



## Review

## Non coeliac gluten sensitivity – A new disease with gluten intolerance

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## SUMMARY

Until recently gluten intolerance has been believed to be typical of celiac disease (CD) and wheat allergy (WA). In the last few years, however, several study results have been published that have proved that gluten intolerance can also affect people who do not suffer from any of the above mentioned diseases. The new syndrome has been named non-coeliac gluten sensitivity (NCGS) or gluten sensitivity (GS). It has been included in the new list of gluten-related disorders published in 2012. Researchers believe that NCGS is the most common syndrome of gluten intolerance. This review discusses many aspects of NCGS epidemiology, pathophysiology, clinical spectrum, and treatment and current tools to identify patients suffering from CD, WA, and NCGS.

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Non-coeliac gluten sensitivity (NCGS) is a new syndrome of gluten intolerance. In literature some other names have been suggested for this disorder, such as gluten sensitivity (GS), gluten hypersensitivity or non-coeliac gluten intolerance [1–5]. Its first name was GS and it was proposed in 2011 by members of the First Expert Meeting on GS [1]. Later, a group of 16 experts who announced a new definition (the Oslo Definition) of celiac disease suggested that instead of GS the disorder should be named NCGS, which made it distinguishable from CD [4]. The Second Expert Meeting on GS that was held in Munich in 2012, decided to change the name of this disorder to NCGS in order to avoid confusion with CD [6].

The first reports about this diseases date back to 30 years ago, but not until recently have numerous reports appeared, primarily about adults, which demonstrate that there is a group of patients whose symptoms have disappeared with gluten withdrawal from diet and they are not affected with either celiac disease (CD) or wheat allergy (WA) [7]. The first case reports of NCGS in children were described in 2012 [8].

NCGS can be diagnosed in those patients with gluten intolerance who do not develop antibodies that are typical neither of CD nor of

WA and who do not suffer from lesions in the duodenal mucosa, which is characteristic of CD. The gluten-free diet leads to complete regression of symptoms [1,3,9]. The overall prevalence of NCGS in the general population is still unknown, mainly because many patients are currently self-diagnosed and start a gluten-free diet (GFD) without medical advice or consultation [6]. The disorder seems to be more common in females and in young/middle age adults [6]. Some authors think that the incidence of NCGS seems to be higher than CD and WA, its estimated numbers reaching 0, 63–6% of the population [5,10–12].

### 1. Genetic background

Half of the NCGS patients have the genes encoding DQ2 or DQ8 molecules in their HLA system [1,6]. It has also been reported that HLA-DQ2 genes are frequently observed in patients with NCGS and with the diarrhoea-predominant irritable bowel syndrome (IBS) [13]. The genes encoding DQ2 or DQ8 molecules (their markers are commonly used in the disease diagnostics) are present in 95% of the CD patients. Negative results for both HLA-DQ2 and HLA-DQ8 excluded the diagnosis of CD in at least 95% (>95% negative predictive value). These genes are present in healthy people as well (30%), but less frequently than in the case of the NCGS patients (50%) [1].

### 2. Clinical manifestation

NCGS is characterized by symptoms that usually occur after gluten ingestion, disappear with gluten withdrawal from diet and

*Abbreviations:* AGA, antigliadin antibodies; ASD, autism spectrum disorders; CD, celiac disease; DGP, deamidated gliadin peptide; EMA, endomysium antibodies; GFCF, gluten-free casein free; GFD, gluten-free diet; GS, gluten sensitivity; IBS, irritable bowel syndrome; NCGS, non-coeliac gluten sensitivity; tTG, transglutaminase antibodies; WA, wheat allergy.

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relapse following gluten challenge [1,3,9,13,14]. Patients suffering from NCGS are a heterogeneous group, composed of several subgroups, each characterized by different pathogenesis and clinical course.

The typical presentation of NCGS is a combination of IBS-like symptoms, and systemic manifestations such as headache, joint and muscle pain, muscle contractions, leg or arm numbness, chronic fatigue, “foggy mind”, body mass loss and anaemia or they can include behaviour disturbances such as the disturbance in attention and depression (Table 1) [3,5,6,10,15]. IBS-like symptoms including abdominal pain, nausea, bloating, flatulence, diarrhoea or constipation. In children, NCGS manifests with intestinal symptoms (abdominal pain and chronic diarrhoea), the extra-intestinal manifestations seem to be less frequent – the most common extra-intestinal symptom being tiredness [8,16].

