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REVIEW



Considering histamine in functional gastrointestinal disorders

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ABSTRACT

In westernized countries, adverse reactions to ingested foods are reported to affect up to 20% of the population. Functional, nonspecific, non-allergic gastrointestinal complaints are mainly due to the intolerance/malabsorption of carbohydrates (lactose and fructose), proteins (gluten), and biogenic amines (histamine). Food intolerance/malabsorption is defined by one or several of the above mentioned food components not being degraded and/or absorbed properly within the gastrointestinal tract. Food intolerance/malabsorption causes variable, functional, nonspecific, non-allergic gastrointestinal and extra-intestinal complaints, and a detailed diagnostic workup for all possible etiologic factors in individual patients is essential. Usually, evaluation for histamine intolerance is not included in differential diagnoses of patients with functional, nonspecific, non-allergic gastrointestinal complaints. A targeted dietary intervention for single or possibly combined intolerance/malabsorption is required. In this article, we review currently discussed differential diagnoses and available tests for intolerance/malabsorption. Accordingly, we aim to outline why including histamine and, histamine intolerance, should be considered in differential diagnoses of patients with functional, nonspecific, non-allergic gastrointestinal complaints.

KEYWORDS

Histamine; lactose; fructose; diamine oxidase; food intolerance; food malabsorption; mastocytosis

Introduction

Adverse reactions to ingested foods causing functional, non-specific, non-allergic gastrointestinal complaints are due to the intolerance/malabsorption of carbohydrates (lactose and fructose), proteins (gluten), and biogenic amines (histamine). However, there is a lack of understanding of these functional, nonspecific, non-allergic symptoms and diagnoses are limited by the lack of accepted standardized tests for the underlying mechanisms (Talley 2020). Due to these disorders being increasingly discussed in the media, a growing number of people change their diets. Nevertheless, intolerance/malabsorption is causing variable gastrointestinal (GI) and extra-intestinal complaints (Mitchell et al. 2019). Generally, symptoms are observed subjectively, and intolerance/malabsorption-caused symptoms are not dependably confirmed by medical tests. Scientific evidence to support this postulated link is increasing, but reliable comprehensive evaluations and/or laboratory tests for definite diagnoses are still needed (Reese et al. 2017).

Food intolerance/malabsorption requires detailed diagnostic examination with available tests for all possible etiologic aspects of each individual patient and, subsequently, personalized treatment with individual dietary plans. Only the targeted dietary intervention for each single, or possibly combined, intolerance/malabsorption may help to provide sustained relief (Enko et al. 2016). Here we review currently discussed differential diagnoses and available tests, and outline why including histamine intolerance (HIT) in the

differential diagnoses of intolerance/malabsorption should be considered for patients with functional, nonspecific, non-allergic GI and extra-intestinal complaints.

Food intolerance and malabsorption

There is growing public interest in food intolerance/malabsorption for people who experience reactions to food. Food intolerance/malabsorption causes functional, nonspecific, non-allergic GI complaints and extra-intestinal symptoms. In westernized countries, adverse reactions that may influence and impair digestion are reported to affect up to 20% of the population (Mitchell et al. 2019).

Recent investigations have led to an improved understanding of food components, particularly of sugars (lactose and fructose), proteins (gluten), and biogenic amines (including histamine). In most cases of intolerance/malabsorption one or a combination of the above described food components cannot be degraded and/or absorbed properly within the GI tract. GI bacteria then use various catabolic enzymes to degrade and ferment ingested food. However, experiments suggest that the quantity, type and composition of dietary carbohydrates and proteins change the metabolic output of these microbes (Schink et al. 2018; Albenberg and Wu 2014).

