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Review

Celiac disease and headache in children: a narrative state of the art

Luca Sabino[1, 3], Silvia Marino[1], Raffaele Falsaperla[1], Francesco Pisani[2], Carmen Massimino[3], Piero Pavone[3]

[1] Pediatric and Pediatric Emergency Department, University Hospital "Policlinico-Vittorio Emanuele", Catania, Italy; [2] Child Neuropsychiatric Unit, Department of Medicine and Surgery, University of Parma, Parma, Italy; [3] Pediatric Clinic, Department of Clinical and Experimental Medicine, University Hospital "Policlinico-Vittorio Emanuele", Catania, Italy

Summary. Celiac disease (CD) is one of the most important entity of the wide spectrum of gluten-related disorders (GRDs). It is well known that neurological manifestation can be present either at the onset of CD, or appear during the development of the pathology, and different can be the neurologic findings. Clinical features are very variable, ranging from typical manifestations of gastrointestinal involvement to neurologic symptom. The most frequent neurologic signs reported were headache, epileptic seizure, migraine, mental retardation, ataxia and attention deficit and hyperactive disorder. Headache either in form of migraine, or in non-specific form represents one of the main clinical presentation in CD. The aim of this work is to provide a narrative review of the pediatric literature focused on the cephalalgic features of children with CD evaluating the potential benefits of a gluten free diet (GFD). Papers were identified by searching for related literature in Medline (PubMed) and Embase using the words "Celiac Disease" and "Headache" or "Migraine" by specifying "children"/"paediatric age" for reports published since 1972 till 31th October 2018. According to our inclusion criteria, a total of 25 papers has been evaluated. Although it is still controversial if headache is prevalent in CD children a correct compliance to a GFD seems to improve the neurological symptoms even if the underlying pathogenic relationship between CD and neurologic system involvement is still not fully understood. (www.actabiomedica.it)

Key words: celiac disease, childhood, headache, therapy

Introduction

Celiac disease, also called non-tropical sprue, is probably the most important entity of the wide spectrum of gluten-related disorders (GRDs) (1). With GRDs are intended a group of characteristic pathologies in which the alimentary assumption of nutrients containing gluten can trigger, in genetically predisposed subjects, different and heterogeneous symptoms (1-2).

Celiac disease (CD), the best-studied of GRDs, is represented by an autoimmune inflammatory condition with main, but not exclusive, involvement of small bowel. In patient with genetical sensibility, the presence of gluten related proteins in ingested food can cause an abnormal activation of immune system which can turn out mainly as a autoimmune chronic enteropathy with diarrhoea, in the typical form, or with an 'atypical' presentation with constipation, or involvement of other districts as cutaneous or neurologic (1-3).

About this last point, is well known that neurological manifestation can be present either at the onset of CD, or appear during the development of the pathology, and different can be the neurologic find-

ings. In fact, patients can have ataxia (suggesting an involvement of the cerebellum), peripheral neuropathy, epilepsy and/or headache (1-5).

Gluten-related disorders

GRDs are a wide spectrum of enteropathies in which ingestion of nutrients containing gluten trigger several grades of alterations, ranging from mild form of intolerance to a clear autoimmune response. In the first brunch are included the so called 'non-celiac gluten sensitivity' (NCGS), describing patients with mainly gastrointestinal manifestation related to gluten ingestion but not causing a real modification of mucosae and with benefits after a gluten free diet (6).

On the other hand we have the Celiac Disease (CD), defined as a chronic autoimmune inflammatory pathology, in which in genetically predisposed individuals expressing HLA class antigens DQ2 or DQ8 (7) the ingestion of nutrients, mainly wheat, rye and barley, containing high percentage of gluten proteins (especially gliadin), can trigger an anomalous activation of the immune system. The main target of this autoimmune response is the proximal small intestine mucosae where typical abnormal findings (infiltration of plasma cells, hypertrophy of crypts and progressive flattening of villi) can be observed together with the contemporary presence of serum antibodies such as anti-gliadin IgG/IgA, anti-translgutaminase (tTG) or endomysial (EMA) antibodies, essential biomarkers for clarifying the diagnosis (6-7).

Clinical characteristics

Clinical features are very variable, ranging from typical manifestation of gastrointestinal involvement (as post prandial bloating, diarrhoea with steatorrhea, malabsorption and weight loss) to an "atypical" gastrointestinal manifestation (with constipation, gastroesophageal reflux, recurrent abdominal pain). Sometimes the symptoms can be either soft or absent (with only a mild elevation of transaminases) or can be characterized by an extraintestinal involvement of any part of the body (alopecia, Dermatitis Herpetiformis) including the nervous system (8-9).

According to recent studies of prevalence, the mean frequency of CD in USA and Europe is estimated around 1% of general population, even if it remains still undetected a wide slice of patients corresponding to the 'celiac iceberg' with a ratio of 1:3-5 between known and undiagnosed cases (10-11).

About the prevalence of neurological manifestations it has been estimated to be around 26% of adult patients (12), while its prevalence in pediatric age is still not well defined, but presumably less frequent than adults. Isikay et al. (3) estimated through a prospective cross-sectional study that 13.5% (40 of 297) of the celiac children examined showed neurologic symptoms. The most frequent neurologic signs reported were headache, epileptic seizure, migraine, mental retardation, ataxia and attention deficit and hyperactive disorder. Headache either in form of migraine, or in non-specific form represents one of the main clinical presentation in CD.

