Immunoglobulin A Deficiency in Celiac Disease

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Goals: To determine the prevalence and significance of immunoglobulin A (IgA) deficiency and partial deficiency in patients with celiac disease (CD).

Background: Selective IgA deficiency is a common primary immunoglobulin deficiency and has a higher prevalence in patients with CD. The prevalence and significance of IgA deficiency and partial deficiency in patients with CD in the United States has not previously been examined.

Study: A retrospective, cohort study of 1498 adults and 317 children seen in a University Medical Center was conducted.

Results: There were 26 patients (22 adults, 4 children) with CD who were IgA deficient and 11 (9 adults, 2 children) with CD who were partially IgA deficient. The prevalence of IgA deficiency/partial deficiency was similar among adults and children (2.1% and 1.9%, respectively, $P = 0.99$). Among adults, concomitant autoimmune disease was present in 29% of IgA-deficient/partially deficient patients versus 12% of CD patients with normal IgA levels ($P = 0.0081$). All 4 IgA-deficient patients who had persistently positive IgG celiac serologies while adherent to a gluten-free diet and were rebiopsied had a normal repeat biopsy. Both positive tissue transglutaminase IgG and antigliadin IgG were found in these patients.

Conclusions: Selective IgA deficiency/partial deficiency is present in 2% of CD patients at this referral center and is equally prevalent among adults and children. IgA-deficient/partially deficient adults had a higher prevalence of concomitant autoimmune disease than those without IgA deficiency. In patients who are IgA deficient, IgG serologies may be persistently elevated despite histologic recovery.

Key Words: celiac disease, IgA deficiency, partial IgA deficiency

(*J Clin Gastroenterol* 2012;46:850–854)

Selective IgA deficiency is the most common primary immunoglobulin deficiency in the general population.[1] Prevalence depends on ethnic background, but in the United States the prevalence of IgA deficiency is estimated to be from 1:223 to 1:1000 in community studies and from 1:400 to 1:3000 in healthy blood donors.[1,2] In patients with celiac disease (CD), the prevalence of IgA deficiency has been found to be greater than that in the general population, occurring in about 1 in 40 patients with CD.[3,4] However, there are limited data about IgA deficiency in patients with CD in the United States. Although gluten intake by patients with CD and normal IgA levels can be monitored through tissue transglutaminase IgA (TTG IgA),[5] the reliability of following IgG levels in patients with IgA deficiency has not been previously explored. Available data show an association between autoimmune diseases and IgA deficiency,[6–8] but this is not well described among patients with CD.

We aimed to determine the prevalence of IgA deficiency, both total (selective) and partial, in our institution's population of adults and children with CD and to investigate the serological and histologic response to a gluten-free diet (GFD) in this cohort. We also intended to compare the presenting symptoms and prevalence of associated autoimmune diseases in IgA-deficient/partially deficient patients with CD with those with normal IgA levels.

MATERIALS AND METHODS

We undertook a single-center retrospective study of the 1815 patients (1498 adults and 317 children) with CD at the Celiac Disease Center at Columbia University. All patients diagnosed with CD had biopsy findings consistent with CD, positive antibody, and/or human leukocyte antigen (HLA) DQ2/8 testing, and the majority responded to a GFD. Total serum IgA levels were measured by nephelometry. Patients were determined to have selective IgA deficiency if they had undetectable levels of total serum IgA (< 6 mg/dL). Those patients who had total serum IgA levels that were detectable but below the lower limit of normal (< 70 mg/dL in adults, < 24 mg/dL in children up to the age of 13) were considered to be partially IgA deficient. The control group consisted of patients at our institution with CD and normal levels of serum IgA. All CD patients were seen and educated by an experienced nutritionist. Patients with IgA deficiency combined with subnormal levels of either IgG or IgM were not included in this analysis.

