The frequency of autoimmune thyroid disorders in juvenile idiopathic arthritis

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Few studies have been performed to investigate autoimmune diseases associated with organ non-specific rheumatological disorders in children, such as juvenile idiopathic arthritis (JIA). The objective in this study was to determine the frequency of autoimmune diseases of the thyroid gland in children with JIA. Eighty patients with JIA and 81 healthy sex- and age-matched controls were enrolled in the study. Serum free T3, free T4, thyroid stimulating hormone (TSH), anti-thyroglobulin antibodies, and anti-peroxidase antibodies were evaluated. The mean age was 11.5±5.5 years in the patient group and 10.5±4.9 years in the control group. Twenty-seven of the cases were classified as oligoarticular, 26 as polyarticular, 17 as enthesitis-related, 6 as systemic, and 4 as psoriatic arthritis. Autoimmune thyroid disease was found in 4 patients in the JIA group (5%). There were no significant differences between the study and control groups regarding the existence of anti-thyroid antibodies (p=0.17). Girls were more likely to develop autoimmune thyroiditis (3 girls, 1 boy). Autoimmune thyroiditis was more frequent in patients who had a family history of thyroid disease (p=0.02). There was no statistical correlation between rheumatoid factor (RF) and antinuclear antibody (ANA) positivity and autoimmune thyroiditis (p>0.05). We conclude that there is no need for routine screening of serum thyroid function tests and thyroid antibody levels in patients with JIA in the absence of clinical symptoms.

Key words: autoimmune thyroid disease, juvenile idiopathic arthritis.

Autoimmune thyroiditis is more frequent than in the normal population in the course of rheumatoid autoimmune diseases such as rheumatoid arthritis, in which specific organ involvement is rare. A common autoimmune pathogenesis or a strong genetic association among these diseases, such as the expression of certain types of major histocompatibility complexes, has been put forward[1,2]. However, there are very few studies about the association of autoimmune thyroid disorders and juvenile idiopathic arthritis (JIA), which is a rheumatoid autoimmune disease of childhood[3-6]. The goal of this study was to determine the frequency of autoimmune diseases of the thyroid gland in a group of children with JIA.

Material and Methods

This prospective study was performed at the Department of Pediatrics, Division of Immunology and Rheumatology of Dokuz Eylül University, Faculty of Medicine, and İzmir Tepecik Training Hospital between September 2004 and June 2005. During this period, 80 patients (41 male, 39 female) (mean age: 11.5±4.1 years) who were diagnosed as JIA between January 1999 and January 2005 according to the revised criteria of JIA[7] were enrolled in the study after informed parental consent was obtained.

For each patient, demographic data, JIA subgroup, and family history of thyroid diseases up to second-degree relatives were recorded.

Rheumatoid factor (RF) and antinuclear antibody (ANA) titers were examined in the JIA group.

Thyroid Function and Autoimmunity Screening

Serum concentrations of free T3, free T4, thyroid stimulating hormone (TSH), and thyroglobulin (TgA) and thyroperoxidase antibodies (TPOA) were determined by chemiluminescence assays (Diagnostic Products Corporation, Los Angeles, CA, USA). Reference values were 0.35-4.9 μIU/L for TSH, 0.8-2.3 ng/dl for fT4 and 2.1-4.4 pg/ml for fT3. TgA values >50 IU/ml and TPOA values >50 IU/ml were considered as positive. Patients with positive autoantibodies were further evaluated with thyroid ultrasonography. Hypothyroidism was defined as low fT3 and/or fT4 with elevated TSH levels; subclinical hypothyroidism was defined as elevated TSH with normal thyroid hormone levels; and thyrotoxicosis was defined as high fT3 and/or fT4 levels accompanying suppressed TSH. Hypothyroid and thyrotoxic patients also had signs and symptoms of thyroid dysfunction, while subclinical hypothyroid and euthyroid groups were clinically symptom-free. Autoimmune thyroiditis was defined as positive TPOA and/or TgA.

Control group: 81 patients (41 male, 40 female, mean age: 10.5±4.9 years) who were admitted to our hospital for non-autoimmune diseases served as control group. None of these patients had the signs and symptoms of thyroid disease or a chronic disease.

The study protocol was approved by the Ethics Committee of Dokuz Eylül University, Faculty of Medicine.

Statistical Analysis

SPSS 10.0 version was used. Results are expressed as mean ± SD. The Mann-Whitney U test was used for non-normally distributed variables whereas Yates chi-square test and Fisher's exact test were used for normally distributed data. P value <0.05 was considered significant.

Results

The sex and age distribution were comparable in the study and control groups. The mean age at JIA diagnosis was 8.6±3.8 years and the mean age at study entry was 11.4±4 years. The mean disease duration at study entry was 34.7±31 months. Twenty-seven out of 80 JIA patients had oligoarticular, 26 RF-negative polyarticular, 17 enthesitis-related, 6 systemic onset, and 4 psoriatic type of the disease (Table I).

Anti-thyroid antibodies were detected in 4 of 80 (5%) JIA patients. The onset of JIA was systemic in 1 of them, enthesitis-related in 1, and polyarticular in the remaining 2. None of the 27 cases with oligoarthritis (OA) had anti-thyroid antibodies; 7 were ANA-positive. Four cases with psoriatic arthritis also did not have antibodies.

