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Review article

Coeliac disease, epilepsy and cerebral calcifications

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Abstract

Coeliac disease, epilepsy and cerebral calcifications (CEC) syndrome is a rare clinical condition. One hundred and seventy-one patients have been reported in the literature. Patients are mostly from Italy, Spain, and Argentina, suggesting a geographically restricted condition. Epilepsy is more frequently characterized by occipital seizures. It may be benign or drug-resistant, sometime evolving into severe epileptic encephalopathy. Gluten free diet (GFD) efficacy seems to be inversely related to the duration of epilepsy and the young age of the patient. Patients with cerebral calcifications (CC) and coeliac disease (CD) without epilepsy are considered as having an incomplete form of CEC syndrome. Some patients with epilepsy and CC without CD are supposed to have a CEC syndrome with silent or latent CD.

Whether CEC syndrome is a genetic condition, or whether epilepsy and/or CC are a consequence of an untreated CD is unknown yet. Since histopathological findings seem to be the expression of vascular calcifyied malformation, CEC syndrome may be considered a genetically determined entity, such as a type of Sturge-Weber-like phacomatosis. Moreover, CEC, as well as CD, is associated with HLA-DQ2 and HLA-DQ8 phenotype and genotype. The progressive growth and late occurrence of CC before beginning a GFD, the demonstration of anti-gliadin antibodies in the cerebro-spinal fluid and the association with HLA class II genes, suggest that an immune reaction originating from the jejunal mucosa, triggered by gliadin in gluten intolerance predisposed subjects (HLA phenotype) may be responsible for seizures and CC. Moreover, a long-lasting untreated CD folic acid deficiency may cause calcifications.

Probably, CEC is considered a genetic, non-inherited, ethnically and geographically restricted syndrome associated with environmental factors.

Keywords: Coeliac disease; Cerebral calcifications; Occipital calcifications; Epilepsy; Occipital epilepsy

1. Historical perspective and definition

Coeliac disease (CD) is an autoimmune disease characterized by chronic inflammation in the wall of the small intestine [1] due to a permanent intolerance to gluten protein (gluten intolerance, GI). CD is defined by crypt hyperplasia, jejunal mucosa villous atrophy, and inflammatory infiltrate in the lamina propria associated with an increased number of intraepithelial lymphocytes; resolution of villous atrophy and clinical improvement on gluten-free diet (GFD); and relapse of clinical symptoms and biopsy features withdrawing GFD.

In the dynamic process of the development of the CD, the first architectural change is the crypt hyperplasia. Initially, the elongated crypts are covered by normal villi, and later on, when the lesion is more advanced, by shortened villi which may be absent in more severe stage, the flat mucosa [2].

Clinically, in the 'classical or typical' form, which appears in the first two years of life, chronic diarrhoea, weight loss, dystrophic appearance and anorexia occur in all patients, while irritability and vomiting in about one-third [3]. In GI predisposed subjects, CD may be silent, latent or potential [4]. These 'atypical' forms are more frequent in children over two years and in adults, and are characterized by non-bowel involvement. Extraintestinal symptoms such as dermatitis herpetiformis and dental enamel defects may be present alone without gastrointestinal symptoms, and they are considered as extraintestinal markers of CD [5,6].

Abbreviations: CEC, coeliac disease, epilepsy and cerebral calcifications; GFD, gluten free diet; CC, cerebral calcifications; CD, coeliac disease; GI, gluten intolerance; SWS, Sturge-Weber syndrome; IMS, Italian Multicentric Study; IWG, Italian Working Group; ESPGAN, European Society Pediatric Gastroenterology Hepatology and Nutrition; EmA, Antiendomysium antibodies; CSF, cerebral spinal fluid; tTG, tissue transglutaminase; Th, pro-inflammatory cytokine; IL, interleukin; IFN, interferon; TNF, tumor necrosis factor.

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Several neurological disorders have also been extensively reported in CD patients [7–12] and they may precede the diagnosis of CD in 7% of newly diagnosed CD cases [13]. Among them epilepsy is the most frequent [8,14–20], and its prevalence in CD patients has been estimated to be between 1.2 and 5% [20–22].