The aim of this work is to provide a narrative review of the pediatric literature focused on the cephalalgic features of children with CD evaluating the potential benefits of a gluten free diet (GFD).

Methods

Our papers were identified by searching for related literature in Medline (PubMed) and Embase using the words "Celiac Disease" and "Headache" or "Migraine" by specifying "children"/"paediatric age" for reports published since 1972 till 31th October 2018. The search was limited to English language articles only with available full-text. Through the research emerged a total of 91 papers, from which original articles, clinical trials, systematic reviews were selected. Titles and abstracts of papers were screened by reviewers to determine whether they met the eligibility criteria, and full texts of the selected articles were retrieved. At the end of the process, a total of 25 papers has been evaluated.

Headaches

As regards headache, possible causes involved in cephalalgic phenomena occurring in celiac disease

have been reviewed (13), suggesting a possible role of immune imbalance with prevailing of proinflammatory cytokines, but also pointing out how even vascular tone regulation can determine headache, especially if combined with lack of vitamins and elements as magnesium as in case of malabsorption in celiac patients. The real impact of headache in celiac children have been estimated in a case-control hospital-based study (14) where headache was significantly higher in CD children compared with controls (24% vs 8%; p<0.001). But very interesting is that in the prospective part of this study, only 5% of the patients admitted to neurological services for headaches was found to be affected from celiac disease and an improvement of headache was noted in 76.4% of children on GFD. This suggest how important should be the screening for CD, in a complete assessment of young patients complaining headaches. In 2008, our group (15) performed a research on the the frequency of neurologic features in children with gluten sensitivity (GS) and the frequency of GS in children with neurologic disease. A total of 835 children with GS (based on positive titers for serum anti-gliadin antibody (AGA), EMA, and anti-tTG antibodies and a positive gut biopsy), representing the local childhood GS population in the town of Catania, Italy, were recruited, prospectively followed up, and screened for neurologic and psychiatric disturbances between 1991 and 2004. Serum AGA, EMA, and anti-tTG antibody titers were estimated in a prevalence sample of 630 consecutive children with neurologic disorders of unknown cause despite full investigation, 300 children with known neurologic syndromes, and 300 healthy children who served as controls. Neurologic or psychiatric problems were noted in 15 of 835 children with GS (1.79%) with previously diagnosed GS enteropathy. In 7 of 630 children (1.1%) with a cryptogenic neurologic disorder, GS was identified based on GS autoantibody screening. These 22 children had febrile seizures, epilepsy, headache, mental retardation, neuropathy, and bipolar disorder; no children had ataxia or cerebellar disturbances. Two of the 300 healthy controls (0.66%) had GS. Based on these findings, the prevalence of neurologic/psychiatric manifestations in this group of children with GS was low but slightly higher than that in the controls (P=.041). Children with known (P=.772) and cryptogenic (P=1.0) neurologic disorders did not exhibit a higher prevalence of GS.

In 2016, a prevalence of CD was 2.04 % in a large cohort of children with recurrent headache versus 1.2% reported in a general population screening study and all demonstrated resolution or improvement of the symptoms after starting a gluten-free diet (16). This improvement is confirmed by others that observed after 6 months of the institution of a gluten-free diet a resolution of the headache in five children on seven and a significant improvement of the symptoms in the remaining two children. (17). Furthermore, a population-based study (18) investigating the association between CD and various comorbidities, revealed an odds of suffering from migraine higher in adolescents with CD when compared to controls (OR 2.3, 95% CI 2.1-2.5, p<0.0001). However, data on the prevalence of headache in CD patients are controversial: Lahat et al. did not find a significant association (19) as well as the prevalence of migraine among children with CD (5, 20), although the suggestion of a positive relation in one patient with CD and migraine in a series of 87 subjects (21). Furthermore, a recent meta-analysis reports a pooled mean prevalence of headache in children and adolescents with CD of 18.3% (95% CI 10.4-30.2%), (2) therefore, it seems that overall an increased prevalence of headache, mainly migraine, in children with CD exists. Nevertheless, a clear pathogenic mechanism has not been clearly expressed. As previously reported, a gluten-free diet is related to a significant clinical improvement as well as to a normalization of the cortical hypoperfusion abnormalities seen in SPECT (22) but this finding was not confirmed in children studied by PET scan. Although some evidence that brain hypoperfusion and perivascular inflammation might play a role in the pathogenesis of GS-related headaches more studies on the likely pathogenetic mechanisms are needed. Some main mechanisms have been supposed: deficiency of vitamins or other nutrients due to malabsorption (23); an immune dysregulation which involves the nervous system, response in the brain and gut mucosa, exposure of neuronal cells to pathogenic antibodies due to a compromised blood-brain barrier, and gluten peptides crossing the blood-brain barrier with a consequent disorder of the neurotransmission (24).

Although it is still controversial if headache is prevalent in CD children a correct compliance to a GFD seems to improve the neurological symptoms even if the underlying pathogenic relationship between CD and neurologic system involvement is still not fully understood.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Correspondence:
Francesco Pisani
Child Neuropsychiatric Unit,
Department of Medicine and Surgery, University of Parma,
Via Gramsci 14 - 43126 Parma, Italy
Tel. +35 0521 702205
E-mail: francesco.pisani@unipr.it