Table II presents important demographic and laboratory data of the four patients with anti-thyroid antibodies: Girls were more prone to develop autoimmune thyroiditis (3 girls vs 1 boy). The four patients had subclinical hypothyroidism, hypothyroidism, hyperthyroidism and euthyroidism, respectively. In the control group, one patient had a positive TPOA with normal FT3, FT4, and TSH, and one patient had subclinical hypothyroidism without thyroid antibodies. There were no

Table I. Characteristics and Presence of Thyroid Disease in JIA vs Control Group

	JIA					Total no. of patients	Control group	
	OA	PA	Sys	JPsA	ERA			
	27 (33%)	26 (32%)	6 (8%)	4 (5%)	17 (22%)	80	81	JIA vs controls
Subclinical hypothyroidism	0	1	0	0	1	2 (2.5%)	1 (1.2%)	p=0.67
Autoimmune thyroid disease (ATD)	0	2	1	0	1	4 (5%)	1 (1.2%)	p=0.17
Family history of ATD	6	5	1	0	1	13 (16%)	3 (4%)	p=0.08

JIA : Juvenile idiopathic arthritis.
OA : Oligoarticular.
PA : Polyarticular.
Sys : Systemic onset.
JPsA: Juvenile psoriatic arthritis.
ERA: Enthesitis-related arthritis.
ATD: Autoimmune thyroid disease.

Table II. Clinical and Laboratory Data of JIA Patients with Positive Anti-Thyroid Antibodies

Patient	Sex	Age (yr)	JIA Subgroup	FT4 (ng/dl)	FT3 (pg/ml)	TSH (μIU/L)	TGA (IU/ml)	TPOA (IU/ml)	Thyroid hormone status
1	Male	16	ERA	0.97	4.1	5.4	42	52	Subclinical hypothyroid
2	Female	14.9	PA	0.4	1.1	50	3000	688	Hypothyroid
3	Female	12	PA	7.5	9.0	0.01	500	300	Thyrotoxic
4	Female	8.3	Sys	1.39	3.2	2.9	23	57	Euthyroid

JIA: Juvenile idiopathic arthritis. ERA: Enthesitis-related arthritis. PA: Polyarticular. Sys: Systemic onset. TSH: Thyroid stimulating hormone. TGA: Thyroglobulin antibody. TPOA: Thyroperoxidase antibody.

significant differences between the study and control groups regarding the existence of anti-thyroid antibodies (p=0.17).

Autoimmune thyroiditis was more frequent in patients who had a family history related to thyroid disease (p=0.02).

There was no statistical correlation between RF and ANA positivity and autoimmune thyroiditis (p>0.05).

Discussion

The association between rheumatoid arthritis and autoimmune thyroid disease is well established; however, most literature studies on this topic are focused on adult series[9-12]. There are only a few studies evaluating the relationship between JIA and autoimmune thyroiditis[3-6]. All of them have reported a high prevalence of anti-thyroid antibodies in JIA when compared to healthy controls. This study could not demonstrate any significant differences between the JIA patients and age-matched healthy controls regarding the existence of anti-thyroid antibodies. Autoimmune thyroiditis is four to seven times more frequent in girls than in boys[13]. Similarly, three of four patients with autoimmune thyroiditis were female in this study.

In the previous studies[3-6], the majority of the patient population was female. However, in our study, 51% of the patients were male. Özdoğan et al.[14] also reported a male predominance among JIA patients in a Turkish population. The rate of male patients was 56% in their 147 patients. The male predominance due to patients with enthesitis-related arthritis (ERA), a subgroup mostly defined in boys, might explain the low frequency of autoimmune thyroiditis in our study. Twenty-two percent of the study population consisted of patients with ERA. None of the mentioned studies included patients with ERA except the study of Harel et al.[3]. Only a minority of 66 patients (3%) had ERA in that study and 75% of the study population was female.

Recently, Harel et al.[3] reported a higher incidence of anti-thyroid antibodies in patients with oligoarticular JIA. All of the patients with positive anti-thyroid antibodies, which composed 39% of the patient population, had OA. Another study by Alpigiani et al.[4], in which 66% of patients were female, demonstrated significantly higher anti-thyroid antibody

positivity, particularly in the OA type. The majority of the patients (64%) were OA. The largest series investigating the coexistence of JIA and autoimmune thyroiditis was reported by Stagi et al.[5]. They evaluated 151 patients, of whom 80% were female, and found a higher prevalence of autoimmune thyroiditis as well as subclinical hypothyroidism in OA type. Fifty-eight percent of the patients had OA. In contrast to these studies, none of the patients with OA had autoimmune thyroiditis in this study. The lower incidence of OA (33%) and female ratio than previous reports may contribute to the lower frequency of autoimmune thyroiditis in this study.

In conclusion, this study demonstrated that there was no significant increase in autoimmune thyroiditis in a group of JIA patients, when compared to a sex- and age-matched control group. Despite the statistical insignificance, the presence of four patients with autoimmune thyroiditis should not be underestimated regarding the evaluation of JIA patients for autoimmune thyroid diseases. Screening for anti-thyroid antibodies is recommended in the presence of clinical symptoms and a positive family history. Further studies with a larger group of patients are needed to demonstrate the frequency of autoimmune thyroiditis in JIA.

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