We obtained information on the primary mode of presentation, the age at diagnosis with CD, and presence of concomitant autoimmune disorders. For the IgA-deficient and partially deficient patients, we also looked more closely at how they were diagnosed with CD and their follow-up biopsies and serologies after starting a GFD.

Patients were considered to have a positive biopsy if histology demonstrated partial (Marsh 3A) or subtotal/total villous atrophy (TVA) (Marsh 3B/C).

We used the χ^2 and Fisher exact tests to compare proportions, and the Mann-Whitney test to compare ages of the groups, as this variable was found to be non-normally distributed. SAS version 9.2 (Cary, NC) was used for all statistical calculations. This analysis used a prospectively maintained patient database that was approved by the Institutional Review Board of Columbia University Medical Center.

RESULTS

There were 26 patients (22 adults, 4 children) who were IgA deficient and 11 patients (9 adults, 2 children) who were partially IgA deficient. The prevalence of IgA

Received for publication September 15, 2011; accepted January 13, 2012.

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The authors declare that they have nothing to disclose.

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deficiency/partial deficiency among adults and children with CD was 2.06% and 1.89%, respectively ($P = 0.99$). Demographic information for adults and children is summarized in Tables 1 and 2, respectively. There were no significant differences in sex or mean age of diagnosis between the IgA-deficient (total and partial) patients and those with normal IgA levels in both adults and children.

Overall, a greater proportion of patients with IgA deficiency presented with diarrhea; however, this was not significant. For adults, 51% of IgA-deficient/partially deficient patients presented with diarrhea, as compared with 35% of those with normal IgA levels ($P = 0.086$). There was also no significant difference between the percentage of totally IgA-deficient versus partially deficient adults who presented with diarrhea (45% vs. 66%, $P = 0.430$). Among children, 33% who were IgA deficient/partially deficient presented with diarrhea, compared with 9% of those with normal IgA levels; however, this was also not statistically significant ($P = 0.095$). Other less common modes of presentation in the adult cohort included iron deficiency anemia (13%), dyspepsia (13%), weight loss (6%), fatigue (6%), screening in a family member with CD (3%), growth problems as a child (3%), and small bowel adenocarcinoma (3%). For the children, other presentations included growth issues (33%), familial screening (16%), and abdominal pain (16%).

Among adults with CD and total/partial IgA deficiency, concomitant autoimmune disease was present in 29% of patients compared with 12% of CD patients with normal IgA levels ($P = 0.0081$). There was no significant difference between totally and partially IgA-deficient patients with regard to concomitant presence of autoimmune disease (27% vs. 33%, $P = 1.0$). Autoimmune disorders that were seen in both the IgA-deficient populations included Hashimoto thyroiditis, Grave disease, vitiligo, psoriasis, type I diabetes, antiphospholipid antibody syndrome, Addison disease, Sjorgren syndrome, and autoimmune neuropathy. None of the totally or partially IgA-deficient children had another known autoimmune disease. Although dermatitis herpetiformis (DH) was not classified as a separate autoimmune disorder in this study, it is interesting to note that no IgA-deficient patients had DH compared with 9% of adult patients with normal levels of IgA ($P = 0.17$).

DISEASE COURSE (TABLES 3–7)

IgA-deficient Adults

Among the 22 adults with total IgA deficiency, only 18 patients (81.8%) had positive initial antibody testing: 17 patients were positive only for IgG antibodies and 1 patient had both IgG and IgA antibodies (Table 7). Of the 4 patients who had negative initial serological testing, 2 had a positive biopsy at the time of diagnosis that improved on repeat biopsy after following a GFD (no HLA testing was performed), and 2 already carried a diagnosis of CD and were following a GFD (with symptom improvement) when they were first seen (1 was positive for HLA DQ2, the other was not tested). Of those in whom there was a positive diagnostic biopsy (n = 19), 52% had TVA and 48% had partial villous atrophy (PVA).