In people with dyspepsia the increased incidence of NCGS was not observed [17]. Yet, NCGS is increasingly often diagnosed in patients with IBS, especially in those with its diarrhoea-predominant and mixed form [9,18]. Then it is referred to as gluten-sensitive irritable bowel syndrome [18]. Massari et al. report that NCGS is also frequently observed in allergic subjects with allergic disorders [19]. Volta et al. have also proven that NCGS is frequent (13%) in the CD patients' first degree relatives [20].

### 3. Histological manifestation

The NCGS patients' gastrointestinal tracts and their intestinal permeability are normal and the lesions in the histological picture of their duodenal mucosa are minor [21]. They present the IEL growth in epithelium ( $\gamma$  and  $\delta$  class) [10]. Additionally, lymphocytic infiltrations in mucosa were observed which are rated at 0 or I in Marsh's classification [1,3,10,15,21].

Partial or subtotal villous atrophy with crypt hyperplasia is typical of CD and is rated as Marsh III and IV [22]. The CD patients had increased numbers of CD3+ IELs ( $>25/100$  enterocytes), while NCGS and WA patients had a number of CD3+ IELs intermediate between CD patients and controls.

**Table 1**  
Symptoms of non-celiac gluten sensitivity disorders (NCGS).

Disturbances
Intestinal
• Abdominal pains (68%) <sup>a</sup>
• Diarrhoea (33%) <sup>a</sup>
• Nausea
• Body mass loss
• Bloating, flatulence
Cutaneous 40% <sup>a</sup>
• Erythema
• Eczema
General
• Headache (35%), bone and joint pain (11%) <sup>a</sup>
• Muscle contractions (34%) <sup>a</sup>
• Numbness of hands and feet (20%) <sup>a</sup>
• Chronic tiredness (33%) <sup>a</sup>
Haematological
• Anaemia (20%) <sup>a</sup>
Behavioural
• Disturbance in attention <sup>a</sup>
• Depression (22%) <sup>a</sup>
• Hyperactivity
• Ataxia
Dental
• Chronic ulcerative stomatitis

<sup>a</sup> 347 patients treated at the Center for Celiac Research University of Maryland in 2004–2010 [1].

Minor abnormalities (mildly inflamed mucosa) in the histological picture, i.e. Marsh I, are observed much more frequently than CD itself. They have been recently referred to as lymphocytic enteropathy. They occur in NCGS and in other diseases, e.g. in food allergy [23]. Marsh I and II lesions can also be the initial phase of mucosal atrophy in CD, but then patients develop more antibodies characteristic of the CD, mainly anti-transglutaminase (tTG) and anti-endomysium (EMA) antibodies, which does not take place in the case of NCGS [24]. Recently, increased infiltration of duodenal lamina propria with eosinophils and activation of circulating basophils have been described in NCGS patients [25,26].

### 4. Diagnosis

The major dilemma in clinical practice is how to recognise the syndrome that is gluten-dependent but does not meet the criteria of CD and WA [5]. The diagnosis cannot be made until CD and WA have been eliminated (Table 2). The diagnosis is confirmed by a food provocation test, i.e. the same test which is applied in the WA diagnostics. The food challenge procedure is performed by means of an open test (if the symptoms are objective – vomiting, diarrhoea) or a blind test (when the symptoms are subjective – abdominal pain, nausea, headache, tiredness). In NCGS the adverse symptoms appear several hours or days after gluten consumption, while in IgE-dependent WA symptoms appear within 2 h from the food intake [3,6]. In scientific studies, as well as in the diagnostics of other adverse reactions to food, food challenge must be performed by means of a double-blind placebo controlled test. However, the standards of food challenge tests in NCGS patients have not been yet developed, therefore the researchers use the protocols adopted in the diagnostics of adverse reactions to food. Experts recommend food challenge with wheat to be performed after at least 3 weeks of the gluten-free diet [6].

There are no laboratory markers specific to NCGS. It is still a major limitation of clinical studies, making the differential diagnosis with other gluten-related disorders difficult. The only known antibodies observed in the NCGS patients are IgG antigliadin antibodies (IgG-AGA) which, unfortunately, occur in only a half of the patients [20].

