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Review

Migraine as a Common Extra-Intestinal Presentation of Celiac Disease

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Abstract

Celiac disease (CD) is a common gluten-related enteropathy that presents several extra-intestinal manifestations. Migraine is globally recognized as one of the most diffuse primary headaches. The present paper aims to review the current evidence on the possible association between CD and migraine. Both adults and children having CD exhibit a high prevalence of migraine. However, screening for CD in an unselected population of migraineurs demonstrated contrasting results. Brain imaging may reveal cerebral calcifications and/or white matter abnormalities in a small number of patients having migraine with underlying CD. Limited data are available on the effects of gluten-free diet (GDF) on migraine in the patients affected by CD, suggesting the efficacy of such intervention on the migraine symptoms in both adults and children. Nonetheless, this inference requires verification with high-quality trials conducted with larger sample sizes and longer follow-up periods.

Keywords
Celiac disease; headache; migraine

1. Introduction

Celiac disease (CD) is a peculiar disorder that manifests as an autoimmune enteropathy triggered by gluten ingestion in genetically predisposed individuals [1]. Tissue transglutaminase is the auto-antigen involved in CD, while human leukocyte antigen (HLA)-DQ2 and HLA-DQ8 are the key genetic elements [1]. The positivity of serological tests is suggestive of CD. The anti-tissue Transglutaminase (anti-tTG) and anti-Endomysium antibodies (EmA) exhibit higher diagnostic accuracy compared to deamidated gliadin peptide antibodies, which are currently used for identifying CD in early childhood (age < 2 years) [1]. However, the gold standard for CD diagnosis is the duodenal biopsy that reveals the mucosal damage of the small intestine [ranging from minimal lesions that are characterized by an isolated increase in the intraepithelial lymphocytes to complete villous atrophy] [1].

CD is one of the most common autoimmune disorders worldwide. According to a recent meta-analysis, the pooled global prevalence of CD is 1.4% when determined using serologic screening and 0.7% when determined using duodenal biopsy. The prevalence is slightly higher in Europe and Oceania compared to the other continents. In addition, the disorder is more prevalent in females than in males. The rates of initial diagnosis are higher in children compared to the adult population [2].

The immune-inflammatory process is reported to specifically affect the gut mucosa, although its presentation is extremely variable and ranges from different gastrointestinal symptoms to various extra-intestinal symptoms [3]. Migraine is reported as one of the most common neurological diseases associated with CD, both in infants and adults [3-5].

Second, only to the tension-type headache, migraine is the most prevalent among the primary headaches on a global scale. The global prevalence of migraine is 11.6% (10.4% in Africa, 10.1% in Asia, 11.4% in Europe, 9.7% in North America, and 16.4% in Central and South America). In adults, migraine occurs mostly in the age range of 25-55 years, with females being significantly more affected compared to males. In young children, migraine is the most common subtype of recurrent headache [6], while in late childhood, migraine is the second most frequent (9%) among the primary headaches after the tension-type headache [6].

The present report aimed to review the literature to find the existing pieces of evidence for the possible association between CD and migraine. In order to achieve this objective, a literature search was performed on two databases/search engines-PubMed and Google Scholar-until August 2020, using the following search string: ("Celiac disease" or "Gluten") and ("Migraine" or "Headache" or "Neurological"). In addition, a manual search was conducted by examining the bibliography provided in every included study and the related references. All the research papers identified in these two search steps were evaluated in relevance to the topic of concern, and the clinically significant articles were selected for inclusion in the present review.

2. Prevalence of Migraine in both Adult and Pediatric Patients with Celiac Disease

According to a large retrospective population-based study conducted by Lebwohl et al., headache-related health care visits were significantly more common in patients with CD in comparison to controls (4.7% vs. 2.9%) [7].

In a meta-analysis conducted in 2018, which included five cohort and four case-controlled studies, a pooled mean prevalence of headache in the adults with CD was reported to be 26% (95% CI 19.5-33.9%), with the odds of experiencing a headache significantly higher in the CD patients compared to controls (OR 2.7, 95% CI 1.7-4.3, $p < 0.0001$) [8]. However, none of the above-stated studies provided information regarding the headache subtypes.