We were interested in determining the most appropriate way to follow these patients. We had follow-up information in 14 (63%) of these patients (mean duration of follow-up, 5.14 y; range, 1 to 15 y). Of these patients in which follow-up data were available, 54% with initially positive serologies had normalized their serologies at follow-up after treatment with a GFD in a mean of 7.25 years (range, 3 to 15 y). However, the remaining 46% had persistently positive serologies, despite being on a GFD—either TTG IgG, antigliadin (AGA) IgG, or both. Follow-up biopsies were performed in 11 patients. All patients who underwent a repeat biopsy after starting a GFD showed signs of histologic improvement, normalizing in 5. This included 4 of the 5 patients who had persistently positive serologies.

TABLE 1. Demographics for Adults

	Normal IgA (n = 1467)	IgA d/pd (n = 31)	*P*
Male sex	406 (28%)	14 (45%)	0.077
Mean age of CD diagnosis (y)	41.5	39.9	0.800
Presented with diarrhea	517 (35%)	16 (51%)	0.086
Concomitant autoimmune disease	171 (12%)	9 (29%)	0.008

CD indicates celiac disease; IgA, immunoglobulin A; IgA d/pd, IgA deficient/IgA partially deficient.

TABLE 2. Demographics for Children

	Normal IgA (n = 311)	IgA d/pd (n = 6)	*P*
Male sex	130 (42%)	4 (67%)	0.222
Mean age of CD diagnosis (y)	8.2	9.7	0.564
Presented with diarrhea	24 (9%)	2 (33%)	0.095

CD indicates celiac disease; IgA, immunoglobulin A; IgA d/pd, IgA deficient/IgA partially deficient.

TABLE 3. Serologies and Histology at dx (Adult)

	IgA Deficient (n = 22)	IgA Partially Deficient (n = 9)
Pos serologies at time of dx	18 (82%)	9 (100%)
IgG only	17	1
IgG and IgA	1	8
Neg serologies	4	0
With pos bx and improvement on GFD	2	N/A
With neg/no bx; already on GFD with improvement in symptoms	2	N/A
Pos biopsy at time of dx	19 (86%)	8 (88%)
PVA (Marsh 3A)	9	4
TVA (Marsh 3B/C)	10	4
Neg biopsy (patient already on GFD)	1	0
Biopsy not performed	2	1
Pos serologies	1	1
Neg serologies; already on GFD	1	0

Bx indicates biopsy; dx, diagnosis; GFD, gluten-free diet; IgA/G, immunoglobulin A/G; neg, negative; pos, positive; PVA, partial villous atrophy; TVA, total villous atrophy.

TABLE 4. Follow-up Serologies and Histology (Adult)

	IgA Deficient (n = 22)	IgA Partially Deficient (n = 9)
Follow-up information available	14 (63%)	9 (100%)
Mean duration of follow-up (y)	5.14	4.5
Repeat serologies tested	13	9
Pos to neg	6	8
Persistently pos	5	1
Persistently neg	2	0
Mean time to convert from pos to neg (y)	7.25	2.9
Repeat biopsy performed	11	3
Normalized	5	2
TVA to PVA	3	0
PVA to mild PVA	2	0
No improvement (patient not on GFD)	0	1
Pos f/u serologies that were re-bx	4	0
Histologic improvement	4	NA

Bx indicates biopsy; f/u, follow-up; GFD, gluten-free diet; IgA, immunoglobulin A; NA, not applicable; neg, negative; pos, positive; PVA, partial villous atrophy; TVA, total villous atrophy.

Partially IgA-deficient Adults

All partially IgA-deficient adults had positive antibody tests at diagnosis, the majority (88%) IgA based; only 1 patient had positive IgG antibodies and negative IgA-based serological tests (Table 7). Positive biopsy findings revealed PVA in 50% and TVA in 50%.

Follow-up was available in all 9 of these patients. Serological tests normalized in all but 1 patient who was noncompliant with a GFD at a mean of 2.9 years. Follow-up biopsy improved or normalized in all 8 patients who followed a GFD.