### 5. Antigliadin antibodies, AGA

AGA are produced in response to wheat gliadin. They have been used in diagnostics since 1980. For some time the IgA AGA ELISAs were used to diagnose CD but today, due to the fact that their sensitivity and specificity are lower (60.9%–96% and 79.4%–93.8%) than EMA ( $\geq 90\%$  and  $\geq 94.7\%$ ) and tTG ELISAs antibodies ( $\geq 90\%$  and  $\geq 90\%$ ), they are not recommended in the CD diagnostics where they are employed only to diagnose children younger than 18 months whose IgA-AGA sensitivity is high (97.2%) and specificity is lower (83.2%) [27–30].

Also, the IgA-AGA antibodies are present in patients with some autoimmune diseases including the conditions that are both gluten-sensitive (Dühring's disease, gluten ataxia) and gluten-insensitive (rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, sarcoidosis) [18].

Healthy people develop AGA antibodies only in the IgG class with the frequency of 2–8%. They are observed in ¼ of patients presenting with increased intestinal permeability, that is in inflammatory gastrointestinal disorders, food allergy and atopic dermatitis [20]. In these groups of patients high levels of AGA antibodies only in the IgG class have been observed.

The IgG-AGA antibodies are also present in some patients with NCGS, yet their share is smaller than in the case of CD. As Volta et al. observed, IgG-AGA were detected in 56.4% of the NCGS patients and

**Table 2**  
Characteristics of gluten-dependent disorders.

Characteristics	Celiac disease	Non-celiac gluten sensitivity	IgE-dependent wheat allergy
Morbidity	1%	Unknown, possibly 0.6%–6%	1%
Genetic background	In 95%: HLA-DQ2 or HLA-DQ8	In 50%: HLA-DQ2 or HLA-DQ8	In 100% atopy
Pathogenic mechanisms	Disturbances in the acquired immune response to gluten depend on the combination of HLA-DQ2 and HLA-DQ8	Unknown, probably the disturbances in the primary immune response to gluten	IgE-dependent reactions, prevalent Th2 combination in the immune response to wheat allergens
Antibodies in serum	tTG <sup>a</sup> , EMA <sup>a</sup> , DGP <sup>a</sup> , AGA primarily in the IgA class, less frequently in the IgG class	In 50%: IgG-AGA <sup>a</sup>	sIgE for wheat sIgE for $\omega$ 5-gliadin (in anaphylaxis) in 25%: IgG-AGA
Histology of duodenal mucosa	Marsh I-IV, prevalent Marsh III i IV	Marsh 0,I	Marsh 0,I,II
Atrophy of duodenal villi	Present	Absent	May be present
Symptoms	Intestinal and extraintestinal	Intestinal and extraintestinal	Intestinal and extraintestinal
Mortality	Increased	Unknown	Increased <sup>b</sup>
Time of gluten-free diet duration <sup>c</sup>	Lifelong	Unknown	The average of 6 years, individual; lifelong in anaphylaxis

<sup>a</sup> tTG – Tissue transglutaminase, EMA – Endomysium antibodies, DGP – Deamidated gliadin peptide, AGA – Antigliadin antibodies.

<sup>b</sup> In anaphylaxis after wheat consumption.

<sup>c</sup> In wheat allergy only wheat is eliminated from the diet.

in 81.2% of the CD patients, whereas IgA-AGA - in 7.7% and 75% respectively [20]. Thus IgG-AGA cannot be regarded as the NCGS marker, although they can be useful when there is a need to confirm the syndrome in the situation when CD and WA have been ruled out and a patient responds to a gluten-free diet. The IgG-AGA concentrations in the CD and NCGS patients do not differ significantly [20]. The vast majority of NCGS patients showed IgG-AGA disappearance after gluten withdrawal. The same antibodies persisted in 40% of CD patients after gluten-free diet [31]. In NCGS patients the negativization of IgG-AGA was significantly related to good clinical response to gluten-free diet [31].

## 6. Irritable bowel syndrome, IBS

At present it is recommended to perform serological screening for CD in patients with IBS, particularly in those who suffer from its diarrhoea-predominant and mixed form, as it has been proven that in their case the incidence of CD is 4 times higher [32–34].

