Headache in Patients with Celiac Disease and Its Response to the Gluten-Free Diet

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Aims: To describe headache characteristics among celiac disease (CD) patients and to analyze the relationship between CD and headache. **Methods:** An online survey analyzing the characteristics of headache and its response to the gluten-free diet (GFD) in celiac patients was published on Argentinean Celiac social networks, open to the public to complete. The results were analyzed using chi-square test or Mann-Whitney test accordingly. **Results:** A total of 1,517 subjects completed the survey, and 866 (55.2%) met the inclusion criteria (headache and CD confirmed with positive biopsy). The subjects were predominantly female (94.5%) and had a median age of 39 ± 11.27 years. Tension-type headache was the most prevalent headache type (52%), followed by migraine without (32.5%) and with aura (15.4%), respectively. Of the included participants, 24% reported headache as the main symptom that resulted in the diagnosis of CD. Following initiation of GFD, headache frequency and intensity improved significantly more in participants with migraine than tension-type headache ($P = .02$ and $P = .013$, respectively). Compliance to GFD was higher among subjects with severe manifestations (77% vs 66%, $P = .05$), and compliant individuals showed a 48% improvement in headache frequency ($P = .049$). An association between food transgressions and headache was better recognized by migraineurs ($P = .02$). **Conclusion:** These results suggest that strict compliance to the GFD could improve headache in celiac patients with headache, even in those without gastrointestinal symptoms. This observation could provide an additional factor when convincing patients to follow a GFD, thus reducing the morbidity related to CD.
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Keywords: *celiac disease, gluten, gluten-free diet, headache, migraine, migraine with aura*

Celiac disease (CD) is a systemic autoimmune illness triggered by gluten, a protein complex found in wheat, barley, and rye. This disease develops in genetically predisposed people (HLA DQ2 and -DQ8 genes) in any age range. The spectrum of gluten disease is wide and includes CD, gluten sensitivity (gastrointestinal [GI] symptoms after gluten intake without positive antibodies or biopsy diagnosis), and gluten allergy (confirmed by allergy testing).[1,2] The diagnosis of CD requires a bowel biopsy with histopathologic analysis using the Marsh score (with which results are considered to be positive with a score of IIIA or more), positive antibodies (anti-transglutaminase, anti-endomysial, anti-deamidated gliadin peptides, and anti-gliadin), and may include a molecular biology test (HLA DQ2 and -DQ8).[2] The worldwide prevalence of CD is about 0.6% to 1.0%,[1,3,4] and it is more frequent in women than in men (1.5:1 to 2:1).[1] Argentina seems to share the same prevalence (1.26% [1:79; 95% confidence interval [CI] 0.84 to 1.81) and female predominance.[5] Clinical manifestations are more evident in pediatric patients than in adults, with the former frequently developing GI symptoms such as abdominal distention, nausea, vomiting, diarrhea, and weight loss, and the latter tending to be frequently oligosymptomatic (just presenting anemia, asthenia, or hypocalcemia) or even asymptomatic in some cases.[1]

Since CD presentation can be diverse, arriving at an accurate diagnosis can be challenging. Indeed, it has been hypothesized that for every patient diagnosed with a symptomatic CD, a great number of subjects remain undiagnosed or asymptomatic. However, there has been a dramatic increase in the number of patients diagnosed with CD during the last 50 years. Previous studies have determined that undiagnosed patients with positive antibodies have a 2- to 4-times greater risk of mortality than the general population,[6,7] although another study failed to replicate these findings.[8]

