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Original Article

Serological screening for celiac disease in children with systemic lupus erythematosus

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Abstract

Objective: The aim of the present study was to investigate the frequency of celiac disease (CD) in patients with juvenile systemic lupus erythematosus (JSLE) and the potential association of JSLE and CD.

Methods: This was a cross-sectional study performed from October 2015 to October 2017. A total of 50 patients with JSLE were included in the study. The levels of total IgA and tissue transglutaminase (tTG) IgA antibody were measured in all patients. Subjects with increased tTG were further evaluated for anti-endomysial antibodies (EMAs). Gastroduodenoscopy and intestinal biopsy were performed in those with increased EMA levels to confirm the diagnosis of CD.

Results: The study included 44 (88.0%) female and 6 (12.0%) male patients. Of the 50 patients, 30 (60.0%) received corticosteroids, and only 4 (8.0%) received no therapy at the time of the study. Only 3 (6.0%) patients were positive for tTG IgA. Patients with positive tTG IgA were then tested for EMA IgA antibodies, and none of them had a positive result.

Conclusion: We did not find CD in children with systemic lupus erythematosus. Studies with more patients with JSLE are needed to conclude a more precise result.

Keywords: Celiac disease, children, juvenile systemic lupus erythematosus

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Introduction

Systemic lupus erythematosus (SLE) is a chronic, multisystemic autoimmune disease with different clinical and serological manifestations that can affect almost any organ and involvement patterns dramatically change from one patient to another. The prevalence of SLE ranges from 20 to 150 per 100,000 individuals depending on the ethnic population (1, 2). Approximately 15% of patients with SLE will have the onset of their disease prior to the age of 18 years (3). Gastrointestinal manifestations are not uncommon in patients with SLE. Previous studies reported that 10% of patients with SLE has gastrointestinal involvement (4, 5). Furthermore, gastrointestinal manifestation could be adverse effects of treatments used in SLE (e.g., non-steroidal anti-inflammatory drugs, corticosteroids, and azathioprine). Rarely, even abdominal pain may be seen as the only presenting symptom of SLE (6).

Celiac disease (CD) is an immune-mediated systemic disease triggered by gluten intake in genetically susceptible individuals characterized by the presence of variable clinical manifestations and intestinal villous damage. The prevalence of CD is estimated to be between 0.5% and 1.0% worldwide. However, the risk of developing CD is higher in Down syndrome, autoimmune disorders, such as type 1 diabetes mellitus and autoimmune thyroiditis, and the relatives of patients with CD because of sharing the same HLA type. CD may present with gastrointestinal symptoms, extraintestinal symptoms, or without symptoms (7). In addition, it has been reported that abdominal pain is the most commonly seen complaint in 52.7% of patients with CD (8).

A possible association between CD and SLE was reported in case reports and case series (9-12). The pathogenesis of both SLE and CD is still unclear. Both of the diseases are clinically heterogeneous autoimmune diseases in which a variety of genetic and environmental factors play a role in the etiology (13). The determination of CD in patients with SLE is clinically important because patients with SLE and CD share a variety of autoantibodies, common HLA types, and may frequently have overlapping symptoms and findings (1).

The number of study investigating the prevalence of CD is limited in patients with SLE (14-19). The prevalence of CD in patients with SLE is still unknown. To our knowledge, there is only one study investigating

the prevalence of CD in JSLE (20). The aim of the present study was to evaluate the frequency of CD in children with SLE.

Methods

Study groups

This was a cross-sectional study performed from October 2015 to October 2017. A total of 50 patients with JSLE were included in the study. The levels of total IgA and tissue transglutaminase (tTG) IgA antibody were measured in patients. Subjects with increased tTG were further evaluated for anti-endomysial antibodies (EMA). Gastroduodenoscopy and intestinal biopsy were performed in those with increased EMA levels to confirm the diagnosis of CD. All patients were evaluated with regard to the clinical and laboratory findings of CD.

