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The role of hyperhomocysteinemia in neurological features associated with coeliac disease

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ABSTRACT

Although a range of neurological and psychiatric disorders are widely reported to be associated with coeliac patients, their pathogenesis remains unclear. Some such disorders are believed to be secondary to vitamin deficiency due to malabsorption, others to immune mechanisms. We hypothesise that hyperhomocysteinemia might, by damaging the blood–brain barrier, expose neuronal tissue to all neuro-irritative metabolites, such as homocysteine itself, a neurotoxic excitatory and proconvulsant amino acid. Neurons respond to these stimuli through hyperexcitability, thereby predisposing subjects to neurological disorders such as epilepsy and headache. Furthermore, persisting endothelial damage may cause blood extravasation and subsequent deposition of calcium salts. We suggest that this might be the pathogenesis of the CEC syndrome, which is characterized by the association of coeliac disease, epilepsy and cerebral calcifications. Indeed, homocysteine plays a well-known role in cardiovascular endothelial dysfunction, with high serum and cerebrospinal fluid levels often being reported in coeliac patients. Moreover, data in the literature show a strong, growing association of homocysteine with epilepsy and migraine in non-coeliac subjects.

Despite these findings, homocysteine has never been held directly responsible for neuronal functional features (neuronal hyperexcitability underlying epilepsy and migraine) and structural brain damage (expressed as cerebral calcification) in coeliac patients. Damage to the blood–brain barrier might also facilitate immune reactions against neuronal tissue to a considerable extent. This hypothesis combines the two afore-mentioned theories (vitamin deficiency due to malabsorption and immune mechanisms).

We also wish to point out that no studies have yet investigated the prevalence of neuronal hyperexcitability and subclinical electroencephalic abnormalities in children and adults with newly-diagnosed coeliac disease before the introduction of a gluten-free diet, and in particular any changes following the introduction of the diet. We believe that the onset of clinical symptoms such as migraine and convulsions is preceded by a period in which damage is expressed exclusively by subclinical electroencephalic abnormalities; persisting damage to neuronal tissue subsequently leads to clinical manifestations. We propose two types of investigations: the first is to determine whether newly-diagnosed coeliac patients with hyperhomocysteinemia are a subgroup at risk for neurological features (clinical and subclinical); the second is to determine whether appropriate treatment of hyperhomocysteinemia and vitamin B status deficiency improves neurological abnormalities and reduces the risk of cerebral calcifications.

The aim of these investigations is to develop new therapeutic strategies designed to prevent neuronal damage and increase the quality of life in children affected by such disorders.

Background

Coeliac disease

Coeliac disease (CD) is a chronic and autoimmune disorder of the small intestine that occurs in genetically predisposed individuals expressing the HLA class II molecules DQ2 (90–95%) or DQ8 (5–10%). It is caused by an inflammatory reaction to gliadin, a gluten protein found in some cereals, including wheat [1].

CD, one of the most common life-long disorders in Europe and the United States, is characterized by crypt hyperplasia, jejunal mucosa villous atrophy and inflammatory infiltrate in the lamina propria associated with an increased number of intraepithelial lymphocytes [2]. A gluten-free diet (GFD) leads to the resolution of villous atrophy and consequently to a clinical improvement, while the suspension of a GFD results in a relapse of the clinical symptoms and biopsy features [3].

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CD can occur in subjects of any age, including the elderly, while the clinical manifestation/spectrum of this disease varies widely depending on the patient's age.

In the 'classical' or 'typical' form, which appears above all in the first 2 years of life, chronic diarrhea or constipation, failure to thrive or weight loss, abdominal cramping, pain and distension, dystrophic appearance and anorexia occur in all patients, while irritability and vomiting occur in about one third [4]. The 'atypical' form is more frequent in children over 2 years of age and in adults; it is characterized by non-bowel involvement and may lead to minimal or unusual intestinal complaints.

The main extraintestinal symptoms are dermatitis herpetiformis and dental enamel defects, short stature, pubertal delay, iron deficiency, abnormalities in liver function tests and migraine.

CD can also occur in apparently healthy subjects (silent CD) or, later in life, in those with positive CD-related autoantibodies but a normal to minimally abnormal intestinal mucosa (potential CD) [5]. The overall prevalence of CD ranges from 0.7% to 2% in the general population and from 0.4% to 1.3% in children [6].

Although its target organ is the gut, gluten-sensitive enteropathy is a typical example of a systemic disorder with involvement of many other tissues and organs, including skin, thyroid, pancreas, liver, heart, joints, muscles, bones, and the central and peripheral nervous systems [7].

Neurological disorders related to coeliac disease

Several neurological and psychiatric disorders have also been widely described in CD patients [8,9]; in 7% of newly-diagnosed cases, such disorders have been reported to precede the diagnosis of CD [10]. They include migraine, febrile seizures, encephalopathy, chorea, brainstem dysfunction, autism, myopathy, neuropathy with positive antiganglioside antibodies, cerebellar ataxia, dementia, white matter lesions, depression and, lastly, epilepsy, which is the most frequent disorder associated with CD [11,12].