IgA-deficient Children

Among the children studied, 3 of 4 demonstrated positive IgG antibody subtype alone; 1 patient was seronegative (Table 7). The 1 patient with negative serologies had a positive small bowel biopsy for CD. All children had an initial small intestine biopsy at the time of diagnosis; 1 had TVA and 3 had PVA. None had a repeat biopsy.

TABLE 5. Serologies and Histology at dx (Children)

	IgA Deficient (n = 4)	IgA Partially Deficient (n = 2)
Pos serologies at time of dx	3 (75%)	2 (100%)
IgG only	3	1
IgG and IgA	0	1
Neg serologies (pos bx)	1	0
Pos biopsy at time of dx	4	2
PVA (Marsh 3A)	3	1
TVA (Marsh 3B/C)	1	1

Bx indicates biopsy; dx, diagnosis; IgA/G, immunoglobulin A/G; neg, negative; pos, positive; PVA, partial villous atrophy; TVA, total villous atrophy.

TABLE 6. Follow-up Serologies and Histology (Children)

	IgA Deficient (n = 4)	IgA Insufficient (n = 2)
Follow-up information available	0	1
Repeat serologies tested	0	1
Positive to negative	NA	1
Time to negative serologies	NA	2 y
Repeat biopsy performed	0	0

IgA indicates immunoglobulin A; NA, not applicable.

Partially IgA-deficient Children

Both patients had positive serologies: 1 had positive IgG antibodies and negative IgA antibodies, and 1 had both positive IgG and IgA antibodies (Table 7). Both patients had initial biopsies that were positive (PVA, TVA). One patient had repeat antibody testing: IgA serologies reverted to negative, but IgG serologies remained positive. Neither patient had a repeat biopsy.

DISCUSSION

Selective IgA deficiency and partial deficiency are present in 2% of CD patients in this referral center, and is equally prevalent among adults and children. This is comparable to the range that has been previously reported (2.3% to 2.6%).[3,4] Our data support the conclusion that these conditions are not common in CD and question the need for routine measurement of total serum IgA when assessing a patient for the diagnosis of CD. Testing total serum IgA levels only in those patients whose initial screening panels are positive for IgG antibodies and negative for IgA antibodies may be more cost effective.

We also examined the significance of IgA deficiency (both total and partial) in our celiac cohort. Our results indicate that adult IgA-deficient patients are more likely to have concomitant autoimmune diseases (29% vs. 12%, $P = 0.0081$). We also found that a higher percentage of patients presented with diarrhea, but this was not statistically significant, which was similar to the results reported by Heneghan et al.[4]

None of the patients who were IgA deficient was diagnosed with DH compared with 9% of the CD patients with normal IgA levels. As granular IgA deposits at the basement membrane are diagnostic for DH,[9] it is not surprising that patients who produce suboptimal levels of IgA would not be affected by this disorder.

The majority of CD patients with IgA deficiency produce IgG antibodies. However, some seronegative patients were encountered. Most patients had AGA IgG measured, whereas a few had TTG IgG antibodies measured. However, no patients in our study had deamidated gliadin peptide antibodies measured; these have been assessed in a population of IgA-deficient patients with CD and found to be a reliable marker of CD.[10] Regardless, there needs to be a high index of suspicion for CD when IgA deficiency is encountered, even in the absence of IgG celiac-related antibodies, as we observed both adults and children with IgA deficiency and CD who were seronegative at diagnosis.

Most adults with partial IgA deficiency produce IgA class AGA and TTG antibodies; however, not all do so, as we encountered 1 patient with only IgG antibodies.

