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Research Submission

Prevalence of Migraine in Patients With Celiac Disease and Inflammatory Bowel Disease

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Objective.—To assess the prevalence of headache in clinic and support group patients with celiac disease and inflammatory bowel disease (IBD) compared with a sample of healthy controls.

Background.—European studies have demonstrated increased prevalence of headache of patients with celiac disease compared with controls.

Methods.—Subjects took a self-administered survey containing clinical, demographic, and dietary data, as well as questions about headache type and frequency. The ID-Migraine screening tool and the Headache Impact Test (HIT-6) were also used.

Results.—Five hundred and two subjects who met exclusion criteria were analyzed – 188 with celiac disease, 111 with IBD, 25 with gluten sensitivity (GS), and 178 controls (C). Chronic headaches were reported by 30% of celiac disease, 56% of GS, 23% of IBD, and 14% of control subjects ($P < .0001$). On multivariate logistic regression, celiac disease (odds ratio [OR] 3.79, 95% confidence interval [CI] 1.78-8.10), GS (OR 9.53, 95%CI 3.24-28.09), and IBD (OR 2.66, 95%CI 1.08-6.54) subjects all had significantly higher prevalence of migraine headaches compared with controls. Female sex ($P = .01$), depression, and anxiety ($P = .0059$) were independent predictors of migraine headaches, whereas age >65 was protective ($P = .0345$). Seventy-two percent of celiac disease subjects graded their migraine as severe in impact, compared with 30% of IBD, 60% of GS, and 50% of C subjects ($P = .0919$). There was no correlation between years on gluten-free diet and migraine severity.

Conclusions.—Migraine was more prevalent in celiac disease and IBD subjects than in controls. Future studies should include screening migraine patients for celiac disease and assessing the effects of gluten-free diet on migraines in celiac disease.

Key words: headache, migraine, celiac disease, gluten sensitivity, secondary headache disorders, autoimmune disease

Abbreviations: C control, CI confidence interval, GFD gluten-free diet, GS gluten sensitivity, HIT-6 Headache Impact Test, HRT hormone replacement test, IBD inflammatory bowel disease, LP lumbar puncture, NSAID nonsteroidal anti-inflammatory drug, OCP oral contraceptive pill, OR odds ratio, PPV positive predictive value, SSRI selective serotonin re-uptake inhibitor, UC ulcerative colitis

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Over the past 40 years, many studies have supported an association between celiac disease and neurological conditions, such as ataxia, peripheral neuropathy, and headaches.[1-4] Celiac disease, present in about 1% of the population worldwide,[5] is an autoimmune condition occurring in genetically predisposed individuals as a response to dietary gluten. The association of celiac disease and neurological disorders has been extended to gluten sensitivity (GS), a disorder considered to be present when patients report improvement in symptoms upon withdrawal of dietary gluten, even though they do not meet diagnostic criteria for celiac disease. While the public awareness of this condition is high,[6] GS has been termed a "no man's land" for physicians.[7]

Studies have suggested that headache is an atypical presentation of celiac disease, with good response to gluten-free diet (GFD).[8,9] Increased prevalence of celiac disease was found in a cohort of patients with migraine compared with controls in an Italian study.[2]

In the present study, we sought to investigate the prevalence of headache and migraine in celiac disease patients encountered in our clinics and local support groups by conducting a survey containing validated migraine evaluation instruments. Patients with inflammatory bowel disease (IBD) – either ulcerative colitis (UC) or Crohn's disease – and healthy controls were chosen for comparison.

METHODS

Subjects.—Subjects age 18 or older were recruited from the Celiac Disease Center at Columbia University, as well as celiac disease support groups in New York (Westchester and Suffolk Counties) and in California (Los Angeles and San Francisco). Patients with IBD were recruited from gastroenterology clinics at Mount Sinai Medical Center and New York-Presbyterian Hospital, both in New York City. Controls were recruited from the staff at Columbia University Medical Center (physicians, nurses, and administrative staff), as well as friends, relatives, and spouses of patients attending the hospital and support group meetings. Clients at a spa in Queens, New York, were also asked to serve as controls for this study. Survey forms were distributed in common areas in the said locations and dropped off in anonymous drop boxes after completion. No identifying information was collected as part of the survey. There was no financial compensation for the study. All participants signed Institutional Review Board (IRB)-approved informed consent forms.

