

Autoimmune endocrine disorders and coeliac disease in children and adolescents with juvenile idiopathic arthritis and rheumatic fever

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Abstract

Objectives

There have been few studies on the association between childhood autoimmune and rheumatic diseases. Therefore, this study aims to assess the frequency of autoimmune thyroiditis (AT), coeliac disease (CD) and type 1 diabetes mellitus (T1DM) in children and adolescents with juvenile idiopathic arthritis (JIA) and rheumatic fever (RF).

Methods

This cross-sectional study includes 53 patients with JIA, 66 patients with RF and 40 healthy subjects controls. All subjects were evaluated for thyrotropin (TSH), triiodothyronine (T3), free thyroxine (FT4), antithyroglobulin (Tg) and antiperoxidase antibodies, fasting glucose, C-peptide, anti-glutamic acid decarboxylase (GAD), anti-islet cell (IA) and antitransglutaminase IgA (tTG) antibodies. Patients with thyroid dysfunction, positive anti-thyroid antibodies or tTG underwent thyroid ultrasonography and jejunal biopsy, respectively.

Results

In group 1 (n=53), 21 patients presented thyroid disorders (40%; 42% oligoarticular), either subclinical hypothyroidism (13%) or positive anti-thyroid antibodies (26%, 50% oligoarticular), significantly higher than in control group ($p<0.009$, $OR=10.5$, $CI\ 1.29-85.2$). In group 2 (n=66), thyroid disorders were identified in 11 patients, four (6%) with subclinical hypothyroidism and seven (11%) with positive anti-thyroid antibodies ($p=0.06$, compared with the control group). There were no cases of clinical overt hypothyroidism, positive anti-GAD or anti-IA, nor changes in serum C-peptide and glycemia. CD was confirmed in one patient from each group.

Conclusion

Patients with JIA (especially the oligoarticular form) and RF should be investigated for thyroid dysfunction. Longitudinal studies could establish screening protocols for CD in patients with JIA and RF. The cost effectiveness of T1DM screening is not justified in this population.

Key words

juvenile idiopathic arthritis, rheumatic fever, autoimmune thyroid disease, type 1 diabetes mellitus, coeliac disease, children, adolescent

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Introduction

Diseases such as type 1 diabetes mellitus (T1DM), autoimmune thyroid disease and coeliac disease (CD) have been reported in adults with systemic autoimmune diseases (systemic lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis) (1-4). However, little is known about the association between those diseases and rheumatic disorders during childhood, such as juvenile idiopathic arthritis (JIA) and rheumatic fever (RF).

There are few studies evaluating the association between thyroid dysfunction and RF, and those that have been done refer only to adults with rheumatic heart disease (5-11). There are also no published data on the association between RF, CD and T1DM.

The purpose of this study was to evaluate the frequency of autoimmune thyroid diseases, CD and T1DM in children and adolescents with JIA and RF.

Patients and methods

Patients

This cross-sectional study included 53 outpatients with JIA (n=53, 25 girls) and 66 outpatients with RF (n=66, 25 girls) from the two existing Paediatric Rheumatology Services and the Paediatric Cardiology Reference Centre in Salvador, Bahia, Brazil, between January 2008 and January 2010.

Patients with JIA fulfilled the criteria for the disease (12), and patients with RF were diagnosed using the guidelines for the diagnosis of rheumatic fever (13).

To evaluate inactivity and clinical remission of JIA, the following criteria were proposed by Wallace *et al.* (14).

This study was approved by the local Research Ethics Committee (protocol 161/2007) and the children's parents or legal guardian signed an informed consent allowing participation. During a routine follow-up visit, all subjects were evaluated for thyroid function and auto-immunity (TSH, T3, free-T4, antithyroglobulin [Tg] and antiperoxidase [TPO] antibodies); for T1DM (glutamic acid decarboxylase [GAD] and islet cell or [IA] antibodies, C-peptide and glycaemia); and for CD (antitransglutaminase [tTG] antibodies). For each patient, demographic data,

age at diagnosis, duration of illness, clinical features of RF, type of JIA, disease activity, family history of autoimmune diseases in first and second degree relatives (including autoimmune thyroid diseases, rheumatological disorders, CD, T1DM, vitiligo, alopecia areata, multiple sclerosis, inflammatory bowel disease), signs and symptoms of thyroid diseases, CD and T1DM and current medication were recorded. Rheumatoid factor by immunonephelometry (cut-off value of 15 IU/mL) and antinuclear antibody (ANA) by indirect immunofluorescence on human cell epithelioma (HEp-2) cells (Euroimmun AG, Germany) titers were performed in the JIA group.