It also is a well-known fact that persistent minor inflammation of duodenal mucosa can lead to IBS. Such lesions are observed in patients with both WA and NCGS, so their presence can predispose such patients to IBS. As early as in 1993 Arranz and Ferguson confirmed that some IBS patients could develop NCGS [35]. They demonstrate a high level of IgA-AGA and a gluten-sensitive diarrhoea, but there is no enteropathy typical of CD. Recently many authors have pointed out that NCGS is frequent in patients with IBS, especially presenting with its diarrhoea-predominant and mixed form [9,11,13,14,18]. The disorder is then called a gluten-sensitive irritable bowel syndrome. In the large study performed by Carroccio et al., 30% subjects with IBS-like symptoms were suffered from wheat sensitivity [25]. Vazquez-Roque et al. proved that in IBS patients gluten altered intestine barrier functions, particularly in HLA-DQ2/8–positive patients. GFD may improve patient symptoms in IBS [36].

The IBS patients who respond well to a GFD can suffer from one of the three diseases: CD, WA or NCGS, where NCGS is the most likely option (Fig. 1). The presence of IgA-tTG and –EMA and the atrophy of duodenal villi (Marsh III and IV) support the CD diagnosis in patients without IgA deficiency. The presence of sIgE for wheat, a positive food challenge and minimal histological lesions (Marsh 0,1) confirm WA, while the absence of markers typical of CD and WA and minor histological lesions (Marsh 0,1) accompanied by a good response to a GFD indicate NCGS [9]. The presence of AGA antibodies is an additional marker for NCGS in those patients.

## 7. Neuropsychiatric syndromes: autism spectrum disorders (ASD) and schizophrenia

In the past two decades several studies have been published discussing the incidence of NCGS in subjects with Schizophrenia and autism spectrum disorders (ASD).

One of the most popular interventions for ASD is the gluten-free casein free (GFCF) diet. Marcason et al. hypothesized that some symptoms may be caused in the ASD patients by opioid peptides formed from the incomplete breakdown of foods containing gluten and casein [37].

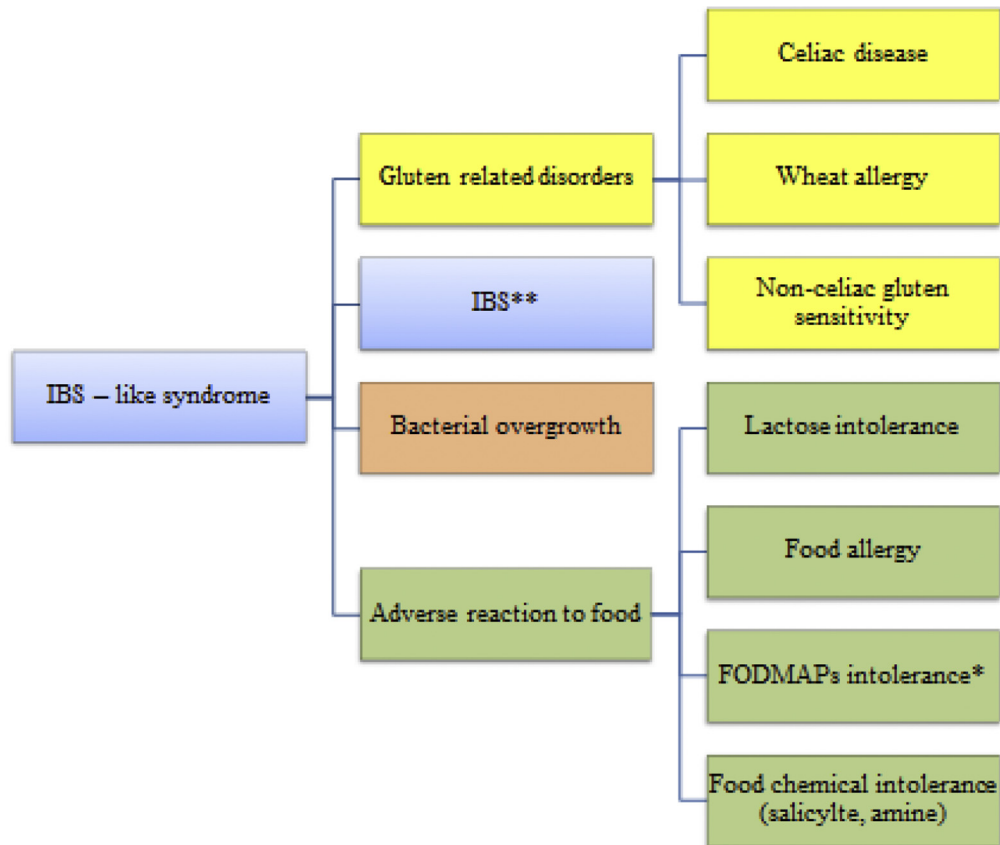
Increased intestinal permeability which occurs in children with ASD allows these peptides to cross the intestinal membrane, enter the blood, and cross the blood-brain barrier, affecting the endogenous opiate system and neurotransmission within the nervous system. The resulting excess of opioids is thought to lead to behaviours noted in ASD. Removal of these substances from the diet could determine a change in autistic behaviours. In the fact only a small group of children affected by ASD may benefit from an GFCF diet indicating that autism may be part of the spectrum of NCGS, at least in some cases. Despite its popularity, the efficacy of this diet in improving autistic behaviour remains not proven [38].

