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Serology of celiac disease in gluten sensitive ataxia or neuropathy; Role of deamidated gliadin Antibody

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Abstract

The role and relevance of deamidated gliadin antibodies specific for celiac disease in gluten-sensitive ataxia/ neuropathy is unknown. We investigated the association of celiac-specific serology with gluten-sensitive ataxia/neuropathy, in patients with and without gliadin-induced enteropathy. 51 patients with unexplained ataxia/neuropathy suspected to have gluten sensitivity were included in the study and their serum celiac specific markers were measured. Deamidated-gliadin-IgA (83% vs 22%), deamidated-gliadin-IgG (50% vs 3%), tissue-transglutaminase-IgA (78% vs 11%), and anti-endomysial-IgA (70% vs 0%), were significantly more positive in ataxia/ neuropathy patients with celiac disease versus those without enteropathy (P <0.001). Our findings suggest that the serological profile of gluten-sensitive ataxia/neuropathy without intestinal involvement lacks the recognition of deamidated-gliadin and tissue-transglutaminase epitopes.

Keywords

Ataxia; Neuropathy; Gluten sensitivity; Celiac disease; Deamidated gliadin Antibody

1. Introduction

Gluten sensitivity develops in response to wheat gluten and related proteins in genetically predisposed individuals. Patients with this condition present with a broad spectrum of manifestations that ranges from clinically asymptomatic features to the disabling disorders such as, wheat allergy, celiac disease, and neuropathies. Celiac disease is an autoimmune enteropathy occurring in susceptible (HLA-DQ2+ or HLA-DQ8+) individuals as a result of sensitivity to wheat storage protein (gluten).(Green and Jabri, 2006; Schuppan, 2000) The extra intestinal manifestations of celiac disease are diverse and include neurologic complications.(Barton and Murray, 2008) Cerebellar ataxia and peripheral neuropathy are the most common neurologic presentations, occurring in 6–10% of celiac patients.(Bushara, 2005; Green et al., 2005)One of the earliest reports was by Cooke *et al* in 1966, describing

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16 cases of celiac disease with severe ataxia and peripheral neuropathy.(Cooke and Smith, 1966) Subsequently, several studies described a variety of other neurologic disorders in association with celiac disease, including epilepsy (with cerebral calcification), headache, depression, neuromuscular complications, movement disorders, cerebral vasculitis, dementia and autism.(Bushara, 2005; Gabrielli et al., 2003; Gobbi et al., 1992; Green et al., 2005; Hadjivassiliou et al., 1997; Hadjivassiliou et al., 2007; Hadjivassiliou et al., 2001; Hu et al., 2006; Murray and Ross, 2004)

A high prevalence of positive anti-gliadin antibodies (AGA) has also been reported in patients with idiopathic ataxia or peripheral neuropathy, conditions commonly referred to as “gluten ataxia” or “gluten neuropathy”.(Hadjivassiliou et al., 1996; Hadjivassiliou et al., 2003b) Nonetheless, the importance and relevance of gliadin antibodies in the absence of intestinal damage in such patients is questionable, as a high prevalence of these antibodies are also found in hereditary ataxia, Huntington’s disease, multiple system atrophy and healthy controls.(Abele et al., 2003; Bushara et al., 2004; Pellecchia et al., 2002)

Recent studies have shown that antibodies against altered deamidated gliadin peptides are more specific for celiac disease than the conventional native gliadin antibodies.(Aleanzi et al., 2001; Osman et al., 2000; Rashtak et al., 2008b; Sugai et al., 2006) However the efficacy of Deamidated Gliadin Peptide (DGP) antibody testing in detection of gluten sensitive neurologic disorders has remained unclear. The aim of our study was to determine the prevalence of these DGP antibodies in a series of patients with so called “gluten ataxia/ neuropathy”. We also evaluated the prevalence of other celiac-specific serologic markers, celiac-predisposing HLA, and the neurologic response to gluten free diet in the treated patients.