Patients who had a coexisting condition and those who refuse to voluntarily participate were excluded from the study. All patients were diagnosed according to the American College of Rheumatology classification criteria that was revised in 1997 (21). All included patients were followed up for at least 6 months at our clinic.

Study design

A total of 50 patients with a diagnosis of SLE, followed up at the Department of Pediatric Rheumatology, were included in the study. The study protocol was approved by the İstanbul University-Cerrahpaşa School of Medicine Review Board (313644, October 6, 2015).

Written informed consent was obtained from the patients and their parents prior to the initiation of the study. All patients have normal gluten-containing diet. All patients were evaluated for CD. Venous blood samples were collected from the patients. Each sample was divided into aliquots, and samples were stored at –80 °C until analysis.

Immunoturbidimetric method (Roche Diagnostics GmbH, Mannheim, Germany) was used for determination of total IgA, and enzyme-linked immunosorbent assay was performed to assess tTG IgA (catalog no. 3503; Aesku.Diagnostics Gmbh, Wendelsheim, Germany).

The cut-off value for tTG IgA was 12 U/ml. Patients with positive tTG IgA results underwent investigation for EMA IgA, which was performed by IFA technique (Inova Diagnostics, Inc., Lübeck, Germany) at the Düzen Laboratory Group in İstanbul, Turkey. Gastroduodenoscopy and small intestinal biopsy were planned for patients with positive EMA antibodies in making a definitive diagnosis of CD.

Statistical Analysis

Statistical analysis was performed using Statistical Package for Social Sciences software version 13.0 (SPSS Inc; Chicago, IL, USA). Categorical data were expressed as percentage (%). Continuous data were expressed as mean±standard deviation or median (range). Independent samples t-test was used for nominal data. Chi-square test was used for comparison of categorical variables. Mann–Whitney U test or Kruskal–Wallis test was used for parameters with non-normal distribution. A p value <0.05 was considered as statistically significant.

Results

A total of 50 patients with JSLE were included in the study. The mean age of the patients at the time of investigation was 15.49±3.39 years. The study included 44 (88.0%) female patients (Table 1).

Of the 50 patients, 30 (60.0%) received corticosteroids, and 4 (8.0%) received no therapy at the time of the study. The mean duration of steroid treatment was 36.07±30.06 months. In addition, 27 (54.0%) patients received immunosuppressive medications (azathioprine, mycophenolate mofetil, and cyclophosphamide).

Only 3 (6.0%) patients were positive for tTG IgA. Patients with positive tTG IgA were further evaluated for EMA, and none of them were found to have an increased level of EMA. IgA deficiency was detected in only three patients to whom tTG IgG was tested, and no positivity was found. After 6 months, tTG IgA, EMA IgA antibodies, and HLA-DQ2/DQ8 testing were analyzed for three patients with positive tTG IgA. All of the tests were found to be negative. There was no difference between patients who did and did not use steroids with regard to tTG levels (p>0.05) (Table 2). In addition, there was no difference between patients who did and did not use immunosuppressants with regard to tTG levels (p>0.05) (Table 3).

Table 1. Demographic and laboratory characteristics of patients

	Patients (n=50)
Age (years)*	15.49±3.39
Sex (female/male)	44/6
Height (cm)**	158.00 (IQR 11.00)
Weight (kg)*	50.72±13.31
tTG IgA (U/mL)**	0.90 (IQR 2.10)
Total IgA (mg/dL)**	181.00 (IQR 141.00)
Age at diagnosis (years)*	11.94±3.42

tTG: tissue transglutaminase; IQR: interquartile range
*Data are presented as mean±standard deviation
**Data are presented as median (interquartile range)

Table 2. Comparison of SLE subgroups with regard to tTG levels

	Patients using steroids (n=30)	Patients without steroids (n=16)	p
Age (years)*	15.88±2.78	16.00±3.76	0.400
tTG IgA (U/mL)**	0.55 (IQR 2.90)	1.05 (IQR 1.60)	0.320
Total IgA (mg/dL)**	183.00 (IQR 141.00)	167.50 (IQR 198.00)	0.854

tTG: tissue transglutaminase; IQR: interquartile range; SLE: systemic lupus erythematosus
*Data are presented as mean±standard deviation
**Data are presented as median (interquartile range)