A recent study found that some schizophrenic patients present high level of AGA IgG and anti-tTG antibodies, but only 2% of schizophrenic patients fulfilled the CD diagnostic criteria (both anti-tTG and anti-EMA positive) [39,40]. Additional studies revealed that most of the tTG positive subjects were tTG-6 positive. Anti-tTG-6 is mostly expressed by a particular subset of neurons in the CNS. It is thought to be a biomarker of neuro-inflammation [41]. Other studies confirmed the high prevalence of antibodies to AGA among people with schizophrenia [42]. In some patients on the GFD the improvement of symptoms was observed. The authors believe that a subgroup of schizophrenics may suffer from food intolerances or that circulating food-derived peptides (exorphins) exert an influence on physiological processes in their brains through the same mechanism as in the autism patients.

Today the role of NCGS in diseases affecting the nervous system still remains a controversial and requires additional studies [6].

## 8. Pathogenesis

Aetiologically NCGS is a disorder with poorly recognised pathogenesis [5]. It has not been determined yet what grain ingredients are responsible for the symptoms of the disease. Upon incubation



\*FODMAPs – fermentable oligosaccharides, disaccharides, monosaccharides and polyols

\*\*IBS – irritable bowel syndrome

Fig. 1. Clinical presentation of irritable bowel syndrome (IBS).

with gliadin, mucosa in the patients with NCGS – unlike the duodenal mucosa in the patients with CD – does not express markers of inflammation and their basophils are not activated by gliadin [43]. Another studies suggest that wheat amylase trypsin inhibitors (ATIs) could play a major role as triggers of the innate immune response leading to NCGS [44]. Eswaran et al. believe that this role can be played by the poorly absorbed carbohydrates in wheat grains – fructo-oligosaccharides, fructans (FODMAPs) [45]. In all NCGS patients gastrointestinal IBS-like symptoms significantly improved during reduced FODMAP intake. During fermentation gas is produced and short-chain fatty acid are formed. What is more, changes in microbiota take place resulting in gastrointestinal symptoms. FODMAPs are also present in many other plants. Today, it is believed that they trigger IBS symptoms [46,47].

Contrary to CD, where the secondary immune response is up-regulation, the NCGS patients demonstrate mainly up-regulation of the primary response [10,21]. There is no increased expression of the genes of the secondary immune response including IL-6, IL-21 and INF $\gamma$ , which is characteristic of CD [1]. In the intestinal mucosa there is an increased expression of toll-like receptors 1, 2 and 4 of the primary immune response. Other relevant differences between the CD and NCGS patients are observed in the intestinal barrier function on the level of the epithelial cell tight junction. The CD subjects manifest increased intestinal permeability and raised claudin-1 and zonulin expression, while the NCGS patients demonstrate normal intestinal permeability and a normal level of

the above proteins, but the expression of CLDN4 gene, which synthesizes claudine-4, is high. In the NCGS patients TGF $\beta$ 1 and the FoxP3 markers for regulatory lymphocytes 3 are significantly reduced, which indicates the likelihood of the recruitment of the regulatory T lymphocytes to the small intestine to be smaller than in healthy people. Brottveit et al. showed that after gluten challenge NCGS patients only had increased IFN- $\gamma$  levels and increased density of intraepithelial CD3(+) T cells at baseline but CD patients had a concomitant innate and adaptive immune response [48]. This indicates that the adaptive immune response may play a role in the NCGS pathogenesis.

