking antibody; TSAB, thyroid-stimulating antibody.

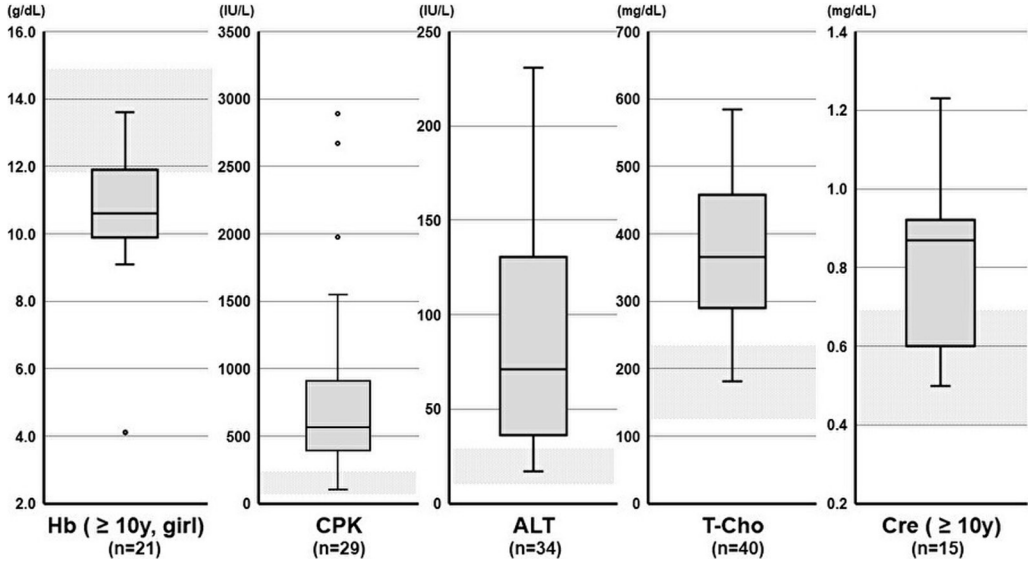

Fig. 4. Boxplot for the selected laboratory data. The shaded area represents the reference range.

Japanese vs. non-Japanese patients

No significant differences were identified in age at diagnosis, Ht-SDS, TSH, Free T3, or Free T4 between Japanese and non-Japanese patients (data not displayed).

Discussion

In English literature and textbooks, HT and AT are often described as differing only in thyroid volume, with no qualitative differences noted between them in both adults and children (1–5). In contrast, pediatric endocrinologists in Japan view HT and AT as distinct entities (7–17). Given this context, we conducted a comprehensive literature review, including both English and Japanese sources. As a result, 45 of the 54 patients recruited were of Japanese descent. This study aimed to delineate the clinical features of pediatric AT and may serve as a preliminary step in discussing the significance of differentiating autoimmune thyroiditis into AT and HT.

The patients displayed the cardinal features typical of autoimmune hypothyroidism. These included a female predominance, prepubertal onset, frequent thyroid-related family history, a high rate of coexisting autoimmune diseases and Down syndrome, and a high prevalence of positive thyroid autoantibodies. A direct

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comparison of these characteristics between AT and HT is challenging because demographic and epidemiological data on Japanese children with HT are limited. However, it has been reported that pediatric HT exhibits female predominance, prepubertal onset in hypothyroid cases, and a high prevalence of autoimmune diseases and chromosomal aberrations (22–24). Decreased echogenicity in US was also similar to that observed in HT (25). Thus, AT and HT during childhood share many similarities.

Notably, the prevalence of TSBAB was 63% among our patients. This finding contrasts with that of a previous report by Matsuura *et al.* (7), which noted an absence of TSBAB in 21 Japanese children with AT and suggested differing pathophysiological underpinnings for AT and HT. Our results align more closely with those of a recent study by Nagasaki *et al.* (8), which discovered that one-third of children with AT had TSBAB. However, considering that very high TSH levels might lead to false-positive TSBAB results is important. Furthermore, TSBAB measurements were typically conducted only once and rarely repeated in our study cohort.

As expected, children with AT exhibited profound hypothyroidism. The patients had short stature and poor growth velocity. Frequently encountered abnormal laboratory values, such as IGF-1, Hb, CPK, ALT, and T-Cho, likely stemmed from profound hypothyroidism. Additionally, a high incidence of obesity, BMI >+1 SD, delayed BA, pericardial effusion, and enlarged pituitary glands were noted. The severity of the disease did not differ significantly between Japanese and non-Japanese patients, indicating that profound hypothyroidism may be a universal characteristic of pediatric AT.