Carbohydrate intolerance/malabsorption

Carbohydrate intolerance/malabsorption is mainly caused by lactose intolerance and fructose malabsorption. Lactose intolerance, with an estimated global prevalence of approximately 70 percent in the world's population, is present in most countries. It is the inability to digest the disaccharide lactose which is mainly found in milk and dairy products. Lactose malabsorption is due to the deficiency of the lactose-degrading enzyme lactase, which hydrolyzes lactose into two monosaccharides, namely glucose and galactose (Storhaug, Fosse, and Fadnes 2017; Ugidos-Rodríguez, Matallana-González, and Sánchez-Mata 2018). If the ingestion of lactose is accompanied by GI symptoms, then it is referred to as lactose intolerance. The clinical diagnosis of lactose intolerance is mainly performed with a hydrogen breath test. During this test a drink containing 50 g of lactose is ingested and the exhalation of hydrogen (H_2) is measured subsequently. Genetic testing for lactase persistence may be performed, but the clinical use of genetic tests has been criticized. It does not describe clinical manifestations or symptoms, and it is limited due to an increasing number of known single nucleotide polymorphism mutations (Casellas et al. 2010).

As outlined below, the diagnosis of histamine intolerance (HIT) may be supported by measurements of a serum diamine oxidase (DAO) value. During H_2 breath tests, performed in patients with lactose intolerance and serum DAO values < 10 U/mL, higher end-expiratory H_2 levels were observed. In addition, these patients reported more symptoms during the H_2 breath tests when compared to lactose-intolerant patients with DAO values > 10 U/mL. This study described the effect of HIT on the perception of functional, nonspecific, non-allergic GI symptoms and concludes that HIT needs to be considered in lactose-intolerant patients (Enko et al. 2017).

The growing amount of ingested fructose, particularly high-fructose corn sirup, is resulting in an increasing occurrence of complaints caused by fructose malabsorption. In this malabsorption the monosaccharide fructose is not adequately absorbed by the epithelial glucose transporters, GLUT-5 and GLUT-2, in the intestinal mucosa (Gibson et al. 2007). Fructose malabsorption is described in several studies and detailed reviews (Latulippe and Skoog 2011; Tuck et al. 2017).

With intolerance/malabsorption, the sugars lactose and fructose reach the large intestine where they are a bacterial substrate. This results in fermentation with hydrogen production. Therefore, the clinical diagnosis of fructose malabsorption is also performed with the H_2 breath test. Usually, the breath test for diagnosis of fructose malabsorption is performed with a drink containing 25 g fructose. There is a dose-dependent and limited absorption capacity with 50 g fructose described in up to 80% of healthy individuals (Jones, Butler, and Brooks 2011).

Evaluations have reported combined lactose intolerance and fructose malabsorption in more than 30% of patients with carbohydrate intolerance/malabsorption and functional, nonspecific, non-allergic GI disorders (Wilder-Smith et al.

2013). We described a high prevalence of 55% serum DAO values < 10 U/mL, indicative of HIT, occurring in patients with carbohydrate intolerance/malabsorption. Seven various combinations of intolerance/malabsorption were described in patients with functional, nonspecific, non-allergic GI symptoms (Enko et al. 2016). Further descriptions and studies on symptom perception and clinical differences also the changes of the microbiome, in these various combinations of intolerance/malabsorption, including HIT, are needed.

Irritable bowel syndrome-like disorders

There is an imprecise clinical overlap between irritable bowel syndrome (IBS) and other IBS-like disorders. The most commonly reported symptom-oriented conditions are IBS, functional dyspepsia (FD) and small intestinal bacterial overgrowth (SIBO). All of these present with various functional, nonspecific, non-allergic GI symptoms, predominantly abdominal pain, bloating and diarrhea (Borghini et al. 2017). These GI symptoms, including multiple combinations of these, are also reported by patients with HIT (Schnedl, Schenk, et al. 2019).

