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Alimentary Tract

Celiac disease in a large cohort of children and adolescents with recurrent headache: A retrospective study

Raffaella Nenna*, Laura Petrarca, Paola Verdecchia, Matteo Florio, Nicoletta Pietropaoli, Gerarda Mastrogiorgio, Maria Bavastrelli, Margherita Bonamico, Salvatore Cucchiara

Department of Paediatrics and Infant Neuropsychiatry, "Sapienza" University of Rome, Rome, Italy

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ABSTRACT

Background: The clinical picture of celiac disease is changing with the emergence of subclinical forms and growing evidence reporting associated neurological disorders.
Aims: To establish the prevalence of celiac disease in children suffering from recurrent headache.
Methods: In our retrospective study we collected charts from 1131 children attending our tertiary care Centre for Paediatric Headache over the period 2001–2012. They were screened for celiac disease and positive patients were referred to our Operative Unit for Coeliac disease and confirmed positive children underwent upper endoscopy with multiple duodenal biopsies. Celiac children started a gluten-free diet.
Results: 883 children (481 females; median age, 9.8 years, range 3–19) performed celiac disease screening, and among them, 11 children (7 females; median age, 8.2 years, range: 4.8–13.9) were diagnosed with celiac disease. Seven children (5 females, median age, 11.9 years, range: 10.3–13.9) had been diagnosed as celiac prior to the neurological evaluation. The prevalence of celiac disease in our sample is 2.04% vs. 1.2% of the general population ($p = 0.034$).
Conclusions: Our study demonstrates, on a large series, that celiac disease prevalence is doubled in patients with chronic headache. Screening for celiac disease could be advised as part of the diagnostic work-up in these paediatric patients, particularly among pharmacological non-responders.
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1. Introduction

Headache is a painful syndrome characterized by variable intensity and location, which can present as continuous, intermittent or occasional, sometimes accompanied by nausea, vomiting or transient neurological symptoms. Headache in children is generally benign, transient, and with a favourable prognosis; longitudinal studies demonstrate an acceptable percentage of symptom remission [1], although some of the subjects continue to be affected in adulthood, assuming the shape of a chronic disease and considerably reducing the quality of life [2].

Recent epidemiological studies on headache in children, based on the International Headache Society (HIS) clinical criteria, show that its prevalence is around 10% [3,4]. In children, as for adults, there is often the coexistence of different types of headache, for example, migraine and tension headache in the same subjects, making it difficult to define an exact diagnosis. For these reasons, and due to the acquisition of new knowledge, HIS compiled a new Classification in 2004 called "International Classification of Headache Disorders (ICHD-II)" [5].

Headache may sometimes represent an extra-intestinal symptom of celiac disease (CD), a chronic, autoimmune, gluten-dependent enteropathy that occurs in genetically predisposed subjects [6]. CD can manifest itself in a typical form, with gastrointestinal symptoms, in an atypical form characterized by extra-intestinal manifestations such as iron-deficiency anaemia or short stature, or can be asymptomatic assuming a "silent form" [7]. CD has a prevalence of 1.2% in the Italian general population, largely in an asymptomatic form [8], and the long-lasting CD can cause complications. As an autoimmune disease, CD may cause the so called "hyperactivation" of the immune system. This may explain the occurrence of "organ-related complications": autoimmune thyroid disease [9], hepatitis [10], type I diabetes [11], psoriasis [12], Addison's disease [13] and dermatitis herpetiformis [14]. Other potential complications include osteoporosis [15] caused by poor bone mineralization and infertility [16].

Among the extra intestinal manifestations, some studies, carried out mostly in adults, show the existence of neurological diseases, such as peripheral neuropathy with paraesthesia, tremor

* Corresponding author at: Department of Paediatrics, "Sapienza" University of Rome, Viale Regina Elena 324, 00161 Rome, Italy. Tel.: +39 3384636804.
E-mail address: raffaella.nenna@uniroma1.it (R. Nenna).

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and weakness [17], autoimmune ataxia [18], brain atrophy [19] and epilepsy with cerebral calcifications [20,21]. While the possibility that CD could manifest with recurrent headache has been studied [17,22–25], very few evidence-based data investigating the prevalence of CD in patients with headache are available. In addition there are very discordant data about this association in paediatric patients and whether the gluten-free diet (GFD) could improve pain and quality of life of celiac patients with headache [17,22,23].

Our aim was to evaluate the prevalence of CD in a large cohort of children and adolescents with recurrent headache, and to characterize the clinical and epidemiological features. We also aimed to investigate the effects of the GFD on headache in patients with a diagnosis of celiac disease.

2. Materials and methods

In this retrospective study, we reviewed charts from 1131 consecutive children and adolescents attending the Centre for Paediatric Headache of the "Sapienza" University of Rome between January 2001 and November 2012.

