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SHORT COMMUNICATION - FOOD FOR THOUGHT

Screening of celiac disease in children with Henoch-Schoenlein purpura

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Abstract Prevalence of celiac disease (CD) is 2.42 % in healthy Turkish children. The frequency of IgA-associated disorders is increased in CD. Henoch-Schoenlein purpura (HSP) is an IgA-associated vasculitis. Association of HSP with CD has not been evaluated. We aimed to evaluate whether CD prevalence is increased in children with HSP. Children with HSP were evaluated for demographic, anthropometric, clinical, and laboratory data including urinalysis, complete blood count, albumin, creatinine, and IgA levels. In addition, tTG-IgA, EMA-IgA, anti-DGP-IgA, and IgG antibody levels were measured. Seropositive patients were evaluated by endoscopic small bowel biopsy. The rate of CD seropositivity and confirmed CD in HSP patients was compared to the rate in healthy Turkish children. There were 42 children (25 male) with HSP. No patient had classical CD symptoms, but two patients had growth failure. None of them had IgA deficiency, anemia or hypoalbuminemia. Celiac serology was positive in five (12 %) children. Endoscopic evaluation was performed in four patients, and two (5 %) of them were confirmed to have CD. Prevalence of both CD seropositivity and histologically confirmed CD in children with HSP was significantly higher compared to healthy Turkish children ($p < 0.001$ and $p = 0.019$, respectively). CD seropositivity rate in children with HSP (12 %) is significantly higher than the rate in healthy children. Although the number of children with HSP is small in this preliminary study, this result suggests that celiac screening may be considered in children with HSP.

Keywords Anti-endomysium IgA · Anti-tissue transglutaminase IgA · Celiac disease · Henoch-Schoenlein purpura

Abbreviations

CD	Celiac disease
DGP-IgA	Anti-deaminated gliadin peptide IgA
DGP-IgG	Anti-deaminated gliadin peptide IgG
EMA-IgA	Anti-endomysium IgA
HSP	Henoch-Schoenlein purpura
IgAN	Immunoglobulin A nephropathy
KD	Kawasaki disease
tTG-IgA	Anti-tissue transglutaminase IgA

Introduction

Celiac disease (CD) is an immune-mediated enteropathy caused by sensitivity to gluten proteins. It develops in genetically susceptible individuals carrying HLA DQ2 and/or DQ8 haplotypes. The prevalence of CD in children in the USA and Europe is around 1 % [1]. Among Turkish school children, seropositivity for CD is 2.5 % and biopsy-proven CD is 1/212 [2]. CD can manifest itself at any age after gluten is introduced into the diet. However, asymptomatic forms of CD in the pediatric population are estimated to be sevenfold higher than the symptomatic forms [1]. There are reliable screening tests for diagnosing CD that are recommended in all symptomatic children, children with a family history of CD, and asymptomatic children with associated conditions [1].

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CD is associated with some autoimmune diseases. The mechanism is probably the disruption of intestinal mucosal integrity by CD leading to unmasking of cryptic autoantigens [3]. CD prevalence is also increased in patients with IgA nephropathy (IgAN) who have rectal mucosal sensitivity to gluten [4]. Gluten-free diet lowers circulating IgA immune complexes in these patients [5].

Henoch-Schoenlein purpura (HSP) is a systemic vasculitis characterized by non-thrombocytopenic purpura, arthritis, bowel angina, and hematuria/proteinuria. Deposition of IgA and C3 along with neutrophil infiltration in small vessel walls and increased serum IgA levels are the other characteristics. The etiology and pathogenesis are still yet to be determined. The disease frequently appears following an infectious episode; however, environmental antigens have triggering roles rather than being directly causative [6]. HSP and IgAN are closely related. Both diseases are characterized by deposition of immune complexes containing aberrantly glycosylated IgA_1 in the tissues [7]. Almost 30 % of HSP patients develop mesangial proliferative glomerulonephritis that cannot be differentiated from IgAN [8]. However, the presence of CD in HSP patients has not been evaluated yet. There are only two adult case reports regarding the coexistence of HSP and CD in the literature [9, 10]. We hypothesized that CD frequency may be increased in children with HSP and aimed to make a serological screening for CD in those children.

Patients and methods

Study protocol

Hospital files of children over 3 years of age with a diagnosis of HSP according to EULAR/PReS criteria [11] were evaluated retrospectively for age, gender, renal involvement, and medications. Patients who consented for the study protocol were evaluated for anthropometric development, complete blood count, serum creatinine, albumin and IgA levels along with CD screening.