2. Material and Methods

Patients and Study design

Subjects were selected from patients with suspected gluten ataxia and/or neuropathy who were referred to the division of Gastroenterology and Hepatology for assessment of gluten sensitivity, between February 2002 and July 2007. The criteria for patient inclusion were presence of idiopathic ataxia and/or neuropathy in the setting of diagnosed celiac disease, or presence of positive celiac serologic tests (AGA, TTG) or celiac predisposing HLA (HLA-DQ2 or -DQ8). Serum samples were collected from these patients as part of their clinical work-up. We measured serum DGP IgA and IgG in all 51 gluten ataxia/neuropathy subjects. The majority of these patients were included in the study because they had AGA IgA or IgG levels greater than the reference range (N=45). The remainder were suspected for gluten-sensitive ataxia/neuropathy because they had a positive TTG antibody (N=3) or a predisposing HLA-DQ2 (N=3). Patients were referred to gastroenterology to confirm or rule out the diagnosis of celiac disease as a potential contributor to the patient’s neurologic syndrome. Data on the application of the gluten-free diet and follow-up of neurologic and serologic outcomes were extracted from each patient’s medical record.

Serology

Deamidated Gliadin peptide (DGP) IgA and IgG antibodies were measured in all subjects by ELISA using kits provided for in vitro diagnostic use (QUANTA Lite Gliadin-IgA II and Gliadin-IgG II, INOVA Diagnostics Inc., San Diego, CA; reference range<20 U).[22] Gliadin (AGA) IgA and IgG antibodies were also measured in all subjects by ELISA using kits provided by the manufacturer for in vitro diagnostic use (Scanlisa Anti-Gliadin-IgA Antibody and Anti-Gliadin-IgG Antibody, Scimedx Corporation, Denville, NJ; reference range<25 EU). All other serologic tests were performed as part of each patient’s clinical

work-up. The test results for Tissue Transglutaminase (TTG) IgA (INOVA Diagnostics Inc, San Diego, CA, positive ≥20 U/mL), Anti-Endomysial Antibodies (EMA) (indirect immunofluorescence on monkey esophagus; BINDAZYME; The Binding Site Ltd, Birmingham, UK) and HLA class II genotyping (polymerase chain reaction, One Lambda Inc, Canoga Park, CA) were extracted from each patient's medical record.(Rubio-Tapia et al., 2008)

Histopathology

Thirty-eight patients underwent upper endoscopy and small intestinal biopsy to rule out celiac disease. Biopsies were performed as part of each patient's clinical workup. Based on histopathologic reports of the duodenal biopsies, subjects were classified according to modified Marsh criteria.(Marsh, 1992)Patients with increased number of intraepithelial lymphocytes, crypt hyperplasia, inflammation, and any degree of villous atrophy (Marsh IIIa-c) (N=12) comprised the definite celiac group.(Marsh, 1992; Rostami et al., 1998) HLA genes predict the possibility of celiac disease, and in the absence of these genes there would be no point in undertaking intestinal biopsies. As such subjects who had no evidence of enteropathy (Marsh 0) (N=24) or had not undergone intestinal biopsy due to lack of genetic predisposition (NO HLA DQ2 or DQ8) to celiac disease (N=13) comprised non-celiac group. Patients with only increased number of intraepithelial lymphocytes (Marsh I) (N=2) were not categorized into either group.

Statistics

Statistical analysis was conducted using JMP™ version 8.0.0 software (SAS Institute Inc.; Cary, North Carolina). The student's T test assuming equal variances was employed to compare age and Chi square or Fisher's exact test (as appropriate) were employed to compare qualitative variables. Logistic regression was used to test for association between titer of anti gliadin antibody titer and deamidated gliadin antibody test results. Statistical significance was inferred at P values < 0.05 for all comparisons.

3. Results

Subjects' Characteristics

Based on the inclusion criteria, fifty-seven adult patients, with median (range) age of 54 (27–83) years, entered the study. Of these, six patients were excluded for serologic analysis because they had started a gluten free diet before serum sample collection. However, they were included in the analysis to study the effect of gluten free diet on neurologic outcome. Of the remaining 51 patients with suspected gluten-sensitive ataxia and/or neuropathy (mean age 57 years, 49% female) Ataxia alone and neuropathy alone were present in 30 and 15 patients, respectively. Six patients had both disorders together. Thirty-eight subjects underwent small intestinal biopsy; of these 12 had evidence of celiac disease on histopathology. Table 1 shows the characteristics of subjects based on the histopathology of intestinal biopsy. Subjects who did not undergo intestinal biopsy were not different from those who had a normal biopsy in age, gender, or presenting neurologic symptoms. For the simplicity of analysis, we categorized these two groups into the non-celiac group. There was no significant difference in age or gender between celiac and non-celiac subjects. However, neuropathy was more frequent in celiac group whereas ataxia was more frequent in non-celiac group (P =0.03, Fisher's exact test, excluding those with both disorders).