Thyroid function and thyroid autoimmunity screening

Thyroid autoimmunity was evaluated by chemiluminescence assays for Tg (reference value <40 IU/mL; Abbott, Lisnamuck, Longford, Ireland) and TPO (reference value <35 IU/mL; Siemens, Llanberis, Gwynedd, UK) auto-antibodies. Also, chemiluminescence assays for TSH (reference values <1 year: 0.4–8.6 µIU/mL, 1–2 years: 0.36–7.6 µIU/mL, 3–6 years: 0.34–6.3 µIU/mL, 7–12 years: 0.36–5.6 µIU/mL, >12 years: 0.4–4.0 µIU/mL; Siemens, Llanberis, Gwynedd, UK), T3 (reference values <1 year: 101.5–181.2 ng/dL, 2–5 years: 101.5–198.9 ng/dL, >6 years: 90.9–177 ng/dL; Abbott, Lisnamuck, Longford, Ireland) and free T4 (reference values 0.70–1.48 ng/dL; Abbott, Lisnamuck, Longford, Ireland) dosages were used.

All patients with abnormal TSH and/or thyroid hormone levels or positive Tg and/or TPO antibodies were further studied through a high resolution thyroid echography examination.

Hypothyroidism was defined as low T3 and/or FT4 with elevated TSH levels; subclinical hypothyroidism was defined as TSH levels above normal limits with normal thyroid hormone levels; and thyrotoxicosis was defined as high T3 and/or FT4 levels with suppressed levels of TSH.

Autoimmune thyroiditis was defined as elevated TPO and/or Tg antibody values associated with abnormal TSH levels

Competing interests: none declared.

and/or a typical hypoechogenic thyroid ultrasound (15). The thyroid was considered hypoechogenic when its signal was equal to or below the echogenicity of the surrounding neck muscles.

Type 1 diabetes mellitus screening

The following laboratory exams were performed for T1DM screening: fasting glycaemia (reference value 60–99 mg/dL, enzymatic; Labtest, Belo Horizonte, Brazil); serum GAD autoantibodies (reference value <10 U/ml, enzyme-linked immunosorbent assay – ELISA; Euroimmun, Lübeck, Schleswig-Holstein, Germany); IA autoantibodies (reference value <0.5, standard indirect immunofluorescence procedure; RSR Ltd, Cardiff, UK); and C-peptide serum (reference value <1.1–4.4 ng/ml, chemiluminescence assay; Roche, Baden-Württemberg, Germany).

Coeliac disease screening

Serum IgA anti-transglutaminase (tTG) antibodies were assayed by a specific ELISA (reference value: <7 U/mL; Orgentec, Diagnostika, Mainz, Germany). A small intestinal biopsy was performed to confirm the diagnosis of coeliac disease in those whose specific autoantibody profile was found to be positive. The Marsh-Oberhuber histological classification was used for reference (16).

Healthy controls

Data from the studied population were compared to those obtained from two control groups of healthy outpatients pediatrics (18 [8 girls] for group 1 and 22 [8 girls] for group 2), matched by sex and age (± 0.3 years) at a 1:3 ratio. None of these subjects had genetic syndrome, congenital disease, signs or symptoms of thyroid disease or any other chronic disease. Informed consent was obtained from their parents or legal guardians.

Statistical analysis

SPSS 17.0 version was used. To describe the data in continuous variables, mean and standard deviation were used. Categorical variables were described using percentages. The data were also presented using tables and graphics. In the statistical analysis, for compari-

son of categorical variables, the chi-squared test (χ^2) was used, and Fisher's exact test was substituted when the assumptions required for the chi-squared test were not met.

Results

Demographics and joint disease

Group 1 (JIA patients) included 53 patients with JIA (25 girls). Demographic and clinical data of 53 patients with JIA at the time of the screening are summarised in Table I. In this sample no other subtype (enthesitis related arthritis, psoriatic or the undifferentiated) of the disease was identified. Rheumatoid factor was positive in 8 (15%) and ANA was found in ten (19%) patients.