Generally, there is a lack of specificity of symptoms, therefore symptoms alone or symptom complexes are hardly, if ever, diagnostic (Verdu, Armstrong, and Murray 2009). It is suspected that various pathogenetic mechanisms may be responsible for IBS (Chey 2016). However, 80% of IBS patients identified food, including histamine, as a possible trigger for their symptoms (Böhn et al. 2013). Currently IBS is defined and discussed within the Rome IV criteria (Schmulson and Drossman 2017). These clinical conditions, such as IBS, FD and SIBO continue to be nebulous and were therefore recently re-named IBS-like disorders (Borghini et al. 2017). Finally, the triggers of these symptom-focused disorders are not well understood and HIT, with its plethora of symptoms, may play a role.

In the search for etiologic factors, dietary nickel (Ni) was recently described as a possible causative factor in patients with IBS-like symptoms (Borghini et al. 2016). Interestingly, several foods described as containing Ni, including tomatoes, cocoa, mushrooms, shellfish, nuts, and canned foods contain histamine, and are consequently not well digested by HIT patients.

Celiac disease

Celiac disease (CD) or gluten malabsorption is a well-defined autoimmune disorder characterized by a reaction to ingested gluten proteins that occurs in genetically predisposed persons. Gluten proteins are mainly found in wheat, rye and barley. The diagnosis of celiac disease is performed with serologic testing and needs histologic confirmation in duodenal biopsies. Although there are a number of undetected "silent" celiac patients suspected, the frequency of biopsy-proven CD was found to be approximately 1% in the general population (Mustalahti et al. 2010). In celiac disease the gluten-free diet is the only effective treatment (Valenti et al. 2017). Patients with CD who do not comply

with a gluten-free diet are at risk for concomitant diseases including osteoporosis, lymphoma, and autoimmune disorders (Ventura, Magazzù, and Greco 1999). Histamine- and other inflammatory mediators releasing mast cells have also been linked with CD, showing that mast cells infiltrating the mucosa were associated with the severity of mucosal damage (Frossi et al. 2017).

Non-celiac gluten sensitivity (NCGS)

The range of gluten-related disorders has expanded with the description of a new clinical condition, non-celiac gluten sensitivity (NCGS) (Dale, Biesiekierski, and Lied 2019). Typically, patients with NCGS test negative with all available diagnostic tests for celiac disease (CD). However, since there are no diagnostic criteria available for NCGS, affected people were also named “people without celiac disease avoiding gluten” (Choung et al. 2017). Currently, up to 20% of the westernized world’s population are avoiding gluten because of self-diagnosed NCGS with GI and/or extra-intestinal symptoms. Unproven hypotheses of supposed health benefits due to gluten-free eating are being spread (Vici et al. 2016).

A recently created term, non-celiac wheat sensitivity, has been proposed as more accurate. It allows for the inclusion of other suspicious symptom-causing non-gluten wheat components such as fructane, galactane, and amylase–trypsin inhibitors (Zevallos et al. 2017). In addition, it has been proposed that people with NCGS 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 (Catassi et al. 2017; De Giorgio, Volta, and Gibson 2016).

Gluten-containing bakery goods and beers are frequently made with yeast, which produces histamine (Qi et al. 2014; Verheyen et al. 2015). Universally consumed food including pasta, pizza and bulgur are commonly consumed with tomatoes and seasonings which, because of their histamine content (Bolygo et al. 2000), are not digested well in people with HIT. Moreover, we reported that in NCGS the GI and extra-intestinal symptoms resemble those found in HIT. However, the reduction of gluten-containing food and drinks cuts the quantity of parallel histamine consumption (Schneidl et al. 2018). This may help explain the current extraordinary popularity of gluten-free food intake.