Table 3. Comparison of SLE subgroups with regard to tTG levels

	Patients using immunosuppressants (n=27)	Patients without immunosuppressant (n=19)	p
Age (years)*	16.30±2.81	15.37±3.51	0.348
tTG IgA (U/mL)**	1.10 (IQR 4.60)	0.80 (IQR 1.50)	0.173
Total IgA (mg/dL)**	184.00 (IQR 133.00)	152.00 (IQR 161.00)	0.409

tTG: tissue transglutaminase; IQR: interquartile range; SLE: systemic lupus erythematosus
*Data are presented as mean±standard deviation
**Data are presented as median (interquartile range)

Discussion

The underlying mechanism for the relationship between CD and SLE is unknown. Both diseases have an autoimmune etiopathogenesis (22). Disorders with autoimmune pathogenesis are seen at an increased frequency in patients with another autoimmune disease history (23).

Systemic lupus erythematosus and CD tend to be associated with many autoimmune diseases, including type 1 diabetes, autoimmune thyroid diseases, and connective tissue diseases (23, 24).

Potential genetic basis with common genetic factors may possibly explain an increased frequency of CD among patients with JSLE. HLA similarities between SLE and CD have been described to support a common genetic factor hypothesis (25, 26). Many HLA and non-HLA risk genes are shared between CD and SLE and can act independently or synergistically in the pathophysiology of the disease. Ninety percent of patients with CD have the DQ2 allele usually presenting with the DR3 haplotype, and two-thirds of patients with SLE carry the DR2 or DR3 haplotype (1, 25, 26). The ancestral haplotype B8-DR3-DQ2 is also strongly associated with IgA deficiency seen in both diseases (27). Recent study has revealed that many new CD genetic risk variants in genetic loci related to non-HLA immunity play a role in other immune-mediated diseases, including SLE (28).

Gastrointestinal symptoms are not uncommon in patients with SLE during the course of the disease, and most of them are caused by adverse reactions to medications and viral or bacterial infections (22). In addition, according to the literature, 10% of patients with SLE have findings of gastrointestinal malabsorption (4).

It should be kept in mind that the clinical and laboratory features of CD may be masked in patients with SLE treated with corticosteroids and/or immunosuppressants (1, 9). In the current study, 30 (60.0%) patients received corticosteroids, and 4 (8.0%) patients received no therapy at the time of the study. In addition, 27 (54.0%) patients received immunosuppressive medications. Owing to the small number of patients without steroids and/or immunosuppressants, all the patients were included in the study.

The prevalence of CD appears to be increased in the last 20 years due to the use of serological tests. Unfortunately, approximately 10% of patients with CD are symptomatic. Despite the recommendation for CD screening among risk groups, the majority of patients remain unrecognized (29).

The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) recommends total IgA and tTG IgA tests for the initial screening of CD. EMA and small intestinal biopsy are suggested in patients with positive tTG antibody (7). In patients with IgA deficiency, tTG IgG or EMA IgG is helpful in making a decision for small intestinal biopsy. However, neither tTG IgG nor EMA IgG is specific as much as IgA antibodies (30). When EMA and tTG are used in combination, they have a sensitivity and specificity of 95% (31).

The prevalence of antigliadin antibodies in SLE was reported to be between 23.3% and 29.0%, but very low rates of histologically confirmed CD were reported (14, 15).

Rensch et al. (14) reported that antigliadin antibodies are found to be positive in 24 (23.3%) of 103 patients with SLE, none of them have positive EMA, and no pathological findings are compatible with CD.

Abdelghani et al. (15) evaluated the frequency of CD in 24 patients with SLE. Antigliadin and tTG antibody positivity were detected in 7 (29%) and 2 (8%) patients, respectively. All patients with positive antibodies underwent endoscopy. Of these, only 1 (4%) patient who was positive for both antigliadin and tTG antibody was diagnosed with CD.