Gliadin Antibodies

Serum DGP IgA and IgG were present in 35% and 14% of all subjects, respectively. There was a significant difference in serum positivity for DGP antibodies between celiac group

and non-celiac group. DGP IgA was present in 83% of ataxia/neuropathy patients who also had celiac disease versus 22% of those without celiac disease (*P* <0.001, Fisher's exact test). Conversely, AGA IgA was not significantly different between celiac (75%) and non-celiac (84%) group as it was expected. Positive DGP IgG was detected in 50% of celiac patients but only 3% of non-celiacs (*P* <0.001, Fisher's exact test). This was in contrast to AGA IgG that was equally present among celiac (42%) and non-celiac (41%) patients. We did not find any significant difference between subjects who had a normal intestinal biopsy and those who did not undergo biopsy regarding AGA and DGP antibodies. Interestingly, both subjects with Marsh I enteropathy were positive for AGA IgA and IgG, but negative for DGP IgA and IgG. These results are summarized in table 2. There was no significant difference between the serologic test results among patients with neuropathy and those with ataxia, except that DGP IgA was more prevalent among neuropathic patients (67%) than ataxic patients (20%) (P=0.002, Chi-square test). After a disease-stratified analysis, this association remained significant in the non-celiac group (50% vs 12% for neuropathy vs Ataxia, P=0.04) but was lost in celiac group (86% vs 75% for neuropathy vs Ataxia). Higher titer of AGA was not associated with positive DPG antibodies as no statistically significant correlation was detected between the titer of anti gliadin antibody and probability of being positive for deamidated gliadin antibody in logistic regression analysis. (OR = 1.004, 95%CI: 0.996 – 1.011, P value = 0.32)

Celiac Autoantibodies and HLA Genotyping

The results of TTG IgA, EMA and HLA genotyping were extracted from each patient's medical record (Table 3). Forty-six patients had been tested for TTG IgA, of those 24% had a positive test. Similar to DGP antibodies, TTG IgA was mainly present in those ataxia/ neuropathy patients who also had intestinal pathology (78%); whereas only a few of non-celiac patients (11%) had a positive TTG IgA (*P* <0.001, Fisher's exact test). Thirty-seven patients had also been tested for EMA antibodies. Interestingly, EMA was exclusively found in those ataxia/neuropathy patients that had biopsy-confirmed celiac disease (*P* <0.0001, Fisher's exact test). The two subjects with Marsh I enteropathy were negative for both TTG IgA and EMA. There was no significant difference in the frequency of serum positivity for TTG IgA (15% vs. 30%) or EMA (7% vs. 17%) among ataxic versus neuropathic patients.

HLA class II genotyping was also performed in most patients (N=47); among those 30 patients (64%) had celiac predisposing HLA (51% HLA-DQ2, 11% HLA DQ8, and 2% HLADQ2/DQ8). All the patients with confirmed celiac disease had either HLA DQ2 or HLA DQ8. Among non-celiac group, 70% of those with normal biopsy had a celiac predisposing HLA versus 31% of those who did not undergo biopsy. This can be explained by knowing in advance that these patients lacking HLA DQ2 or DQ8 and therefore were not subjected to intestinal biopsy in the absences of gastrointestinal symptoms. None of the patients with biopsy proven celiac disease had HLA DQ8 as compared to 23% (6/26) of patients with normal biopsy that expressed HLA DQ8. Of the subjects with Marsh I enteropathy, one had HLA-DQ8, but the other one did not have any celiac predisposing HLA. The prevalence of HLA DQ2 and/or DQ8 was not significantly different in ataxia (59%) versus neuropathy (67%) patients.