An online survey promoted on the Argentinean Celiac social networks investigated the characteristics of the headache in celiac patients, with a total of 866 individuals fulfilling the inclusion criteria of headache and CD confirmed with a positive biopsy. It was revealed that the tension-type headache was the most prevalent headache type (52%), followed by migraine without aura (32.5%) and with aura (15.4%), respectively. Interestingly, 24% of the subjects included in this survey reported headache as the main symptom leading to the diagnosis of CD [9].

Only two case-control studies on the topic of concern are available in the literature. In one of these studies, 28% of the 72 adult patients with biopsy-proven CD presented migraine as one of the neurological symptoms [10]. In another study, Dimitrova et al. reported that 40 patients among the 188 patients with CD had a concomitant migraine, in contrast to only 13 patients among the 178 controls (OR = 3.79). The authors reported that this association was stronger in women and those aged < 65 years [11]. In addition, a trend toward more severe headaches in CD patients compared to the controls was observed by the authors.

In regard to the pediatric population, the meta-analysis conducted by Zis et al. reported an 18.3% (95% CI 10.4%-30.2%) pooled mean prevalence of primary headaches in children and adolescents with CD [7]. In regard to migraine specifically, the data reported for pediatrics were similar to those observed in adults. In a large, cross-sectional, population-based study conducted on Israeli adolescents (median age of 17.1 years), the multivariate analysis revealed that migraine was significantly more common in CD patients compared to controls (OR 2.3) [12].

Two retrospective studies reported 18.6% (16 among 86 subjects) and 25% (33 among 132 subjects) prevalence of migraine among the children with CD [13, 14].

Case-control studies on the topic of concern are also available in the literature, with a significantly higher prevalence of migraine reported in CD patients compared to controls (12.6% among 111 subjects versus 5.7% among 211 subjects) [15].

3. Prevalence of Celiac Disease in both Adult and Pediatric Patients with Migraine

A few case reports have suggested migraine as the possible first presentation of CD [16-20]. In a study conducted by our group with 90 adults having migraine and the 236 sex-matched and age-matched controls, CD (screened using anti-tTG and EmA, and the positive cases confirmed by biopsies) was diagnosed in 4.4% of the patients with migraine and 0.4% of the controls ($p < 0.05$) [21]. No other data are available regarding the screening for CD in the adults affected by migraine.

Relatively greater evidence is available from the pediatric population. In a study by Lahat et al., it was observed that the anti-Endomysial antibodies were negative in all 41 children with migraine

headache (1-16 years of age) [22]. Five related case-control studies are available in the literature [23-27], two of which, both conducted with the Turkish population, reported negative findings [23, 24]. In one of these studies, no difference was observed in the positivity of anti-tTG between the migraine patients and the healthy controls (2% in both; 2/100 versus 30/1500, respectively) [23]. The other study, conducted by Balci et al., reported similar results, with 2 among the 81 patients having migraine exhibiting positivity for anti-tTG antibodies compared to 1 among the 176 controls (p = ns). In the same study, the duodenal biopsy was negative in all the subjects, who were then considered 'potential celiacs' [24].

In another Turkish study conducted with children in the age range of 6-17 years, a significantly higher prevalence of positive anti-tTG antibodies was reported in the 73 patients with migraine (5.5%) compared to the 147 controls (0.6%, $p < 0.05$). However, the patients with positive serology exhibited normal duodenal histology, suggesting a condition of 'potential CD' [25].

On the other hand, two case-control studies concerning the Italian population reported a positive association between migraine and CD. Lionetti et al. reported that 4 among the 79 (5%) patients with primary headaches had CD. The prevalence was significantly higher compared to the 0.6% prevalence observed in the general pediatric population in the same geographical area. Jejunal biopsy confirmed the diagnosis of CD in all children included in the study [26]. It is noteworthy that, in this study, the patients with a combined diagnosis of migraine and tension headaches were enrolled, as according to the authors, a clear distinction between these two forms of headache in children and adolescents was difficult and often confusing [28].