Data Collected.—Data were collected between April 2010 and September 2011. Participants filled out a 4-page questionnaire. Data on age, sex, medical conditions, current medications, alcohol, coffee, and illicit drug use were collected. Diagnoses of celiac disease and IBD were self-reported, and were defined as the presence of positive serology and/or biopsy in celiac disease, and the presence of biopsy/colonoscopy, barium enema, or upper gastrointestinal (GI) series in IBD. Participants answered questions on method of diagnosis of celiac disease or IBD, type of IBD, date of celiac disease/IBD diagnosis and adherence to GFD, years on GFD if applicable, as well as any other dietary restrictions. Respondents without biopsy or serology-proven celiac disease were given the option to classify themselves as gluten-sensitive (GS).

All survey responses pertaining to medical problems and current medication use were reviewed, with particular attention to anxiety/depression and use of selective serotonin re-uptake inhibitors/other psychiatric medications, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, trazodone, contraceptives, or hormone replacement therapy (HRT), as these are known contributors to migraine headaches.

Subjects were asked if they experienced frequent headaches, and if they had been diagnosed by a physician with any of the following: migraine, tension headache, cluster headache, hemicrania continua, or trigeminal neuralgia. Those who reported chronic headaches completed the ID-Migraine tool,[10] a validated survey that has been shown to be highly sensitive and specific in the diagnosis of migraine, with a positive predictive value of 0.93.[10] The Headache Impact Test (HIT-6) was used to assess the degree of headache-related disability among the subjects who tested positive on the ID-Migraine test. HIT-6 is a 6-question survey shown to be a reliable screening tool in monitoring patients or in clinical research, and has been validated in 27 countries.[11]

Statistical Design and Analyses.—This study was conducted as a cross-sectional survey of clinic and support group patients with celiac disease and IBD, as well as a convenience sample of controls, consisting of friends, family and spouses of patients, hospital employees, and spa clients in New York City.

The chi-square test and Fisher's exact test were used to compare proportions, and the Student's *t*-test and analysis of variance to compare continuous variables. Logistic regression was used to assess for an association between headache severity, as measured by the HIT-6 test, and duration of GFD (in years) among subjects with celiac disease who suffered migraine headaches.

In the earlier analysis, GFD duration was treated as a continuous variable, and headache severity as a dichotomous variable, defined as an HIT-6 score of ≥4.

Multivariate logistic regression was performed to test for independent associations among celiac disease, GS, IBD, and the presence of migraines. The outcome, migraine disorder, was defined as a positive score on the ID-Migraine questionnaire (2 out of 3 questions answered with "Yes"). The following covariates were included in the multivariate model a priori: gender, age group (18-30, 31-50, 51-65, >65), the presence of depression/anxiety, use of opioids or NSAIDs/trazodone, and use of oral contraceptive pills (OCP) or HRT.

All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). *P* values less than .05 were considered statistically significant. All reported *P* values are 2-tailed.

The study was approved by IRBs of Columbia University Medical Center and Mount Sinai Medical Center.

RESULTS

Study Participants.—Seven hundred twenty-eight adults were enrolled in this study – 281 subjects with celiac disease; 38 subjects claimed non-celiac GS and were studied separately (GS); 151 subjects with IBD, of which 84 (56%) had Crohn's disease, 55 (37%) had UC, and the remaining 12 did not report the type of IBD. All IBD patients were analyzed together. There were 243 controls. Fifteen additional subjects had dual diagnoses (7 with celiac disease and IBD, and 8 with GS and IBD).

Exclusion Criteria.—Subjects with past medical history of a disorder, commonly contributing to headache such as head trauma, brain tumor, neck injury and chronic neck pain, vision problems uncorrected by glasses, vascular problems in the head and neck, lumbar puncture within the past 3 years, and past surgeries of the head and neck, were excluded from analysis. The 15 subjects who had dual diagnoses (as described earlier) were also excluded from analysis. Subjects who reported alcohol consumption exceeding 14 drinks per week or failed to report the number of alcoholic drinks per week were also excluded. Additionally, subjects who reported consuming more than 4 cups of coffee per day or failed to report daily caffeine consumption were excluded. Subjects who reported any current drug use were also excluded (Figure).

Group Characteristics.—Of the 728 enrolled subjects, 502 met exclusion criteria and were analyzed (178 controls, 188 celiac disease, 25 gluten intolerance, and 111 IBD). The study groups differed significantly in gender ($P < .0001$) and in mean age ($P < .0001$). Sixty-two percent of the controls were women compared with 79% of celiac disease, 84% of the GS, and 52% of the IBD groups. While the celiac disease, GS, and control groups were similar in age, the IBD group was significantly younger (Table 1).