***Helicobacter pylori* (H.p.)**

H.p. causing a change of the gastric environment and with this affecting the absorption of certain nutrients has been described (Franceschi et al. 2014). Although the involvement of an infection with *H.p.* in functional dyspepsia is controversial, some studies support the connection of *H.p.*-induced gastritis in the pathogenesis of dyspeptic symptoms. Recently, in areas with a high prevalence of *H.p.*, it was reported that *H.p.* eradication improves dyspepsia. Additionally, conflicting associations of *H.p.* with gastroesophageal reflux disease were published (Jonaitis, Pellicano, and Kupcinskas 2018). An association between *H.p.*

infection and CD was demonstrated because CD patients had significantly lower rates of gastric *H.p.* compared to healthy patients (Lebwohl et al. 2013). In patients with functional, nonspecific, non-allergic GI symptoms, an *H.p.* infection needs to be considered and eradication therapy is required (Tomita, Oshima, and Miwa 2018). Evaluations of HIT in *H.p.* infection are needed because the main stimulants of gastric acid secretion are gastrin and histamine, which in concert with *H.p.* may increase or decrease acid secretion (Schubert 2017).

Generally, GI endoscopy with histologic evaluation of GI mucosa and ultrasound of the abdomen are valuable extra options for the evaluation of patients, especially aged >50 years with functional, nonspecific, non-allergic GI symptoms (Bai et al. 2018). If signs of infection are evident, then GI infections need consideration to start specific antimicrobial or anti-parasitic treatments that may reverse disease.

Mast cell activation syndrome (MCAS)

Intra-corporeal produced histamine appears to have less influence on HIT except in cases of mastocytosis. Mast cells (MCs) are heterogeneous, multifunctional cells basically involved in immunity and inflammation. Blood MCs produce various inflammatory and vasoactive mediators, and store them in intracellular, metachromatic granules (Varricchi et al. 2019). MCAS is a condition where an increased number of mast cells, inadequately, due to still unknown factors, release histamine and other mediators, resulting in a variety of symptoms. Generally, symptoms in MCAS are nonspecific and include: urticaria, flushing, abdominal cramps, diarrhea, collapse, and tachycardia. These may range from mild to severe, potentially life-threatening, especially in patients with mastocytosis and concomitant allergy. Recently, consensus criteria were defined for MCAS with severe, recurrent symptoms that, affect more than one organ, frequently in combination with hypotension and anaphylaxis. However, there certainly is a relation of functional, nonspecific, non-allergic GI and extra-intestinal complaints in MCAS and HIT. Nevertheless, HIT predominantly causes GI symptoms (Schneidl, Schenk, et al. 2019; Valent et al. 2019). Helpful for diagnosis in MCAS patients are serum tryptase values and, it was reported that DAO and tryptase significantly increase during anaphylaxis in MCAS patients (Boehm et al. 2019).

The Mas-related G protein-coupled receptor family (Mrgprs) members were identified as itch receptors in cutaneous sensory neurons. Now, they have become a target in abdominal pain research. Recently, a novel function for Mrgprc11 in the mouse gut nociceptive innervation was found (Van Remoortel et al. 2019) and in mice phenothiazine antipsychotics were shown to increase histamine levels over Mrgprb2 (Hou et al. 2019). Given these functions of Mrgprs in humans, the mentioned findings therefore deserve future research and may also help to elucidate pathology of HIT.

Eosinophilic gastroenteritis (EGE)

EGE is a digestive disorder that is characterized by eosinophilic infiltration into the gastrointestinal mucosa. The underlying mechanisms to this disease are still unknown. However, eosinophils and mast-cells recruitment and activation seem codependent. Mast cells induce eosinophils in the mucosa, and eosinophils in turn can activate mast cells. This is commonly accepted as the eosinophil–mast cell axis, involved in functional GI disorders, associated with increased visceral sensitivity and disordered motility. Although, in EGE corticosteroids seem the mainstay of effective therapies, alternative therapeutic regimens include mast-cell stabilizers and antihistamines. Symptoms in EGE like abdominal pain, nausea, vomiting, dyspepsia, diarrhea, eczema and rhinitis (Sunkara et al. 2019), resemble several complaints of HIT (Schnedl, Schenk, et al. 2019).