Among the patients, 37.7% were in clinical and laboratory remission (28.3% and 9.4% with and without medication, respectively).

Demographic and clinical data of 66 patients with RF at the time of the screening are summarised in Table II. Seventy-six percent (50/66) of the patients had rheumatic heart disease, the most frequent being mitral insufficiency (28.8%), followed by associated mitral and aortic insufficiency (22.7%), mitral and tricuspid insufficiency (12.1%) and aortic insufficiency (4.5%).

Positive history of arthritis, chorea and subcutaneous nodules was present in 74 (49/66), 27 (18/66) and 4.5 (3/66) percent of the patients, respectively. There were no cases of identified erythema. Among the patients, five (7.6%) had the following signs of active disease: arthritis (1), carditis (1), chorea (1), and both arthritis and carditis (2).

Family history of autoimmune diseases

Group 1 (JIA patients) included twenty patients (37.3%) diagnosed with JIA (especially oligoarticular [10 patients, 50%]) who had a family history of autoimmune diseases, namely rheumatic disease (n=10), hypothyroidism (n=15), psoriasis (n=1), type 1 diabetes mellitus (n=3), multiple sclerosis (n=1), inflammatory bowel disease (n=1), vitiligo (n=1), and alopecia areata (n=1). When compared with the control group (37.3% vs. 5.8%), this difference was statistically significant ($p < 0.013$).

Table I. Demographic and clinical data of 53 patients with juvenile idiopathic arthritis at the beginning of the study.

| Sex | n (%) |
|--------------------------|---------------------------|
| Male | 28 (53) |
| Female | 25 (47) |
| | Mean (limits) |
| Age at diagnosis, years | 7.5 \pm 3.8 (1.1–15.9) |
| Age at study, years | 10.4 \pm 4.0 (2.3–17.9) |
| Disease duration, months | 41.3 \pm 37 (2–156) |
| Initial presentation | n (%) |
| Oligoarticular | 17 (32) |
| Polyarticular | 18 (34) |
| Systemic | 18 (34) |
| Clinical remission | 20 (38) |
| Without medication* | 5 (9) |
| With medication** | 15 (28) |
| Drug therapy | |
| NSAIDs | 43 (81) |
| Methotrexate | 31 (59) |
| Steroids | 17 (32) |
| Immunobiological | 8 (15) |
| No therapy | 5 (9) |

mean \pm SD.

NSAIDs: non-steroidal anti-inflammatory drugs.
*Inactive disease, defined as no joints with active arthritis; no fever, rash, serositis, splenomegaly or generalised lymphadenopathy attributable to JIA; no active uveitis, confirmed by ophthalmological examination; normal erythrocyte sedimentation rate or negative C-reactive protein; physician's global assessment of disease activity (*i.e.* best score attainable on the visual analogue scale), for 12 consecutive months while the patient is not using any medication
**Inactive disease, defined as above, for 6 consecutive months while the patient is using medications.

Table II. Demographic and clinical data of 66 patients with rheumatic fever at the beginning of the study.

| Sex | n (%) |
|--------------------------|--------------------------|
| Male (%) | 41 (62) |
| Female (%) | 25 (38) |
| | Mean (limits) |
| Age at diagnosis, years | 8.5 \pm 2.6 (2.4–15.5) |
| Age at study, years | 11.5 \pm 2.7 (6.1–18) |
| Disease duration, months | 32 \pm 27 (0.1–120) |
| Active disease | 5 (7.6) |
| Clinical characteristics | |
| Rheumatic heart disease | 50 (76) |
| Arthritis | 49 (74) |
| Chorea | 27 (18) |
| Subcutaneous nodules | 3 (4.5) |
| Erythema | 0 (0) |

mean \pm SD.

