Pediatric Goiter: Can Thyroid Disorders Be Predicted at Diagnosis and in Follow-Up?

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Objective To investigate the prevalence of thyroid dysfunction, autoimmune thyroid disease (AITD), and simple goiter at goiter diagnosis, and to analyze the natural course of simple goiter and predictors for progression to AITD and/or thyroid dysfunction.

Study design In total, 939 patients (770 females, 5.0-17.9 years) with goiter were reviewed retrospectively. Anthropometrics, pubertal status, goiter grade, and family history (FH) of thyroid disease were investigated. Simple goiter was defined as euthyroid goiter without pathologic cause, after excluding AITD and isolated nonautoimmune hyperthyrotropinemia (iso-NAHT).

Results At diagnosis, 36.9% of children showed thyroid dysfunction and/or AITD (euthyroid AITD [9.9%], hyper- or hypothyroid AITD [18.4%], iso-NAHT [8.6%]). Risk for subsequent medication was higher in euthyroid AITD than simple goiter (20.4% vs 0.3%, $P < .001$). Hashimoto thyroiditis (HT) and iso-NAHT developed in 5.2% and 6.6% of patients initially diagnosed with simple goiter during the median 2.0-year follow-up. Compared with the persistent simple goiter group, the HT group had greater FH (54.8% vs 23.6%) and unchanged or increasing goiter size (89.3% vs 71.8%), and the iso-NAHT group had a higher proportion of patients within the upper tertile range of baseline thyrotropin levels (71.8% vs 24.9%) and unchanged or increasing goiter size (86.8% vs 71.8%; all $P < .05$).

Conclusions Thyroid disorders were detected in one-third of pediatric patients presenting with goiter. The higher risk for thyroid dysfunction needing medication in patients with euthyroid AITD emphasizes the importance of autoantibody evaluation at diagnosis. During simple goiter follow-up, progression to HT or iso-NAHT occurs, especially in patients with FH or persistent goiter. *(J Pediatr 2016;170:253-9)*.

The term "goiter" refers to a thyroid gland that is enlarged,[1] with or without symptoms of hyper- or hypothyroidism. Inflammation or infiltration resulting from autoimmune thyroid diseases (AITDs), infection, and/or neoplasms can induce goiter with or without hyper- or hypothyroidism.[2] If a euthyroid goiter is not due to inflammatory or neoplastic processes, it is initially diagnosed as a "simple" goiter.[3]

A diagnosis of simple goiter may change later to Hashimoto thyroiditis (HT) because simple goiter appears to be a forerunner of HT.[3,4] Some patients may develop subclinical or overt thyroid dysfunction in the form of hyper- or hypothyroidism. A 10-year follow-up of adult patients with simple goiter revealed a 3.8% incidence of HT over the 10-year observation period.[3] A 20-year follow-up of the Whickham Survey showed that antithyroid antibodies newly developed in 17.3% of adult female and 6.6% of adult male patients initially diagnosed with goiter.[5] Few studies have assessed the natural course of children and adolescents initially diagnosed with simple goiter.[6,7]

Goitrous AITD usually presents in adolescents but occurs rarely in very young infants.[8,9] When these patients have hypo- or hyperthyroid symptoms, there is no disagreement that thyroid autoantibodies should be checked. However, when a euthyroid goiter is detected without symptoms, it has not yet been established whether antibodies should be determined to differentiate euthyroid AITD from simple goiter at diagnosis.

In this study, we investigated the prevalence of thyroid disorders in children and adolescents with an initial diagnosis of goiter. In particular, we investigated whether the presence of initial thyroid autoimmunity in euthyroid patients at diagnosis predicted

AITD	Autoimmune thyroid disease
BMI	Body mass index
FH	Family history
FT4	Free thyroxine
GD	Graves disease
HR	Hazard ratio
HT	Hashimoto thyroiditis
iso-NAHT	Isolated nonautoimmune hyperthyrotropinemia
TSH	Thyroid stimulating hormone
T3	Triiodothyronine
WHO	World Health Organization

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subsequent development of hypothyroidism needing medication. During follow-up of patients initially diagnosed with simple goiter, we analyzed the prevalence of and predictors for later development of AITDs and/or thyroid dysfunction.

Methods

The medical records of 1370 patients (5-17.9 years of age) diagnosed with goiter between January 2009 and May 2014 at Seoul National University Children's Hospital were reviewed retrospectively. Of them, 147 patients with other underlying diseases (chromosomal disorders, chronic diseases, and malignancies) and those taking drugs related to thyroid dysfunction were excluded. An additional 284 patients who did not have a second visit were also excluded. In total, 939 children with goiter were included. None of the included patients had histories of previous neck radiation or abnormal results on neonatal congenital hypothyroidism screening. Our study protocol was approved by our center's institutional review board (1502-012-644).

