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Hypergammaglobulinemia is a marker of extraintestinal manifestations in pediatric inflammatory bowel disease

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ABSTRACT

Background/Aims: The significance of hypergammaglobulinemia as a phenotypic feature of inflammatory bowel disease is unknown. Thus, we aimed to analyze the magnitude and significance of hypergammaglobulinemia in newly diagnosed pediatric inflammatory bowel disease patients.

Materials and Methods: The medical records of 296 pediatric onset inflammatory bowel disease patients who were evaluated from 2002 to 2015 were retrospectively reviewed. Patients with recorded immunoglobulin G (IgG) levels were categorized as either normal or high IgG levels at diagnosis. Baseline characteristics included age at onset, sex, severity indices, laboratory data, extraintestinal manifestations, endoscopic findings, and anthropometric measurements.

Results: Of 184 subjects [mean age, 13.2±2.8 years; 105 (60%) males] with recorded IgG levels, 129 (70%) had Crohn disease, 46 (25%) had ulcerative colitis, and 9 (5%) had unclassified inflammatory bowel disease. Overall, 46 patients (25%) had hypergammaglobulinemia, including 30 (23%) with Crohn disease, 14 (30%) with ulcerative colitis, and 2 (22%) with unclassified disease. Hypergammaglobulinemia was associated with the female sex (55% vs. 35%; p=0.03) and extraintestinal manifestations (70% vs. 10%; p<0.0001), including arthritis, skin disorders, and primary sclerosing cholangitis but not with arthralgia. It was also associated with corticosteroid induction (68% vs. 45%; p=0.02) and maintenance with an immunomodulator (61% vs. 21%; p=0.0001) after diagnosis. In ulcerative colitis patients, hypergammaglobulinemia was associated with a high pancolitis prevalence (p=0.002).

Conclusion: Hypergammaglobulinemia is a marker of extraintestinal manifestations in pediatric inflammatory bowel disease and may assist in distinguishing arthritis from arthralgia.

Keywords: Children, Crohn disease, immunoglobulin G, ulcerative colitis

Original Article

INTRODUCTION

Polyclonal hypergammaglobulinemia in adult patients is related to infections, autoimmune diseases, chronic liver diseases, and malignancies (1). The clinical significance of hypergammaglobulinemia in children has not been thoroughly characterized. Nevertheless, in children having fever of unknown origin, high gamma globulin levels were shown to be associated with a diagnosis of an autoimmune disease (2). Elevated immunoglobulin G (IgG) level is an established feature of adult and pediatric autoimmune liver diseases (3). The significance of hypergammaglobulinemia in inflammatory bowel disease (IBD) has not yet been evaluated; hence, whether elevated IgG levels at IBD diagnosis simply is a consequence of an autoimmune process, a marker of disease activity, or a feature of distinct phenotypic characteristics remains unexplored. This study aimed to analyze the magnitude of hypergammaglobulinemia in newly diagnosed pediatric IBD patients and to investigate its clinical significance at the time of diagnosis.

MATERIALS AND METHODS

Patients

We retrospectively reviewed the medical records of all pediatric onset IBD patients who were diagnosed up to the age of 18 years at a referral hospital between 2002 and 2015. Diagnosis of IBD was performed according to the accepted criteria (4,5).

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Description of Variables

Age; sex; and clinical, laboratory, histological, and anthropometric variables at diagnosis were thoroughly investigated by reviewing the medical records. The disease activity of Crohn disease (CD) and ulcerative colitis (UC) was assessed using the pediatric Crohn's disease activity index and pediatric ulcerative colitis activity index, respectively. The disease phenotype at diagnosis was categorized according to the Paris classification (6). Hypergammaglobulinemia was defined as IgG levels of ≥1470 mg/dL for children aged <10 years, ≥1560 mg/dL for those aged 10-14 years, and ≥1600 mg/dL for those aged >14 years.

Statistical Analysis

Continuous variables were evaluated for normal distribution using histogram, Q-Q Plots, and Kolmogorov-Smirnov test and were reported as median (interquartile range) for non-normally distributed variables or as mean (standard deviation, SD) for normally distributed variables. Categorical variables were reported as frequency and percentage. Continuous variables were compared using independent simple t-test or Mann-Whitney U test, whereas categorical variables were compared using the chi-square or Fisher exact test. Correlation among continuous variables was evaluated using Spearman rho correlation coefficient.

