Endocrine autoimmunity in young patients with juvenile chronic arthritis

M.G. Alpigiani, M. Cerboni, I. Bertini, G. d'Annunzio[1], R. Haupt[2], A. Iester, R. Lorini

Department of Pediatrics, University of Genoa, G. Gaslini Institute, Genoa; [1]Department of Pediatrics, IRCCS Policlinico San Matteo, Pavia; [2]Epidemiology and Biostatistics Unit, Scientific Directorate, G. Gaslini Institute, Genoa, Italy.

Maria G. Alpigiani, MD; Monica Cerboni MD; Irene Bertini PhD; Giuseppe d'Annunzio MD; Riccardo Haupt MD; Aldo Iester MD; and Renata Lorini MD.

Please address correspondence and reprint requests to: Renata Lorini, MD, Department of Pediatrics, University of Genoa, Gaslini Children's Hospital, Largo G. Gaslini no. 5, I-16148 Genova, Italy. E-mail: reumatologia@ospedale-gaslini.ge.it

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ABSTRACT

Objective. *The aim of our study was to investigate the coexistence of autoimmune diseases (autoimmune thyroid disease and type 1 diabetes mellitus, T1DM) in patients affected by Juvenile Chronic Arthritis (JCA).*

Methods. *We studied 66 patients affected by JCA, 42 females and 24 males: 42/66 patients had a pauciarticular form of JCA, 13/66 had a polyarticular form and 11/66 had a systemic form. All the patients underwent autoimmune thyroid screening through determination of anti-thyroglobulin (TgA) and anti-peroxidase (TPOA) autoantibodies. Patients with TgA and/or TPOA, underwent thyroid sonography. T1DM screening included determination of anti-glutamic acid decarboxylase (GADA), anti-insulin (IAA), anti-tyrosine phosphatase-like protein (IA-2A) and anti-islet cell (ICA) autoantibodies. Oral glucose tolerance test (OGTT) was performed only in patients with autoantibody positive values. HLA typing for risk of T1DM was performed in 43 patients.*

Results. *Nine female patients (14%) showed anti-thyroid autoantibodies, in particular: TgA in 3 cases, TPOA in 5, TgA and TPOA in only 1. In 3 of these patients, ultrasound examinations showed thyroid abnormal pattern, suggesting Hashimoto's thyroiditis. As regards T1DM, only 2 patients showed positive levels of GADA. As regards HLA typing, one or more T1DM susceptibility heterodimers were detected in 20 patients (46%) (13 with 1 heterodimer, 7 with 2 heterodimers).*

Conclusion. *Our study showed that anti-thyroid autoantibody frequency (9/66, 14%) was higher in JCA than in the general population, while T1DM markers (islet autoantibodies and genetic markers) were not frequent. These results suggest to investigate specific markers of thyroid autoimmunity in patients with JCA, in particular in females with JCA pauciarticular form.*

Introduction

The association of rheumatoid arthritis (RA) with several autoimmune diseases has been described mainly in adults. A common autoimmune pathogenesis or a strong genetic association between these diseases and the expression of certain types of major histocompatibility complex have been hypothesized. The association between RA and endocrine autoimmunity, in particular type 1 diabetes mellitus (T1DM) or thyroid autoimmunity (1-6) has been reported in adults, but little is known about the association of juvenile chronic arthritis (JCA) with T1DM and thyroid autoimmunity (7-10).

The aim of this study was to describe the prevalence of endocrine autoimmunity in a group of young JCA patients followed in the Department of Pediatrics of the University of Genoa.

Patients and methods

Patients with JCA diagnosed in the Department of Pediatrics of the University of Genoa between January 1979 and December 2000 and still in follow-up (date of last visit > 01/01/1998) were considered eligible for the study. JCA diagnostic criteria were those proposed by the European League Against Rheumatism (EULAR) (11, 12), namely: the first clinical signs before 16 years of age, arthritis lasting for more than 3 months and exclusion of any other known causes.

After receiving internal ethics committee approval and the parents' informed consent, during a routine follow-up visit all subjects were tested for thyroid and T1DM autoantibodies. For each patient, demographic data, JCA type, age at JCA diagnosis and family history up to second degree relatives were collected.

Thyroid autoimmunity screening

Thyroid autoimmunity was evaluated by fluorescence enzymatic immunoassays of anti-thyroglobulin (TgA) and anti-peroxidase autoantibodies (TPOA). TgA values > 50 IU/ml and TPOA values > 100 IU/ml were considered as positive. At the time of autoantibody determination, each patient also underwent immunometric assay of TSH, free-T3 (fT3) and free-T4 (fT4) serum levels. Patients with TgA and/or TPOA positive values were further studied with thyroid sonography.