Celiac disease screening

Anti-endomysium IgA (EMA-IgA) and anti-deaminated gliadin peptide IgA (DGP-IgA) antibodies were tested by indirect immunofluorescence test (IFAT) with a $\geq$1:10 titer determined as positive (Euroimmun, Lübeck, Germany). Anti-tissue transglutaminase IgA (tTG-IgA) and DGP-IgG were tested using a commercial enzyme-linked immunosorbent assay with a titer above 20, and 25 relative units were evaluated as positive, respectively (Euroimmun, Lübeck, Germany).

Table 1 Demographic, anthropometric, clinical, and laboratory features of the patients

Gender (male/female)	25 (60 %)/17 (40 %)
Age (month)	126 ± 49
Height SDS	0.6 ± 1.3
Weight SDS	0.6 ± 1.2
Body mass index SDS	0.4 ± 1.2
Growth failure	2 (5 %)
Serum albumin (g/dL)	4.1 ± 0.4
Serum creatinine (mg/dL)	0.58 ± 0.19
Hemoglobin (g/dL)	13.5 ± 1.2
Serum IgA (mg/dL)	201 ± 111

The study was approved by the local ethics committee. Written informed consent was obtained from the patients and/or their parents. CD prevalence in HSP patients was compared with CD frequency in Turkish school children [2] by significance test for the difference between two percentages.

Results

Among the children fulfilling the inclusion criteria, 42 who consented to the study protocol were enrolled. Nineteen patients (45 %) had renal involvement, and renal biopsy was performed in 14 of them. Ten of these patients required immunosuppressive treatment, and all of them recovered renal function with only three patients requiring angiotensin-converting enzyme inhibitors for persistent non-nephrotic proteinuria. All patients were in remission and off immunosuppressive treatment when they were evaluated for CD serology.

Demographic, anthropometric, and laboratory features of the patients are summarized in Table 1. Azotemia, anemia, hypoalbuminemia, and low serum IgA level were not present in any of the patients. There were only two patients with growth failure (height and BMI SDS < -2). These patients were seronegative for CD.

Seropositivity for CD was determined in five patients (12 %) (Table 2), and it was not different among the patients with nephritis (1/19) and without nephritis (4/23) (Chi-square test, $p = 0.227$). CD was confirmed histologically in two patients (2/42; 5 %), while non-specific inflammation was determined in two patients. One of the patients did not accept endoscopic evaluation and refused further follow-up. With gluten-free diet, specific antibody profiles became negative in patients 1 and 5 with confirmed CD. However, serological abnormalities persisted in patients 2 and 3 with normal histology who were not given gluten-free diet.

Table 2 Clinical, laboratory, and histopathological findings of the seropositive patients

No.	Sex	Age (month)	Clinical findings	Renal pathology	Celiac serology	Endoscopy
1	Female	144	Arthritis Bowel angina	–	tTG-IgA[a]	Villous atrophy, crypt hyperplasia, cryptitis
2	Female	59	Bowel angina	–	tTG-IgA[a]	Chronic gastritis, *Helicobacter pylori* (+)
3	Male	54	Arthritis	–	tTG-IgA[a] EMA-IgA[b]	Chronic duodenitis
4	Male	107	Nephritis Bowel angina	Mesangial proliferative glomerulonephritis with predominant IgA deposition	tTG-IgA[a]	Not performed
5	Female	131	Bowel angina	–	EMA-IgA[b] DGP-IgA[c] DGP-IgG[d]	Villous atrophy, crypt hyperplasia, cryptitis

[a] Anti-tissue transglutaminase IgA

[b] Anti-endomysium IgA

[c] Anti-deaminated gliadin peptide IgA

[d] Anti-deaminated gliadin peptide IgG

Seropositivity for CD antibodies in children with HSP (12 %) was significantly higher than the previously defined prevalence of CD serology in healthy Turkish school children (2.5 %) ($p < 0.001$) [2]. Furthermore, confirmed CD prevalence was significantly higher in patients with HSP (2/42) compared to healthy school children (1/212) in the same study (Chi-square test, $p = 0.019$). This indicates an OR of 10.5 for the presence of CD in children with HSP compared to healthy children.

Discussion

There are only two adult cases of CD in subjects with a history of HSP [9, 10]. Since CD is a frequent condition in the general population, this association might be coincidental. However, our data suggest that children with HSP display increased prevalence of CD, both serologically and histologically, compared to healthy children.