The association between IgG levels at diagnosis and multiple outcomes such as different types of therapies was examined using multivariate logistic regression analysis. Age, sex, and IgG levels were forced into the regression, whereas the other potential confounders were selected using forward step-wise likelihood ratio. p values of <0.05 were considered to be statistically significant. IBM Statistical Package for the Social Sciences version 23 (IBM Armonk, NY, IBM Corp, USA) was used for all statistical analyses.

The study protocol was approved by the Rabin Medical Center Ethical Committee. Because of the retrospective design of the study, patients' informed consent was not required.

RESULTS

Of the 296 newly diagnosed pediatric IBD patients who were followed up from 2002 to 2015 at a large referral hospital, 184 (62%) [mean age, 13.2±2.8 years; 105 (60%) males] had recorded IgG levels. Of these, 129 (70%) had CD, 46 (25%) had UC, and 9 (5%) had unclassified IBD. Overall, 46 (25%) patients had hypergammaglobulinemia, of which, 30 (23%) had CD, 14 (30%) had UC, and 2 (22%) had unclassified IBD. The mean IgG level was 1310±295 mg/dl. The cohort was analyzed as a whole and independently for CD and UC patients. For the entire population, hypergammaglobulinemia was associated with the female sex [27/47 (55%) vs. 48/137 (35%); p=0.03] and extraintestinal manifestations (EIMs) [33/47 (70%) vs. 14/137 (10%); p<0.0001], mainly arthritis or sacroileitis [31/47 (66%) vs. 10/137 (7%); p<0.0001]. Four (3%) patients with normal IgG blood levels and two (4.5%) with hypergammaglobulinemia had either erythema nodosum or pyoderma gangrenosum. Two (4%) patients with hypergammaglobulinemia had primary sclerosing cholangitis, whereas no patient with normal IgG blood levels had primary sclerosing cholangitis. Hypergammaglobulinemia was also associated with corticosteroid induction [32/47 (68%) vs. 61/137 (45%); p=0.02] and maintenance with an immunomodulator [28/47 (61%) vs. 29/137 (21%); p=0.0001] after diagnosis. The phenotypic, clinical, anthropometric, and biochemical features of patients according to the type of disease and IgG category are specified in Table 1 for CD patients and in Table 2 for UC patients. For both diseases, hypergammaglobulinemia was not associated with most variables (including disease location in CD patients), except for EIMs and medical therapies at diagnosis. For UC patients, hypergammaglobulinemia was

Table 1. Characteristics of CD patients with or without hypergammaglobulinemia at diagnosis (n=129)

	Normal IgG (n=99)	Increased IgG (n=30)	Significance (p)
Male, n (%)	65 (65%)	12 (40%)	0.02
Family history of IBD (1st degree relative), n (%)	21 (21%)	9 (30%)	0.2
Anthropometric measurements, median (IQR)			
Weight z score	-0.76 (-1.8-0.2)	-1 (-1.9-0)	0.5
Height z score	-0.45 (-1.3-0.35)	-0.3 (-1-0.4)	0.6
BMI z score	-0.67 (-1.5-0.3)	-0.9 (-1.8-0)	0.2
Disease behavior, n (%)			
Inflammatory (B1)	71 (72%)	18 (60%)	
Stricturing (B2)	25 (25%)	11 (37%)	0.2
Penetrating (B3)	3 (3%)	1 (3%)	
Perianal disease, n (%)	11 (11%)	4 (13%)	0.7
Granuloma in histology, n (%)	42 (43%)	9 (30%)	0.2
Extraintestinal manifestations (any), n (%)	10 (10%)	22 (73%)	
Arthritis, n (%)	7 (7%)	20 (67%)	<0.0001
Skin, n (%)	3 (3%)	2 (7%)	
Positive ASCA, n (%)	38 (55%)	12 (50%)	0.7
Positive ANCA, n (%)	15 (20%)	5 (21%)	0.9
ESR, mean (SD)	49±26	62±29	0.07
CRP, mean (SD)	4.4±3	6±3.5	0.06
Albumin, (g/dL), mean (SD)	3.6±0.4	3.6±0.5	0.5
Hemoglobin (g/dL), mean (SD)	11.2±1.2	10.8±1.3	0.15
PCDAI	36±9	50±15	0.07
Treatment following diagnosis, n (%)			
Corticosteroid induction	48 (48%)	21 (70%)	0.04
Maintenance with immunomodulators	20 (20%)	19 (63%)	<0.0001

ANCA: anti-neutrophil cytoplasmic antibodies; ASCA: anti-Saccharomyces cerevisiae antibodies; BMI: body mass index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate;
IgG: immunoglobulin G; IQR: interquartile range; PCDAI: pediatric Crohn's disease activity index; SD: standard deviation