So far there are no reports comparing the immunological disorders in the intestinal mucosa in WA and NCGS.

## 9. Gluten-related disorders

In 2011 in London a panel of 15 experts announced a new classification of gluten-related disorders that was then published in February 2012 (Fig. 2) [1]. Catassi et al. expressed the opinion that the term “gluten-related disorders” is the umbrella-term to be used for describing all the conditions related to ingestion of gluten-containing food [6]. The classification covers a wide range of disorders including allergies (food allergy, anaphylaxis, wheat-dependent exercise induced anaphylaxis, baker’s asthma, contact dermatitis), autoimmune diseases (celiac disease, dermatitis herpetiformis, gluten ataxia) and the diseases that are likely to be immune

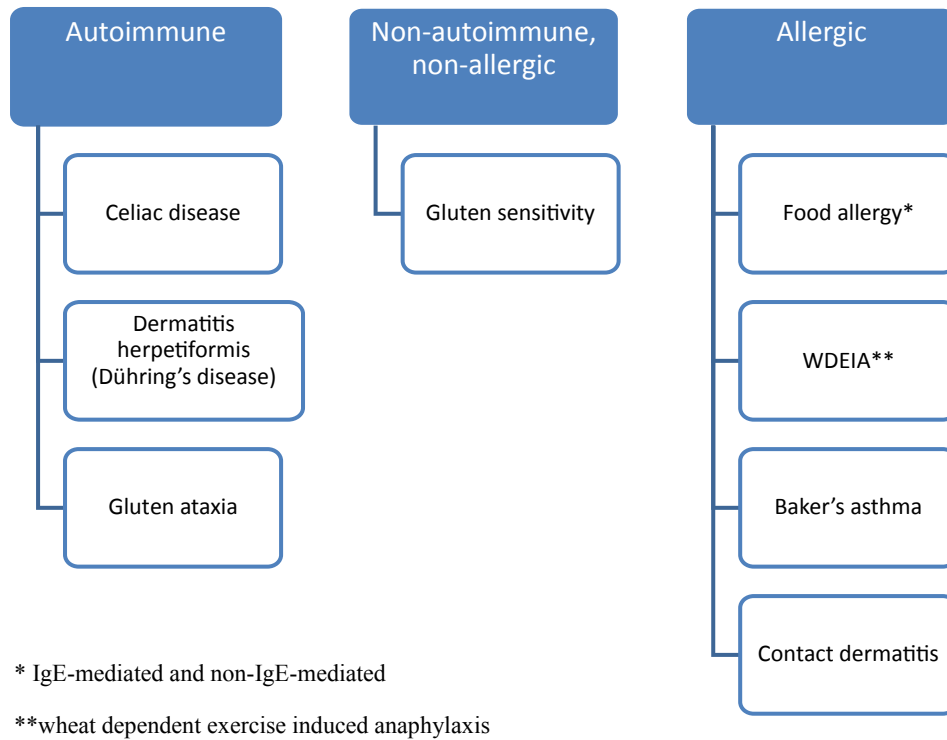


Fig. 2. Classification of gluten-related disorders.

mediated (gluten sensitivity). At the Second Expert Meeting on GS that was held in Munich in 2012, it was noted that besides the IgE-mediated WA the non-IgE-mediated WA existed as well [6]. This form of WA may be difficult to distinguish from NCGS [6].

Groups of gluten-related disorders are manifested not only by disturbances in the gastrointestinal tract, but also by dermatological, haematological, endocrinological, rheumatological, gynaecological, dental and neurological symptoms. After the administration of a GFD the symptoms disappear. However, when the diet is abandoned, all the symptoms recur [1].

What is critical for making right diagnostic decisions is to carefully define the symptoms and choose such serological tests and histological imaging of duodenal mucosa that make it possible to distinguish between different gluten-dependent disorders with their varying courses, diet protocols, prognoses and complications [49,50].

### Conflict of interest

None.

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