Height was measured with a standard stadiometer (Holtain Ltd, Crymych, Wales, United Kingdom) to the first decimal place, and body mass index (BMI) was calculated. Age- and sex-specific z-scores for height, weight, and BMI were assigned based on the 2007 Korean National Growth Charts.[10] Subjects were classified according to BMI as follows: lean (<85th BMI percentile), overweight (85th-95th BMI percentile), or obese (≥95th BMI percentile). All subjects underwent physical examinations by 3 pediatric endocrinologists (S.Y., C.S., and Y.L.) and pubertal status was assessed by Tanner staging for breasts (females) and genitals (males). Symptoms related to hyper- or hypothyroidism, such as palpitations, exophthalmos, sweating, heat intolerance, agitation, tremor, weight change, fatigue, constipation, and developmental delay were evaluated, and any family history (FH) of thyroid diseases in first- and second-degree relatives was investigated (**Table I**; available at www.jpeds.com). Goiters were graded according to the World Health Organization (WHO) criteria: (0) not palpable and not visible; (1) palpable but not visible (1a: not visible with neck extension; 1b: visible with complete neck extension); and (2) palpable and visible.[1] Once a goiter was identified clinically by a pediatric endocrinologist, neck ultrasound was performed at the discretion of the clinician evaluating the patient, especially in cases with a considerably enlarged (WHO grade 1b or 2) and/or firm thyroid gland in which palpation for nodules was difficult. Neck ultrasound was performed in 254 (27.1%) patients by a pediatric radiologist. No subject with thyroid nodules or malignancies was included in our study.

All the patients with goiter underwent regular follow-up evaluations of serum thyroid function and thyroid autoantibodies every 4-6 months. Serum concentrations of free thyroxine (FT4) and thyroid stimulating hormone (TSH) were measured using immunoradiometric kits (RIAKEY; Shin Jin Medics, Seoul, Republic of Korea). The serum levels of triiodothyronine (T3), antithyroglobulin antibodies, antithyroid peroxidase antibodies, and TSH receptor antibodies were measured using radioimmunoassay kits (Brahms DYNOTest; Diagnostica GmbH, Berlin, Germany). The normal ranges of serum FT4, TSH, and T3 are 0.70-1.80 ng/dL (9.01-23.2 pmol/L), 0.4-4.1 mIU/L, and 87-184 ng/dL (1.34-2.83 nmol/L), respectively.

All subjects were categorized by their TSH levels as euthyroid (TSH 0.4-4.1 mIU/L), hypothyroid (TSH >4.1 mIU/L), or hyperthyroid (TSH <0.4 mIU/L). Subclinical hypothyroidism was defined as a serum TSH concentration above the upper limit of the reference range when the serum FT4 concentration was within the reference range.[11,12] Levothyroxine treatment was indicated in patients with subclinical hypothyroidism who had a serum TSH concentration >10 mIU/L and in patients with overt hypothyroidism.[13]

AITDs occur in 2 common forms: Graves disease (GD) and HT. GD is an autoimmune condition caused by TSH receptor-stimulating antibodies that stimulate the thyroid resulting in hyperthyroidism.[4,14] HT is a chronic autoimmune thyroiditis, characterized by lymphocytic infiltration of the gland and high titers of circulating antithyroid peroxidase and/or anti thyroglobulin antibodies. Hypothyroidism and goiter are common presenting features but may be absent. Transient episodes of thyrotoxicosis (hashitoxicosis) in patients with HT may occur, caused by unregulated release of stored thyroid hormone during inflammation-mediated destruction of the thyroid gland.[15,16] A diagnosis of isolated nonautoimmune hyperthyrotropinemia (iso-NAHT) was based on the finding of isolated TSH elevation with normal FT4 and T3, no sign or symptom of hypothyroidism, and the absence of thyroid autoantibodies.[17] Finally, a diagnosis of simple goiter was arrived at by the exclusion of other causes and the presence of small, soft, or diffuse euthyroid goiters in the absence of thyroid autoantibodies and inflammatory or neoplastic processes.[3,4]

Statistical Analyses

All statistical tests were performed using the SPSS software (v 21.0 for Windows; SPSS Inc, Chicago, Illinois). Data are presented as means ± SDs. Differences in continuous variables between the 2 groups were compared using Student *t* test. Categorical variables were analyzed using the χ^2 test or the χ^2 test for trends. Medication-free survival and event-free survival plots were constructed using the Kaplan-Meier method and groups were compared using the log-rank test. An event was defined as the development of HT or iso-NAHT (**Figure 1**). The Cox proportional hazard model was used to assess predictors of medication-free survival or event-free survival. Hazard ratios (HRs) are presented with 95% CIs. *P* values of <.05 were deemed to indicate statistical significance.

Results

Initial clinical characteristics of the 939 patients (770 females, 435 prepubertal children) with goiter at initial presentation