

Increased Prevalence of Antithyroid Antibodies and Subclinical Hypothyroidism in Children with Juvenile Idiopathic Arthritis

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ABSTRACT. Objective. To estimate the occurrence of antithyroid antibodies (ATA) and hypothyroidism in children with juvenile idiopathic arthritis (JIA) compared to matched healthy controls.

Methods. The occurrence of ATA, including antithyroglobulin (anti-TG) and antithyroid peroxidase (anti-TPO) antibodies, was evaluated by quantitative immunometric ELISA in children with JIA and in a healthy matched control group. Thyroid function was assessed in both groups.

Results. The study group included 66 patients with JIA (50 girls, 16 boys) of mean age 11.7 ± 4.4 years (range 2–23). The control group included 89 children (71 girls, 18 boys) of mean age 10.8 ± 4.2 years (range 2–18). Mean age at onset of joint disease was 7.3 ± 3.6 years (range 1–15). Anti-TG antibodies were found in 7 of 62 patients (11.3%) in the JIA group and 2 of 89 controls (2.2%) ($p = 0.03$); anti-TPO antibodies were found in 5 of 65 patients (7.9%) and one of 89 controls (1.1%) ($p = 0.08$). All patients with ATA had oligoarticular type JIA ($p = 0.01$). Mean thyroid stimulating hormone (TSH) levels were higher in the study group than in controls (2.6 ± 2.3 vs 1.9 ± 1.0 mIU/l; $p = 0.01$); levels were above normal range (0.4–4 mIU/l) in 8 study patients (12%) and 3 controls (3.4%) ($p = 0.055$). Overall, ATA were found in 9 of the 150 study participants, 4 (44%) of whom had TSH levels above 4 mIU/l ($p = 0.001$).

Conclusion. Children with JIA have a higher than normal incidence of ATA and subclinical hypothyroidism and should be routinely screened for these variables. (J Rheumatol 2006;33:164–6)

Key Indexing Terms:

JUVENILE IDIOPATHIC ARTHRITIS ANTITHYROID ANTIBODIES HYPOTHYROIDISM

There is a large body of cumulative data on coexisting organ-specific and systemic autoimmune diseases with numerous series reporting a higher prevalence of antithyroid antibodies (ATA) and hypothyroidism in adults and children

with systemic lupus erythematosus (SLE)^{1,2} and rheumatoid arthritis (RA)^{3,4} than in the general population. However, this association remains unclear in children with juvenile idiopathic arthritis (JIA) and the prevalence of ATA in this population compared to healthy controls has not been established.

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MATERIALS AND METHODS

Children diagnosed with JIA from 4 pediatric rheumatology centers in Israel were evaluated for the occurrence of ATA, including antithyroglobulin (anti-TG) and antithyroid peroxidase (anti-TPO) antibodies, using a quantitative immunometric ELISA. The same tests were performed concurrently in an age and sex matched group of healthy children with no known thyroid or autoimmune diseases. Thyroid function was assessed in both groups by measurement of free thyroxine (FT₄) and thyroid-stimulating hormone (TSH) levels. Subclinical hypothyroidism was defined by TSH above normal and normal values of FT₄. Rheumatoid factor (RF) and antinuclear antibody (ANA) titers were examined in the JIA group. The data were analyzed by analysis of variance (ANOVA) for continuous variables and Pearson's chi-square test or Fisher's exact test for discrete variables, as appropriate.

RESULTS

Demographics. The study group included 66 patients with JIA (50 girls, 16 boys) of mean age 11.7 ± 4.4 years (range 2–23). The control group included 89 children (71 girls, 18 boys) of mean age 10.8 ± 4.2 years (range 2–18).

Joint disease. Mean age at onset of joint disease was 7.3 ± 3.6 years (range 1–15). The subsets of JIA included polyarthritis (36%), oligoarthritis (39%), systemic arthritis (20%), enthesitis-related arthritis (3%), and psoriatic arthritis (1.5%). RF was found in 5 of the 58 children tested (8.6%); ANA were found in 20 of 62 (32.3%).

Antithyroid antibodies. The rate of occurrence of both anti-TG and anti-TPO antibodies was higher in the JIA group than in the controls (Table 1). All patients with either anti-TG and/or anti-TPO antibodies had oligoarticular-type JIA ($p = 0.01$).

There was no association between the anti-TPO or anti-TG findings and the presence of either ANA ($p = 0.42$) or RF ($p = 1.00$).