Gliadin antibodies have lower specificity and sensitivity than tTG and EMA antibodies; therefore, positive gliadin antibodies support less the association between SLE and CD (32).

The prevalence of EMA antibodies was found to be 0%–5.6% in patients with SLE in previous studies (16-18). In these studies, all patients with positive EMA antibodies underwent endoscopy, and small intestinal biopsies were obtained, but none of them were diagnosed with CD.

Feighery et al. (18) analyzed EMA antibody test in 46 patients with SLE. None of them had positive EMA, and no small bowel biopsy was performed.

In the study by Koehne et al. (16), EMA test was first analyzed in 69 patients with SLE, then tTG was measured in patients with positive EMA antibodies. Only 3 (4.3%) patients had EMA positivity, but none of them had positive tTG. Endoscopy was performed on patients with positive EMA, but no CD was detected.

In 2013, Picceli et al. (17) investigated the gastrointestinal organ-specific autoantibodies in 194 patients with SLE and 103 healthy controls. In their study, small intestinal biopsy was obtained from 11 (5.6%) patients with EMA positive. None of them were diagnosed with CD. In addition, 5 of 11 EMA positive patients had tTG positivity. Only EMA positivity was statistically different when compared with controls. However, it has been shown that there is no significant relationship between EMA antibodies and CD after intestinal biopsy.

In addition, Aikawa et al. (20) investigated the gastrointestinal organ-specific autoantibodies in 41 patients with JSLE. EMA antibodies were analyzed in all patients, and only 1 (2.4%) patient had EMA positivity. Gastroduodenoscopy was performed on this patient. The result of duodenal biopsy was compatible with CD; therefore, the patient without clinical manifestations of CD was diagnosed with CD.

In a case–control study investigating 100 patients with SLE, only three patients had positive tTG antibodies, and one of them was diagnosed with CD by small intestinal biopsy (33).

There are some common limitations of all the previously mentioned studies. First, all studies did not have pediatric patients except the study by Aikawa et al. (20). Second, the ESPGHAN criteria were not used for diagnosis of CD.

In a study using the ESPGHAN criteria similar to our study, tTG positivity was found in 3 (3.0%) of 100 patients with SLE, and one of them had EMA positivity (19). This patient was diagnosed with CD by intestinal biopsy. The patient had no complaints of gastrointestinal symptoms.

Our study used the updated ESPGHAN criteria for asymptomatic child or adolescent with CD-associated conditions. Only 3 (6.0%) patients were positive for tTG IgA in the present study. Patients with positive tTG IgA were further tested for EMA IgA antibodies, and none of them had positive EMA antibodies; therefore, further assessment was unnecessary. According to the updated ESPGHAN guideline, we followed up three patients with positive tTG IgA. After 6 months, tTG IgA, EMA IgA antibodies, and HLA-DQ2/DQ8 testing were analyzed for those patients. All of the tests were found to be negative. None of our patients were diagnosed with CD. We have not detected the association between CD and JSLE.

Although controversial, many authors have suggested that prednisone and other immunosuppressants may reduce antibody production, especially at high doses (34). In contrast

with that, we detected no difference between patients who did and did not use steroids, and patients who did and did not use immunosuppressants with regard to tTG levels in the current study (p>0.05).

The presence of celiac antibodies in patients with SLE may be explained by genetic and epigenetic changes, leading to the production of autoantibodies instead of a true disease association (20). In addition, it is likely to represent non-specific polyclonal B cell activation (35). If there is a clinical suspicion, screening tests for CD should be performed.

As a result, we did not find CD in children with SLE, but further studies with more patients with JSLE are needed to conclude a more precise result.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of İstanbul University-Cerrahpaşa School of Medicine (313644/06.092015).

Informed Consent: Written informed consent was obtained from the parents of the patients who participated in this study.

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