The groups also differed significantly in rates of hormone use, defined as OCP, patch, or HRT, with the celiac disease and GS groups being significantly higher ($P < .0001$). There was no significant difference among the 4 groups in rates of anxiety and depression, opioid, NSAID, or trazodone use.

Headache Results.—All 3 patient groups – celiac disease, GS, and IBD – reported significantly higher prevalence of chronic headaches compared with controls. The GS group reported the highest rates of chronic headaches (56%), followed by celiac disease (30%), IBD (22%), and control (14%) groups. (Table 2).

There was a significantly higher prevalence of migraine by ID-Migraine criteria in the GS and celiac disease groups (40% and 21%, respectively)

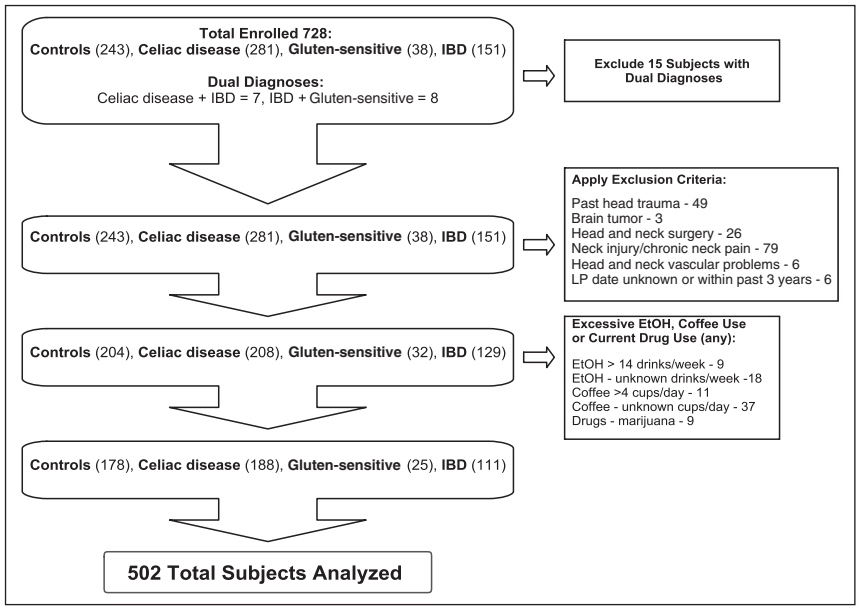

Figure.—Enrollment flowchart. IBD = inflammatory bowel disease; LP = lumbar puncture.

Table 1.—Subject Characteristics

	Controls (n = 178)	Celiac Disease (n = 188)	Gluten-Sensitive (n = 25)	IBD (n = 111)	*P* value
Sex = female (%)	109 (62%)	150 (80%)	21 (84%)	58 (52%)	<.0001
Age (mean)	47.8	45.3	49.5	36.5	<.0001
Depression/anxiety	16 (9%)	31 (16%)	4 (16%)	10 (9%)	.0987
Use of opioids/NSAIDs/trazodone	3 (2%)	6 (3%)	1 (4%)	6 (5%)	.3772
OCP or HRT use	4 (2%)	29 (15%)	4 (16%)	6 (5%)	<.0001

HRT = hormone replacement therapy; IBD = inflammatory bowel disease; NSAID = nonsteroidal anti-inflammatory drug; OCP = oral contraceptive pill.

Table 2.—Headache Results – Self-Reported and ID-Migraine Criteria

	Controls (C)	Celiac Disease (CD)	Gluten-Sensitive (GS)	IBD	*P* value
Chronic headaches	25 (14%)	57 (30%)	14 (56%)	25 (23%)	<.0001
Migraine	13 (7%)	40 (21%)	12 (48%)	11 (10%)	<.0001
Tension headache	11 (6%)	24 (13%)	5 (20%)	8 (7%)	.0362
Cluster headache	1 (<1%)	4 (2%)	1 (4%)	3 (3%)	.2448
Hemicrania continua	0	1 (<1%)	0	1 (<1%)	.7343
Trigeminal neuralgia	0	1 (<1%)	0	1 (<1%)	.7343
Migraine disorder (ID-Migraine criteria)	10 (6%)	40 (21%)	10 (40%)	15 (14%)	<.0001

Migraine disorder (by ID migraine criteria) in CD vs C: $P < .0001$; IBD vs C: $P = .0211$; GS vs C: $P < .0001$; GS vs CD: $P = .0464$; IBD vs CD: $P = .0941$; GS vs IBD: $P = .0042$.
IBD = inflammatory bowel disease.

