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LETTERS TO THE EDITOR

Can *Campylobacter jejuni* play a role in development of celiac disease? A hypothesis

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Abstract

Celiac disease (CD) is an entropathy with malabsortive condition in which an allergic reaction to the cereal grain-protein (gluten) causes small intestine mucosal injury. CD is a multifactorial disorder in which both genetic and environmental factors contribute to the disease development. Mechanisms have been described to explain the pathology of CD. T cells specific for multiple gluten peptides are found in virtually all patients. Generation of such a broad T cell response may be a prerequisite for disease development. CD is associated with multiple extraintestinal presentations, including neurological deficits. Recent studies have shown a significant correlation between anti-ganglioside antibodies and neurological disorders in patients with underlying CD. Gangliosides are glycosphingolipids which are abundant in nervous system and in other tissues including gastrointestinal tract. It is not known what triggers the release of anti-ganglioside antibodies in people with gluten sensitivity. But, the mechanism is likely to involve the intestinal immune system response to ingested gliadin, a component of wheat gluten. Studies showed that mechanisms different from gluten exposure may be implicated in antibody formation, and other environmental factors may also exist. In addition, considering the fact that genetic predisposition dysregulating mucosal immune responses in the presence of certain environmental triggers like gastrointestinal infections may be strong etiological factors for developing chronic intestinal inflammation including CD, the hypothesis raised in our mind that antiganglioside antibody formation in CD may play a role not only in development of neurological complications in celiac patients, but also in development of CD itself. As presence of Campylobacter jejuni in other diseases with antigangliosides antibody formation has been established, we propose the possible role of Campylobacter jejuni in development of CD in association with other genetic and environmental factors by the mechanism that molecular mimicry of gangliosides-like epitopes common to both lipo-polysacharide coats of certain strains of Campylobacter jejuni and gangliosides in cell structure of gastrointestinal mucosa may cause an autoimmune response and consequently lead to atrophy and degeneration of mucosa possibly by apoptosis.

Key words: Celiac disease; Gangliosides; Campylobacter jejuni; Molecular mimicry

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TO THE EDITOR

Celiac disease (CD) is an entropathy with malabsorptive condition in which an allergic reaction to the cereal grain-protein (gluten) causes small intestine mucosal injury. CD is a multifactorial disorder in which both genetic and environmental factors contribute to the disease development[1]. Most of CD patients carry human leukocyte antigens (HLA)-DQ2 or HLA-DQ8. But, this genetic predisposition cannot fully explain the pathogenesis of CD, as CD just develops in minority of HLA-DQ2 and HLA-DQ8 positive individuals[2]. Several mechanisms have been described to explain the pathology of CD. Gluten proteins have several unique factors that contribute to their immunogenic properties. They are extremely rich in amino acid proline and glutamine. Due to high proline content, gluten is highly resistant to proteolytic degradation within the gastrointestinal tract. Moreover, high glutamine content makes gluten a good substrate for tissue transglutaminase (Ttg), which can convert glutamine into negatively charged glutamic acid. Such modified gluten peptides can bind to HLA-DQ8 and subsequently cause T cell response. T cells specific for multiple gluten peptides are found in virtually all patients. Generation of such a broad T cell response may be a prerequisite for disease development[3]. CD is associated with multiple extraintestinal presentations, including bone disease, endocrine disorders and neurological deficits[4].

Neurological disorders and CD

Limited neurological disorders are recognized in association with CD. But, their spectrum becomes wider as complications of prediagnosed CD and/or as an initial manifestation of CD. Neurological disorders include cerebellar ataxia, peripheral neuropathy, epilepsy, dementia, migraine, encephalopathy and Guillain-Barre-like syndrome. Vitamin deficiency due to malabsorption was a first described as the etiology of neurological manifestations. But, it could not explain neurological disorders in patients with normal level of vitamins or in individuals with vitamin deficiency, but without neurological syndromes[5]. Recent studies have shown a significant correlation between anti-ganglioside antibodies, and neurological disorders in patients with underlying CD. Gangliosides are glycosphingolipids which are abundant in the nervous system and in other tissues including gastrointestinal tract[6]. It is not known what triggers the release of anti-ganglioside antibodies in people with gluten sensitivity. But, the mechanism is likely to involve the intestinal immune system response to ingested gliadin, a component of wheat gluten. Two mechanisms have been postulated for the release of anti-ganglioside antibodies: one is the presence of ganglioside-like epitopes in gliadin and the other is the potential for complex formation between gliadin and GM1 ganglioside. One study evaluated the feasibility of these two mechanisms, and found that certain gliadin spices are glycosylated. But, they do not appear to carry GM1-like carbohydrate moieties[7]. In contrast, *in vivo* formation of gliadin-GM1 complexes is probably feasible, since abundant GM1 is found in gut epithelial cells[7].

It was reported that antibody titer is reversed in some patients after gluten-free diet, whereas it increases in other patents after such a diet[8], suggesting that mechanisms different from gluten exposure may be implicated in antibody formation, and other environmental factors may exist.

Hypothesis

The above findings, and the fact that a genetic predisposition dysregulates mucosal immune responses in the presence of certain environmental factors such as gastrointestinal infections are strong etiological factors for development of chronic intestinal inflammation including CD (We can define the hypothesis in our mind that anti-ganglioside antibody formation in CD may play a role not only in developing neurological complications of celiac patients, but also in developing CD itself).

Among disorders associated with anti-ganglioside antibody formation, we focused on an autoimmune disorder with some neurological presentations like CD, and Guillain-Barre syndrome (GBS). In GBS a preceding infection may trigger an autoimmune response through molecular mimicry in which the host generates an immune response to an infectious organism which shares ganglioside-like epitope with the host's peripheral nervous system. Among bacterial organisms which have a role in development of GBS, Campylobacter jejuni has been best studied, showing that about 25% of patients with GBS have a recent Campylobacter. jejuni infection. Now, it is well established that lipo-oligosacharide located in the wall of Campylobacter jejuni cross-reacts with ganglioside in axonal membrane of neurons.

We proposed a possible role of Campylobacter jejuni in development of CD in association with other genetic and environmental factors by the mechanism that molecular mimicry of gangliosides-like epitopes common to both lipo-polysacharide coats of certain strains of Campylobacter jejuni and gangliosides in cell structure of gastrointestinal mucosa may cause an autoimmune response, and consequently lead to atrophy and degeneration of mucosa damage possibly by apoptosis in a manner similar to nerve tissue injury in GBS. The proposed mechanism can also explain the presence of neurological manifestations of CD.

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