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Circadian profiling reveals higher histamine plasma levels and lower diamine oxidase serum activities in 24% of patients with suspected histamine intolerance compared to food allergy and controls

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Abstract

Background: Histamine intolerance is thought to trigger manifold clinical symptoms after ingesting histamine-rich food due to reduced activity of diamine oxidase (DAO). No study has hitherto systematically assessed daily fluctuations of histamine levels and DAO activities in symptomatic patients. The aim of the study was to investigate the presence of histamine intolerance, to therefore establish day profiles of histamine levels and DAO activities, and to compare the results between patients with suspected histamine intolerance, food allergy and healthy controls.

Methods: We determined day profiles of histamine plasma levels and DAO serum activities in 33 patients with suspected histamine intolerance, in 21 patients with proven food allergy and in 10 healthy control patients. Clinical symptoms, food intolerances and further clinical and laboratory chemical parameters were evaluated.

Results: Twenty-four percent (8 of 33) suspected histamine-intolerant patients showed elevated histamine levels during the day. That might be caused by constantly and significantly reduced DAO activities in these patients compared to food-allergic and control patients. The remaining 25 patients presented normal histamine levels and DAO activities, but an increased prevalence of multiple food intolerances compared to the other subgroup of suspected histamine-intolerants. There was no correlation between subjective complaints and serological histamine parameters in patients with suspected histamine intolerance.

Conclusions: We determined by daily profiling that decreased DAO activities correlated with elevated histamine levels in a subgroup of suspected histamine-intolerants. This finding discriminates these patients from food intolerant individuals with similar clinical symptoms and strongly suggests the presence of histamine intolerance.

Abbreviations: 95% CI, 95% confidence interval; BSA, Body surface area; DAO, Diamine oxidase; ELISA, Enzyme-linked Immunosorbent Assay; FODMAP, Fermentable Oligo-, Di-, Monosaccharides And Polyols; IBS, Irritable bowel syndrome; RAST, Radioallergosorbent test; REA, Radio Extraction Assay.

Clinical trial registration number: NCT02293343.

KEYWORDS
diamine oxidase activities, day profile, food allergy, histamine intolerance, histamine levels

1 | INTRODUCTION

Abdominal pain, diarrhoea, pruritus—adverse food reactions appear in a multifaceted manner with a broad range of symptoms. Due to the increasing incidence of food intolerances in industrial nations and the associated restriction of quality of life, a close look at nutrition becomes increasingly important.[1-3]

There is a much evidence of food hypersensitivity—either expressed as immunological food allergy or nonimmunological food intolerance.[4] The prevalence of the latter averages between 15% and 20% and is thus about four times higher than the prevalence of food allergy.[4-6] Among the most common food intolerances are intolerances against fructose and lactose as well as histamine.[4,7] The frequency of histamine intolerance is not fully understood yet, but indirect evidence suggests that about 1%-3% of the population is affected.[8] Reduced activity of diamine oxidase (DAO), the key enzyme in histamine metabolism, has been hypothesized as the main factor in the development of histamine intolerance leading to the accumulation of histamine above the individual critical value.[9-12] Consequently, this is provoking disorders within a short time lag from hours up to days. High histamine levels in the body are not only caused by reduced DAO activities but also by the ingestion of histamine-rich and histamine-releasing foods such as meat, dairy products and alcohol.[2,13,14]

Histamine intolerance has already been reported as a causal trigger for cardinal gastrointestinal disorders like abdominal pain, diarrhoea and flatulence.[2,15,16] On the one hand, the patients' clinical presentation can resemble other food intolerances or allergy and is usually diagnosed under the umbrella of irritable bowel syndrome (IBS).[2,7] On the other hand, histamine intolerance is also characterized by extra-intestinal symptoms such as headache,[15] pruritus,[16] urticaria,[17] atopic eczema,[18] cardiac arrhythmia[19] and asthma[13,14] that exceed the diagnosis of IBS. As both the aetiology and the course of histamine intolerance are not sufficiently investigated, the knowledge and treatment in the medical field are not always uniform. Thus, affected patients do doctor shopping to find an appropriate explanation for their diversified complaints.

According to the current recommendations,[20] a provocation test with increasing concentrations of histamine hydrochloride can be applied under strict medical supervision for the determination of a histamine intolerance. However, side effects can be very severe and hospitalization might be required so that a provocation test should probably be limited to patients with an urgent suspicion. A simple, fast-tracked diagnostic tool could provide the first evidence for a histamine intolerance and might be helpful to select patients for a provocation test.