Table 3.—Multivariate Logistic Regression of Independent Predictors of Migraine Disorder

	OR	95%CI	*P* value
Sex			
Male	1.0	(ref)	(ref)
Female	2.69	1.27-5.70	.0101
Age group			
18-30	1.0	(ref)	(ref)
31-50	1.13	0.58-2.20	.7194
51-65	0.94	0.45-1.96	.8622
>65	0.11	0.01-0.85	.0345
Depression/anxiety	2.55	1.31-4.96	.0059
Use of opioids/NSAID/trazodone	1.93	0.59-6.30	.2766
OCP or HRT use	1.29	0.58-2.84	.5352
Control	1.0	(ref)	(ref)
CD vs control	3.79	1.78-8.10	.0006
GS vs control	9.53	3.24-28.09	<.0001
IBD vs control	2.66	1.08-6.54	.0328

CD = celiac disease; CI = confidence interval; GS = gluten-sensitive; HRT = hormone replacement therapy; IBD = inflammatory bowel disease; NSAID = nonsteroidal anti-inflammatory drug; OCP = oral contraceptive pill; OR = odds ratio; ref = reference value.

compared with controls (6%), $P < .0001$. The IBD group also reported significantly higher prevalence of migraine (14%) compared with controls ($P = .0211$).

Multivariate Analysis.—A multivariate logistic regression analysis was performed to assess independent predictors of migraine disorder (Table 3). Female sex ($P = .0101$), depression or anxiety ($P = .0059$), celiac disease ($P = .0006$), GS ($P < .0001$), and IBD ($P = .0328$) were all independent predictors of migraine. Conversely, age >65 ($P = .0345$) had a protective effect (odds ratio 0.11).

Migraine Severity/HIT-6.—Of the subjects who met the ID-Migraine criteria for migraine, patients with celiac disease were most severely afflicted, based on the HIT-6 – 72% scored as "very severe" headache impact compared with 60% of the IBD group, 50% of the control group, and 30% of the GS group, with a trend toward statistical significance (Table 4).

Effect of GFD.—In the celiac disease and GS groups, duration of GFD in years was not a predictor of headache severity (Table 4). Eight of the celiac disease patients on a GFD reported that their past migraines improved significantly since the diet was adopted (Table 5). As these patients denied current migraines, they were not considered to have migraine in the analysis.

DISCUSSION

This study suggests that patients with celiac disease report increased headache prevalence compared with controls without known celiac disease. Recent international studies have also described higher rates of headaches in celiac disease compared

Table 4.—Headache Impact Test (HIT-6) Score Among Migraineurs in All Groups

	Number of Subjects Meeting ID-Migraine Criteria			
HIT-6 Score	Controls (n = 10)	Celiac Disease (n = 39)†	Gluten-Sensitive (n = 10)	IBD (n = 15)
1-Little/no impact	2 (20%)	3 (7.7%)	0	0
2-Some impact	3 (30%)	4 (10.3%)	6 (60%)	3 (20%)
3-Substantial impact	0	4 (10.3%)	1 (10%)	3 (20%)
4- Very severe impact*	5 (50%)	28 (71.8%)	3 (30%)	9 (60%)
GFD duration (in years) as a predictor of HIT-6 score of 4				
	N/A	OR 1.01 95%CI 0.81-1.26 *P* = .9482	OR 4.26 95%CI 0.33-54.62 *P* = .2660	N/A

*$P = .0919$.
†One patient with migraine disorder was excluded from this analysis due to lack of HIT-6 score.
CI = confidence interval; GFD = gluten-free diet; IBD = inflammatory bowel disease; N/A = not applicable; OR = odds ratio.