Response to Gluten Free Diet

In order to find out if a gluten-free diet is beneficial for patients with suspected gluten ataxia or neuropathy, we searched patients' medical records for instruction of gluten free diet and response to the diet. Those 6 patients that had started the gluten free diet prior to serum sample collection and therefore were excluded from the serologic analysis of the study were entered in the analysis for evaluation of response to the diet. 9 patients did not have diet instruction in our evaluation. Of the 48 remaining patients, 25 had adopted a gluten-free diet

and 23 had not. The follow-up on neurologic symptoms was reported in 30 patients. This was primarily based on clinical impression of the neurologist physician and objective measurements that has been performed in some patients. Two third of patients who were lost to follow-up belonged to the group that had not adopted a gluten-free diet. Of patients on gluten-free diet, the neurologic symptoms improved in 16%, remained stable in 37%, and worsened in 47% (Table 4). Of those who were not treated with gluten-free diet, 9% improved, 18% remained stable and 73% worsened. However, these differences were not statistically significant. None of the patients had an improvement of ataxia on a gluten-free diet. Studying brain MRI of the six unresponsive patients with progressive ataxia demonstrated that four of them had evidence of cerebellar atrophy and the two others had vascular degeneration and ischemic changes. One patient had small chronic infarcts noted in the superior aspect of the right and left cerebellum as well as small vessel ischemic changes of moderate severity throughout the hemispheric white matter. The second patient had focal and confluent areas of abnormality in the white matter of both cerebral hemispheres considered most like suggestive of small vessel degenerative change. Three out of 10 patients with neuropathy improved on a gluten-free diet, 2 of those had a biopsy-confirmed celiac disease, and the other one had a high titer of DGP IgA despite a normal biopsy.

Serologic follow up

Along with neurologic evaluation, 14 patients (9 on GFD and 5 on GCD) have been followed for celiac specific serology. Anti gliadin IgA levels were primarily considered for the characterization of serologic profile. In those cases that did not have anti gliadin IgA levels evaluated, anti TTG IgA was applied for categorization. Normal range serologic values or seroconversion from positive values to the values close to the normal range has been classified as desired serologic profile while worsening or unchanged positive serologic markers were considered to be undesired.

Of seven patients who had desired serologic testing, three patients had worsening neurologic symptoms, two patients had improvement, and other two patients remained unchanged. One patient of this group had increased level of antigliadin antibody and that occurred while she was on strict gluten free diet. In evaluation of the seven patients in the other group, with undesired serologic profile, only one patient remained stable and all of the six remaining patients showed exacerbated neurologic outcome. No clinical improvement was evidenced in this group. In comparison of the two groups, a trend of correlation between the overtime neurologic outcomes and serologic profiles can be seen, however this association did not reach to statistical significance. (P value 0.18)

4. Discussion

Cerebellar ataxia and peripheral neuropathy are the most common neurologic findings in celiac disease(Chin et al., 2003). Conversely, celiac disease is found in 2–17% of patients with unexplained cerebellar ataxia and in 1.5–8% of those with neuropathy.(Bushara, 2005; Chin et al., 2003)The association between celiac disease and these neurologic disorders as well as the observation of high prevalence of antibodies to native gliadin in patients with idiopathic ataxia/neuropathy has led to the description of a syndrome termed gluten-sensitive ataxia/neuropathy.(Bushara, 2005; Hadjivassiliou et al., 2006a) However, it is not clear whether gliadin antibodies in the absence of enteropathy are relevant to or play any role in the development of these neurologic symptoms. This is particularly because antibodies to native gliadin are commonly found in healthy controls as well as in patients with known causes of neurologic disorders. (Abele et al., 2003; Bushara et al., 2004; Pellecchia et al., 2002)On the other hand; some studies have refuted any association between gliadin antibodies and sporadic ataxia when compared to healthy controls.(Wong et al.,

2007) So whether the presence of these antibodies is indicative of true gluten sensitivity is questionable.(Combarros et al., 2000; Wills and Unsworth, 2003)

In this study, we evaluated serum deamidated gliadin antibodies in a relatively large number of patients with gluten-sensitive ataxia and/or neuropathy. Our results of serologic testing in ataxia/neuropathy patients with and without enteropathy indicates that celiac serologic markers might be irrelevant findings in so called “gluten-sensitive ataxia/neuropathy” in the absence of intestinal pathology. These findings suggest that patients who have gluten-sensitive neurologic symptoms with enteropathy might recognize different epitopes of gliadin molecule from those who have isolated gluten-sensitive ataxia/neuropathy.

