



Non-celiac gluten sensitivity: people without celiac disease avoiding gluten—is it due to histamine intolerance?

Wolfgang J. Schnedl^{1,2} · Sonja Lackner¹ · Dietmar Enko³ · Michael Schenk⁴ · Harald Mangge⁵ · Sandra J. Holasek¹

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Abstract

Introduction Food intolerance/malabsorption is caused by food ingredients, carbohydrates (mainly lactose and fructose), proteins (gluten), and biogenic amines (histamine) which cause nonspecific gastrointestinal and extra-intestinal symptoms. Here we focus on possible etiologic factors of intolerance/malabsorption especially in people with non-celiac gluten sensitivity (NCGS) or the so-called people without celiac disease avoiding gluten (PWCDAG) and histamine intolerance.

Methods Recognizing the recently described symptoms of NCGS (PWCDAG) we review correlations and parallels to histamine intolerance (HIT).

Results We show that intestinal and extra-intestinal NCGS (PWCDAG) symptoms are very similar to those which can be found in histamine intolerance.

Conclusions After a detailed diagnostic workup for all possible etiologic factors in every patient, a targeted dietary intervention for single or possibly combined intolerance/malabsorption might be more effective than a short-term diet low in fermentable oligo-, di- and monosaccharides and polyols (FODMAP) or the untargeted uncritical use of gluten-free diets.

Keywords Histamine intolerance · Diamine oxidase · Food intolerance · Food malabsorption · Non-celiac gluten sensitivity

Introduction

Food malabsorption syndromes and non-immunological food intolerances are reported in approximately 20% of the population in westernized countries and they cause nonspecific gastrointestinal symptoms and several extra-intestinal

symptoms [1, 2]. Food intolerance/malabsorption is caused by certain food ingredients, carbohydrates (mainly lactose and fructose), proteins (gluten), and biogenic amines (histamine) which impair digestion [3]. Here we describe possible etiologic factors of intolerance/malabsorption, especially in people with non-celiac gluten sensitivity (NCGS) and people without celiac disease avoiding gluten (PWCDAG), and their link to histamine intolerance. Recognizing the recently described symptoms of NCGS (PWCDAG) we discuss correlations and parallels to histamine intolerance (HIT). Food malabsorption or intolerance requires personalized treatment and an individual dietary intervention for sustained relief of symptoms. After a detailed diagnostic workup for all possible etiologic factors in each patient, a targeted dietary intervention for single or possibly combined malabsorption might help more than an untargeted diet low in fermentable oligo-, di- and monosaccharides and polyols (FODMAP) or the widespread uncritical use of gluten-free diets.

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✉ Wolfgang J. Schnedl
w.schnedl@dr-schnedl.at

¹ Institute of Pathophysiology, Centre for Molecular Medicine, Medical University of Graz, Heinrichstrasse 31a, 8010 Graz, Austria

² Department of Internal Medicine, Practice for General Internal Medicine, Dr. Theodor Körnerstrasse 19b, 8600 Bruck/Mur, Austria

³ Institute of Laboratory Medicine, General Hospital Steyr, Sierninger Straße 170, 4400 Steyr, Austria

⁴ Das Kinderwunsch Institut Schenk GmbH, Am Sendergrund 11, 8143 Dobl, Austria

⁵ Clinical Institute of Medical and Chemical Laboratory Diagnosis, Medical University of Graz, Auenbruggerplatz 30, 8036 Graz, Austria

Non-celiac gluten sensitivity: people without celiac disease avoiding gluten

Celiac disease or gluten malabsorption is an autoimmune disorder that occurs in genetically predisposed persons as a reaction to ingested gluten proteins, which are mainly found in wheat, rye, and barley. Celiac disease can be diagnosed with serologic testing and histologic confirmation, and has an estimated global prevalence of up to 5% in the general population. A gluten-free diet is the only effective treatment [4].