TABLE 7. Initial Serologies at Diagnosis

Patient No.	Classification	TTG IgA	AGA IgA	EIgA	TTG IgG	AGA IgG	Unknown IgG
1	Adult IgAd	–	–	NT	NT	+	
2	Adult IgAd	–	–	NT	+	+	
3	Adult IgAd	–	–	NT	NT	–	
4	Adult IgAd	–	NT	NT	+	NT	
5	Adult IgAd	–	–	NT	NT	+	
6	Adult IgAd	–	–	NT	–	–	
7	Adult IgAd	NT	–	NT	+	+	
8	Adult IgAd	+	–	NT	+	NT	
9	Adult IgAd	–	–	NT	+	+	
10	Adult IgAd	–	–	NT	+	+	
11	Adult IgAd	–	–	NT	+	+	
12	Adult IgAd	–	–	NT	NT	+	
13	Adult IgAd	–	–	NT	+	+	
14	Adult IgAd	–	–	NT	+	–	
15	Adult IgAd	–	–	NT	NT	+	
16	Adult IgAd	–	–	NT	NT	+	
17	Adult IgAd	–	NT	NT	–	NT	
18	Adult IgAd*	NA	NA	NT	NA	NA	+
19	Adult IgAd	–	–	NT	NT	+	
20	Adult IgAd	NT	NT	NT	+	+	
21	Adult IgAd	–	–	NT	NT	–	
22	Adult IgAd	–	–	NT	NT	+	
23	Child IgAd	–	–	NT	NT	+	
24	Child IgAd	–	–	–	NT	–	
25	Child IgAd	–	–	NT	NT	+	
26	Child IgAd	–	–	NT	+	–	
27	Adult IgApd	+	–	NT	NT	+	
28	Adult IgApd	+	+	NT	NT	+	
29	Adult IgApd	+	NT	NT	NT	NT	
30	Adult IgApd	+	–	NT	NT	+	
31	Adult IgApd	+	–	NT	–	+	
32	Adult IgApd	NT	–	NT	–	+	
33	Adult IgApd	–	+	NT	NT	+	
34	Adult IgApd	–	–	+	NT	–	
35	Adult IgApd	+	+	NT	NT	+	
36	Child IgApd	+	+	NT	NT	+	
37	Child IgApd	–	–	NT	NT	+	

*This patient was noted in chart to have positive IgG serologies, but no laboratory values could be found in the chart.

Adult IgAd indicates adult IgA deficiency; adult IgApd, adult partial IgA deficiency; AGA, antigliadin; child IgAd, child IgA deficiency; child IgApd, child partial IgA deficiency; EIgA, endomysial IgA; IgA/G, immunoglobulin A/G; NA, not available; NT, not tested; TTG, tissue transglutaminase.

Additionally, 1 of 2 children who were partially IgA deficient did not produce IgA antibodies. It is noteworthy that we observed 1 patient who produced IgA antibodies in the face of documented IgA deficiency as a child, which has been reported previously.[11]

In patients who are IgA deficient, IgG serologies may be persistently elevated despite histologic recovery. Therefore, it is unreliable to monitor disease course and/or compliance with a GFD in the IgA-deficient population by IgG serologies. This was also noted in a study by Cataldo et al[12] who found that 4 of 34 IgA-deficient patients on a strict GFD still had TTG IgG antibodies, yet none had AGA IgG. However, in our study, patients continued to have both TTG IgG and AGA IgG antibodies on a GFD, supporting the fact that neither AGA IgG nor TTG IgG is a reliable marker for following disease course in the IgA-deficient population. Timely follow-up biopsy is the only reliable method to confirm disease regression.

We conclude that selective IgA deficiency/partial deficiency is present in 2% of CD patients in this referral center, and appears to be equally prevalent among adults and children. There needs to be a high index of suspicion for CD in the setting of IgA deficiency as we found both adults and children with IgA deficiency and CD who were seronegative at diagnosis. Patients who are partially IgA deficient can still usually be diagnosed by IgA antibody testing. In patients who are IgA deficient, IgG serologies may be persistently elevated despite histologic recovery. Therefore, IgG serologies alone are an unreliable gauge of disease activity and/or adherence to the GFD in the IgA-deficient population; follow-up biopsy is necessary.

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