The main treatment for CD is the gluten-free diet (GFD), which must be followed thoroughly every day. Gluten is a key ingredient in many different foods and beverages (bread, pasta, beer, whiskey, etc), and many products contain flour or may undergo gluten contamination during the manufacturing process. Hence, maintaining the GFD is not an easy task. Any kind of gluten consumption can potentially damage the intestinal mucosa; as little as 10 to 50 mg per day can cause intestinal mucosa injury.[1] The association between CD and neurologic symptoms was first described in 1966 by Cooke and Smith, who paid special attention to gluten ataxia.[9] In 1996, Hadjivassiliou et al calculated that the prevalence of neurologic manifestations related to CD varied from 5% to 8%[10]; however, in 2001, another study reported a higher prevalence of 8% to 36%.[11] The most frequent neurologic symptoms associated with CD are gluten ataxia and peripheral neuropathy.[9,12–14] Nowadays, a great number of different clinical manifestations are considered to be related to CD, including epilepsy,[15] occipital calcifications,[15] myoclonus, cognitive impairment,[16] dementia,[16] myopathy,[17] and the one that motivated this study: headache.[18]

There are few papers addressing the association between CD and headache, especially in adults.[18–23] These studies reported that the prevalence of CD in patients with migraine is four times higher than that of the general population worldwide,[18] that more CD patients suffer headache than healthy subjects (21% to 6%, respectively),[18] that a majority of CD patients (72%) experience migraine as being of "very severe impact" (as measured by the Headache Impact Test [HIT-6]) compared to 50% of controls, and that CD was an independent predictor for migraine ($P < .001$).[18] A substantial percentage of the CD patients had either chronic headache (n = 57, 30%) or migraine (n = 40, 21%), while a low percentage had tension-type headache (TTH) (n = 24, 13%).[18]

Gabrielli et al reported headache improvement following the GFD.[19] However, the efficacy of the GFD in headache amelioration is still controversial and poorly studied. A case report described a patient whose first manifestation of CD was headache (migraine with aura [MWA] and nausea, vomiting, and anemia). Her symptoms responded well to the GFD.[20]Additionally, Bürk et al observed a decrease in the frequency and intensity of headache after the introduction of a GFD in 28% of the patients (20 of 72).[21] Finally, a large, recently published study reported an increased risk (1.66-fold) of headache-related visits of patients after CD diagnosis compared to controls[22]; however, the GFD response was not assessed in this study, as was later pointed out by Petrarca and Nenna in a letter to the editor.[23] Of note is that prospective or case-control studies with a representative number of adults are lacking and that the papers published to date[18–23] have analyzed patients with different kinds of intestinal disorders, such as inflammatory bowel disease, CD with or without bowel biopsy confirmation, and gluten sensitivity. The contention is that these patients present different aspects of the disease and therefore do not behave in the same manner. Biopsy confirmation is very important in this regard.

The objectives of this study were to describe the characteristics of headache among CD patients, to recognize headache as a possible potential clinical manifestation of CD, and to analyze the relationship between CD and headache, as well as to acknowledge the impact of the GFD on headache to appraise this relationship. Since clinical manifestations of CD are variable, it seems especially interesting to define the characteristics of headache in patients with CD, as this can provide information to decide whether to exclude CD in patients consulting with headache. To the best of the authors' knowledge, this is the first research project focusing on the response to the GFD with a considerable number of adult patients with headache and CD confirmed by intestinal biopsy.

Materials and Methods

An online survey was developed consisting of 35 questions addressing demographic data, features of headache (location, type, intensity measured with a numeric rating scale [NRS] of 1 to 10, frequency, duration, presence of aura, incapacity scale [MIDAS[24]], triggers, familial history, treatment, and whether headache appeared before the diagnosis of CD was made); characteristics of CD (age of diagnosis, positive or negative antibodies, last antibodies test, familial history of CD, duodenal biopsy result, histologic classification [Marsh scale], reasons that resulted in the diagnosis of CD, years following the GFD, presence and frequency of transgressions); and the response to the GFD for the different types of headache (regarding intensity, frequency, and duration after following the GFD and if the subject noticed a relationship between gluten intake and headache). Subjects were

1. Birthdate:

2. Sex:
   a. F
   b. M

3. Do you usually have headaches?
   a. Yes
   b. No

4. Since how long have you been suffering from headache?
   a. < 10 years
   b. 10-20 years
   c. 20-30 years
   d. 30-40 years
   e. 40-50 years
   f. > 50 years

5. How long do the episodes of headache last?
   a. < 30 minutes
   b. 30-4 hours
   c. 4-24 hours
   d. > 24 hours

6. On a scale of 1 to 10, where 1 is pain of mild intensity and 10 is pain of severe intensity, mark the intensity of your pain.