The use of gluten-free diets has rapidly increased in popularity and are followed by up to 20% of the population in Europe and the United States, mainly by people without celiac disease [5]. Therefore, a new symptom-based disorder related to the consumption of gluten-containing products, namely non-celiac gluten sensitivity (NCGS), is under discussion [6–9]. Since there are no diagnostic criteria available for these people they may be called “people without celiac disease avoiding gluten” (PWCDAG) [10]. So far, the diagnosis of NCGS (PWCDAG) solely relies on self-reported symptoms by patients and is self-diagnosed and then self-treated [11]. Although symptoms alone or symptom complexes are rarely, if ever, diagnostic [12], NCGS (PWCDAG) is characterized by a combination of a wide variety of intestinal and extra-intestinal symptoms (Table 1). However, since no specific blood test or radiological and/or endoscopic examination is known for NCGS (PWCDAG), factors other than gluten are suspected to cause NCGS (PWCDAG). A recent study demonstrated that gluten-containing cereals have a high content of amylase–trypsin inhibitors and this increased intestinal inflammation via activation of the toll-like receptor of myeloid cells [13]. There is some evidence that other factors, for example, the oligosaccharides fructane or galactane in wheat, might cause the reported symptoms [14]. It is also

suspected that people with NCGS (PWCDAG) constitute a group of patients with irritable bowel syndrome (IBS) who are self-diagnosed and perform self-treatment by adhering to a gluten-free diet [15].

Withdrawal of wheat products reduces the symptom severity and improves the quality of life in persons with NCGS (PWCDAG) [16] and novel plant breeding strategies are being used to produce gluten-reduced grains. However, a gluten-free diet is expensive, usually high in fat and low in fibre [17], and is therefore, not recommended for healthy people because it may even lead to adverse health effects, as it may be associated with a higher risk of type 2 diabetes mellitus [18]. So far, it seems that gluten-containing food triggers the symptoms in NCGS (PWCDAG) despite the fact that NCGS (PWCDAG) is not well defined.

Gluten-containing grains are found in many foods, including bread, pasta, pizza, bulgur, couscous, and drinks such as beer [4]. However, most of these foods and drinks also contain the biogenic amine histamine [19] and/or they are usually consumed with additional histamine-containing seasonings. Many gluten-containing bakery goods and beers contain yeast [20, 21], and bulgur, pasta and pizza [22] are consumed regularly with tomatoes and other seasonings which because of their high histamine content are not digested and metabolized properly in people with histamine intolerance (HIT) [19, 23, 24]. Here we show that intestinal and extra-intestinal NCGS (PWCDAG) symptoms are very similar to those which can be found in histamine intolerance [25, 26]. Gastrointestinal nonspecific symptoms in HIT include postprandial fullness, flatulence, bloating, abdominal pain, loose stools, diarrhea and/or obstipation. Extra-intestinal symptoms include headache, migraine [27], foggy mind, chronic fatigue [28], joint and muscle pain, tingling of extremities, leg or arm numbness [29], eczema [30], asthma [31] and depression [28]. All of these may be associated with NCGS (PWCDAG), too (Table 1). However, withdrawal of gluten-containing wheat products reduces the

Table 1 Symptoms reported in NCGS (PWCDAG) with possibly corresponding histamine receptors

Intestinal symptoms in NCGS	Histamine receptors	Extra-intestinal symptoms in NCGS	Histamine receptors
Bloating [6–9], gas [5], flatulence [8]	H ₂ R, H ₄ R	Fatigue [5, 7], tiredness [6, 9], lack of wellbeing [8]	H ₃ R
Abdominal pain [5–8], stomach-ache [9], acidity [9], reflux [9]	H ₂ R	Headache [5, 6, 8], migraine [5], confusion [8, 9], foggy mind [5]	H ₂ R, H ₃ R
Nausea [6, 8, 9], vomiting [9]	H ₂ R, H ₃ R	Eczema [5, 6], rash [8], hives [9], dermatitis [9], erythema [6]	H ₁ R, H ₄ R
Belching [8], abdominal discomfort [8, 9]	H ₂ R	Depression [5, 6, 8], anxiety [9], disturbance in attention [6], confusion [8, 9], hyperactivity [6]	H ₃ R
Distension [5], irregular bowel movements [5]	H ₄ R	Joint and muscle pain [5, 6, 8, 9], tingling of the extremities, leg or arm numbness [5, 6, 9]	H ₄ R
Diarrhea [6–9], constipation [8, 9]	H ₂ R, H ₄ R	Rhinitis [9], angioedema [9]	H ₃ R
		Trouble breathing [9]	H ₄ R

