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Original Article

Elevated tissue transglutaminase antibodies in juvenile idiopathic arthritis children: Relation to neutrophil-to-lymphocyte ratio and disease activity

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ABSTRACT

Background: Subclinical gut inflammation is described in juvenile idiopathic arthritis (JIA), so has joint involvement been related to celiac disease (CD). The well-known involvement of tissue transglutaminase (tTG) in the pathogenesis of CD stimulated progress in the field of autoimmune diseases. *Aim of the work*: To screen JIA children for tTG antibodies and to detect its relation to the neutrophil-lymphocyte ratio (NLR) and disease activity. *Patients and methods*: The study included 44 JIA children with 44 matched controls. All subjects had no GIT symptoms suggestive of CD. Disease activity was assessed using the juvenile arthritis disease activity score in 27 joints (JADAS-27). The tTG antibodies (IgA and IgG) were assessed. *Results*: The patients mean age was 12.5 ± 2.8 years and disease duration 5.01 ± 2.9 years; Female:Male 3.4:1. The mean JADAS-27 score was 12.6 ± 2.04. tTG antibodies were positive in 43.2% of the patients compared to 18.2% control ($p = 0.01$). Antibodies positivity was comparable according to gender and subtypes. The NLR in JIA children (1.62 ± 0.58) was significantly higher than in control (1.3 ± 0.5) ($p = 0.006$). Those with positive tTG antibodies had a significantly reduced body mass index ($p = 0.02$) and increased NLR ($p = 0.02$) compared to those with negative tTG. Only NLR and JADAS-27 would significantly predict antibodies positivity ($p = 0.037$ and $p = 0.04$, respectively). *Conclusion*: Increased tTG antibodies are frequent in JIA children raising the possibility of an associated subclinical CD. Markedly reduced BMI and increased NLR could forecast the presence of these antibodies. In addition to the JADAS-27, the NLR is a simple test that could predict this association and could be a useful biomarker.

1. Introduction

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in childhood [1,2] that often persists into adulthood and can result in significant long-term morbidity, including physical disability [3]. Its pathogenesis is thought to be the result of a combination of host genetic and environmental triggers. However, the precise factors that determine one's susceptibility to JIA remain to be unraveled [2]. Inflammatory cytokines including tumor necrosis factor-α (TNF-α) and interleukins play an important role in the pathogenesis and prognosis of JIA [4]. The 'microbiome' has received increasing attention as a potential contributing factor to the development of a wide array of immune-mediated diseases including JIA. It may influence the development of the immune system, the integrity of the intestinal mucosal barrier and the differentiation of T cell subsets which in turn might lead to further immune dysregulation [2].

Gastrointestinal (GI) symptoms are frequent among JIA children and are associated with a lower quality of life [5]. A high percentage of JIA children and adolescents treated with non-steroidal anti-inflammatory drugs show signs of GI involvement [6] and GI symptoms were reported in 58% of JIA [5] and almost 40% complained of chronic abdominal pain [6,7]. The most common GI indications for endoscopy in JIA children are persistent abdominal pain and diarrhea where 85% showed gut mucosal inflammation [7]. Subclinical gut inflammation has been described in two-thirds of spondyloarthritis patients. Also, arthritis, peripheral or axial, represents an extra-intestinal manifestation of several GI diseases including celiac disease (CD) [8]. Celiac sprue, a gluten-sensitive enteropathy, is a common autoimmune disease [9] that occurs in

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about 1% of the Western population with the highest prevalence reported in Finland (2.4%), yet there is currently an ongoing debate on how to define CD [10]. Neutrophils and lymphocytes are key cells in inflammatory processes and cellular immunity obviously plays a major role in intestinal damage in CD. The main pathogenesis of CD is believed to be related to a gluten specific T-lymphocyte-mediated response [11]. Occult CD is present [12] and frequently coexists with other autoimmune diseases [13]. The prevalence of CD is increasing as the consumption of gluten-containing foods is increasing worldwide [14].

Juvenile idiopathic arthritis children have an increased prevalence of CD [15]. Moreover, JIA and associated autoimmune antibodies are frequent in CD and their first-degree relatives indicating a shared genetic susceptibility [12]. Most sufferers from CD show atypical symptoms and may remain undiagnosed which makes screening justified in high-risk patients with autoimmune diseases [16].

Although the diagnosis of CD is confirmed by a small bowel biopsy, autoantibodies directed against tissue transglutaminase (tTG) may serve as helpful biomarkers. The frequency of false positive tTG test in JIA is comparable to that in controls and thus may be used to screen patients at risk who require further evaluation for the presence of CD [17]. Neutrophil-to-lymphocyte ratio (NLR) seems to be linked with inflammation and cytokines and was introduced as a useful index for diagnosis or prognosis of different diseases including CD [11]. The present study was performed to screen JIA children for CD by assessment of the tissue transglutaminase (tTG) antibodies and to detect its relation to the neutrophil-lymphocyte ratio (NLR) and disease activity.

2. Patients and methods

The study included 44 consecutive children with JIA diagnosed according to the classification criteria [18]. They were 10 male and 34 female from those attending the Rheumatology Clinics of Cairo University Hospitals and National Research Centre outpatient pediatric clinic. 44 age and sex matched normal children chosen from the children of staff members and workers in the department were included in the study and served as controls.