Very mild 1 2 3 4 5 6 7 8 9 10 Very severe

7. How would you describe your pain as?
   a. Pulsatile
   b. Stitches
   c. Oppressive
   d. Pulsatile and oppressive

8. Which part of the head hurts?
   a. The whole head
   b. Right or left half
   c. Forehead
   d. Eyes
   e. Hindhead

9. When you have pain, is it accompanied by one or more of the following symptoms?
   a. Nausea or vomiting
   b. Discomfort with light (Photophobia)
   c. Abdominal pain
   d. Discomfort with loud sounds
   e. It is not accompanied by any additional symptoms

10. How many days per month do you have pain?
   a. 1-4 days
   b. 5-9 days
   c. 10-14 days
   d. > 15 days

11. Have you ever experienced transient symptoms such as seeing lights or spots of colors or dark; tingling or weakness of a limb; or difficulty speaking before an episode of headache?
   a. Yes
   b. No

12. If you had them, how long did they last?
   a. < 5 minutes
   b. 5- 60 minutes
   c. > 60 minutes

13. Do you recognize factors that trigger your headache?
   a. Lack of sleep
   b. Fasting
   c. Stress
   d. Types or special food
   e. Hormonal changes

14. How many days have you had to miss work or place of study because of the headache in the last three months?

15. How many days do you think your work or study performance has been reduced by half or more in the last three months due to headache?

16. How many days have you been unable to attend social or leisure activities in the last three months due to headache?

17. Do you have relatives who suffer from headache?
   a. Yes
   b. No

18. Have you ever had a brain image (tomography or magnetic resonance imaging)?
   a. Yes, normal
   b. Yes, abnormal or pathological
   c. No

19. What treatment do you use for pain?

20. Do you have a diagnosis of celiac disease?
   a. Yes
   b. No

21. At what age were you diagnosed with celiac disease?

22. Why did you consult a doctor?
   a. Gastrointestinal symptoms (diarrhea, vomiting, abdominal pain, bloating)
   b. Fatigue
   c. Anemia
   d. Weight loss
   e. Familiar screening
   f. Headache
   g. Other neurological symptoms

23. Did you have positive antibodies at the time of diagnosis?
   a. Yes
   b. No

24. Have you been diagnosed with celiac disease by biopsy (endoscopy)?
   a. Yes
   b. No

25. Do you remember the histological classification (Marsh)?

26. Do you have celiac relatives?
   a. Yes
   b. No
   c. I do not know

27. When was the last antibodies level determination?
   a. < 6 months
   b. 6 months to 5 years
   c. > 5 years

28. Do you remember the results?
   a. Positive
   b. Negative
   c. I do not remember

29. How many days per month do you incur in food transgressions or you do not comply with the gluten-free diet?
   a. None, I do the strict diet
   b. Less than 5 days
   c. 5-15 days
   d. More than 15 days
   e. Every day

30. Have you had headache before the diagnosis of celiac disease?
   a. Yes
   b. No

31. How did your headache behave in terms of intensity, after starting the gluten-free diet?
   a. Increased
   b. Without change
   c. Decreased

32. Was the frequency of headache modified with the gluten-free diet?
   a. Increase
   b. Without change
   c. Decrease

33. Did the duration of the headache change with the gluten-free diet?
   a. Increase
   b. Without change
   c. Decrease

34. Does the headache coincide with food transgressions?
   a. Yes
   b. No

35. And when you eat gluten?
   a. Yes
   b. No

Fig 1 Survey questionnaire.

asked directly about intensity, duration, and frequency of headache and whether it had increased, decreased, or presented no changes after starting the GFD. Intensity was rated on a 1- to 10-point NRS, where 1 corresponded to pain of mild intensity and 10 to pain of severe intensity. The questionnaire (Fig 1) was developed in collaboration with the Headache Section of the Neurology Department of the Raúl Carrea Institute for Neurological Research (FLENI), and its aim was to classify the different types of headache according to the International Classification of Headache Disorders, 3rd edition (ICHD-III)[25] to collect the characteristics of CD and the clinical response (headache modification) to the GFD.

