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ORIGINAL ARTICLE

Asymptomatic celiac sprue in juvenile rheumatic diseases children

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Abstract

Background: Celiac disease (CD) is the most frequent enteropathy in adults and its coexistence with other autoimmune diseases is frequent.

Objective: To detect asymptomatic CD in children with rheumatic diseases by measuring tissue transglutaminase (tTG) antibodies and finding any relation to disease activity.

Patients and methods: Setting and study design: The study included 60 children with juvenile rheumatic diseases consecutively from those attending the Rheumatology Clinics of Cairo University Hospitals: 30 juvenile rheumatoid arthritis (JRA), 10 juvenile systemic lupus erythematosus (SLE), 12 juvenile seronegative spondyloarthropathy and eight juvenile systemic sclerosis/polymyositis (SSc/PM) overlap syndrome were recruited during 2010. There were 22 male and 38 female patients. Thirty matched healthy controls were included. All children were subjected to thorough history taking, clinical examination and laboratory investigations. The body mass index (BMI) for age was used. All subjects had no gastrointestinal tract symptoms suggestive of CD and the tTG antibodies (IgA and IgG) were assessed.

Results: The mean age of patients was 12.03 ± 3.3 years and disease duration 4.18 ± 3.24 years. The demographic, clinical and laboratory features of the children were studied and compared. The tTG was positive in 32 (53.3%) patients compared to 20% of the controls ($P = 0.03$), being higher in females. In tTG-positive patients, the BMI was significantly lower, while white blood cell count, erythrocyte sedimentation rate and disease activity were significantly higher.

Conclusions: tTG antibodies may be used as a screening test to identify asymptomatic CD associated with juvenile rheumatic diseases, especially those with active JRA or marked reduction in BMI.

Key words: asymptomatic celiac disease, juvenile rheumatic diseases.

INTRODUCTION

Juvenile rheumatoid arthritis (JRA) children have an increased prevalence of celiac disease (CD).[1] It is characterized by chronic arthritis and an autoimmune etiology. The gene locus 4q27 associated with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and CD has been found to be also associated with susceptibility to JRA.[2] CD (gluten enteropathy) is a chronic inflammatory malabsorption disease of the gastrointestinal tract (GIT) of autoimmune etiology in genetically predisposed individuals after ingestion of wheat gluten. It is the most regular enteropathy in adults and frequently coexists with other autoimmune diseases, having common symptoms which can delay its diagnosis and the introduction of a gluten-free diet, which improves the quality of life and protects from dangerous GIT complications.[3,4] In addition to intestinal symptoms, CD is associated with various

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extra-intestinal complications, including bone and skin disease, anemia, endocrine disorders and neurologic deficits.[5] The prevalence of CD is increasing as the consumption of gluten-containing foods is increasing worldwide.[6]

Juvenile rheumatoid arthritis and associated autoimmune antibodies are frequent in CD patients and their first-degree relatives, indicating a shared genetic susceptibility.[7] This enigma, being an epiphenomenon or pathogenic, remains unresolved and presents a challenging area for upcoming research.[8] Although the diagnosis of CD is often confirmed by a small bowel biopsy, autoantibodies directed against tissue transglutaminase (tTG) are highly correlated with biopsy-proven disease and serve as a valuable screening marker. Furthermore, CD coexists with other rheumatic diseases as RA, such as systemic lupus erythematosus (SLE), systemic sclerosis (SSc), Sjögren syndrome.[9] inflammatory bowel disease[10] and polymyositis (PM).[11] The frequency of false positive tTG tests in these diseases is similar to that in controls and thus may be used as a screening test to identify patients at risk who require further evaluation for the presence of CD.[9]

Most CD patients show atypical symptoms and may remain undiagnosed, which makes screening justified in high-risk patients with autoimmune diseases.[12] However, when the clinical suspicion of CD is high, small bowel biopsy should be performed if tTG antibody tests are negative.[13] The incidence of CD has increased considerably during the last two decades and is diagnosed in adults as frequently as in children. Besides the typical symptomatic presentation, silent, latent and potential CD is found. Asymptomatic courses are increasingly found in all age groups.[14] Although primarily affecting the small bowel, CD is a multisystem disorder that may initially present to a wide range of clinical specialties.[15]

The present study was performed for the screening of tTG antibodies for CD in children with rheumatic diseases, including JRA, SLE, seronegative spondyloarthropathy (SpA) and SSc/PM or dermatomyositis (DM) overlap syndrome and to find any relationships between the presence of the antibodies with disease activity in these children.