In a larger study, Nenna et al. screened 883 children (481 females, median age 9.8 years) attending a tertiary care Centre for Pediatric Headache for the presence of CD. Among these children, eighteen (18, 2.04%) received a final diagnosis of CD (positive serology confirmed by duodenal biopsy). The prevalence was significantly higher compared to the 1.2% prevalence observed in the general population ($p = 0.034$). The most common type of headache observed in this sample was migraine (without aura 50%, and with aura 11%), followed by tension-type headache and migraine with aura (38.9%) [27].

4. Imaging in Migraine and Celiac Disease

Computed tomography (CT) is usually a norm in primary headaches, including migraine headaches. Interestingly, a few case reports demonstrate that newly diagnosed CD, migraine-like headache, and occipital or parieto-occipital calcifications in adults and children are well evident in CT scans [8, 16, 19, 29]. In certain pediatric cases, cerebral calcifications were associated with both migraine and epilepsy, thereby resembling what is referred to as the 'epilepsy and cerebral calcification syndrome' [8]. The association between these two diseases could be based on the "vascular" pathophysiological mechanism. Indeed, the pathological specimens exhibit various cortical vascular abnormalities, such as venous hemangiomas in deep cortical layers, subcortical calcification of the vessel walls, and large jagged microcalcifications, among others [30]. Such abnormalities are similar to but not identical with those observed in Sturge-Weber syndrome, another condition with the possible coexistence of migraine and epilepsy [31].

Non-specific white matter abnormalities (WMA) detected in magnetic resonance imaging (MRI) could be an incidental finding in normal control populations, although these are significantly more common in individuals with cerebrovascular risk factors [32]. An increased rate of WMA was

reported in migraine patients [33], suggesting a risk of future cerebrovascular events such as ischemic stroke [34]. Interestingly, WMA are common in CD patients, particularly those with concomitant migraine. A study reported 12 among the 33 adults (36%) with CD and neurological comorbidities to have WMA compared to none among the controls [35]. The strongest association was observed in the sub-group with migraine-like headache, with four among the six patients exhibiting WMA. Moreover, this category also exhibited the greatest number of WMA per scan. No major cardiovascular risk factor was present in these patients. Similar findings were reported by Hadjivassiliou et al., who observed that all four subjects with episodic migraine-like headache and CD exhibited WMA [36]. Only one study concerning children is available in the literature, and it reports the presence of WMA in one among the four patients with positive anti-tTG serology [25].

The etiology of WMA in CD remains unknown so far, although an immune-mediated vasculitis is suggested [35]. The common detection of WMA in patients with migraine and CD, particularly in adults, suggests that this category might be at a higher risk of future cardiovascular disease, including ischemic heart disease, ischemic stroke, and vascular dementia [37, 38].

In regard to Single Photon Emission Computed Tomography (SPECT) imaging, the available data are from a study conducted with two groups of patients, one with four adults having migraine and untreated CD and the other with five controls having migraine without CD, involving the administration of 740 MBq of 99 mTc hexemethyl-propylene-amineoxime in a headache-free period. All the patients in the first group exhibited evident abnormalities in regional cerebral blood flow, which was characterized by a circumscribed area of cortical hypoperfusion. In contrast, no interhemispheric asymmetries of cortical regional blood flow were observed in the group of controls [21]. Interestingly, complete disappearance of the SPECT abnormalities was observed at the 6-month follow-up performed during the gluten-free diet (GFD) period.

5. Effect of Gluten-Free Diet in Adults and Pediatrics

Currently, the data on the effect of GFD on migraine symptoms are scarce. It is reported that after commencing GFD, the migraine disappears or significantly improves only in a proportion of CD patients [16-20].

In a small series of adult patients with both CD and migraine, GFD was reported to be associated with the disappearance of headache in one subject and a marked improvement in the intensity, frequency, and duration of attacks in the other subjects [21].

Nenna et al. reported a successful GFD, which resulted in a significant improvement in the headache symptoms in all 18 children affected with a recurrent primary headache that was diagnosed as CD after the serological screening and histological confirmation [27].

The other cohort studies assessing the effect of GFD on headache in adult and pediatric CD patients [10, 11, 39] did not distinguish the results according to migraine or the other subtypes [15, 26, 40, 41], and all these studies reported a substantial amelioration of headache in a substantial proportion of patients.