Cerebral occipital calcifications, radiologically identical to those of Sturge-Weber syndrome (SWS), but without portwine facial naevous, were firstly described by Garwicz and Mortensson 1976 [18] in two children. Between 1983 and 1987 several further patients have been reported and supposed as having an atypical (without facial naevous) SWS [23–30].

The first description of the syndrome 'coeliac disease, epilepsy and cerebral calcifications' (CEC) is probably from Sammaritano et al. in 1985 [25]. A severe type of progressive occipital epilepsy in patients with bioccipital cortico-subcortical calcifications was reported between 1985 and 1988 [31,32]. An unexpected series of similar cases of atypical SWS with occipital epilepsy, in which CD was casually observed [18,25,33–40], prompted the organisation of an Italian Multicentric Study (IMS) by child neurologists and gastroenterologists to determine the association between CD and epilepsy. Several previously described Italian 'atypical SWS' cases were included in this study. The results showed that 77.4% of patients with epilepsy (especially occipital epilepsy) and cerebral calcifications (CC) more frequently located in occipital regions were affected by CD. Since there was no reason for a higher frequency of CD in subjects with cerebral calcifications and epilepsy than in the normal population, it has been considered that this association is not casual [41]. Then, further patients with CEC were published in Italy [42–45] and outside Italy [46–55], demonstrating the large distribution of this syndrome all over the world.

Reviewing the literature data up to 1996 [56], three groups of patients were identified: (1) patients with, CEC or 'typical form'; (2) patients with CD and epilepsy without CC; (3) patients with CD and CC without epilepsy. The latter two groups are considered 'atypical forms.' There is the fourth group of patients with epilepsy and CC without CD, who are supposed to be affected by a latent or silent form of CD [57].

2. Typical CEC syndrome

In typical CEC syndrome CD may appear at any time during a lifetime and it can evolve in silent or paucisymptomatic forms. Epilepsy is a localization-related epilepsy, usually occipital in type. CT-scan features consist of bilateral cortico-subcortical occipital calcifications without contrast enhancement, and brain atrophy.

2.1. Gastrointestinal complaints

In the Italian Working Group (IWG) series (42 patients, 16 males) [57], the mean age at diagnosis of CD was 15.7 ± 6.6 years. In eight cases, CD was investigated because of gut complaints. In the remaining 34 cases, CD was investigated and diagnosed only because of epilepsy and cerebral calcifications. Adopting an ad hoc anamnestic investigation, it was possible to detect gastrointestinal symptoms suggesting an atypical early childhood CD in some of these patients. These symptoms were abdominal distension, vomiting, diarrhoea, recurrent aphthous stomatitis, iron deficiency anaemia and short stature. In 14/42 patients, CD was previously diagnosed, and 10 out of these 14 subjects underwent gluten-free diet for a mean period of 3 years, but the diet was then stopped by the parents.

2.2. Epilepsy and EEG findings

Age at onset of epilepsy ranged between 1 and 28 years (mean 6.64; SD 5.45) in the IWG series [56], and between 1 and 16 years (mean 6.13) in a more recent Argentinean series [53]. In IWG series, 13 children had epilepsy before the age of 3, 25 from 4 to 13 years, and only in four cases epilepsy started in adulthood. In all but three CEC patients, epilepsy started before the diagnosis of CD and the beginning of GFD.

Among 171 literature CEC patients, 127 were available for epilepsy analysis (Table 1). On the basis of clinical and EEG findings and evolution, the epilepsy was classified as localization-related in 109. Among them, 78 patients had occipital epilepsy. The semeiology of the seizures may consist of versive and/or visual seizures (simple hallucinations, amaurosis), visual seizures followed by complex seizures or secondary generalization. Two anecdotal cases had reflex epilepsy: reading reflex seizures in one [56], and eating induced seizures in the other [22]. The remaining 31 cases showed other varieties of partial epilepsy, with

Table 1
Types of epilepsy and evolution in literature CEC patients (127 cases)

Type of epilepsy	Total of cases
Localisation-related	109
Occipital epilepsy	78
Other localisation-related	31
Complex seizures	15
Partial motor seizures	9
Partial seizures with secondary generalization	7
Generalised	10
Progressive myoclonic epilepsy	2
Occasional seizures (febrile convulsions)	1
Evolution	
Benign	22
Drug resistant	38
Severe epileptic encephalopathy	18