PATIENTS AND METHODS

Patients

The study included 60 consecutive children attending the Rheumatology Clinics of Cairo University Hospitals, Egypt, with rheumatic diseases diagnosed according to the relevant classification criteria for the diseases. There were 30 with JRA,[16] 10 with juvenile SLE,[17] 12 with juvenile SpA[18] and eight with juvenile SSc/PM or DM overlap syndrome[19,20] recruited during 2010. There were 22 male and 38 female patients. Thirty age- and sex-matched healthy children chosen from the children of staff members and workers Clinics were included in the study and served as controls.

Study design

All juvenile patients and control children were not known to have CD and had no significant GIT symptoms suggestive of it (malabsorption such as diarrhea, constipation, flatulence, growth retardation, abdominal colics, anorexia, nausea and vomiting, change in the color of stools) during the 6 months preceding the study. All children were subjected to thorough history taking, special detailed history for GIT, clinical examination and laboratory investigations. The body mass index (BMI) for children was used, taking into account their age and gender. Disease activity in JRA cases was assessed by the use of the Disease Activity Score (DAS28)[21] and in juvenile SLE using the Systemic Lupus Disease Activity Index (SLEDAI).[22] Combined serum immunoglobulin G (IgG) and IgA tTG antibodies levels were detected using a commercially available enzyme-linked immunosorbent assay (ELISA) kit semi-quantitative method (Immuno-Biological Laboratories, Hamburg, Germany). Informed consents were given by the parents and the study was approved by the local ethics committee.

Statistical analysis

SPSS program version 15 was used for analysis of data (SPSS Inc., Chicago, IL, US). Data was summarized as means $\pm$ SD. Non-parametric test was done for two independent variables. Pearson's correlation was also used. Student's *t*-test was used to detect a significant difference. *P*-values were considered significant at ≤ 0.05. A semi-quantitative interpretation of IgA and IgG tTG antibody results was available by using the 25 U/mL standard as a cut-off control. Results are expressed in Binding Index (BI), the ratio between the sample and the cut-offs optical density (OD): BI = Sample OD/Cut-off OD (a sample is negative when BI ≤ 1; a sample is positive when BI ≥ 1).

RESULTS

The mean age of the children with rheumatic diseases was 12.03 $\pm$ 3.3 years and the disease duration was

4.18 ± 3.24 years with an age at disease onset of 7.83 ± 3.58 years. The mean BMI for children was 17.97 ± 3.8. There were 38 female and 22 male patients with a ratio of 1.72 : 1.00. The 30 children with JRA had a mean morning stiffness (MS) of 16.79 ± 26.29 min, the tenderness score was 5.73 ± 3.35, number of swollen joints 2.47 ± 1.57 and DAS-28 of 4.05 ± 0.85. There were 10 systemic onset, four polyarticular and 16 oligoarticular onset. They were receiving methotrexate at a dose of 14.33 ± 4.1 mg/week. There were 12 juvenile SpA patients, including 10 with ankylosing spondylitis (AS) and two PsA who were receiving methotrexate at a dose of 10 mg/week. The demographic and laboratory features of the studied patients are shown in Tables 1 and 2.

Tissue transglutaminase was positive in 32 (53.3%) and negative in 28 patients (46.7%). Six (20%) out of the 30 control children had positive tTG which was significantly different from the juvenile rheumatic diseases patients ($P = 0.03$). tTG was present in 16 (53.3%) of the JRA patients, being more in the systemic onset. tTG was positive in 60% of juvenile SLE and 50% of juvenile SpA and SSc/PM patients. tTG positivity was seen in 12 males (54.54%) but was much higher in females, being present in 20 (71.43%). BMI for children was significantly lower in juvenile rheumatic diseases patients with positive tTG compared to those with negative tTG (16.94 ± 3.76 *vs.* 19.14 ± 3.55) ($P = 0.023$).