Table 5.—Patient Reports of Headache Improvement on GFD

Case	Age	Sex	PMH	Current Medications	Celiac Disease Diagnosis	Years on GFD	Past Chronic HA	Current Chronic HA	Patient Comments
1	56	F	–	–	10/2006	4	Yes	"Not anymore"	"I had severe chronic headaches my entire way until I was diagnosed [with celiac disease] in October 2006, age 52. And now, I only get a headache when I need to eat (resulting from a 'blood' sugar level)."
2	42	F	Dermatomyositis, lymphocytic colitis, anemia, osteoporosis	Iron supplement, Ca + Vit. D, multivitamin	9/2009	2	Yes	"Not anymore"	"I used to get chronic headaches before GFD, not anymore."
3	46	F	–	–	2004	6	Yes	"No"	"I used to get migraine a lot before going GF."
4	49	F	Hypertension, hypothyroidism, arthritis, insomnia, anxiety	Labetalol, Celebrex, Ambien	8/2003	7	Yes	"Not so bad anymore on GF diet"	At time of CD diagnosis "Chronic headaches, abdominal bloating, pain, chronic diarrhea" She suffered chronic headaches in the past."
5	61	F	Hypertension	Metoprolol	2/2005	5	Yes	"No"	"Migraines ended within 1 year of diagnosis."
6	52	F	GERD	Vitamins	1997	1	Yes	"No"	"Headaches for months years ago"
7	74	F	Hypothyroidism, psoriasis, osteoporosis	Levoxyl	6/2008	2	Yes	"Greatly improved"	"Note: I had severe migraine headaches for 60 years. Since starting the gluten-free diet 2 years ago, my severe migraines stopped. Now I occasionally have a migraine or tension headache but it is far less severe and can be remedied usually with cold compress and rest."
8	47	F	–	–	4/2006	4	Yes	"No"	"Not anymore since eating gluten-free diet. If accidentally served gluten (eg, cross-contamination), I get a headache within 15-30 minutes."

GERD = gastroesophageal reflux disease; GFD = gluten-free diet; HA = headache; PMH = past medical history.

with controls in both pediatric[8,9] and adult[2] subjects. We used screening criteria for migraine contributors, including past medical history, present medical conditions, medication use, alcohol and coffee consumption, and illicit drug use. After applying the described exclusion criteria and screening all reported headaches with the ID-Migraine questionnaire, we found a 21% prevalence of migraine in the celiac disease group. The 2 published studies investigating the prevalence of headache in adults with celiac disease were from Italy and showed widely different results: Cicarelli et al[2] reported 32% prevalence of migraines compared with only 5.6% reported by Briani et al.[12]

We chose to use patients with IBD as another control group with GI disease, and found a significantly increased prevalence of headache and migraine in this group, similar to the celiac disease group. Little is known about the prevalence of headache and other neurological symptoms in patients with IBD. Most of the neurological manifestations of IBD appear to be related to cerebral vasculitis, causing a hypercoagulable state that could manifest as headache.[13-15] Cases of peripheral neuropathy, myelopathy, myopathy, myasthenia gravis, and stroke have been described.[15,16] Additionally, there may be an increased prevalence of demyelinating diseases, such as multiple sclerosis and optic neuritis in IBD.[17]

Headache was found to be the most common neurological complaint among IBD patients in a Brazilian study,[18] with a self-reported prevalence of 54.8% and 56.9% among Crohn's and UC patients. Twenty-five percent of these headaches were determined to be migraines, with migraine rates of 13% for Crohn's disease and 14% for UC.[18] Our findings of 14% prevalence of migraine in the IBD group are similar.

Our study is the first to survey the prevalence of headaches in US adults with celiac disease and IBD. The available publications to date have studied pediatric and adult populations in Europe, Israel, and South America, and vary greatly in the method of diagnosis, sample sizes, and types of controls used (if any) (Table 6).

It is not surprising that the celiac disease and IBD groups were somewhat discrepant in sex and age, as this reflects these diseases' demographics. Women predominated in the celiac disease group. According to a recent study,[19] the overall prevalence of undiagnosed celiac disease in a northern American population is 0.8% (ranging from 0.6% to 1.1%), depending on age group, with 65% of patients being women. Women typically account for more outpatient care visits than men, with 60.5% of primary care visits in 1994.[20] In contrast, IBD affects roughly equal percentages of men and women, which was reflected in our IBD cohort. While the highest prevalence of IBD appears to be among people in their 40s and 50s, increasing numbers of patients are diagnosed earlier in life,[21] which may account for the significantly lower age of the IBD group in our study. The higher rates of OCP/HRT use in the celiac disease and GS groups are likely attributed to the higher percentages of women participants.