The thyroid volumes of these patients were notably small. Although accurate assessment using US-based volumetry was only feasible in a limited subset of patients, 13 out of 14 lobes measured were smaller than the 25th percentile. Radioactive uptake, reported in 13 patients, was extremely low. In adults with AT, 12 out of 55 patients demonstrated no radioactive uptake (26), while uptake was quite variable in those with HT (27). Thus, the low uptake observed in our study may suggest a small thyroid gland. These results differ from those observed in adult cases of autoimmune hypothyroidism, where thyroid volume typically displayed a unimodal pattern (6).

Taken together, despite some similarities to HT, pediatric AT appears to have distinct characteristics marked by profound hypothyroidism and a small thyroid gland. However, a diagnostic bias exists as HT can be detected early through the evaluation of goiter, whereas AT may not be. Consequently, many patients with AT and mild to subclinical hypothyroidism may remain undiagnosed. In a population-based survey of adults, a small subgroup with subclinical AT was identified (28).

Surprisingly, we discovered only nine case reports of pediatric AT by non-Japanese authors. No reports have been available from Eastern Asia, where the prevalence of autoimmune hypothyroidism is higher than that in other regions (4, 29). Several factors contribute to the scarcity of non-Japanese reports on AT, including the availability of US, the incidence of AT, and the acceptance rate of case reports. Although the exact reason for this discrepancy is unclear, we speculate that AT is not always recognized as a distinct disease entity in other countries. As previously mentioned, no qualitative differences between HT and AT, other than thyroid size, have been described in English literature and textbooks (1–5). For instance, a 1988 United States. study focusing on the final height in "juvenile hypothyroidism" did not consider thyroid size at all (30). Moreover, in a recent review of Van Wyk–Grumbach syndrome —a severe form of hypothyroidism associated with LHRH-independent precocious puberty— Spanish authors did not address thyroid size (31). Notably, Van Wyk-Grumbach syndrome has been reported worldwide. These examples indicate that some specialists believe thyroid size is unrelated to disease severity in autoimmune hypothyroidism. A comprehensive epidemiological survey is necessary to accurately compare disease severity between AT and HT.

Apart from discussing the significance of distinguishing AT from HT, several issues remain unresolved. First, the height prognosis for children with AT, particularly those diagnosed during pre- or early puberty, is largely unknown. A small-scale study on juvenile hypothyroidism, which did not consider thyroid size, observed inadequate catch-up growth in cases diagnosed late (30). Second, optimizing the treatment regimen is crucial. Although initial doses of L-T4 were substantially low with gradual dose increments, the effectiveness of this strategy, particularly for height prognosis, has not been studied. Two patients with precocious puberty had Down syndrome, similar to findings in Van Wyk-Grumbach syndrome, where 10 out of 99 patients were identified with Down syndrome (31). Although one of our patients exhibited LHRH-dependent precocious puberty, not typical of Van Wyk-Grumbach syndrome, an unidentified link may be present between Down syndrome and precocity in the context of hypothyroidism. Finally, if we assume a distinction between pediatric AT and HT, the underlying causes of these differences remain an open question. Although AT was once considered the end stage of HT, the transition from HT to AT has rarely been demonstrated. In our study, progressive thyroid atrophy was confirmed in only one recent report (20). Qualitative differences between AT and HT have been suggested, including antibody-dependent cell-mediated cytotoxicity in AT (32, 33), HLA types (HLA-DR3/B8 in AT vs. HLA-DR5 in HT) (34), specific autoantibodies (TRAb in AT vs. TPO-Ab/TG-Ab in HT) (35), and T cell function (Th2 predominance in AT vs. Th1 predominance in HT) (36). Pathological differences are also notable; AT with TBII is characterized by perifollicular fibrosis, small follicles, and flattened follicular epithelium, whereas HT exhibits lymphocytic infiltration with interlobular fibrosis, conspicuous follicles, and tall epithelium (37).

This study had several limitations, mainly due

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to its retrospective design. First, due to the scarcity of English literature on pediatric AT, we employed an unconventional review method to collect both English and Japanese literature, resulting in 83% of the patients being Japanese. This mirrors our previous work on hyponatremia in severe atopic dermatitis. Even though numerous reports exist in Japanese literature, hyponatremia with atopic dermatitis has not garnered much global attention (38). When differences exist between Japan and other countries, a review of domestic reports becomes significant. Second, a publication bias potentially exists, where patients with severe symptoms are preferentially reported. Third, methods for measuring laboratory data, including TSH, Free T3, and Free T4, are seldom disclosed. As such, we utilized the reported values for statistical analysis. Nonetheless, methodological differences did not appear to impact our conclusions significantly, given the gross abnormalities observed in thyroid hormone levels.

In conclusion, our study highlights the clinical features of pediatric AT, characterized by profound hypothyroidism and a small thyroid gland. However, considering the limited literature from foreign countries and potential biases in finding and reporting cases of AT, further studies are needed to clarify whether AT and HT are distinct disease entities.

Conflict of interests: The authors have nothing to declare.

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