The differences in JRA patients with positive and negative tTG antibodies regarding demographic and laboratory features are shown in Tables 3 and 4. DAS-28 was significantly higher in those with positive tTG (4.35 ± 0.46 *vs.* 3.7 ± 1.06) at $P = 0.047$. Rheumatoid factor was positive in only 10 JRA cases (16.7%) and antinuclear antibody (ANA) was positive in 22 (36.7%). Lymphocytosis was higher in tTG-positive JRA patients (41.2%) compared to those with a negative test (33.6%) but this was not significantly different. Again, the same was found when considering all the juvenile rheumatic diseases with positive and negative tTG.

All the juvenile SLE cases had positive ANA and anti-double stranded DNA (anti-ds-DNA). There was no correlation between tTG positivity and either rheumatoid factor or ANA. The mean SLEDAI was 12.8 ± 4.94, being significantly higher in those with positive tTG at $P = 0.016$ (15.67 ± 3.5 *vs.* 8.5 ± 3.42). All the juvenile SpA cases were rheumatoid factor and ANA negative and they all had clinical and radiological sacroilitis. There were 10 with AS and two with PsA. Enthesiopathy was present in six cases (50%) in which tTG was positive in three. ESR was significantly higher (39.67 ± 19.81 *vs.* 8.67 ± 3.61 mm/1st hour) ($P = 0.012$) in those with positive tTG compared to those who were negative. All juvenile SSc/PM overlap syndrome patients gave histories of Raynaud's phenomenon, manifestations of scleroderma and polymyositis was present in two. All the patients were inactive during the study.

DISCUSSION

An association between CD and other autoimmune disorders such as SLE and RA has been described.[23] Furthermore, sub-clinical gut inflammation is described in patients with AS and PsA and joint involvement is reported to be related to CD.[24] The diagnosis of CD in systemic rheumatic diseases can be difficult because they are often associated with a number of GIT symptoms and diseases.[9] This trigger incidence of anti-TG in children with autoimmune rheumatic diseases goes along with a recent study that supports its association to multiple sclerosis, although the specific role of these antibodies in the pathogenesis remain uncertain and require additional research.[25]

In the present study, regarding tTG antibody positivity, there was a significant difference between patients and controls. This is in agreement with the results of

Table 1 Demographic features and steroids used by study children with rheumatic diseases

Features (mean ± SD)	JRA (30)	Juvenile SLE (10)	Juvenile SpA (12)	Juvenile SSc/DM (8)
Age (years)	11.87 ± 3.93	12.2 ± 2.15	13 ± 2.89	11 ± 2.39
Age at onset (years)	5.33* ± 3.74	11.1 ± 1.09	8.83 ± 3.43	7.25 ± 1.75
Disease duration (years)	6.5* ± 3.8	1.3 ± 0.69	4 ± 1.35	3.75 ± 2.87
BMI	17.87 ± 4.18	17.64 ± 1.02	16.93* ± 2.22	21.45 ± 3.97
F : M	2.75 : 1.00	4 : 1	1 : 2	1 : 1
Steroid dose (mg/day)	4.67 ± 4.44	18.5 ± 6.99	2.08 ± 3.17	8.75 ± 6.94

*Significantly different from the corresponding values at $P < 0.05$. BMI, body mass index; F : M, female : male ratio; JRA, juvenile rheumatoid arthritis, SLE, systemic lupus eryhtematosus; SpA, spondylarthropathy; SSc/DM, systemic sclerosis/dermatomyositis overlap.