Type 1 diabetes mellitus screening
Screening for the risk of T1DM included fasting glycemia and assay of autoantibodies against glutamic acid decarboxylase (GADA), insulin (IAA), tyrosine phosphatase-like protein (IA-2A) and islet cell (ICA). GADA, IAA and IA-2A were determined with radiobinding techniques, while ICA were tested with standard indirect immunofluorescence procedure (13). GADA values > 0.9 U/ml, IAA > 10.18%, IA-2A > 0.75 U/ml and ICA ≥ 5 Juvenile Diabetes Foundation Units (JDFU) were defined as positive, as previously described (14). If positive autoantibodies were detected, oral glucose tolerance test (OGTT) and intravenous glucose tolerance test (IVGTT) (15, 16) were performed.

HLA typing
Patients were further tested for T1DM susceptibility heterodimers by HLA-DQ and DQ polymorphism analysis. Hybridization with sequence-specific oligonucleotide probes (PCR-SSO), polymerase chain reaction and sequence specific primers (PCR-SSP) were the techniques used (17).

Healthy controls
Data obtained in the study population were compared with those obtained in three groups of controls. One consisted of 66 subjects (24 males, 42 females) comparable by sex and age to our study population, admitted to our Clinic for non-hematologic and non-autoimmune diseases; this group was tested for thyroid autoantibodies. The second group was tested for T1DM autoantibodies and consisted of 185 subjects, some of them admitted to our hospital because of minor surgical procedures, others being students of a secondary school. As for HLA typing, the control group consisted of 179 bone marrow donors enrolled in the Italian Blood Donors Registry of Pavia (18).

Statistical analysis
The –test or the Fisher's exact test were used to compare differences between cases and controls. Statistical tests were two-tailed, and tests were considered significant when $p < 0.05$.

Table I. Features of 66 JCA patients admitted to the Department of Pediatrics of the University of Genoa (1979-2000).

Sex		
Males (%)	24	(36%)
Females (%)	42	(64%)
JCA form		
Pauciarticular (%)	42	(64%)
Polyarticular (%)	13	(19%)
Systemic (%)	11	(17%)
Family history		
Thyroid disease	5	
Psoriasis	3	
Rheumatoid disease	2	
T1DM	1	
Median age at diagnosis, years (range)	5.5	(0.9 - 16)
Median age at study, years (range)	12	(1.8 - 25)
Median of disease duration, years (range)	6.75	(0.3 - 22.5)

Results
A total of 143 patients were diagnosed with JCA in our department during the study period. Of these, 81 had at least one visit after 01/01/98, and 66 (81%), 42 females and 24 males, agreed to be enrolled in this study. The median age at JCA diagnosis was 5.5 years (yrs) (range 11 months - 16 yrs) and the median age at study entry was 12 yrs (range 1.9 – 25 yrs). Disease duration at study entry ranged from 4 months to 22.5 yrs., median 6.8 yrs. According to the EULAR classification, 42 patients (64%) had a pauciarticular form, 13 (19%) a polyarticular form, and 11 (17%) a systemic form of JCA; none had ankylosing spondylitis nor psoriatic arthritis. Eleven patients had a positive family history of autoimmunity or thyroid disease, namely: 5 had a family history of goiter and/or nodule, 3 of psoriasis, 2 of rheumatoid arthritis and 1 of T1DM (Table I).

Thyroid autoimmunity
Anti-thyroid autoantibodies were detected in 9 patients (14%), all females, with a significant difference between males and females ($p < 0.05$) (Table II). In particular, they were detected in 19% (8/42) and in less than 1% (1/13) of patients with pauciarticular and polyarticular forms, respectively. No anti-thyroid autoantibodies were found in the 11 cases with JCA systemic form (not significant).
Five cases were found positive for TPOA, 3 for TgA and 1 for both. All these patients, as the rest of our JCA population, had normal values of thyroid hormones. In 3 patients (#37, 61, 66), thyroid ultrasound showed unhomogeneous thyroid parenchyma without nodules and Hashimoto's thyroiditis was diagnosed. Only in 1 case (#37, Table II) thyroid autoantibodies were detected before JCA diagnosis; in fact, a pauciarticular form of JCA was diagnosed nine months after diagnosis of Hashimoto's thyroiditis. The patient had family history of thyroid disease, in particular her paternal grandfather and aunt had goiter; she presented enlargement of the thyroid gland showing an unhomogeneous parenchyma on ultrasound and unhomogeneous left lobe parenchyma on 99TC scan. At the moment of JCA diagnosis, she was not under hormone substitution therapy. All the controls had normal values of thyroid hormones without anti-thyroid autoantibodies, thus no statistical test was done.

Type 1 diabetes mellitus autoantibodies
Only 2 patients (3%) were positive for GADA (Table II), while none were positive for ICA, IA-2A and IAA. Of the 2 GADA positive patients, one (#13) showed impaired glucose tolerance on OGTT, but normal values on IVGTT, while the other one (#61), with T1DM family history (her maternal uncle) and positive values for anti-thyroid autoantibodies, had normal glucose tolerance test. Among controls,

Table II. Clinical, immunological and immunogenetic features of 10 JCA patients with positive levels of anti-thyroid and/or T1DM autoantibodies.