The survey was published using Google Forms in May 2014 through June 2014 on the Argentinean Celiac Association's official Facebook page and in another celiac patients' social network (Argentinean celiac patients' Facebook page).

The resulting data were analyzed and submitted to an inclusion-exclusion filter. All subjects with defined CD (compatible pathologic anatomy analysis on duodenal biopsy) and headache were included. The different types of headache (TTH, MWA, and migraine without aura [MoA]) were classified according to the guidelines of the ICHD-III.[25] Subjects with no clear classification were subjected to a consensus of experts in headache (M.T.G. included) to address their classification, which was recorded accordingly.

Subjects whose headache was not classifiable were excluded, along with those with abnormal findings in computed tomography [CT] scans or magnetic resonance imaging [MRI]. Subjects under 18 years of age were also excluded.

The protocol was approved by the Raúl Carrea Institute for Neurological Research Ethics Committee and Institutional Review Board. All participants signed an informed consent form.

Statistical Analyses

The chi-square test and Fisher exact test were used to compare proportions, and Student *t* test and Mann-Whitney test were used to compare continuous variables. A P value ≤ .05 was considered significant. All statistical analyses were performed using Stata version 12.1 (Statacorp).

Results

During the 2-month period in which the survey remained available in the social networks, 1,569 subjects completed the form. A total of 1,142 (72.8%) reported being diagnosed with CD, and 1,015 (88.8%) met the criteria for a defined diagnosis (with compatible biopsy). Of these individuals, 969 (95.5%) reported having headache. Subjects under 18 years of age, those with a pathologic finding on head CT or MRI, those with unclassifiable headaches, and those with an incomplete form were excluded (n = 103).

Finally, 866 (55.2%) individuals met the inclusion criteria (headache and defined CD) with a median age of 39 ± 11.27 years. A female predominance was observed (819 women [94.5%], 46 men [5.3%], and 1 subject refused to provide sex) (Fig 2).

It was possible to classify the different types of headache in 604 (70%) subjects. The classification of the remaining 262 (30%) was obtained by consensus. A total of 452 subjects (52%, 425 women) met the criteria for TTH, 281 (32.5%, 268 women) for MoA, and 133 (15.4%, 126 women) for MWA.