Using multivariate regression analysis, we found age and female sex to be independent predictors of migraine. These findings are expected as migraine is 3 times more common among US women compared with men – 18.2% and 6.5% prevalence, respectively – as reported by the American Migraine Study.[22] Our finding that age >65 has some protective effect against migraine is consistent with prior epidemiological studies showing an overall decline in migraine prevalence in women older than 65.[23] There is significant psychopathology associated with headache, as reviewed by Green.[24] Our finding that depression and anxiety are independent predictors of migraine is well established in the literature.[24,25]

Interestingly, while both celiac disease and IBD were independent predictors of migraine, we did not find a significant difference in the prevalence of migraine between the celiac disease and IBD groups ($P = .0941$). It is unclear why celiac disease and IBD groups both have higher prevalence of migraine headache compared with controls. Abdominal complaints, regardless of their etiology, have been associated with depression, somatization, conversion disorders, and headaches.[26,27] The presence of abdominal complaints in both celiac disease and IBD may be a factor in the increased incidence of headache in these patient populations. The question still remains whether there are any mechanistic differences of migraine pathogenesis between celiac disease and IBD.

Table 6.—Overview of Publications on Headache Prevalence in Patients With Celiac Disease and Inflammatory Bowel Disease (IBD)

Authors	Population Studied	Method of Diagnosis	Prevalence of HA in CD Group	Controls	Prevalence of HA in Controls	Statistical Significance
Arroyo et al 2002[40]	32 Argentinian children with CD, seizures, and occipital calcifications	Modified ESPGHAN criteria: Antibodies Jejunal biopsy	42.4% headache "migraine-like"	–	–	–
Briani et al 2008[12]	71 Italian adults with CD	Jejunal biopsy	5.6% headache	–	–	–
Cicarelli et al 2003[2]	176 Italian adults with CD	Antigliadin antibodies Antiendomysial antibodies Jejunal biopsy	46% headache 32% migraine	52 age-matched controls	29% headache 25% migraine	Yes ($P < .05$) (headache) No (migraine)
Hadjivassiliou et al 2001[32]	10 British adults with gluten sensitivity and CNS white matter changes on MRI	Antigliadin antibodies HLA DQ2 or DQ8	60% headache	–	–	–
Lionetti et al 2009[9]	354 Italian children with CD	Modified ESPGHAN criteria: Antibodies Jejunal biopsy	24.8% headache	200 age- and sex-matched controls	8% headache	Yes ($P < .001$)
Zelnik et al 2004[8]	111 Israeli children with CD	Antiendomysial IgA antibodies Jejunal biopsy	27.9% headache 12.6% migraine	211 age- and sex-matched controls	8.1% headache –	Yes ($P < .01$) (headache) –

Authors	Population Studied	Method of Diagnosis	Prevalence of HA in IBD Group	Controls	Prevalence of HA in Controls	Statistical Significance
Lossos et al 1995[15]	638 Israeli adults with IBD	Upper and lower GI biopsy	1 patient with headache	–	–	–
Oliveira et al 2008[18]	82 Brazilian adults with Crohn's or UC	Upper and lower GI biopsy	54.8% headache in Crohn's (13.7 migraine) 56.9% headache in UC (14.2% migraine)	–	–	–

CD = celiac disease; CNS = central nervous system; ESPGHAN = European Society of Pediatric Gastroenterology, Hepatology and Nutrition; GI = gastrointestinal; HA = headache; IBD = inflammatory bowel disease; MRI = magnetic resonance imaging; UC = ulcerative colitis.

There may be a generalized inflammatory response triggering migraine in both celiac disease and IBD. There is considerable research on the inflammatory aspects of migraine. Specifically, inflammatory reactants, such as CRP, MMP-9, cytokines, adhesion molecules NF-kB, and iNOS, have all been implicated in migraine.[28-31] Conversely, 2 distinct mechanisms may be responsible for the neurological symptoms (including migraine) in celiac disease and IBD. It is possible that in celiac disease, there is a direct gluten effect, mediated by antigliadin antibody cross-reactivity, in contrast to a generalized inflammatory response in IBD.

Few studies have addressed the underlying mechanisms linking celiac disease and migraine. In a 10-patient case series of patients with celiac disease and migraine headaches, Hadjivassiliou et al reported a possible association among white matter lesions, serum antigliadin antibodies, and the presence of HLA DQ2.[32] Nine of the 10 patients responded to GFD, and 7 of the 10 migraines resolved completely. How these cross-reactivity targets and demyelinating processes are implicated in migraine mechanistically remains to be elucidated because most patients with celiac disease have both antigliadin antibodies and HLA DQ2.

