Markers of autonomic nervous system impairment in celiac disease: we know the questions to ask but we still do not have answers

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Celiac disease is a chronic systemic disease of an autoimmune background, caused by the ingestion of grains (wheat, rye, barley) containing gluten.[1] It is characterized by immune-mediated chronic inflammatory enteropathy, associated with maldigestion and malabsorption of most of nutrients and vitamins. Celiac disease was first described by Samuel Gee in 1888 in a report entitled "On the Coeliac Affection"; however, a similar description of a chronic, malabsorptive disorder by Aretaeus from Cappadocia (now Turkey) was noted in the second century AD.[2]

Celiac disease occurs primarily in whites of northern European ancestry; its prevalence among Europeans ranges between 1:4000 and 1:8000; however, it is increasingly also found in populations of Northern Africa, the Middle East, India, and Northern China.[3,4]

The clinical presentation of celiac disease differs depending on the patient's age. Adult patients usually present with atypical form of the disease. Patients with atypical disease have only minor gastrointestinal complaints, but they can manifest anemia, dental enamel defects, osteoporosis, arthritis, increased liver enzyme levels, infertility, or neurologic symptoms. Interestingly, however, most of these patients, even with no gastrointestinal symptoms, show also severe mucosal damage and display the celiac-specific antibody pattern.

According to recent recommendations, immunoglobulin A (IgA) anti-intestinal transglutaminase 2 antibody is the most sensitive serological marker, and its detection, together with total IgA, should be the first examination in the diagnostic workup for celiac disease.[5] However, the HLA-DQ2 and HLA-DQ8 haplotypes are also helpful, especially in diagnosis without biopsy.[6]

Numerous autoimmune conditions are frequently associated with celiac disease, including dermatitis herpetiformis, type 1 diabetes mellitus, Down syndrome, selective IgA deficiency, and autoimmune thyroiditis.[7,8] Several papers have demonstrated also an association between celiac disease and neurologic or psychiatric symptoms such as headache, peripheral neuropathy, ataxia, depression, dysthymia, anxiety, and epilepsy. Peripheral neuropathy has been described in up to 50% of patients with celiac disease and may precede its diagnosis.[9] The mechanism of this neuropathy is actually unknown, but it has been suggested that it could be associated with lymphoma or consequences of malnutrition such as deficiency of vitamins B_1 (thiamine), B_2 (riboflavin), B_3 (niacin), B_6 (pyridoxine), B_{12} (cobalamine), and E. The association of gluten hypersensitivity and peripheral neuropathy is still unclear. On the one hand, vitamin deficiency syndromes are uncommon in the absence of extensive small bowel involvement, on the other hand, it has not been demonstrated that gluten-free diet can improve peripheral neuropathies.[10] What is more, it has also been determined that more than half of the patients with neurologic symptoms of unknown etiology have positive serological markers typical of celiac disease.[11]

The relative pathogenic importance of humoral immunity versus the established role of cellular immunity in the pathogenesis of celiac disease is uncertain. The intraepithelial T lymphocytes, the levels of which are increased in patients with active gluten-sensitive celiac disease compared with normal subjects, show increased expression of interferon γ and interleukin 10 (IL-10).[12] Inflammatory lesions in patients with active celiac disease

seem to be related to the response to gluten and are associated with the production of proinflammatory and anti-inflammatory cytokines, such as IL-10. The most important role of IL-10 is to maintain the immunological balance within the structures of the gastrointestinal tract and to reduce inflammation.

It has also been demonstrated that antiganglioside antibodies are present in patients with some neurologic disorders and in patients with celiac disease, including patients with no neurologic symptoms.[13] It is also known that some of those antibodies (GM1) and GD1a play a key role in demyelinating processes. The third player, important in the course of immune system disorders, is the concentration of neuron-specific enolase (NSE). Whether these molecules play a role in the pathogenesis of neurologic symptoms in celiac patients, or at least are important as a marker of such symptoms, is still unclear.

The paper by Przybylska-Feluś et al,[14] published in the October issue of the *Polish Archives of Internal Medicine* (*Pol Arch Med Wewn*) discusses a very important issue concerning the different clinical manifestations of celiac disease, especially neurologic conditions. In this interesting preliminary report, the authors evaluated the prevalence of antiganglioside M1 (anti-GM1) antibodies as well as the concentrations of NSE and IL-10 in patients with celiac disease without neurologic symptoms and in the control group of healthy subjects. They also investigated the correlations between anti--GM1 antibodies, NSE, IL-10, and heart rate variability (HRV) and potential changes in electrogastrography in the group of celiac patients.

In those preliminary data, Przybylska-Feluś et al[14] reported that celiac subjects presented with a higher concentration of anti-GM1 antibodies and IL-10 in comparison with the control group. The difference in NSE levels was not significantly higher in patients with celiac disease. They also showed that changes in HRV depend on IL-10 concentrations, but no correlation was found between the changes in gastric myoelectrical activity and the presence of anti-GM1 antibodies, NSE, and IL-10.

What is really new and what is most interesting in the reported data? The presence of anti-GM1 antibodies has so far been demonstrated in the course of gluten-dependent disorders, such as celiac disease or gluten ataxia.[15] Similar and contrary results to those presented by Przybylska-Feluś et al[14] on IL-10 concentrations have also been reported.[16,17] On the other hand, until now, there have been no studies reporting on NSE concentrations in the serum of celiac patients, although some data on the changes in NSE concentrations in the intestinal tissue in the course of celiac disease can be found.

From the clinical point of view, the most important and interesting part of the presented study is an attempt to correlate clinical conditions such as gastrointestinal motility and heart rate with the investigated markers. Gastrointestinal motility

disorders accompanying celiac disease have already been described, but the mechanisms inducing these disorders have not yet been elucidated. Moreover, the correlations between the changes in gastric myoelectrical activity and the presence of anti-GM1 antibodies, NSE, and IL-10 have not been analyzed so far.

In conclusion, according to the paper by Przybylska-Feluś et al[10] and some other data, it seems to be clear that some markers of autonomic nervous system impairment in celiac disease are already known. However, it is still unclear whether those markers are involved in the pathogenic mechanism of neurologic symptoms. Based on the evaluation of the correlation between IL-10 and changes in HRV, the influence of IL-10 on HRV cannot be excluded. For sure, there is a need for further study on the potential markers of autonomic nervous system damage in the course of celiac disease. The limitation of the presented data is the small number of study participants and lack of the correlation of studied markers with celiac disease activity. According to the presented data, despite the fact that all celiac patients declared compliance with dietary recommendations, histopathological changes in biopsy specimens of duodenal mucosa and/or positive results of serological tests were demonstrated in the majority of subjects. It would be interesting to see whether myoelectrical activity disturbances (HRV and electrocardiography) are dependent on positive serology and/or histopathological changes. It is also unclear what is the concentration of the studied markers in a group of patients presenting peripheral neuropathy symptoms. Until the answers to some of these questions become available, it is necessary to continue research on the pathogenesis of different clinical conditions in celiac disease.

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