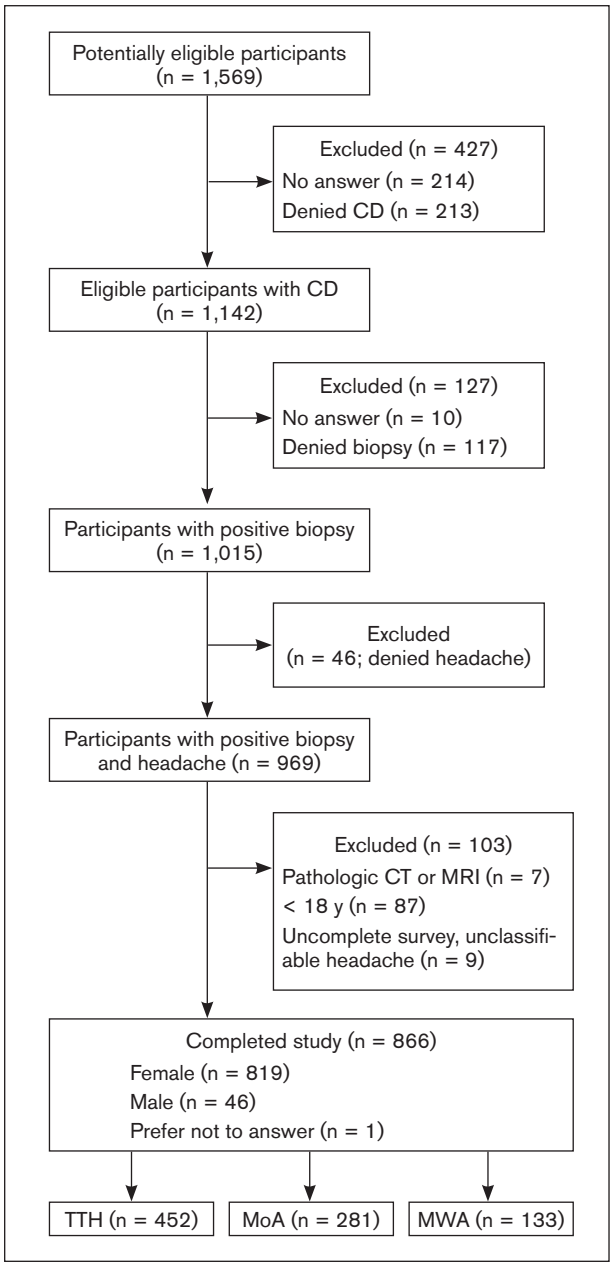

Fig 2 Enrollment flowchart. CD = celiac disease; CT = computed tomography; MRI = magnetic resonance imaging; TT = tension-type headache; MoA = migraine without aura; MWA = migraine with aura.

Most of the subjects reported suffering from headache prior to CD diagnosis: 77% of the subjects with TTH (n = 334); 87% of those with MoA (n = 239); and 84% of those with MWA (n = 107). Almost all of the headache sufferers reported recognizing specific headache triggers such as lack of sleep, hormonal changes, fasting, stress, and certain foods: 96% of TTH sufferers (n = 433); 93% of MoA (n = 262); and 98% of MWA (n = 130). The majority

Table 1 Characteristics of the Different Types of Headache in Celiac Patients

	TTH (n = 452)	MoA (n = 281)	MWA (n = 133)
Age at onset (y), n (%)			
< 10	52 (12)	44 (16)	20 (15)
10–20	102 (23)	90 (32)	41 (31)
20–30	142 (32)	89 (32)	34 (26)
30–40	100 (22)	33 (12)	27 (20)
40–50	44 (10)	19 (7)	8 (6)
> 50	10 (2)	6 (2)	3 (2)
Headache duration with painkillers			
30 min to 4 h	318 (70)	115 (41)	65 (49)
4 to 24 h	89 (20)	114 (41)	41 (31)
> 24 h	45 (10)	52 (19)	27 (20)
Intensity on 0–10 NRS, median	6	8	7
Frequency (headache days per month), n (%)			
1 to 4 d	246 (54)	121 (43)	52 (39)
5 to 9 d	106 (23)	87 (31)	38 (28)
10 to 14 d	49 (11)	34 (12)	24 (18)
> 15 d	46 (10)	34 (12)	17 (13)
Presence of triggers, n (%)	433 (96)	262 (93)	130 (98)
	117 (35)	120 (44)	102 (39)
	130 (39)	119 (44)	93 (36)
	63 (19)	55 (20)	46 (18)
	220 (66)	175 (64)	195 (75)
	94 (28)	98 (36)	69 (27)
Family with headache, n (%)	264 (59)	197 (72)	85 (66)
Headache before diagnosis of CD, n (%)	334 (77)	239 (87)	107 (84)
Age (y) at diagnosis of CD, median (range)	31 (1–75)	32 (1–63)	33 (1–80)
Accompanying symptoms, n (%)			
Nausea and vomiting	47 (10.4)	159 (57)	61 (46)
Photophobia	93 (20.6)	201 (72)	79 (59)
Phonophobia	133 (29.4)	184 (65)	75 (56)
Epigastric discomfort	61 (13.5)	35 (12)	30 (23)

TTH = tension-type headache; MoA = migraine without aura; MWA = migraine with aura; CD = celiac disease.

of subjects presented with episodic headaches (frequency of 1 to 14 days per month): 88.7% of TTH sufferers (n = 401); 86% of MoA (n = 242); and 85% of MWA (n = 114). Of the included subjects, 24% (n = 364) reported headache as the main symptom that resulted in the diagnosis of CD. Individuals with MWA primarily complained about headache, as well as other neurologic symptoms not related to headache, more often than those with TTH ($P < .001$) (Table 1).