Table 2. Characteristics of UC patients with or without hypergammaglobulinemia at diagnosis (n=46)

	Normal IgG (n=32)	Increased IgG (n=14)	Significance (p)
Male, n (%)	20 (62%)	8 (57%)	0.7
Family history of IBD (First degree relative), n (%)	11 (34%)	4 (29%)	0.7
Anthropometric measurements, median (IQR)			
Weight z score	-0.2 (-1.4-0.6)	0.1 (-0.6-0.2)	0.1
Height z score	-0.4 (-1-0.3)	-0.1 (-0.4-0.3)	0.09
BMI z score	-0.1 (-0.9-0.7)	0.1 (-0.8-0.9)	0.3
Disease extent, n (%)			
Proctitis (E1)	9 (28%)	1 (7%)	
Left sided colitis (E2)	10 (31%)	0 (0%)	0.002
Extensive colitis (E3)	1 (3%)	1 (7%)	
Pancolitis (E4)	12 (38%)	12 (86%)	
Elevated liver enzyme levels, n (%)	1 (3%)	6 (43%)	0.002
Extraintestinal manifestations (any), n (%)	3 (9%)	9 (64%)	
Arthritis, n (%)	2 (6%)	7 (50%)	<0.0001
Skin, n (%)	1 (3%)	0 (0%)	
PSC, n (%)	0 (0%)	2 (14%)	
Positive ANCA, n (%)	25 (81%)	9 (75%)	0.7
ESR, mean (SD)	18±13	40±21	0.01
CRP, mean (SD)	0.7±0.4	0.8±0.4	0.3
Albumin, (g/dL), mean (SD)	4.2±0.4	4.1±0.5	0.5
Hemoglobin (g/dL), mean (SD)	11.8±2	11.3± 2.3	0.4
PUCAI	40±15	43±14	0.4
Treatment following diagnosis, n (%)			
Corticosteroid induction	12 (37%)	11 (77%)	0.02
Maintenance with immunomodulators	7 (22%)	8 (57%)	0.03

ANCA: anti-neutrophil cytoplasmic antibodies; BMI: body mass index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IgG: immunoglobulin G; IQR: interquartile range; PUCAI: pediatric ulcerative colitis activity index; PSC: primary sclerosing cholangitis; SD: standard deviation

associated with disease extent because increased IgG levels were more prevalent in pancolitis patients (Table 2). Of note, the erythrocyte sedimentation rate (ESR) was significantly associated with hypergammaglobulinemia in UC patients (Table 2). Although CD patients with hypergammaglobulinemia had higher ESR and C-reactive protein levels than patients with normal IgG levels, they were not statistically significant (Table 1).

When analyzing IgG levels as continues variables against phenotypic, clinical, anthropometric, and biochemical variables, female patients (1405±342 mg/dL vs. 1221±353 mg/dL; p=0.009) had higher IgG levels than male patients. Other variables with significant differences in IgG levels are shown in Figure 1.

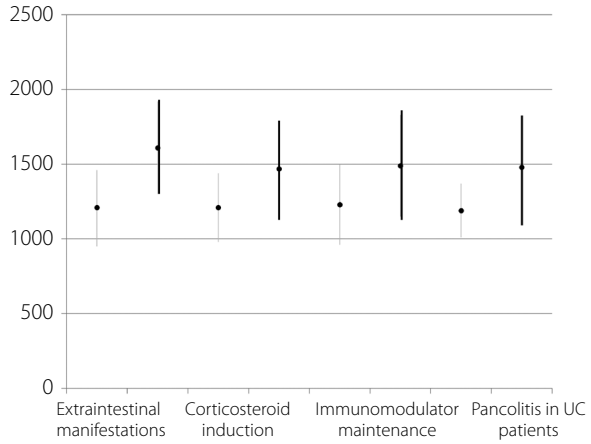

Figure 1. Mean IgG levels for clinical variables in pediatric IBD patients. Analysis of 184 pediatric IBD patients shows that mean (±SD) IgG levels significantly differ for patients with (black line) and without (gray line) extraintestinal manifestations (p<0.0001), corticosteroid induction (p=0.005), maintenance with immunomodulatory (p=0.001) and pancolitis (in UC patients; p=0.01) (mean, black dot; SD, vertical line)

Twenty-three (13%) patients had arthralgia without overt arthritis. A sub-analysis of patients with arthritis or arthralgia showed that arthritis patients had significantly higher IgG levels than arthralgia patients (1621±395 mg/dL vs. 1242±315 mg/dL; p=0.001).