The recognition of gliadin by both T cells and B cells is the central part in the pathogenesis of celiac disease.(Sollid, 2002) Tissue Transglutaminase (TTG) binds to gliadin proteins at the gut level, resulting in gliadin-TTG complexes. Selective deamidation of gliadin peptides presumably by TTG results in increased recognition of gliadin peptides by gluten responsive T cells derived from the intestine of celiac disease patients.(Arentz-Hansen et al., 2000; Quarsten et al., 1999)These T cells then activate the B cells to recognize DGP-TTG complexes leading to generation of antibodies against both antigens.(Marietta et al., 2009; Sollid et al., 1997)The DGP and TTG antibodies have been shown to be more specific for celiac disease as compared to conventional gliadin antibodies.(Aleanzi et al., 2001; Rashtak et al., 2008a; Rashtak et al., 2008b; Schwertz et al., 2004; Sugai et al., 2006)Herein, we demonstrated that in contrast to conventional anti gliadin antibodies, DGP antibodies are specific to celiac disease and are not generally found in patients with gluten ataxia/ neuropathy without enteropathy. Similarly, TTG and EMA antibodies were mainly positive in those ataxia/neuropathy patients that also had biopsy-proven celiac disease. This association could be explained by the deamidation process that exclusively occurs in the intestine of celiac patients and leads to subsequent activation of B cells to generate anti DGP antibodies. We can also speculate that patients who have a positive anti-gliadin antibody, but lack the more specific deamidated gliadin peptide or tissue transglutaminase or endomysial antibodies that are specific for celiac disease actually have a gluten-related neuropathy or ataxia. It is quite possible that this may represent a sensitivity to a different epitope, perhaps in some way similar to gliadin, but which limits their disease to the nervous system.

All of our patients with celiac disease had a positive celiac predisposing HLA (DQ2 and/or DQ8) as compared to about half of the non-celiac patients. In addition HLA DQ8 was more commonly expressed in gluten sensitive patients with normal mucosa as compared to biopsy proven celiac patients that may also suggest different genotypic profiles between the two groups.

In our study, intestinal pathology was defined as presence of villous atrophy with the changes compatible to celiac enteropathy. A previous study on nine patients with unexplained ataxia and increased gliadin antibodies has shown subepithelial deposition of TTG IgA in the jejunum of these patients in a pattern similar to the intestine of celiac patients.(Hadjivassiliou et al., 2006c) In the same study, those gliadin antibody positive patients that had other causes for their ataxia did not have any villous atrophy or deposition of TTG antibody in the intestine. This is consistent with our finding as it suggests that presence of intestinal pathology is an essential component in the development of immune response to gluten and perhaps a better response to gluten free diet.

We also acknowledge it is entirely possible that these individuals had idiopathic neuropathy or cerebellar ataxia and the positive serologic tests, particularly that directed against antigliadin, is a false positive test and does not relate to the mechanism of their neurologic syndrome.

Our findings regarding neurologic response to treatment with gluten free diet is not conclusive. Although, the data may suggest a trend towards benefits from gluten exclusion, the neurologic outcome of the two dietary groups were not significantly different. It appears that neuropathic symptoms in celiac patients may have a better chance of recovery (if any) on gluten free diet than ataxic symptoms. We did not see any improvement of ataxia with gluten free diet either in the celiac patients or in the non-celiacs. Obviously, patients with celiac disease should be encouraged to adhere to a gluten free diet; however, there are inconsistent reports regarding the effectiveness of this treatment for improvement of neurologic symptoms.(Grossman, 2008; Hadjivassiliou et al., 2003a; Hadjivassiliou et al., 2006b; Luostarinen et al., 2003; Tursi et al., 2006)[39–43] Based on our results, especially for the patients without underlying enteropathy, gluten free diet does not have a significant beneficial effect on the neurologic symptoms. In addition we did not observe any correlation between the course of neurologic disorders and serologic outcomes in our patients that may also suggest these are distinct entities. However, it should be noted though that our observation regarding the effect of dietary treatment has a few limitations. First, we were not able to systematically evaluate the degree of neurologic involvement before and after treatment since the outcome measures were retrospectively extracted form patients' medical record. We also lost a fair number of patients to follow-up leading to a small sample size. However, Timeliness of the intervention may be important as it could be suggested that delayed intervention for treatment of ataxia is associated with a reduced chance of response due to irreversible changes in nervous system. This may be especially important when patients already have developed cerebellar atrophy, reducing the likelihood of any improvement in the neurologic symptoms. Also lack of progression of an established neurologic syndrome may in itself be a benefit that is inherently difficult to appreciate.