An own entity seems eosinophilic esophagitis as a chronic immune disease, characterized by a dense eosinophilic infiltrate in the mucosa of the esophagus. Food impaction and reflux-like symptoms are main complaints. The pathophysiology of this localized inflammation is also unknown, but it was suggested that several cytokines and, besides others, a proliferation of eosinophils and histamine-releasing mast cells is involved (D'Alessandro et al. 2015). It remains to be evaluated how a histamine-reduced diet influences MCAS and EGE.

Histamine

Histamine [2-(4-imidazolyl)-ethylamine] was discovered more than 100 years ago and it plays an important role in allergic reactions and inflammation (Jones and Kearns 2011). Histamine belongs to a group of biogenic amines including putrescine, cadaverine and agmatine, which are produced by bacterial decarboxylation of foods (Doeun, Davaatseren, and Chung 2017).

Usually the consumption of low amounts of biogenic amines in humans does not affect their health. In food the amount of histamine is affected by multiple factors, including the manufacturing process, the cleanliness of raw materials, microbial composition, and the duration of fermentation. Histamine is a result of the decarboxylation of the amino acid histidine. Endogenous histamine is stored primarily in mast- and basophil cells. It is an important mediator of immunoglobulin E (IgE) and non-IgE-dependent clinical allergic reactions. The understanding of the histamine pathway in allergies and in immune regulation has led to the development of several antihistamine medications (Chazot 2013). This pathway is described with numerous pharmacogenetic variations and influences disease expression and response to treatment. Food allergies, like peanut allergy, is, with an overall low mortality, the leading cause of death related to food-induced anaphylaxis in the United States (Togias et al., 2017). HIT should be separated from food allergies and is therefore described as a non-allergic adverse reaction causing complaints of intolerance/malabsorption to ingested food (Reese et al., 2017).

Scombroid poisoning is named after the Scombridae family of fish, which includes mackerels, tunas and bonitos (Feng, Teuber, and Gershwin 2016). First descriptions of this disease were noted in association with the ingestion of these fish species (Miya et al. 2013), although it may happen with the ingestion of non-scombroid fish species as well. They naturally contain high levels of histidine, which is, with bacterial growth during e.g. improper storage, converted to histamine. Fermentation can be prevented by the fast refrigeration or freezing of fish immediately after catching (Kovacova-Hanusikova et al. 2015). Additionally, this foodborne disease related to spoiled fish also happens when cooking, smoking, or freezing does not eliminate the histamine. Scombroid toxin is reportedly the most common toxin in poisoning outbreaks associated with imported foods in the United States (Gould et al. 2017). However, scombroid poisoning is caused by the consumption of food, mostly sea animals, contaminated with bacteria that cause very high concentrations of histamine. The European Union set regulatory limits of histamine content of up to a maximum of 200 mg/kg in fresh fish and 400 mg/kg in seafood products (Visciano et al. 2014). Histamine quantity of more than 40 mg per meal (0.75 mg/kg body weight) can significantly increase the risk of poisoning (Doeun, Davaatseren, and Chung 2017).

Histamine intolerance (HIT)

The term “histamine intolerance” is used in a similar way to the term lactose intolerance, which is due to a deficiency in the enzyme lactase, as it is assumed that histamine intolerance is due to a deficiency in the enzyme diamine oxidase (DAO). HIT appears as a metabolic disease because histamine is widely distributed throughout the body (Schwelberger 2010) and it is involved in the etiology of common diseases (Kucher and Cherevko 2018).

Human DAO and histamine N-methyl transferase are enzymes which catalyze the oxidative deamination of mono-, di- and polyamines. Within the GI tract, DAO appears to be the primary enzyme for the degradation of ingested histamine (Smolinska et al. 2014). DAO is synthesized by mature intestinal enterocytes and is constantly released from the intestinal mucosa during digestion as well as into the blood circulation (Ji et al. 2013; Wollin, Wang, and Tso 1998). Impairment of the GI mucosa caused by various diseases and medications may also reduce DAO activity. DAO from the white pea (*Lathyrus sativus*) reportedly prevented histamine toxicity in vitro in human heterogeneous epithelial colorectal adenocarcinoma cells (Jumarie et al. 2017).