Multivariate regression analysis results demonstrated that hypergammaglobulinemia was associated with EIMs with an odds ratio (OR) of 5.5 [95% confidence interval (CI), 2.1-9.2; p<0.001]. The statistical significance of the association between the female sex and hypergammaglobulinemia was not maintained. Hypergammaglobulinemia was also associated with corticosteroid induction (OR, 2.1; 95% CI, 1.2-3.5; p=0.04), immunomodulatory maintenance (OR, 3.5; 95% CI, 1.7-7.2; p=0.001) and with pancolitis (OR, 2.3; 95% CI, 1.3-3.8; p=0.01).

DISCUSSION

In this study, we evaluated the associations of phenotypic and clinical features of pediatric IBD patients with hypergammaglobulinemia. To the best of our knowledge, this is the first study to assess the implications of hypergammaglobulinemia in IBD patients. Hypergammaglobulinemia in children was previously reported to be associated with various autoimmune diseases, including IBD (7). A substantial proportion (25%) of our cohort had hypergammamlobulinemia. The main finding of our study is the striking association between elevated IgG levels and EIMs; the majority (70%) of children with hypergammaglobulinemia had joint, skin, or liver diseases. The vast majority (66%) of these children had peripheral arthritis or sacroileitis. The most common EIMs in IBD affect joints, skin, eyes, and mouth (8). Joint involvement (either peripheral or axial) was observed to be the most common EIM in both adults (9) and children (10) with IBD, which may involve 16%-33% of patients at diagnosis or during

follow-up. In a study evaluating 442 pediatric patients with hypergammaglobulinemia (7), 50% of patients had autoimmune diseases, including systemic lupus erythematosus, mixed connective tissue disease, polyarticular juvenile idiopathic arthritis, systemic onset juvenile idiopathic arthritis, spondyloarthritis, and IBD. Our findings imply that the combination of IBD and EIMs (mainly joint involvement) increases the likelihood for elevated IgG blood levels. In contrast, hypergammaglobulinemia was not associated with arthralgia. Arthralgia in a common feature in IBD patients despite it not being defined as an EIM (9). Dotson et al. (11) reported an arthralgia prevalence of 17% in pediatric IBD patients, which is more common than arthritis (4% of patients in the cohort). Because distinguishing arthralgia from arthritis might not be easy in some cases, measuring IgG levels might assist in differentiating between the two diseases as a complementary measure to clinical and radiological evaluation.

Elevated IgG levels were not associated with disease severity and other phenotypic features except for disease extent in UC patients, implying that luminal inflammation is not a dominant driving force for hypergammaglobulinemia. EIMs were previously shown to behave quite similarly; In CD patients, no correlation was observed between disease distribution and EIMs, whereas in UC patients, EIMs were significantly more associated with pancolitis than with isolated rectosigmoid disease (11).

Our finding demonstrating an association between hypergammaglobulinemia and corticosteroid induction and early maintenance with immunomodulators is plausibly attributed to the fact that patients with either EIMs or pancolitis are usually more aggressively treated during both induction and maintenance (9,11).

The etiology of polyclonal hypergammaglobulinemia in patients with autoimmune diseases is multifactorial. Polyclonal B-cell activation by inflammatory cytokines, including B-cell activating factor and interleukin 6 (IL-6), plays an important role in lupus and other autoimmune conditions (12,13). IL-6 overexpression is a common feature of many autoimmune disorders, including IBD and autoimmune joint diseases (14,15); thus, it is probably a key determinant in the etiology of elevated IgG levels in IBD and EIM patients.

Our study has several limitations. First, our cohort is relatively small; therefore, the findings may be at a risk for type II error. Moreover, as a retrospective study, some data are missing, including those regarding IgG subclasses. The fact that only 60% of our IBD patients had measured IgG levels suggests a selection bias. Nevertheless, this is the first study to assess IgG levels in IBD patients to provide interesting insights on the association between hypergammaglobulinemia and phenotypic features such as EIMs.

In conclusion, hypergammaglobulinemia is prevalent in pediatric IBD patients showing a striking association with EIMs, mainly arthritis but not arthralgia. Thus, an elevated IgG level is a potential marker for EIMs in pediatric IBD and may assist in distinguishing arthritis from arthralgia.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Rabin Medical Center.

Informed Consent: N / A.

Peer-review: Externally peer-reviewed.

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