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SHORT COMMUNICATION

High Prevalence of Celiac Disease in Patients with Immune Thrombocytopenia

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Abstract Celiac disease (CD) is known to be associated with several autoimmune disorders. We studied the prevalence of subclinical CD among patients with immune thrombocytopenia (ITP) as compared to general population. Cases of primary ITP between the age group of 18–60 years were studied. Besides clinical examination, all patients underwent serology testing for tissue transglutaminase antibody (tTG) IgA and anti-endomysial antibodies IgA. The diagnosis of CD was made if both antibodies were positive. Healthy subjects acted as controls and underwent serological testing for tTG IgA. Seventy-nine primary ITP and 316 healthy subjects underwent serology testing for CD. Four patients of primary ITP (4/79) were positive for both serology as compared to 2 (2/316) healthy controls [odds ratio 8.37 (CI 1.50–46.47, $p < 0.005$)]. Among the ITP cases only one had clinical symptoms of CD while none of the healthy controls had symptoms of CD. There is a significantly higher prevalence of subclinical CD in patients with ITP. Since the prevalence of CD is known to vary among different geographical zones, we suggest further studies on screening of ITP patients for CD in areas of high prevalence.

Keywords Celiac disease · Thrombocytopenia · Epidemiology · Screening

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Introduction

Celiac disease (CD) is a multisystem disorder resulting from inflammatory injury to small intestinal mucosa from exposure to dietary gluten. The prevalence of CD in India is estimated to be less than 1%, but a significant proportion of the disease is present among undiagnosed and apparently asymptomatic patients [1]. Our own experience showed that subclinical CD can be a cause of refractory iron deficiency anemia [2]. Celiac disease has proven association with a wide range of auto immune diseases, including Type 1 diabetes, autoimmune thyroiditis and IgA deficiency [3]. There are only anecdotal reports of prevalence of CD in patients of immune thrombocytopenia (ITP), an autoimmune hematological disorder. In the present study we looked systematically at the prevalence of CD in patients with ITP and compared with that of age matched general population.

Materials and Methods

All diagnosed cases of primary ITP, between the ages 18 and 60, who presented to our institute during the 18-month study period were included. Both newly diagnosed and already diagnosed cases of ITP were included. The diagnosis of ITP was based on internationally accepted and published guidelines [4]. Patients with severe thrombocytopenia (platelets $\leq 10 \times 10^9$/L) and patients who received steroids for ITP in the 4 weeks preceding enrolment in the study were excluded.

All patients who consented to the study were asked for symptoms suggestive of celiac disease (diarrhoea, weight loss, short stature, abdominal pain, anemia, arthritis, hepatitis and dermatitis herpetiformis) on the basis of a

structured questionnaire. The signs and symptoms of ITP were assessed using the standard ITP Bleeding score (IBLS) [5]. Serum Immunoglobulin A against tissue transglutaminase (IgA tTG) and Immunoglobulin A against Anti-endomysial antibodies (IgA EMA) were done in all ITP patients. IgA tTG was measured by an indirect non-competitive enzyme immune assay using CELIKEY^{TM}tTG ELISA kit. Values of IgA anti-tTG higher than 8 U/ml were considered positive [6]. IgA EMA were determined by the indirect immuno fluorescence method with human umbilical cord tissue as antigen [7]. Those who were seropositive for both tTG IgA and EMA IgA were diagnosed as having celiac disease and small intestinal biopsy was done wherever feasible. All patients diagnosed with CD were prescribed a gluten free diet (GFD) and were kept on follow up. Four age matched controls were included for each ITP patient. The controls were selected from another study at our institute, in which the prevalence of tTG IgA seropositivity among healthy blood donors was studied [8]. All statistical analyses were done using EPI info software (v.2016). Differences in the proportion of seropositive patients between the patients and matched controls were determined by odds ratio and Fishman's exact test. A p value less than 0.05 was considered as significant.

Results

Seventy-nine (n = 79) cases of primary ITP and three hundred and sixteen (n = 316) age matched healthy controls were included in the study. Basic demographic profile of cases and controls are summarized in Table 1. Sixty three percent (n = 50) of the ITP population had no bleeding manifestations at enrolment with an IBLS score of zero.

Among the seventy-nine cases of ITP, 5% (n = 4) had significant positive titer of tTG IgA and EMA. Among these four, only one patient had symptoms suggestive of CD. The four positive cases had a mean platelet count of 34.5 $\times$ 10^9/L (range 10–80 $\times$ 10^9/L) and a mean hemoglobin level of 11.45 g/dL (range 11.2–11.6 g/dL). Two among the four patients underwent a duodenal biopsy, which revealed Marsh stage III changes, confirming the diagnosis of CD. The other two patients with elevated IgA tTG/EMA levels refused to have an endoscopic biopsy done. All 4 patients were prescribed a gluten free diet to prevent progression of CD. There was 100% concordance between the two antibodies in all the four cases.