Reference numbers mentioning the symptoms of NCGS (PWCDAG)

overall quantity of the parallel consumption of histamine, which also reduces HIT-associated symptoms and this may explain the current wide spread popularity of gluten-free diets.

The only symptom which is described with NCGS (PWCDAG) that was not included in the table of symptoms (Table 1) is anaemia, because there is no correlation to histamine receptors. Additionally, co-incidence data on patients infected with *Helicobacter pylori*, the Gram-negative pathogen in the stomach frequently causing iron-deficiency anaemia [32, 33], are neither known for NCGS (PWCDAG) nor for HIT.

Histamine intolerance

The discovery of histamine [2-(4-imidazolyl)-ethylamine] dates back more than 100 years and histamine plays an important role as a mediator in allergic reactions including inflammation. New receptors of histamine were discovered and its importance in immune regulation leads to the development of selective antihistamine medications. The histamine pathway in allergic disease is described with several pharmacogenetic variations influencing disease expression and a response to treatment [34].

The name “histamine intolerance” is used due to postulated diamine oxidase (DAO) enzyme deficiency with reference to the term lactose intolerance. A scombroid poisoning is caused by consumption of fish contaminated with bacteria that cause high concentrations of histamine. Ingested histamine, even in small quantities, clearly below the dose causing scombroid poisoning, is suspected to cause HIT-related symptoms in affected people [35].

A disproportionate amount of histamine in the body is suspected to result from the consumption of histamine-containing food or drinks, and a reduced ability of enzymes (diamine oxidase and histamine N-methyl transferase) to digest histamine. Histamine is widely distributed throughout the body and within the gastrointestinal tract DAO appears to be the primary enzyme for the degradation of ingested histamine [36]. DAO is synthesized by mature apical enterocytes located in the upper intestinal villi and is continuously released from the intestinal mucosa for digestion and into the blood circulation [37]. Mucosal damage in the small intestine caused by, e.g., gastroenteritis, short bowel syndrome, gastrointestinal surgery and various drugs may also reduce DAO activity [38].

There are polymorphisms identified in the genes coding for DAO [39, 40] and for the known histamine receptors [41] which may help to explain the wide individual variability of symptoms observed in multiple organs. These polymorphisms may also influence disease expression and potentially the response to diets or treatment. Although

these polymorphisms have been identified, their functional and clinical significance has not yet been determined. The clinical diagnosis of histamine intolerance (HIT) is difficult [25], and standardized in vitro diagnostic tests for HIT testing are still lacking, but the diagnosis of HIT may be supported with the measurement of diamine oxidase in serum [42]. Although serum DAO values have not been shown to correlate with gastrointestinal DAO activity, patients with reduced serum DAO activity (< 10 U/mL), two or more typical gastrointestinal symptoms described for HIT, and a reduction of abdominal complaints after following a histamine reduced diet, may be diagnosed with HIT [25, 43]. Concerning all these limitations determinations of serum DAO in well-defined patients with NCGS (PWCDAG) are needed to evaluate if their DAO activity is reduced [44].