The explanations for this potential association might include the following: (1) sharing of common immunological mechanisms in CD and HSP. However, although CD is associated with autoimmune disorders [3], occurrence of a second immunological disorder in patients with HSP is rare. (2) Involvement of intestinal mucosa during HSP leading to alterations in its permeability, and in predisposed subjects, inducing CD development as in other gastrointestinal disorders [12]. (3) However, the most likely hypothesis seems to be intestinal epithelial damage caused by CD leading to the development of HSP just like IgAN [13]. Epithelial damage in early life due to CD may result in sensitization and hyperresponsiveness of systemic IgA immune system to mucosal challenge with subsequent infectious or dietary antigens. This leads to increased production of systemic IgA and accumulation of secretory IgA (sIgA) in glomeruli due to migration of mucosal B cells to bone marrow [13, 14].

Furthermore, development of both CD and IgAN in pediatric population is effected by the feeding practices during infancy. Breast-feeding at the time of gluten introduction into the diet significantly decrease CD development [1] as breast-feeding accelerates the closure of mucosal permeability in the gut [13]. Similarly, we showed that early feeding with formula, cow's milk, and complementary foods might increase the risk of future primary IgAN, while breast-feeding has a protective effect against IgAN in later life [15]. Breast milk also contains probiotic bacteria [16] that stimulate sIgA production and have trophic effects on intestinal mucosa [17]. We also demonstrated that enteric probiotic (*Saccharomyces boulardii*) ingestion prevented development of experimental IgAN induced by oral poliovirus vaccine in mice [18].

A significant proportion of HSP patients develop a glomerulonephritis histologically identical to IgAN [8]. Like IgA_1 in IgAN, recent studies have shown aberrant glycosylation of IgA_1 in HSP patients with nephritis [7]. These data indicate that HSP and IgAN have similar pathogenetic mechanisms and histologic manifestations. Thus, increased rate of CD in HSP might be due to sensitization of systemic IgA immune system due to epithelial damage in the early life in CD just as in IgAN.

Several additional hypotheses cannot be excluded. However, our study, in simply reporting an observed association, is clearly not a proper tool and does not attempt to speculate about these pathogenetic issues.

The accuracy of CD screening tests is influenced by age, amount and frequency of gluten consumption, IgA deficiency, and immunosuppressant medications. Asymptomatic children with risk factors for CD is recommended to be >3 years old and consuming gluten for at least 1 year [13]. Children who have total serum IgA levels <0.2 g/L should have additional testing done with IgG-specific antibodies. We enrolled the patients >3 years of age and off the immunosuppressant medications, and none of the patients had IgA deficiency. Moreover, as involvement of intestinal mucosa during initial stages of HSP may alter its permeability inducing CD development in predisposed subjects as in other gastrointestinal disorders [12], we performed CD screening during remission of HSP in all patients.

Demonstration of intestinal mucosal inflammation on biopsy is the gold standard for CD diagnosis, and two of our patients were confirmed to have CD. On the other hand, positive CD serology and predisposing HLA genotype in the absence of intestinal inflammation is termed as potential CD. One-third of the patients with potential CD develop villous atrophy during the follow-up [1]. We could not study HLA DQ genotype in our patients with positive celiac serology. Thus, we cannot define the two patients with positive serology and normal histology as having potential CD. However, we also cannot exclude the possibility of potential CD, and these patients need close follow-up.

HSP and Kawasaki disease (KD) have been reported to be more common in Asians than whites [19]. On the other hand, CD is quite rare in Japanese populations with a low prevalence of predisposing genes and a diet that contains minimal gluten [20]. The results of our study seem to be contradictory with these data. However, pathogenesis of HSP does not depend only on the dietary factors. Instead, superantigens and/or infectious agents are thought to be the major triggering factors in HSP and KD. On the other hand, we still should not overlook the effect of diet in the low prevalence of CD in Japan as it has been shown that the prevalence of CD (5.5 %) is higher than the normal population in Italian children with KD [21].

In conclusion, we report a higher prevalence of CD in children with HSP. However, as our data are based on a low number of patients, additional and more extensive studies are necessary to confirm this association and clarify possible underlying mechanisms linking CD in HSP patients.

Author contributions Dr. Alper Soylu conceptualized and designed the study, and drafted the initial manuscript. Dr. Yeşim Öztürk performed endoscopic evaluation of seropositive patients. Drs. Yavuz Doğan and Özlem Yılmaz carried out the laboratory analyses for celiac disease screening. Drs. Derya Özmen and Pınar Kayum evaluated the hospital files of the patients to collect clinical and laboratory data, and performed statistical analyses. Dr. Salih Kavukçu critically reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Compliance with ethical standards

Conflict of interest None.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional and/or National Research Committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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