In contrast to these results, a recent study of neurological complications in celiac disease by Briani et al found no clear correlation between the presence of neurological dysfunction and the presence of central nervous system antineuronal antibodies in rat cerebellar sections when tested by immunohistochemistry and Western blot.[12] These findings imply that neurological complications in celiac disease may be caused by a general inflammatory response, rather than directly antibody-mediated. The finding of increased migraine in IBD patients lends support to the role of inflammation in the pathogenesis of migraine in this population.

Our study did not demonstrate the well-established associations between OCP/HRT and migraine,[33-35] nor between the frequent use of opioids, NSAIDs and trazodone, and migraine.[36,37] The low number of subjects who reported taking the said medication prevents us from drawing meaningful conclusions about a possible association with migraine.

Multiple authors have described a positive effect of GFD on neurological symptoms in celiac disease, including reduction of occipital calcifications and improvement in headache severity.[2,9,38,39] All the surveyed participants with celiac disease reported being on a GFD, including those with migraine headaches. There was no correlation between the duration of GFD (in years) and headache severity as measured by the HIT-6, suggesting that GFD is not protective against the development of migraines in celiac disease patients. This contradicts the findings of Gabrielli et al,[39] who showed that, 6 months after initiation of GFD, migraine patients with celiac disease had either resolution of headaches or an improvement in the frequency, duration, and intensity of migraine. In our survey, we asked subjects to report only current headaches and did not collect a detailed migraine history. Therefore, we could have missed improvement in headache symptoms following the initiation of GFD. Of note, 8 study participants reported complete resolution or great improvement in migraine headaches after the initiation of GFD (Table 5). These subjects entered their comments as free text on the survey forms. Such reports suggest a therapeutic value of GFD in celiac disease patients afflicted with migraines.

Our data on migraine severity showed that more celiac disease patients (72%) experienced "very severe impact" migraines as measured by the HIT-6 compared with 50% of controls. While this difference is not statistically significant, it raises the possibility of a more severe migraine phenotype in celiac disease. The daily ingestion of wheat allergens could contribute to migraine severity, either by increased antibody generation or by causing continuous generalized inflammatory response.

The fact that groups are not matched for age and sex is one of the limitations of this study. There was a convenience sample selection bias in subject enrollment. The subject characteristics reflect the differing demographics of patients with celiac disease and IBD, which lead to discrepancies in age, sex, and OCP/HRT use among the 4 groups, and inability to match for age or sex. A multivariate analysis was performed in order to eliminate the effect of these sample disparities. There was a convenience sample selection

bias in the control group as well. While the said selection bias prevents the free application of our findings to the general patient populations with celiac disease and IBD, we believe that further investigation with larger sample sizes is warranted.

The collected information on headaches included only current presence/absence of headaches, without a full headache history (age of onset, duration prior to initiation of GFD, etc). Many more subjects in each group reported the presence of chronic headaches compared with how many met the ID-Migraine criteria. While most frequent headaches represent undiagnosed migraine, without the benefit of a neurological exam and full migraine history, we only used the ID-Migraine survey to identify how many of the chronic headaches reported were migraines, and we may have underestimated the incidence of migraine in all 4 groups.

As this was a self-reported study, we could not monitor and assess dietary compliance to GFD beyond subject report. Because of the paucity of publications and the increasing recognition of GS, we were interested in examining the GS group separately, even though subjects were classified as GS entirely on the basis of self-report, in the absence of celiac disease diagnosis. This group reported the highest frequency of headache and migraine among all groups.

CONCLUSION

In summary, we have shown that patients with celiac disease have increased prevalence of migraine headaches compared with healthy controls. Interestingly, the prevalence of migraine among patients with IBD is similar to that of celiac disease patients. This may imply a general migraine-generating inflammatory mechanism common to both celiac disease and IBD; however, we cannot rule out the presence of a gluten antibody-mediated mechanism of migraine in celiac disease. While there is no correlation between duration of GFD and migraine severity, some patients reported migraine improvement or resolution following onset of GFD. The migraines experienced by celiac disease patients appear to be more debilitating compared with those in the other groups, and thus may represent a separate phenotype. Future studies should test migraine patients for celiac disease, particularly those with severe and treatment-resistant headaches. The effects of GFD on US celiac disease patients with migraine should be studied in an interventional study.

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