Among the patients with a family history of thyroid disease, only two were diagnosed as autoimmune thyroiditis. First-degree relatives accounted for

Table III. Family history of autoimmunity; prevalence of thyroid disorders, coeliac disease and DM1 in 53 patients with JIA.

| Patients | Total n (%) | Oligo- articular n (%) | Poly articular n (%) | Systemic n (%) | Controls n (%) | JIA vs. controls <i>p</i> -value |
|-----------------------------------|----------------|------------------------------|----------------------------|-------------------|-------------------|----------------------------------------|
| Subjects | 53 (100) | 17 (32) | 18 (34) | 18 (34) | 17 (100) | |
| Family history of autoimmunity | 20 (37) | 10 (50) | 7 (35) | 3 (15) | 1 (6) | 0.013 |
| Thyroid disorders | 21 (40) | 9 (42) | 6 (29) | 6 (29) | 1 (6) | 0.009 |
| Subclinical hypothyroidism | 7 (13) | 2 (28) | 4 (57) | 1 (14) | 0 (0) | 0.14 |
| †A-TPO and/or TgA | 14 (26) | 7 (50) | 2 (14) | 5 (36) | 1 (6) | 0.07 |
| Autoimmune thyroiditis* | 06 (11) | 4 (67) | 1 (16) | 1 (16) | 0 (0) | 0.32 |
| Coeliac disease (tTG IgA+ biopsy) | 01 (2) | 0 (0) | 0 (0) | 1 (100) | 0 (0) | 0.56 |
| DM1 | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | |

DM1: type 1 diabetes mellitus; JIA: juvenile idiopathic arthritis; tTG IgA: sérum Ig A anti-transglutaminase; biopsy: small intestine biopsy.

*03 patients with elevated TPO and/or Tg antibody values with abnormal TSH levels and 03 patients with elevated TPO and/or Tg antibody values with a typical hypoechogenic thyroid ultrasound.

Table IV. Family history of autoimmunity and prevalence of thyroid disorders, coeliac disease and DM1 in 66 children with RF.

| Patients | RF | Controls | RF vs. controls <i>p</i> -value |
|-----------------------------------|----------|----------|------------------------------------|
| | n (%) | n (%) | |
| Number of subjects | 66 (100) | 23 (100) | |
| Family history of autoimmunity | 30 (46) | 4 (6) | 0.017 |
| Thyroid disorders | 11 (17) | 0 (0) | 0.06 |
| Subclinical hypothyroidism | 4 (6) | 0 (0) | 0.22 |
| †A-TPO and/or TgA | 7 (11) | 0 (0) | 0.15 |
| Autoimmune thyroiditis* | 2 (3) | 0 (0) | 0.999 |
| Coeliac disease (tTG IgA+ biopsy) | 1 (1.5) | 0 (0) | 0.55 |
| T1DM | 0 (0) | 0 (0) | |

T1DM: type 1 diabetes mellitus; RF: rheumatic fever; tTG IgA: serum IgA anti-transglutaminase; biopsy: small intestine biopsy.

*02 patients with elevated TPO and/or Tg antibody values with a typical hypoechogenic thyroid ultrasound.

36% of reported familial auto-immune disorders, while second-degree relatives accounted for 64%.

Comparing the different onsets of the disease, patients with oligoarticular onset JIA had a higher prevalence of family history of autoimmune diseases (10 out of 20 families, 50%) compared with polyarticular onset patients (7 out of 20 families, 35%) and systemic onset patients (3 out of 20 families, 15%) (Table III).

Group 2 (RF patients) included thirty patients with RF (45.6%) who had a family history of autoimmune diseases, namely, rheumatic diseases (n=20), hypothyroidism (n=5), CD (n=6), psoriasis (n=1), T1DM (n=2), multiple sclerosis (n=2), inflammatory bowel disease (n=1) and vitiligo (n=2). When compared with the control group (45.6% vs. 6.0%), this difference was statistically significant ($p<0.017$).

Thyroid function, thyroid autoantibodies and autoimmune thyroiditis

In group 1 (JIA patients), thyroid abnormalities were identified in 40% (n=21; 9 oligoarticular, 42%) of the patients and in 5.8% (n=1) of controls ($p<0.009$). In 7 (13%) JIA patients (5 girls, mean age 12.3 yr, range 4.2–17 yr) subclinical hypothyroidism was diagnosed. The onset of JIA was systemic in one, polyarticular in four and oligoarticular in two patients. Three patients were positive for thyroid antibodies (5.6%; 3 girls, mean age 15.4 yr, range 14–17 yr), and were diagnosed as autoimmune thyroiditis. No cases of overt clinical and laboratory hypothyroidism were found among children with JIA.