UPN*	Sex	Age at study (yrs, mos)	JCA form	TgA (IU/ml)	TPOA (IU/ml)	Thyroid sonography	GADA (U/ml)	IAA (%)	IA-2A (U/ml)	ICA (JDFU)	Family history	HLA-DQ heterodimers (no.)
9	F	4 y	Pauciarticular	-	113	Normal	23.4	Neg	Neg	Neg	Thy. nodule	Not tested
13	F	8 y	Polyarticular	-	-	Not tested	1.8	Neg	Neg	Neg	Neg	0
23	F	1 yr 11 mo	Polyarticular	71.2	-	Normal	1.8	Neg	Neg	Neg	Neg	2
31	F	14 yr 2 mo	Pauciarticular	221	-	Normal	Neg	Neg	Neg	Neg	Neg	0
37	F	18 yr 1 mo	Pauciarticular	92	1156	Abnormal	Neg	Neg	Neg	Neg	Goiter	2
40	F	14 yr 1 mo	Pauciarticular	-	214	Normal	Neg	Neg	Neg	Neg	Neg	2
42	F	6 yr 11 mo	Pauciarticular	68.8	-	Normal	Neg	Neg	Neg	Neg	Neg	1
57	F	7 yr 3 mo	Pauciarticular	-	131	Normal	Neg	Neg	Neg	Neg	Neg	1
61	F	16 yr 6 mo	Pauciarticular	-	976	Abnormal	23.4	Neg	Neg	Neg	T1DM	1
66	F	12 yr 11 mo	Pauciarticular	-	2345	Abnormal	Neg	Neg	Neg	Neg	Thy. nodule	0

*UPN: unique personal number; Thy. nodule: thyroid nodule.

only 2 cases had IA-2A without other autoantibodies tested. The difference between cases and controls was not significant.

As regards HLA typing (performed only in 43 patients since the remaining ones refused to participate in this part of the study), one or more T1DM susceptibility heterodimers were detected in 20 (46%) patients, 13 of them with 1 heterodimer (30%), 7 with 2 heterodimers (16%), and the remaining 23 (54%) with no T1DM susceptibility heterodimers. Out of the 20 patients positive for T1DM heterodimers, 6 had one or more anti-thyroid or T1DM autoantibodies (Table II). Among controls, the prevalence of 0, 1, 2, or 4 T1DM susceptibility heterodimers was 58%, 26%, 15% and 0.5%, respectively. The difference between our population and healthy controls was not significant.

Discussion

Our data showed a high incidence of anti-thyroid autoantibodies among JCA subjects and an increased risk for endocrine autoimmunity in female patients and in those with JCA pauciarticular form. However, autoimmune activity did not seem to significantly affect thyroid function since all our cases had normal hormone levels.

Most literature studies on this subject are focused on adult series with RA and in this population RA has already been found associated with autoimmune thyroiditis and/or T1DM (1-6). In these series, the prevalence of thyroid autoimmunity ranged between 2% (6) and 16% (1), while for T1DM, except for few case reports (4, 5), only 3% of RA patients (3) were found positive for GADA with no cases positive for ICA.

As regards the pediatric population, few reports have described the association of JCA with autoimmune thyroiditis and/or T1DM (7-10). Concerning thyroid autoimmunity, our data confirm the observation of Mihailova *et al.* (10) that females and subjects with JCA pauciarticular form are at increased risk. However, in our series we demonstrated a lower incidence (14%) compared to that observed by Mihalova (44%) in a smaller group of JCA patients. Only larger studies will allow a more precise estimation of the risk of thyroid autoimmunity in JCA subjects.

Although in our series all the subjects with thyroid autoimmunity had functional euthyroidism, Mihailova *et al.* (10) found that compensated hypothyroidism (11%) and Hashi-toxicosis (4%) might occur. Their data indicate that thyroid functional alteration may occur in some JCA patients with thyroid autoimmunity, and therefore careful follow-up should be planned.

Finally, it is interesting to note that among subjects with thyroid autoimmunity we observed 3 cases of Hashimoto's thyroiditis presenting a higher incidence (4.5%) than the general population (1-2%) (19).

Finally, in our study no significant association was found between JCA and T1DM. This association has been rarely reported in the literature, namely: in 2 case reports (7, 9) and more extensively in a series of 200 diabetic children, 7 of them (3.5%) with JCA (8). Since both JCA (11) and T1DM (15) are autoimmune diseases, this rare association may not be due to chance alone.

In conclusion, we believe that JCA patients, in particular all females with the pauciarticular form, should be regularly tested for thyroid autoimmunity. If thyroid autoantibodies are detected, patients should be closely followed-up in order to minimize the risk of undiagnosed hypothyroidism. Future longitudinal follow-up studies are needed in order to quantify the risk of overt hypothyroidism in the patients with JCA pauciarticular form. Further studies are needed to determine the cost effectiveness of T1DM screening of JCA patients.

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