A disproportionate amount of histamine in the body is suspected to result from the consumption of histamine-containing food or drinks, and the reduced ability of enzymes to digest histamine. Ingested histamine, clearly below the dose of a scombroid poisoning, is thought to cause HIT-related symptoms in affected people.

The clinical diagnosis of HIT is challenging, as standardized diagnostic tests are still lacking. A thorough anamnesis of all complaints which may be linked to HIT experienced

by each individual is the mainstay of HIT diagnosis. However, diagnosis may also be supported with measurement of a serum DAO value <10 U/mL. Two or more typical GI symptoms of HIT and a reduction of complaints subsequent to a histamine-reduced diet may help to support the diagnosis. Serum DAO values are not established to correlate with gastrointestinal DAO activity. Recently, however, a significant increase of serum DAO values due to strict diet compliance was demonstrated in patients with HIT (Lackner et al. 2019). Then, evidence of correlation between low DAO values, symptoms of histamine intolerance, and response to histamine reduced diet and/or to oral diamine oxidase supplementation has been reported (Manzotti et al. 2016; Schnedl, Schenk, et al. 2019).

Currently, DAO is determined using a radio extraction assay based on the spontaneous conversion of oxidized radioactive putrescine into delta-1-pyrroline. This method seems to have limitations because only a relative amount of DAO in serum is quantified. A human DAO standard is not available and absolute DAO quantities cannot be determined. Therefore, it is necessary to develop new assay methods. An enzyme-linked immunosorbent assay (ELISA) using human DAO as a standard was found to be accurate (Boehm et al. 2017). With the widespread availability of this ELISA, the potential of DAO as biomarker for diseases, including reduced serum DAO values in HIT, needs to be reevaluated.

The search for HIT diagnostic tests continues. Double-blind placebo-controlled oral histamine provocation tests also triggered reactions in 50% of healthy controls. However, due to the lack of sufficient data, an oral histamine provocation is not suitable to diagnose HIT at present (Reese et al., 2017). Precise determination of plasma histamine values is an ongoing issue. Radioimmunoassay (RIA) is currently the gold standard method to quantify histamine. However, its limitations include the time expenditure, the specificity of the procedure for technicians and the production of radioactive waste (Poli et al. 2016; Liu et al. 2014). Another approach is the measurement of histamine and methylhistamine in urine. The widespread use of this diagnostic procedure seems limited because of the unpredictable amount of individual protein ingestion before the test (Comas-Basté et al. 2017). Histamine is also a metabolite of intestinal bacteria and this reduces the reliability of diagnostic stool analysis. Skin-prick tests have been validated for food allergy diagnoses (Gomes-Belo et al. 2018), but not for HIT (Kofler, Ulmer, and Kofler 2011).

There are known genetic polymorphisms for lactase (Järvelä, Torniainen, and Kolho 2009), celiac disease (Hunt and van Heel 2009), and a genetic background might also be a factor in fructose malabsorption (Patel et al. 2015). Additionally, polymorphisms in the genes coding for DAO (Maintz et al. 2011; Petersen, Raithel, and Schwelberger 2005) and the histamine receptors (Sadek and Stark 2016) have been identified. The polymorphisms of the four known histamine receptors and polymorphisms of DAO seem associated with multiple clinical symptoms and hundreds of symptom combinations in HIT. This may help to explain

Table 1. Currently available tests to be performed in each individual patient with functional, nonspecific, non-allergic abdominal complaints.