Table 2 Laboratory investigations of the study children with rheumatic diseases

Laboratory investigations (mean ± SD)	JRA (30)	Juvenile SLE (10)	Juvenile SpA (12)	Juvenile SSc/DM (8)
RBCs (million/mm^3)	4.53 ± 0.31	3.71 ± 0.43	4.98 ± 0.72	4.43 ± 0.2
Hemoglobin (g%)	11.19 ± 1.28	11.38 ± 2.47	11.62 ± 0.79	12.05 ± 0.68
Hematocrite (%)	34.56 ± 3.4	30.8 ± 5.11	34.82 ± 1.94	33.28 ± 2.87
MCV (μm^3)	76.52 ± 6.11	83.44 ± 4.48	70.27 ± 7.7	72.06 ± 4.15
WBC (× 10^3/mm^3)	8.97 ± 2.99	7.36 ± 2.66	8.4 ± 1.95	7.7 ± 5.08
Platelet (× 10^3/mm^3)	427.07 ± 129.38	433.8 ± 213.96	370.83 ± 173.02	372.5 ± 89.52
ESR (mm/first hour)	32.73 ± 20.71	86.04* ± 41.89	24.17 ± 3.59	35.25 ± 26.38
AST (U/L)	21.46 ± 7.19	63.6* ± 15.47	21.46 ± 3.59	30 ± 13.03
ALT (U/L)	14.97 ± 5.22	46.4* ± 25.06	18.68 ± 7.77	26.75 ± 13.68
Albumin (g/dL)	3.94 ± 0.34	4.04 ± 0.14	4.17 ± 0.49	4.22 ± 0.29
ALP (IU/L)	247.67 ± 72.92	83.6* ± 12.7	221 ± 39.3	179.75 ± 51.39
Urea (mg/dL)	10.02 ± 3.42	37.4* ± 23.43	17.62 ± 8.86	14.15 ± 8.02
Creatinine (mg/dL)	0.59 ± 0.2	0.61 ± 0.22	0.6 ± 0.2	0.54

*Significantly different from the corresponding values at $P < 0.0001$. ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; ESR, erythrocyte sedimentation rate; JRA, juvenile rheumatoid arthritis, MCV, mean corpuscular volume; RBC, red blood cells; SLE, systemic lupus eryhtematosus; SpA, spondylarthropathy; SSc/DM, systemic sclerosis/dermatomyositis overlap; WBC, white blood cells.

Table 3 Demographic features of the 30 JRA patients with and without positive tissue transglutaminase (tTG) antibodies

Demographic features (mean ± SD)	tTG antibodies		Significance (*P*)
	Positive (16)	Negative (14)	
Age (years)	9.75* ± 3.99	14.29 ± 2.05	0.001
Age at onset (years)	5.19 ± 2.73	8 ± 4.37	0.05
Disease duration (years)	4.56 ± 2.65	6.21 ± 4.64	0.234
Body mass index	15.61* ± 2.6	20.46 ± 4.2	0.001
F : M	7 : 1	1.5 : 1.0	

*Significantly different from the corresponding value at $P < 0.05$.

Table 4 Laboratory investigations of the 30 JRA patients with and without positive tissue transglutaminase (tTG) antibodies

Laboratory investigations (mean ± SD)	tTG antibodies		Significance (*P*)
	Positive (16)	Negative (14)	
RBCs (million/mm^3)	4.62 ± 0.27	4.42 ± 0.33	0.08
Hemoglobin (g, %)	11.07 ± 0.44	11.33 ± 1.85	0.62
Hematocrite (%)	35.63 ± 1.41	33.34 ± 4.53	0.09
MCV (μm^3)	77.03 ± 6.12	75.93 ± 6.28	0.63
WBC (×10^3/mm^3)	10.68* ± 2.55	7.02 ± 2.17	0.000
Platelet (×10^3/mm^3)	457.25 ± 124.94	392.57 ± 130.12	0.18
ESR (mm/1st hour)	40.25* ± 24.39	24.14 ± 11	0.027
AST (U/L)	19.1 ± 5.88	24.15 ± 7.79	0.059
ALT (U/L)	11.83* ± 3.03	18.57 ± 4.9	0.000
Albumin (g/dL)	4.08* ± 0.37	3.78 ± 0.21	0.009
ALP (IU/L)	209.39* ± 51.62	291.43 ± 70.16	0.001
Urea (mg/dL)	9.25 ± 2.97	10.9 ± 3.78	0.2
Creatinine (mg/dL)	0.5* ± 0.1	0.68 ± 0.25	0.021