Data from clinical charts (anthropometric measurements; clinical characteristics of headache such as the type and the localization of pain, the frequency, the intensity, and the duration of the headache attacks and the association with other neurological and gastrointestinal symptoms) anti-gliadin (AGA), anti-endomysium (EMA), anti-transglutaminase antibodies (TG2Ab) and total IgA were recorded for each patient.

The diagnosis and classification of headache was initially based on the criteria of the International Headache Society described in the "Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain" in 1988, and then based on the new criteria presented in the "International Classification of Headache Disease II (ICHD-II)" published in 2004 [5].

The study was conducted in accordance with the principles of the Declaration of Helsinki.

2.1. Statistical analysis

Statistical analysis was performed using SPSS v.20 (Chicago, Illinois).

From quantitative variables means, medians, and standard deviations were computed, and Student *t* test, when possible, was used to compare group means. Qualitative variables were described by counts and percentage. Chi square test and Fisher's exact test, when necessary, were used to compare proportions.

A 2-tailed $p < 0.05$ was considered significant.

3. Results

Among the 1131 patients' charts, 883 (481 females, median age, 9.8 years, range 3–19) reported data about celiac disease antibodies and were included in our study.

The clinical presentations of headache were the following: 547 presented migraine without aura (62%), 292 presented tension type headache (33%), 44 presented migraine with aura (5%); 93.5% reported a family history of headache attacks.

Among the 883 patients with headache, 7 children (0.8%, 5 females, median age, 11.9 years, range: 10.3–13.9) were already diagnosed as celiac and were on a GFD during the first neurological evaluation for headache. In these patients, the most common type of headache was found to be migraine without aura (50%), followed by tension-type headache (38.9%) and migraine with aura (11.1%). In 72.2% duration of attacks ranged from 30 min to 4 h and most of them (83.3%) complained about episodes of mild or moderate intensity even 4 times a week. The most frequently referred location was the frontal area (44.4%).

Overall 11 children (1.25%, 7 females, median age: 8.2 years, range, 4.8–13.9) were found to be positive for TG2Ab and/or EMA and/or AGA (Table 1) at the celiac screening prescribed during the first neurological evaluation.

In all of these children the diagnosis of CD was confirmed by multiple duodenal biopsies: in particular, 10 patients presented type 3c histological lesions and in 1 patient type 3b lesions were observed.

Five patients (45%) had a typical form of celiac disease: one child showed a wide constellation of symptoms (recurrent abdominal pain, iron deficiency anaemia, abnormalities of dental enamel, irregular bowel movements and bloating), four patients complained of recurrent abdominal pain. Six patients had no symptoms correlated with celiac disease. No patient showed evident signs of malabsorption.

Newly diagnosed celiac patients were followed for a period of time ranging from 3 months to 6 years after the start of the GFD. During follow-up patients showed a good weight and height growth and negative antibodies (in three children after 3 months of GFD, in 2 after 6 months, in 4 after 9 months, in the remaining 2 after 12 months).

Among newly-diagnosed celiacs, 6 children (54.5%) reported the complete disappearance of headache (3 after 3 months and the remaining three after 6 months) whereas 5 (45.5%) noticed a clear reduction in both intensity and frequency of attacks (in 3 after 6 months, in a patient after 3 months and in another patient after 12 months). One patient was undergoing treatment with triptans at the time of CD diagnosis. The treatment was suspended after three months of GFD due to the disappearance of headache. The remaining 10 patients (91%) were treated with NSAIDs in case of

Table 1
Clinical data, serology and histology of 11 newly diagnosed paediatric celiac patients.

No.	Age (years)	Sex	IgA TG2Ab (cut-off)	IgA EMA	Clinical presentation	Histology[a]
1	6.5	M	15 U/mL (<9)	3+	Recurrent abdominal pain	3c
2	5.7	M	>100 U/mL (<20)	3+	–	3c
3	10.3	M	31.3 U/mL (<20)	1+	–	3c
4	7.9	F	89.9 U/mL (<20)	3+	Recurrent abdominal pain, iron deficiency anaemia, bloating	3c
5	13.9	F	29.5 U/mL (<5)	1+	–	3b
6	9.9	M	>100 U/mL (<20)	2+	Constipation,	3c
7	10.3	F	>100 U/mL (<20)	3+	Recurrent abdominal pain, weight growth restriction	3c
8	4.8	F	28.9 U/mL (<16)	1+	–	3c
9	6.6	F	143 U/mL (<20)	3+	–	3c
10	8.2	F	>100 U/mL (<16)	3+	–	3c
11	12.4	F	>100 U/mL (<16)	2+	Recurrent abdominal pain	3c

M, male; F, female; TG2Ab, anti-transglutaminase antibodies; EMA, anti-endomysium antibodies.

[a] Marsh classification modified by Oberhuber et al. [26].

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