In 2010, Lionetti et al. [13] published a meta-analysis and systematic review of the few evidence-based data available on these disorders in children. He showed that the relative risk (RR) of epilepsy in individuals with CD, and of CD in individuals with epilepsy, compared with the general population, was 2.1 and 1.7, respectively. The clinical spectrum of epilepsy associated with CD ranges from focal to generalized forms. In the vast majority of these patients, wakefulness EEGs revealed focal abnormalities (spike waves or slow waves), mainly localized in one or both occipital regions [14,15].

The pathogenesis of neurological manifestations in CD is multifactorial and has yet to be fully understood. Such manifestations were initially assumed to be secondary to vitamin deficiencies (e.g. folate, vitamins B12, D and E) due to malabsorption. Vitamins are known to exert neurotrophic and neuroprotective effects. While some patients with cerebellar ataxia are reported to have low vitamin E levels, neurological manifestations may even arise without enteropathy [16,17]. Consequently, immune mechanisms, as opposed to malabsorption, are suspected to be involved in the pathogenesis of these disorders [7]. This hypothesis is supported by evidence of lymphocytic infiltration in the central and peripheral nervous systems [18], as well as by the presence of serum antineuronal antibodies [19], in CD patients with neurological complications.

Antibodies against Purkinje cells [20] and anti-ganglioside antibodies [21,22] have sometimes been found in CD patients with neurological diseases [23]. However, the role of these antibodies in the pathogenesis of neurological dysfunction is not yet fully understood and it is still unclear whether CD contributes to the pathogenesis of these disorders or represents an epiphenomenon.

Nevertheless, it is widely accepted that patients with neurological disorders of unknown cause, particularly those with neuropathy, ataxia, migraine and epilepsy, should be screened for CD. Indeed, neurological symptoms are sometimes the only clue to an underlying gluten-sensitive enteropathy; in such cases, an early diagnosis will prevent the onset of further complications. The description of a more specific condition, known as CEC syndrome, was first made by Sammaritano et al. [24] and subsequently developed by Gobbi et al. [25]. It is a rare and sporadic condition with an undefined prevalence, characterized by the association of CD, epilepsy and cerebral calcifications (CC).

An Italian multicentre study conducted by pediatric neurologists and gastroenterologists first identified the association between CD, CC and epilepsy. The results of that study showed that 77.4% of patients with epilepsy (especially occipital epilepsy) and CC, more frequently located in occipital regions, were affected by CD [26]. In addition to patients who display a 'typical form' of CEC, there are those with CC and CD without epilepsy, who are considered as having an incomplete form of CEC syndrome, as well as those with epilepsy and CC without CD, who are believed to have a CEC syndrome with silent or latent CD [27].

Few studies have investigated the prevalence of occipital calcifications in CD patients. Magaudda et al. [28] demonstrated that the prevalence of occipital calcifications in CD patients without epilepsy is comparable to that in the normal population; by contrast, the prevalence of occipital calcifications is significantly higher in CD patients with epilepsy than in CD patients without epilepsy. These results were not confirmed by another study, in which none of the subjects in a series of 16 CD epileptic adults were found to have CC [29].

Typical CT features of CEC syndrome consist of bilaterally subcortical, roughly symmetrical or asymmetrical occipital calcifications, absence of contrast enhancement and absence of brain atrophy [30]. In some cases, additional calcifications may be encountered in other brain regions, with scattered cases of unilateral occipital calcifications being reported.

The majority of CEC patients have not exhibited a significant change in the size of calcifications in follow-up studies. Calcifications in other patients have appeared in new regions during their evolution. Finally, some patients with an initial normal CT scan develop bilateral parieto-occipital calcifications after approximately 1 year [14].

Kieslich et al. [31], who used brain imaging to study individuals with CD, detected unilateral and bilateral focal T2 hyperintense white matter lesions localized in the biparietal-occipital, uniparietal, frontal and uniparieto-temporo-occipital areas in 20% of diet-treated participants with the disease. Periventricular white matter lesions were also recorded by Ruggieri et al. [32] in 13.6% of children with CD and neurological dysfunctions.

With regard to its pathogenesis, it is not yet known whether CEC syndrome is a genetic condition, or whether epilepsy and/or CC are a consequence of an untreated CD. Since its histopathological findings seem to be the expression of vascular calcified malformations rather than of inflammatory lesions, CEC syndrome may be considered a genetically determined entity, such as a type of Sturge-Weber-like phacomatosis [33]. Moreover, both CEC and CD are associated with the HLA-DQ2 and HLA-DQ8 genotype [34].

However, the progressive growth and late occurrence of CC before a GFD is initiated and the detection of antigliadin and anti-transglutaminase (TG) antibodies in the cerebro-spinal fluid (CSF), all suggest that an immune reaction originating from the jejunal mucosa and triggered by gliadin in gluten intolerance-predisposed subjects may be the cause of CC.

TG6 autoantibodies are believed to be a more specific marker of neurological manifestations, with the median TG6 antibody concentration being significantly higher than that of TG2 antibodies