Recently a high prevalence of low serum DAO values in patients with carbohydrate (lactose and fructose) intolerance/malabsorption was described. In patients with non-specific gastrointestinal symptoms seven combinations of intolerance/malabsorption were described and more than 55% of these patients demonstrated DAO values < 10 U/ml [3]. It was reported that an individual and subjective perception of nonspecific gastrointestinal symptoms, which is often associated with carbohydrate malabsorption, also needs to be considered [45, 46]. Additionally, a so-called visceral hypersensitivity seems to play an essential role in gastrointestinal symptoms, but the triggers of these symptoms are still not understood and HIT may also play a role. Another factor to be considered is that the histamine content in food varies considerably depending on ripeness, storage time, and processing [47]. All of these variables need to be considered and may help to explain each person's unique and even sometimes changing tolerance levels of food intolerance/malabsorption.

Discussion

There is increasing interest in food intolerance/malabsorption syndromes causing nonspecific abdominal complaints and what dietary triggers may be responsible. In recent years advances have led to a better understanding of the role of certain nutrients and food components. The gastrointestinal bacteria use various catabolic enzymes to degrade and ferment carbohydrates and proteins from food [48]. However, several experiments suggest that the amount and type of dietary carbohydrates and proteins affect the metabolic output of these microbes [49]. Food intolerance/malabsorption causes gastrointestinal nonspecific and extra-intestinal symptoms when a particular nutrient or a combination of certain nutrients cannot be absorbed and digested properly.

In fructose intolerance or malabsorption the sugar fructose is not absorbed adequately by glucose transporters in the

small intestine [50]. Lactose intolerance is the inability to digest lactose found in milk and dairy products due to a deficiency of the lactose degrading enzyme lactase. In patients with intolerance/malabsorption, these carbohydrates, fructose and/or lactose, reach the large intestine where they are metabolized by intestinal bacteria, resulting in fermentation and hydrogen production. Therefore, for the clinical testing and diagnosis of lactose and fructose intolerance/malabsorption, using a hydrogen breath test is helpful in patients with nonspecific abdominal complaints [51]. Studies reported combined lactose and fructose intolerance/malabsorption in patients with functional gastrointestinal disorders [52] and demonstrated variable combinations of lactose, fructose and histamine intolerance/malabsorption [3].

One suggested diet for nonspecific abdominal complaints is a diet low in fermentable oligo-, di- and monosaccharides and polyols (FODMAP) which restricts a wide variety of foods from different food groups (cereals, fruits and vegetables, milk and dairy products) [53]. It is stated that patients with food malabsorption should be advised to avoid dietary triggers for as short a time as possible, usually 3–4 weeks, to induce symptom improvement [15]. Since there are several known genetic polymorphisms for lactase [54], celiac disease [55], DAO and histamine receptors [39–41], some genetic background might also exist for fructose malabsorption [56]. There are various combinations of intolerance/malabsorption [3], and a gradual food reintroduction within a short time period may cause the symptoms to return. Some clinical evidence supports the use of a low FODMAP diet for a limited time in clinical practice, but due to the genetic background and various combinations of intolerance/malabsorption, the short-term dietary changes with a low FODMAP diet can have only modest and rapidly reversible effects.

After a detailed individual diagnosis of single or combined food intolerance/malabsorption, a registered dietician is needed to develop an individually tailored diet to ensure nutritional adequacy [57, 58]. Since changes to diet clearly have an effect on the gastrointestinal microbiome, the effect of long-term removal of specific foods or food components is unknown [59]. It also seems important to consider the individual's tolerance level when recommending dietary restrictions to reduce symptoms for a long time, to enlarge dietary variety, ensure nutritional adequacy and cause a minimal impact on the gastrointestinal microbiota [23].

Conclusions

Nonspecific abdominal complaints need to be assessed individually. All etiologic factors of intolerance/malabsorption including fructose, gluten, histamine, lactose, and *Helicobacter pylori* infection must be evaluated. Intolerance/

malabsorption can then be treated by reducing the ingestion of the triggering nutrients and/or treating the *Helicobacter pylori* infection based on a detailed diagnosis and the individual tolerance level to the symptomatology.

Compliance with ethical standards

Conflict of interest Wolfgang J. Schnedl received speaking honoraria from Sciotec. The other authors declare no competing interests.

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