Positivity for TPO and/or Tg antibodies was detected in 14 (26.4%) patients (7

oligoarticular JIA, 8 girls, mean age 10 yr, range 2.3–14.9 yr). Of these, 4 patients were positive for TPO, 4 for TgA and 6 for both. Among these patients, three children had a hypoechogenic ultrasound pattern, which is compatible with the diagnosis of autoimmune thyroiditis.

Autoimmune thyroiditis was more prevalent in oligoarticular JIA (4 patients, 67%).

In the control group, one patient tested positive for TPO and anti-Tg antibodies, with normal levels of T3, FT4 and TSH and without abnormalities on the thyroid ultrasound evaluation.

Despite the high prevalence of thyroid abnormalities in JIA patients in comparison with the control group ($p<0.009$), no statistically significant difference was found when the thyroid abnormalities were analysed separately (Table III).

ANA and rheumatoid factor were present in 10 (19%) and 8 (15%) JIA patients, respectively, but no association was found between them and the presence of antithyroid antibodies ($p<0.84$).

In group 2 (RF patients), thyroid abnormalities were found in 17% (n=11) of the patients and in none of the controls ($p<0.06$). In this group, 4 patients (2 girls, mean age 12.4 yr, range 9.7–14.9 yr) had subclinical hypothyroidism (1 patient with chorea; 1 with arthritis and chorea; and 2 with both arthritis and valvulitis [1 mitral and aortic insufficiency, and 1 mitral and tricuspid insufficiency]). None of these patients had autoimmune thyroiditis. No case of overt clinical and laboratory hypothyroidism was found among these children.

Seven patients (11%) tested positive for TPO and/or Tg antibodies (6 girls, mean age 11.7 yr, range 8.7–14.9 yr). Of these, three patients were positive for anti-TPO and four for both anti-TPO and anti-Tg antibodies. Among these patients, two children had a hypoechogenic ultrasound pattern, compatible with the diagnosis of autoimmune thyroiditis.

In the control group, no patient had positive antibodies and thyroid abnormalities.

There was a higher prevalence of subclinical hypothyroidism and thyroid auto-antibodies in group 2 than in the control group, but these differences were not statistically significant.

Table IV summarises thyroid disease in this group as well as its characteristics.

Coeliac disease

In group 1 (JIA patients), a small intestinal biopsy was carried out to confirm the diagnosis of CD in only one asymptomatic patient (1.9%; systemic JIA; boy; 10 years old; age at diagnosis, 5 years old; clinical and laboratory remission for 24 months; ANA, rheumatoid factor, TPO-A and TgA negative; normal thyroid function) with positive IgA anti-transglutaminase (tTG) antibodies (value: 130 U/mL) and biopsy showing typical villous atrophy and crypt hyperplasia. This patient was classified as type 3c lesion according to Marsh-Oberhuber, which is consistent with the diagnosis of CD. There was no family history of autoimmune diseases and/or coeliac disease.

In group 2 (RF patients), CD was confirmed by small intestinal biopsy in only one asymptomatic patient (1.5%; boy; 14.9 years old; age at diagnosis, 12 years old; subclinical hypothyroidism; mitral and tricuspid insufficiency) with positive IgA tTG antibodies (value: 17 U/mL). The patient had the same histological lesion described above (Marsh-Oberhuber 3c). There was no family history of autoimmune and/or coeliac disease.

The IgA anti-transglutaminase (tTG) antibodies in the other patients and in the control group were within the normal reference values.

Type 1 diabetes mellitus

No patient in the study group had positive GAD or IA, changes in C-peptide serum levels, or glycemic disorders.

Discussion

JIA and thyroid dysfunction

There is a clear association between autoimmune thyroid disease and rheumatic arthritis (RA), although the pathogenic mechanism is uncertain (17). Positivity for thyroid autoantibodies, anti-Tg and/or anti-TPO was detected in about

11% of RA patients (18), which has been confirmed in most studies, ranging from 2% (19) up to 30% (17-20).

The first report on the association between JIA and autoimmune thyroiditis was published in 1968 (21), followed by other case reports (22-25). Cross-sectional studies have been conducted and all of them reported a high prevalence of autoimmune thyroiditis, especially in patients with oligoarticular JIA (26-31).