Since all these studies were uncontrolled, the improvement observed in the migraine symptoms upon using GFD might be a placebo effect. However, it is noteworthy that placebo is reported to have a strong influence on acute migraine (up to 75% response in symptoms scores),

while its effect on chronic migraine remission is estimated to be less significant (approximately 25%) [42].

6. Possible Pathophysiological Mechanisms

Several mechanisms have been proposed for the association between migraine and CD, although none of these has been definitively proven [43-48]. Migraine is a neurovascular condition characterized by the dysfunction of cerebral nerves and blood vessels. Calcitonin gene-related peptide (CGRP) is reported to be strongly involved in the pathophysiology of migraine [43-45]. Migraine-specific triggers cause the dilation of cranial blood vessels, which activates the perivascular trigeminal sensory nerve fibers, ultimately resulting in the release of vasoactive peptides, such as substance P and particularly CGRP. These peptides are reported to exacerbate vasodilation and cause neurogenic inflammation that is characterized by vasodilation, leakage of blood vessels, and degranulation of mast cells [36-38]. Pro-inflammatory cytokines, such as tumor necrosis factor-alpha and interferon-gamma, typically released in CD patients after gluten ingestion, may promote, via complex mechanisms, the synthesis of CGRP, thereby triggering migraine attacks [43-45].

An alternative hypothesis states that the malabsorption associated with CD may lead to a deficiency of vitamins and macro-elements (magnesium), thereby affecting migraine [19, 43]. In particular, folate deficiency, which is known to increase the plasma levels of homocysteine, could play a role in the cerebral vascular dysfunction typical of migraine, as well as in the development of cerebral calcifications detected in certain cases of migraine associated with CD [16, 19].

CD is an autoimmune disease associated with several other autoimmune disorders, and therefore, migraine in CD patients could be the consequence of the neurological damage mediated by anti-neuronal and anti-ganglioside antibodies, which are detected frequently in the CD patients, particularly those with neurological disorders, with cerebellar ataxia and epilepsy being the most common ones [46-48]. These autoantibodies tend to disappear after a strict gluten-free diet, as reported in certain studies [46, 47]. Although no data confirming this inference are available in the literature concerning patients with CD and migraine, it remains a plausible mechanism, recalling the autoimmune hypothesis of WMA in CD.

7. Discussion and Conclusion

In an attempt to summarize the current pieces of evidence regarding the association between migraine and CD, the following key points are highlighted:

a. According to the data in the literature, there is a high prevalence of migraine in CD patients, both adults and children.

b. On the contrary, the screening for CD using serological tests in an unselected patient population with migraine remains debatable due to the conflicting findings of the reported studies. The screening may probably be justified when the other findings also suggest CD diagnosis (i.e., gastrointestinal symptoms, iron-deficiency-based anemia, and autoimmune disorders typically associated with CD) or when cerebral calcifications and/or WMA are revealed in brain imaging.

c. Preliminary data suggest that GFD may improve the intensity, duration, and frequency of headache attacks in patients with the migraine associated with CD. Considering the importance of GFD in treating the CD enteropathy and the majority of the associated extra-intestinal disorders, it

is recommended to motivate the patients to strictly follow the prescribed GFD. In addition, the physicians should strictly monitor their patients and conduct periodical serological testing to assess their compliance with GFD.

d. Although the available literature suggests that migraine should be considered a common extra-intestinal disorders associated with CD, further studies with larger sample sizes, in both adults and children, that assess the prevalence of CD in migraine and the effects of GFD on migraine attacks (possibly with a consistent follow-up) are warranted to confirm this suggestion. Since several of the published trials did not include a proper definition of the diagnosis of primary headache, future trials should take this into consideration. In addition, future studies should focus on unraveling the mechanisms underlying the association of CD and migraine.

Author Contributions

Maurizio Gabrielli and Francesco Franceschi conceived and wrote the paper; Veronica Ojetti, Marcello Candelli and Luca Santarelli analyzed and collected all the available literature; Francesco Franceschi and Antonio Gasbarrini revised the draft of the manuscript.

Competing Interests

The authors have declared that no competing interests exist.

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