Thyroid function. TSH levels were higher and subclinical hypothyroidism was more prevalent in the study group than in the controls (Table 2). No patient had clinical hypothyroidism or symptoms related to the thyroid gland.

Association between presence of ATA and TSH level. Of the total 9 patients in the entire series with anti-TPO and/or anti-TG antibodies, 4 (44%) had TSH levels above 4 mIU/l ($p = 0.001$).

ATA and age/disease duration. No significant association was found between presence of anti-TG and/or anti-TPO antibodies and patient age, although patients with antibodies were older than those without (mean age 12.9 ± 4 , range 7–21 yrs, compared to mean age 11 ± 4.3 , range 2–23 yrs, respectively; $p = 0.19$). The youngest age at which antibodies were detected was 7 years. Disease duration was shorter in patients with anti-TPO and/or anti-TG antibodies than in patients with negative findings, but the difference did not reach statistical significance (mean 3.28 ± 4.4 compared to 4.48 ± 4.2 , respectively; $p = 0.48$).

Goiter. Goiter was found in 3 of 58 children in whom the

Table 1. Antithyroid antibodies in children with JIA and healthy controls.

Antibody	JIA Group, n (%)	Control Group, n (%)	p
Anti-TG	7/62* (11.3)	2/89 (2.2)	0.03
Anti-TPO	5/65** (7.9)	1/89 (1.1)	0.08

* Data were missing in 4 patients; ** Data were missing in one patient. JIA: juvenile idiopathic arthritis; anti-TG: antithyroglobulin antibodies; anti-TPO: antithyroid peroxidase antibodies.

Table 2. TSH levels in children with JIA and controls.

	JIA Group, n = 66	Control Group, n = 89	p
TSH, mIU/l, mean \pm SD	2.6 ± 2.3	1.9 ± 1.0	0.01
TSH > normal*, n (%)	8/66 (12)	3/86** (3.4)	0.055

* Normal TSH 0.4–4 mIU/l; ** data were missing in 3 patients. TSH: thyroid-stimulating hormone.

size of the thyroid gland had been assessed in the study group (5.2%) and in none of the control group ($p = 0.06$). All 3 had ATA.

Family history. Family history of thyroid disease was found in 7 of 66 patients (10.6%) and 4 of 89 controls (4.5%) ($p = 0.21$). There was also a higher incidence of family history of other autoimmune diseases in the patients than in the controls (RA, inflammatory bowel disease), but the difference did not reach statistical significance ($p = 0.43$).

DISCUSSION

We found a high prevalence of ATA in patients with JIA, all in the oligoarticular subgroup, in addition to a high rate (12%) of subclinical (but without any case of clinical) hypothyroidism, compared to healthy controls. To our knowledge this is the first controlled study of thyroid involvement in JIA.

The involvement of the thyroid gland in JIA is not surprising. Autoimmune thyroid disease has been reported in association with other autoimmune diseases, namely, insulin-dependent diabetes mellitus⁵, autoimmune hepatitis⁶, and others. It has also been related to rheumatologic diseases, such as SLE (including juvenile SLE)^{1,2}, RA (with no association with presence of RF or ANA)^{3,4}, and others.

Regarding JIA, there are several case reports of concomitant Hashimoto's thyroiditis⁷⁻⁹, but very few large series have been evaluated, none of them controlled, all reporting a high prevalence of ATA in JIA¹⁰⁻¹², especially in patients with oligoarticular disease¹³. Our results further support the coexistence of thyroid involvement and oligoarticular JIA. Indeed, thyroid disease is not the only autoimmune disease associated with JIA: insulin-dependent diabetes mellitus and myasthenia gravis have also been reported^{14,15}. A higher prevalence of autoantibody production in the oligoarticular type of JIA and its female predominance may serve as an explanation for the association of ATA with this subgroup.

The relationship between antithyroid autoimmunity and the pathogenesis of autoimmune diseases is unknown. Possible underlying mechanisms include (1) immunomodulatory effects of ATA, (2) molecular mimicry between thyroid and disease-specific epitopes, and (3) a genetic link between antithyroid autoimmunity and susceptibility to JIA.

ATA were more prevalent in patients with JIA than in healthy controls. ATA were seen only in the oligoarticular group, but lacked association with ANA positivity. Although none had clinical disease, 12% of our patients with JIA had subclinical hypothyroidism. Therefore, screening for ATA and thyroid function is recommended in all children with JIA, especially in the oligoarticular type.

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