In contrast, Ünsal *et al.* found no case of autoimmune thyroiditis in patients with oligoarticular JIA, nor any significant statistical association between JIA and autoimmune thyroiditis (32). The authors stated that this finding may have been attributable to the lower prevalence of oligoarticular JIA (33%) and the small ratio of girls in this study when compared to the data in the literature. These two variables – oligoarticular arthritis and female sex – as highlighted in other studies (32) are closely related to autoimmune thyroiditis.

The present study showed a higher frequency of thyroid disorders (subclinical hypothyroidism, antithyroid antibodies and autoimmune thyroiditis) in patients with JIA than in the control group ($p < 0.009$, OR=10.5, CI 1.29–85.2).

Many drugs are known to interfere with thyroid function (amiodarone, propranolol, non-steroidal anti-inflammatory drugs [NSAID] and steroids). The NSAIDs may decrease thyroid hormone serum levels by interfering with the connection to the carrier proteins (33-35). This study found no association between thyroid abnormalities and NSAIDs or steroids in JIA ($p < 0.30$).

Girls are found to be more prone to developing autoimmune thyroiditis, subclinical hypothyroidism, and to present antithyroid antibodies.

Unlike most studies on this subject, which include predominantly female patients, and in agreement with the findings of Ünsal *et al.* (32), this study had 53% male patients. Ünsal *et al.* attributed the unusually high male to female ratio to the fact that 22% of the patients had enthesitis-related arthritis, a type mostly affecting boys, which may have modified the frequency of autoimmune thyroiditis. Although we have no pa-

tient diagnosed with enthesitis-related arthritis, the lower female/male ratio may have played a role in the results concerning autoimmune thyroiditis.

In contrast to data reported by other studies, the majority (4/7) of JIA children with subclinical hypothyroidism in this study had a polyarticular onset and almost half of them (3/7) had autoimmune thyroiditis.

By comparing the different types of onset, oligoarticular JIA patients seem to have autoimmune thyroiditis more often than other JIA patients, which is in agreement with the literature.

A family history of autoimmune disorders was present in 37.3% ($p = 0.013$) of the JIA patients, especially in the oligoarticular onset group. The most frequent autoimmune disorders among their relatives were rheumatic disease and autoimmune hypothyroidism, whereas other studies (30, 36) predominantly found the diagnosis of psoriasis, and then autoimmune thyroiditis, respectively. As previously stated, relatives of JIA patients presented a higher frequency of autoimmune disorders than relatives of control patients did.

The increased prevalence of ANA among patients with autoimmune thyroid disease is also well documented, although its clinical significance and pathogenic mechanism remain unknown. Some authors suggest that a polyclonal immune response (specific and nonspecific body) may exist in these patients (17). Atzeni *et al.* demonstrated the presence of ANA in 75% and 69% of patients with anti-TPO and anti-Tg, respectively (17). In the present study, there was no association between ANA and rheumatoid factor positivity and the presence of antithyroid antibodies.

This study found 21 patients with thyroid disorders (40%), including 14 (26.4%) who tested positive for antithyroid antibodies. Due to these numbers, screening for thyroid autoimmunity should be considered in girls with oligoarticular JIA and when the patient has family history of such. If thyroid autoantibodies are detected, patients should be closely followed, allowing for early diagnosis of hypothyroidism. Further studies with larger groups of patients are needed to demonstrate the

real frequency of autoimmune thyroiditis, as well as the risk of hypothyroidism in patients with JIA.

JIA and coeliac disease

Children with JIA may have gastrointestinal symptoms, anaemia, short stature, arthritis, gastrointestinal symptoms, delayed puberty and growth failure. These symptoms can be induced by medications or the disease itself, but can be also attributed to other primary diseases, like CD. Some studies have shown an association between CD and the serological markers for various rheumatic diseases, particularly systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome (30, 37-48). In the present study, the diagnosis of coeliac disease was confirmed by small intestinal biopsy and positive test for IgA tTG antibodies in one symptom-free patient with JIA (1.9%). This is similar to the prevalence found in other studies (41, 47). Different results were described by Stagi *et al.* (6.7%), Lepore *et al.* (3.3%) and Al-Mayouf *et al.* (2.38%), (30, 46, 48). IgA tTG was used in the serological test, described by Dieterich *et al.* in 1977 as having high sensitivity (98%) and specificity (90%) (49). The proposed test is accepted as a reliable screening method for CD. Contrary to Stagi *et al.* (30), this study found no association between CD and autoimmune thyroid disease in patients with JIA.