In conclusion, the serologic profile of patients with ataxia/neuropathy who have celiac disease is different from those without enteropathy. In those patients with celiac disease, the clear benefit of a gluten-free diet in terms of their gut is well established but convincing evidence of the benefit in terms of neurologic outcomes are still lacking. If despite this uncertainty clinicians wish to identify celiac disease in patients with ataxia or neuropathy deamidated gliadin peptide antibody has superior specificity for the detection of enteropathy.

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Table 1

Subjects' characteristics

	N	Age	Female	Ataxia	Neuropathy	Both†
Celiac	12	56 ± 13	7 (58)	4 (33)	7 (58)	1 (8)
Non-Celiac	37	58 ± 14	17 (46)	25 (67)	8 (22)	4 (11)
Marsh 0	24	56 ± 13	13 (54)	15 (63)	6 (25)	3 (12)
No Biopsy	13	61 ± 15	4 (30)	10 (77)	2 (15)	1 (8)
Marsh I	2	47 ± 14	1 (50)	1 (50)	0 (0)	1 (50)
Total	51	57 ± 14	25 (49)	30 (59)	15 (29)	6 (12)

Results are shown as (Mean ± SD) or N (%).

†Both ataxia and neuropathy. None-celiac group comprise patients with normal intestinal biopsy (Marsh 0) and those who did not undergo biopsy (No Biopsy).

Table 2

AGA and DGP antibodies in patients with gluten ataxia/neuropathy

	N	**DGP IgA	**DGP IgG	AGA IgA	AGA IgG
Celiac	12	10 (83)	6 (50)	9 (75)	5 (42)
Non-Celiac	37	8 (22)	1 (3)	31 (84)	15 (41)
Marsh 0	24	6 (25)	1 (4)	21 (87)	8 (33)
No Biopsy	13	2 (15)	0 (0)	10 (77)	7 (54)
Marsh I	2	0 (0)	0 (0)	2 (100)	2 (100)
Total	51	18 (35)	7 (14)	42 (82)	22 (43)

Results are shown as N positive (%).

** P<0.001 for comparison between celiac group (Marsh III) and non- celiac group. None-celiac group comprised patients with normal intestinal biopsy (Marsh 0) and those who did not undergo biopsy (No Biopsy). P values are obtained by Fisher's exact test.

Table 3

Other celiac serologic markers in patients with gluten ataxia/neuropathy

	**TTG IgA	***EMA IgA	*HLA DQ2 or DQ8
Celiac	7/9 (78)	7/10 (70)	9/9 (100)
Non-Celiac	4/35 (11)	0/25 (0)	20/36 (56)
Marsh 0	4/23 (17)	0/17 (0)	16/23 (70)
No Biopsy	0/12 (0)	0/8 (0)	4/13 (31)
Marsh I	0/2 (0)	0/2 (0)	1/2 (50)
Total	11/46 (24)	7/37 (19)	30/47 (64)

Results are shown as N positive/N tested (%).

* P<0.05,

** P<0.001,

*** P<0.0001, for comparison between celiac group and non-celiac group. None-celiac group comprised patients with normal intestinal biopsy (Marsh 0) and those who did not under go biopsy (No Biopsy). P values are obtained by Fisher's exact test.

Table 4

Effect of Gluten Free diet on Neurologic outcome

	N	Improved	Stable	Worsened
Celiac	7	2 (28)	2 (28)	3 (43)
Normal Biopsy	7	1 (14)	3 (43)	3 (43)
Marsh I	5	0 (0)	2 (40)	3 (60)
Total	19	3 (16)	7 (37)	9 (47)

Results are shown as N positive (%). There was no significant difference in neurologic outcome of the patients on gluten free diet vs. those on gluten containing diet