Subjects with a strict GFD compliance tended to show negative antibodies in laboratory analyses more frequently than those with a low compliance to the GFD (52% vs 37%, $P = .03$). There was a lower percentage of subjects with positive antibodies among diet compliants than noncompliants (77% vs 87%, $P = .005$). Migraineurs reported high levels of improvement in headache frequency (MoA: improvement 52.4%, without changes 37.6%, and decrease 10%; MWA: improvement 46.1%, without changes 41.5%, and decrease 12.4%; $P = .02$) and intensity (MoA: improvement 49.6%, without changes 39.4%, and decrease 11%; MWA: improvement 46.2%, without changes 43%, and decrease 10.8%; $P = .013$) following initiation of the GFD that were higher than in TTH subjects (TTH frequency: improvement 41.6%, without changes 48.4%, and decrease 10%; TTH intensity: improvement 38.7%, without changes 48.7%, and decrease 12.6%) (Fig 3). Migraineurs showed improvement in headache frequency following initiation of the GFD regardless of whether they presented GI symptoms ($P = .025$).

A higher compliance to the GFD was observed in subjects with severe headache (77%) than in those with milder manifestations (66%) ($P = .05$). Subjects with MWA who reported high compliance to the GFD showed 48% improvement in headache frequency vs noncompliant subjects (38.7%) ($P = .049$). An association between food transgressions and headache was also better recognized by migraineurs ($P = .02$). No statistical significance according to the MIDAS scale[24] was observed.

Discussion

CD is a systemic autoimmune disease that can affect any organ, not only the gut. Its clinical manifestation is variable, but new neurologic manifestations—such as headache—are being described.

The pathophysiologic mechanisms that may explain the relationship between gluten and neurologic manifestations are still unknown.[26] There are a number of potential mechanisms, including antibody cross-reaction,[13] systemic toxicity, or vitamin deficiency due to intestinal malabsorption.[27] The most frequently studied neurologic manifestation accompanying CD is gluten ataxia, which is considered to be secondary to an antibody-mediated cross-reaction (antigliadin antibodies especially) against cerebellar Purkinje cells (ie, molecular mimetism).[13] CD patients may show cerebellar atrophy on MRI,[28] and some postmortem findings of patients with CD-associated ataxia include gliosis, atrophy, Purkinje cell loss, and degeneration of the posterior columns of the spinal cord.[9,28] However, a recently published study addressing neurologic complications in CD did not find a clear correlation between antibody reactivity and neurologic dysfunction.[29]

Previous studies reported that there is a higher prevalence of headache (especially migraine) among patients with CD,[19] as well as of CD in patients suffering from headache.[18] In addition, patients with CD have a higher risk of headache-related medical visits after CD diagnosis.[22] Although this study focused

on headache types (mainly migraine and trigeminal neuralgia) and headache-related visits, the response to the GFD and its adherence was not addressed.

Other studies analyzed patients with inflammatory bowel disease, CD, and gluten intolerance,[21] but, to the best of the present authors' knowledge, the present study is the first to enroll a high number of patients with CD (confirmed by bowel biopsy and positive antibodies) and headache, which seems to be an important aspect of this study. It is also the first whose aims were to describe the characteristics of headache in those patients and its response to the GFD.

Approximately one out of every four subjects reported headache as the main symptom resulting in the diagnosis of CD. This supports the hypothesis that CD should be considered when diagnosing patients with headache (especially migraine)[22,23] regardless of whether they have GI symptoms. Indeed, celiac patients can suffer from headache in the absence of GI symptoms.[20]

The vast majority of participants (90%) suffered episodic headache (only 10% reported chronic headache). These findings are in line with the lower prevalence (30%) of chronic headache sufferers reported by Dimitrova et al.[18] Moreover, in contrast to a previously published study,[18] there was a higher percentage of TTH sufferers in this study (52% vs 13%), as well as migraineurs (48% vs 21%). These differences are likely due to sample and methodologic differences.