There is no consensus in the literature on the need for routine CD screening in patients with JIA. In the present study, the only CD patient was asymptomatic, which draws attention to the possibility of silent forms of CD and to the wide spectrum of the clinical disease, as well as to the need to monitor the emergence of other autoimmune diseases along the course of JIA. New controlled studies appear to be useful in the clarification of this issue.

JIA and T1DM

The association of T1DM with autoimmune thyroiditis is well documented in the literature, with an estimated prevalence of 4–16% (50), but few reports have described the association of JIA and T1DM: in 8 case reports (22, 23, 25, 51-55) and a series of 200 diabetic

children, 7 were diagnosed with JIA (six with polyarticular onset JIA) (56). However, one case refers to a seven-year old girl who developed T1DM five months after initiating etanercept therapy for systemic onset JIA (53).

No patient in this study showed changes in fasting glucose or C-peptide or was positive for anti-GAD or anti-IA. Apparently, the cost effectiveness of T1DM screening for JIA patients is not justified in this population.

Rheumatic fever and thyroid dysfunction

There are few studies that evaluate the association between thyroid dysfunction and RF, and none of them assessed RF in children and adolescents. The first reference on this association is in 1961, with the study of six women with rheumatic heart disease who developed thyroiditis and hyperthyroidism and were anti-Tg positive (5).

Since 1961 the few studies that have been published have contradictory results, showing either no association between RF and autoimmune thyroid disease (6) or a higher frequency of some kind of thyroid dysfunction and/or thyroid autoantibodies in patients with chronic rheumatic heart disease (7-11). In this study, all the seven patients (with the exception of one) with RF and positive thyroid autoantibodies had clinical history of carditis and valvular heart damage, and all of them had arthritis in the early stages of the disease. The majority of these patients were girls (n=6), two of them with diagnosis of chorea. Recently, Ertgrul *et al.* have showed that adults with rheumatic mitral stenosis have a higher frequency of Hashimoto's thyroiditis (16/55, 29%) than healthy controls (11). This suggests a possible association between rheumatic mitral stenosis and thyroid disease. No case of mitral stenosis was identified in the present study, but this may have been due to the different age groups and the heterogeneity of the sample. Mitral regurgitation was the lesion most commonly found in patients with thyroiditis, followed by the associated mitral and aortic insufficiency.

This study evidenced subclinical hypothyroidism and autoimmune thy-

roiditis in 6% and 11% of cases, respectively, which is not negligible. In spite of the absence of statistical significance ($p=0.06$), this issue deserves attention during the follow-up of patients with RF.

Rheumatic fever, coeliac disease and type 1 diabetes mellitus

There is no report in the literature on the association between T1DM, CD and rheumatic fever. No patient in this study showed changes in fasting glucose, C-peptide or positive anti-GAD and anti-ICA antibodies. On the other hand, the diagnosis of CD was confirmed in a symptom-free patient with RF (1.5%), who also presented subclinical hypothyroidism.

In the absence of other studies evaluating the association between CD and RF and considering that only 1 case (1.5%) of such was found in this series, further prospective controlled studies are needed to assess whether this was an incidental finding or deserves some clinical significance.

Conclusion

The present study found a significant prevalence of autoimmune thyroid disorders in patients with RF and JIA, especially in the oligoarticular subtypes, suggesting that routine screening for thyroid diseases in this group must be considered. The identification of two asymptomatic cases of coeliac disease emphasises the need for health professionals to be attentive toward atypical and oligosymptomatic forms of the disease, which can often manifest themselves in ways similar to rheumatic diseases. With respect to diabetes, the absence of elements that could establish an association with JIA or RF indicates that screening for risk factors for DM1 is unnecessary in this population.

Key messages

- Due to the high prevalence of autoimmune thyroid disorders, patients with juvenile idiopathic arthritis and rheumatic fever should be routinely investigated for thyroid dysfunction.
- Patients with JIA have a 10-fold greater chance of autoimmune thyroid abnormalities indicating that

systematic screening should be routinely performed.

- Organ-specific autoantibodies were observed in 26% of juvenile idiopathic arthritis, particularly in the oligoarticular subtype.
- Organ-specific autoimmune diseases, especially subclinical hypothyroidism and coeliac disease were evidenced in juvenile idiopathic arthritis and rheumatic fever.

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