All juvenile patients and control children were not known to have CD; had no significant GIT symptoms suggesting it (malabsorption such as diarrhea, constipation, flatulence, growth retardation, abdominal colics, anorexia, nausea and vomiting, change in the color of stools) during the six months preceding the study. All children were subjected to thorough history taking, special detailed history for GIT, clinical examination and laboratory investigations with special interest in the differential count of the white blood cells and calculation of the neutrophil-to-lymphocyte ratio (NLR). The body mass index (BMI) for children was used taking into account their age and gender. Disease activity was assessed using the Juvenile arthritis disease activity score in 27 joints (JADAS-27) [19]. Combined serum IgG and IgA tTG antibodies levels were detected using a commercially available ELISA kit semi quantitative method (Immuno-Biological Laboratories, Germany). Informed consents were given by the parents and the study was approved by the local ethical committee.

Statistical analysis of data was performed with a statistical package for the social sciences (SPSS) version 15. Data were presented as mean ± standard deviation and percentage. Mann-Whitney test was used for analysis of two non parametric quantitative data and ANOVA was used for more than two. Spearman's correlation coefficient was used to correlate between 2 non parametric variables. p value was considered significant if <0.05. A standard linear multiple regression analysis of the variables that may influence tTG positivity was performed. A semi quantitative interpretation of tTG IgA and IgG antibodies results was available by using the 25 U/ml standards as a cut off control.

3. Results

The mean age of the 44 JIA children was 12.5 ± 2.8 years and the disease duration was 5.01 ± 2.9 years with an age at disease onset of 9.2 ± 12.1 years. They were 34 females and 10 males with a ratio of 3.4:1. The control were sex and age matched (11.9 ± 2.3 years) (p = 0.28). They were 10 systemic onset, 5 polyarticular and 29 oligoarticular onset. They were receiving methotrexate at a dose of 14.6 ± 4.3 mg/week. 27 patients were receiving steroids at a mean dose of 3.8 ± 3.7 mg/day. 32 children were receiving hydroxychloroquine at a dose of 200 mg/day. The mean JADAS-27 score was 12.7 ± 2.04 and was comparable in the patients according to the subtypes (p = 0.16).

Tissue transglutaminase (tTG) antibodies were positive in 19 (43.2%) JIA children and in 8 (18.2%) of the control and the difference was significantly different (p = 0.01). The tTG antibodies were positive in 60% of systemic onset, 40% of the polyarticular and in 37.9% of the oligoarticular onset cases. The tTG positivity was seen in 3 males (30%) and tended to be higher in females being present in 16 (47.1%) (p = 0.35). The differences in JIA patients with positive and negative tTG antibodies regarding the demographic features, subtypes and laboratory investigations are shown in Table 1. There was a positive consanguinity in 5 patients (26.3%) with positive tTG antibodies and in 3 (12%) of those with a negative tTG (p = 0.25). Positivity was also comparable according to the medications received.

The NLR was 1.62 ± 0.58 in the JIA children and significantly higher than in the control (1.3 ± 0.5) (p = 0.006). The NLR in the JIA patients and controls with and without tTG positivity are presented in Fig. 1. There was a significant difference among the

Table 1
Demographic features, subtypes and laboratory investigations of the juvenile idiopathic arthritis patients with and without positive tissue transglutaminase antibodies.

Parameter mean ± SD or n(%)	tTG antibodies in JIA children		Sig (p)
	Positive (19)	Negative (25)	
Age (years)	12.1 ± 2.5	12.9 ± 3	0.3
Age at onset (yrs)	7.3 ± 2.2	7.6 ± 3.7	0.68
Disease duration (yrs)	4.8 ± 2.3	5.2 ± 3.5	0.7
F:M	3:16	7:18	0.3
BMI	15.6 ± 2.4	17.9 ± 3.8	**0.02**
Subtypes			
Systemic	7 (36.84)	3 (12)	0.3
Oligoarticular	10 (52.63)	19 (76)	
Polyarticular	2 (10.53)	3 (12)	
Hemoglobin (g/dl)	11.1 ± 0.4	10.9 ± 1.5	0.7
WBC ($x10^3/mm^3$)	10.3 ± 2.5	8.3 ± 2.2	**0.008**
Neutrophils (%)	56 ± 7.2	49.4 ± 11.8	**0.04**
Lymphocytes (%)	31.9 ± 7.7	37.3 ± 10.3	0.07
NLR	1.85 ± 0.5	1.45 ± 0.6	**0.02**
Platelet ($x10^3/mm^3$)	451.7 ± 115.7	422.8 ± 90.1	0.37
ESR (mm/1st hr)	40.4 ± 22.5	31.4 ± 13.01	0.13
AST (U/L)	19.5 ± 5.3	20.7 ± 5.3	0.47
ALT (U/L)	13.5 ± 3.8	14.8 ± 4.8	0.3
Urea (mg/dl)	9.1 ± 2.8	9.7 ± 3.2	0.5
Creatinine (mg/dl)	0.5 ± 0.09	0.57 ± 0.1	0.26
RF positivity	2 (10.5)	5 (20)	0.39
ANA positivity	5 (26.3)	8 (32)	0.69
JADAS-27	13.04 ± 1.3	12.2 ± 2.4	0.16

JIA: juvenile idiopathic arthritis, tTG: Tissue transglutaminase, BMI: body mass index, RBC: Red blood cells, MCV: mean corpuscular volume, WBC: White blood cells, NLR: neutrophil-lymphocyte ratio, ESR: Erythrocyte sedimentation rate, AST: Aspartate transaminase, ALT: Alanine transaminase, ALP: Alkaline phosphatase. Bold values are significantly different at p < 0.05.