*Significantly different from the corresponding value at $P < 0.05$. ALP, Alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; ESR, erythrocyte sedimentation rate; MCV, mean corpuscular volume; RBC, red blood cells; WBC, white blood cells.

other studies.[1,10,26] The development of the serological test involving tTG antibodies for the diagnosis of CD made its screening a realistic possibility.[27] Patients with very high tTG antibody titers are positive for CD and a small-bowel biopsy is not necessary to make the diagnosis.[28] Its high diagnostic accuracy confirms CD, a disorder that is eminently treatable.[29,30] A false positive tTG test was not present in any of the systemic rheumatic diseases.[9] On the contrary, in another study, no significant difference in the prevalence of IgA anti tTG was found between patients and controls.[24]

All the present patients were underweight and BMI was significantly lower in those with positive tTG. Adult CD is usually associated with weight loss and an increased number of silent or subclinical cases.[31] The presence of obesity does not exclude CD, and a potential diagnosis on the basis of a patient's body weight should not be discouraged. An obese adult with CD was reported as a rare finding.[32] In the present study there was no significant difference in tTG according to RF positivity. No association between CD and rheumatoid factor was found in RA[33] and about 6% of tTG-positive CD patients had an elevated IgM rheumatoid factor.[34] Anti-tTG antibody positivity correlates with more severe villous atrophy and not the mode of presentation of CD.[35] The exact frequency of the coexistence of gluten entropathy and different rheumatic diseases is not known due to its atypical presentation and underestimated prevalence.[24]

Expression of TG is increased in inflammatory diseases and a reversal of inflammation by TG inhibition has been demonstrated.[36] In the present study, white blood cell count, ESR and DAS-28 were significantly higher in JRA patients with positive tTG Ab and there was lymphocytosis. CD develops gradually from lymphocytosis, crypt hyperplasia and minor villous atrophy to overt villous atrophy and it is not known how such minor mucosal changes predict eventual CD.[37] The incidence of some neoplastic disorders, particularly malignant lymphoma, is increased in CD.[38] Intestinal intra-epithelial lymphocytes are increased in children with JIA and along with their cytotoxicity occur in a similar pattern to CD.[39]

An increased prevalence of autoantibodies was found in CD and SLE as both diseases share the human lymphocyte human leukocytic antigen (HLA)-B8 and HLA-DR3 histocompatibility antigens.[24] Positive tTG was found in 60% of the present juvenile SLE cases. Original presentations and immunological profiles have led to the erroneous diagnosis of SLE and the correct diagnosis of CD was made after years of treatment with steroids and other immunosuppressive drugs.[40] The presence of an enteropathy is no longer a prerequisite for the diagnosis of CD, which can solely present with extraintestinal symptoms and signs. The real prevalence of CD in SLE is unclear as the co-association is based on case reports.[41] The association of CD with juvenile PsA and enthesitis has been reported.[42] There was a significant correlation between serum and synovial fluid anti-tTG which postulated that these antibodies might be synthesized in arthritic joints[10] and ESR was increased in rheumatoid[43] and PsA[44] patients with CD.

All the juvenile SSc/PM or DM overlap syndrome patients in the present study had features of PM and scleroderma as part of their presentation, with DM presenting in two. In clinical practice, overlap features are common in idiopathic inflammatory myopathy (IIM). Systemic sclerosis is the most common connective tissue disease associated with IIM, accounting for 42.6% of overlap myositis. This provided a rationale for positioning overlap clinical features at the core of a new classification system of IIM.[45] The level of TG expression is specifically increased in polymyositis and DM, thus making the targeting of TG inhibition a challenging therapeutic approach.[11] The coexistence of CD and scleroderma has been reported.[12]

Gluten-free diet is currently the only effective mode of treatment for CD, but better understanding of the mechanisms of the disease is likely to add other choices for therapy in the future.[5]

In conclusion, asymptomatic CD is frequent in children with juvenile rheumatic diseases. Active JRA patients are more at risk of developing CD, especially those with lymphocytosis. Marked reduction in BMI of juvenile rheumatic diseases patients should raise the suspicion for CD. It is recommended that tTG antibodies are used as a screening test to identify asymptomatic CD in children with juvenile rheumatic diseases.

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