Among the 316 age matched controls included in the study, 2 patients (0.63%) had significant titer of tTG IgA and duodenal biopsy in both cases showed Marsh stage III changes. Thus the prevalence of CD in ITP patients was eight-time higher when compared with age matched controls [odds ratio 8.37 (CI 1.50–46.47, p = 0.0152)] and this difference in proportion was significant by Fisher's exact test (2 tail) (p = 0.0162). In all the four cases of ITP with CD, steroids were started for ITP treatment and hence we were unable to assess the response of platelet counts to GFD.

Discussion

In this study we analyzed the prevalence of CD in patients with primary ITP and found it to be eight times higher than in an age-matched control population. The seroprevalence of tTG positivity among healthy blood donors was 0.6% in our study which is similar to the estimates in the Indian population [9]. We did an extensive literature search in established databases Pubmed, Medline and Scopus. The

Table 1 Baseline parameters of the ITP patients and healthy controls

	ITP patients	Healthy controls
Number	79	316
Median age in years (range)	34 (21–48)	42 (25–60)
Sex (M:F ratio)	1:2.12	13.28:1
Haemoglobin level (g/dL)	11.4 ± 2.2	14.2 ± 1.7
GI symptoms of CD	1/79	0/316
Duration of symptoms of ITP (in months)	44.66 ± 66.94	NA
Platelet count (range)	43,500 (15,000–70,000)	NA
Phase of ITP	Newly diagnosed: 25.3%	NA
	Persistent ITP: 25.3%	
	Chronic ITP: 49.4%	
IBLS score	0.8 ± 1.067	NA
Steroid usage status at the time of study inclusion		NA
Never received steroids	32 (40.5%)	
Off steroids for > 4 weeks	47 (59.5%)	

Table 2 Published Literature on association between CD and ITP

	Author/place/year	Sample size	Inclusion	Study design	Methodology	Conclusions
1	Altintas et al., Turkey, 2008 [16]	74	Adult	Prospective cohort study	Screening of ITP patients with EMA and anti gliadin antibodies	Among the ITP patient and healthy controls EMA IgG positivity was 8.1% and 5.5% respectively while anti gliadin IgG positivity was 22.9% and 7.2% respectively
2	Olen et al., Sweden [17]	14,347	Adult and pediatric	Retrospective cohort study	Analysis of Swedish national inpatient registry for CD patients who were subsequently diagnosed with ITP	CD leads to subsequent ITP (HR 1.91)
		15,382	Adult and pediatric	Case control study	Analysis of Swedish national inpatient registry for CD patients who had a prior diagnosis of ITP	Prior ITP is a risk factor for CD (OR 2.96)
3	Present study	79	Adult	Case control study	Screening of ITP patients with tTG IgA and EMA IgA	Four cases of CD detected. OR 8.37

OR odds ratio, *ITP* immune thrombocytopenia purpura, *tTG* tissue transglutaminase

existing literature on the coexistence of CD and ITP are restricted to a few studies (Table 2). The first case report of presence of CD in ITP was reported in 1981 [10]. Several reports have been published since then [11–15]. The time period between the diagnoses of these two diseases were variable and ranged up to 30 years and in almost all reports, the diagnosis of CD preceded the diagnosis of ITP.

The association of ITP and CD shows varied results in studies across different populations. Altintas et al. from Turkey screened children with chronic ITP for Anti gliadin antibody (AGA) and EMA. This study showed a higher prevalence of CD among ITP, but the results weren't statistically significant and there was lack of correlation between positivity of AGA and EMA [16]. A retrospective large Swedish registry analysis of celiac disease patients demonstrated an increased risk of developing CD in patients who had a prior history of ITP (odds ratio of 2.96). They also found a bi-directional relationship; that patients of celiac disease had increased risk of developing ITP and vice versa, suggesting a shared pathogenesis with different presenting manifestations [17].

There are four cases reported in literature which have showed improvement of thrombocytopenia after institution of GFD [13–15]. We were unable to demonstrate the same in our study, but this shows us that patient of ITP who are seropositive for CD have a potential therapeutic option in the form of adherence to GFD.

In view of difficulties in obtaining a biopsy in a thrombocytopenic patient, the diagnosis of CD was made on the basis of dual seropositivity in two of our patients of ITP. In the setting of EMA having 100% specificity for CD and tTG IgA providing an additional advantage by superior sensitivity, endoscopy and biopsy maybe deferred in patients with severe thrombocytopenia [18]. The other limitation of the study was that we studied only the point prevalence of CD in ITP whereas time gap between the onset of the two condition ranges from 1 year to 30 years in the available literature. Since the natural history and complications of CD can be markedly altered by the early institution of GFD, it is important for an early diagnosis of CD especially in a high risk population. We propose to carry out studies in different geographical regions, as well as in larger number of ITP cases to clearly know the association between CD and ITP, before incorporating a universal screening for CD in patients with ITP.

In conclusion, in our study, a higher prevalence of CD was demonstrated in patients of ITP when compared to the general population.

Compliance with Ethical Standards

Conflict of interest All authors declare no conflict of interest in writing this manuscript.

Ethical Committee Approval Taken.

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