In the present study, migraineurs showed a higher improvement in headache frequency and intensity following initiation of the GFD compared to TTH patients. Migraineurs also better recognized the association between food transgressions and headache. Why migraineurs report a significant improvement in headache frequency and intensity after following the GFD is still unclear. One possible explanation is that the GFD leads to a reduction in the intestinal inflammatory response, consequently reducing the circulating antibodies levels and decreasing the inflammatory response and systemic toxicity, with resulting improvement in nutrient absorption. Migraineurs seem to be more prone to this improvement compared to TTH patients. Prospective studies are required to determine if there is a causal relationship between headache and GFD and whether the GFD is really beneficial for the management of migraine.

Subjects referring greater improvement in headache were those with a lower percentage of positive autoantibodies, and these were also the subjects who reported higher adherence to the GFD. Considering that approximately 10% of the general population suffers from migraine and that this represents one of the top four neurologic disorders with high annual costs (with 190 million working days lost every year in Europe), it cannot be exluded that adherence to a GFD could have a considerable impact on economics and public health. On the other hand, considering the possibility of the presence of CD in migraineurs could potentially help in diagnosing this disease early, therefore optimizing its treatment.

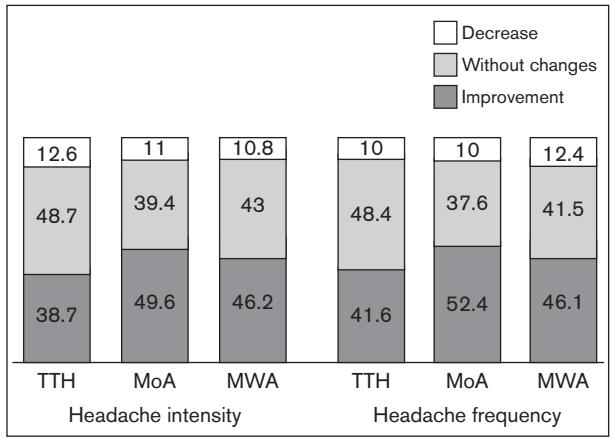

Fig 3 Percent improvement in headache frequency and intensity after following gluten-free diet (GFD). Migraineurs had higher levels of improvement in headache frequency (P = .02) and intensity (P = .013) following initiation of GFD compared to tension-type headache (TTH) patients. MoA = migraine without aura; MWA = migraine with aura.

Strengths of this study include the large sample and the inclusion of subjects only having both diagnoses and with the CD diagnosis supported by duodenal biopsy. A clinical implication of this study could be that the information that headache may decrease with adherence to the GFD may motivate CD patients to initiate or strictly follow a GFD, helping not only to improve this symptom but to prevent long-term complications as well.

The present study has several limitations. First, the investigated population had a high female predominance, which is likely due to two facts: the two diseases (headache and CD) are more frequent in women than in men, and women are more predisposed to complete online surveys.[30] Second, survey recruitment was an open invitation over social media, potentially oversampling more young and health-concerned individuals than older and less health-conscious individuals. Thus, the fact that subjects decided to participate could have introduced some selection bias. Third, headache classification and complementary workup analysis relied solely on the subject's reports and was not confirmed by a clinical examination, which could have led to classification errors. Moreover, aura analysis and its modification after the introduction of the GFD was not addressed. Fourth, the survey did not address other concurrent factors that could have led to headache

amelioration, such as changes in treatment, medical attention, or lifestyle changes. Finally, the prevalence of headache could not be estimated in this population, since it included only participants with both disorders.

Conclusions

The results suggest that strict compliance to a GFD could have a beneficial outcome among celiac patients with headache, even without GI symptoms. Patients with migraine responded better to the GFD than patients with TTH, reporting better improvement in headache intensity and frequency. This is a preliminary study showing that headache improves in subjects with CD in response to a GFD; however, more prospective studies are needed to confirm a causal relation between GFD and headache improvement.

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