Intolerance/malabsorption	Available tests in addition to the thorough anamnesis
Lactose intolerance	Hydrogen breath test
Fructose malabsorption	Hydrogen breath test
Histamine intolerance	Serum diamine oxidase with radio extraction assay or ELISA
Celiac disease	Antibodies against tissue transglutaminase with IgA ELISA
<i>Helicobacter pylori</i> infection	Histologic evaluation of gastric mucosa, C13 breath test, stool antigen tests, determination of antibodies against <i>H.p.</i> with IgA ELISA
IgA ELISA, Immunoglobulin A enzyme-linked immunosorbent assay; <i>H.p.</i> , <i>Helicobacter pylori</i>	

the extensive individual variability of functional, nonspecific, non-allergic GI and extra-intestinal symptoms. Furthermore, this genetic variety might influence symptoms and disease expression and individual response to diets or treatment. Although some of these polymorphisms have been identified, their functional and clinical significance remains unknown. Another factor to consider is that the histamine content in food is frequently not known (Gagic et al. 2019) and varies considerably depending on ripeness, storage time, and processing (San Mauro Martin, Brachero, and Vilar 2016). All of these variables need to be advised and may help to explain each person's unique and even sometimes changing tolerance levels concerning food intolerance/malabsorption.

Discussion

Food intolerance/malabsorption syndromes cause non-allergic, functional, nonspecific GI complaints and scientific advances have led to a better understanding of the role of food ingredients. These functional, nonspecific, non-allergic abdominal complaints may be accompanied by extra-intestinal symptoms when a food or a combination of certain ingredients cannot be absorbed and digested properly. GI bacteria use catabolic enzymes to degrade and ferment carbohydrates and proteins from ingested food (Pimentel, Mathur, and Chang 2013; Reese et al. 2018).

Although there is limited availability of sufficiently sensitive and specific tests it seems essential to assess functional, nonspecific, non-allergic GI complaints individually with all currently available tests (Rezaie et al. 2017). All etiological factors of functional, nonspecific, non-allergic GI complaints including fructose, gluten, histamine, lactose, and *H.p.* infection need to be evaluated in each patient (Table 1). Studies have shown combined lactose and fructose intolerance/malabsorption and variable combinations of lactose-, fructose- and histamine intolerance/malabsorption, including *H.p.* infection. In an evaluation of more than 400 patients with functional, nonspecific, non-allergic GI complaints nearly 80% of the patients suffered from malabsorption/intolerance due to a single food or 7 combinations, and/or *H.p.* infection (Enko et al. 2016). After detailed diagnosis, functional, nonspecific, non-allergic GI complaints can be treated by reducing the ingestion of the triggering single or combined

nutrients and/or eradication of *H.p.* To ensure nutritional adequacy this should only be done after a detailed diagnosis and it should include the careful evaluation of the individual tolerance level to the symptomatology.

Conclusion

In conclusion, histamine seems to play a significant role in functional, nonspecific, non-allergic GI complaints. Diagnostic tools for HIT need improvement but future wide-spread availability of ELISA for determination of DAO in serum seems promising. A detailed diagnosis of single or combined food intolerance/malabsorption, including HIT, with currently available methods is necessary to evaluate patients with functional, nonspecific, non-allergic GI complaints. However, histamine-reduced diets need further evaluation, and a registered, experienced dietician is required to design an individually tailored diet. Each patient's tolerance level should be considered when recommending dietary restrictions for long-term symptom reduction. Dietary advice ought to include nutritional variety, ensure alimentary adequacy and cause negligible impact on the GI microbiome.

Disclosure statement

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Abbreviations

CD	celiac disease
DAO	diamine oxidase
EGS	eosinophilic gastroenteritis
ELISA	enzyme-linked immunosorbent assay
FD	functional dyspepsia
GI	gastrointestinal
<i>H.p.</i>	<i>helicobacter pylori</i>
HIT	histamine intolerance
IBS	irritable bowel syndrome
MCAS	mast cell activation syndrome
NCGS	non-celiac gluten sensitivity
SIBO	small intestinal bacterial overgrowth

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