To some extent, low DAO activities and high histamine levels in the blood are indicators of the disease.[10-12,18] But do the complaints of the patients indeed correlate with the measured histamine parameters? So far, no study has systematically assessed daily fluctuations of histamine levels and DAO activities in symptomatic patients. Wantke et al[21] investigated daily variances of histamine levels and DAO activities in healthy volunteers, but could not observe any differences. However, a single-shot measurement of these parameters may be insufficient to detect intraday variations and clarify the presence of a histamine intolerance. Therefore, more knowledge of the daytime dynamics of histamine and DAO activity is very important. A correct diagnosis, which is ideally based on the determination of serological parameters, is the basis for an adequate therapeutic intervention, and symptom relief can be achieved through histamine-free diet,[10,22,23] antihistamines,[11,13,23] medication that blocks the effects of histamine and supplementation of DAO.[24]

The aims of this project were to determine a day profile of histamine levels and DAO activities and to evaluate differences concerning the serological parameters and clinical symptoms between the investigated study groups—suspected histamine-intolerants, proven food-allergic patients and healthy controls—to offer a better diagnostic tool for histamine intolerance.

2 | METHODS

2.1 | Subjects

Over a 12-month period, a total of 65 adult patients were enrolled in the study. Patients were recruited by special social media platforms and from the ambulance for nutritional medicine of the Department of Medicine 1 of the University Erlangen-Nuremberg, Germany. Three patient groups were acquired: (i) suspected histamine intolerance, (ii) proven food allergy and (iii) healthy controls. The first group comprised patients with reasonable suspicion of histamine intolerance. Clinical complaints under normal histamine-rich diet that resolved completely when consuming a histamine-low diet served as inclusion criterion for this group. When participants further complained about symptoms despite a histamine-low diet, they were rejected from the study. The second group covered patients with increased serum IgE as well as gastrointestinal complaints that did not improve under histamine-low diet. The third group enclosed healthy individuals without any complaints under standard diet. Exclusion criteria comprised pregnancy, lactation, being under age and the current intake of antihistamines or anti-inflammatory medication.

2.2 | Study design and setting

This study was performed in a prospective cohort design. The study protocol was approved by the local ethics committee. All participants provided written informed consent.

Four weeks before study start, all medication possibly interfering with the analyses (antihistamines, corticosteroids and anti-inflammatory medication) was paused. During a period of 1 week prior to and throughout the examinations, all groups had normal mixed diets with the aim of supplying normal amount of histamine by food and drink.

2.3 | Data collection

A 3-day nutritional diary using the Freiburger Diet Protocol (Nutri-Science GmbH, Freiburg, Germany) directly before the time of investigation was itemized in energy value as well as content of protein, fat, carbohydrates and alcohol per day by PRODI (version 6.5 expert, Nutri-Science GmbH). All patients were checked for sugar intolerances in-house or externally by validated H2 breath tests. The survey at the examination day assessed clinical symptoms, underlying diseases and both nicotine and alcohol consumption. Furthermore, IBS symptoms were recorded using questionnaires based on the Rome III criteria.[25,26]

2.4 | Sample collection and analysis

To determine a day profile of both histamine levels and DAO activities at the examination day, blood samples were taken every three hours from 6 AM until midnight by butterfly needles or peripheral venous catheters. Because of the short half-life of histamine, the blood samples were immediately cooled on ice and centrifuged (1780 g) for 10 minutes at 4°C (Rotina 35R, Hettich GmbH, Tuttlingen, Germany). Histamine plasma levels (threshold: 0.35 ng/mL/m^2 BSA, Immundiagnostik AG, Bensheim, Germany) were determined by enzyme-linked immunosorbent assay (ELISA) and DAO serum activities (threshold: 5.73 U/mL/m^2 BSA, Immundiagnostik AG, Bensheim, Germany) by radio extraction assay (REA). Both serological parameters were adapted to the subjects' individual body surface area (BSA).

Additional blood samples were taken for further investigation of a differential blood count (reference range neutrophil granulocytes <75%, eosinophil granulocytes <4%, basophil granulocytes <1%, lymphocytes <40% and monocytes <8%) and for vitamin B6 determination (reference range 5.0-30.0 ng/mL). The total quantity of IgE antibodies (reference value: <100 kUA/L) as well as specific IgE antibodies against food allergens was quantified by radioallergosorbent test (RAST), and serum tryptase (reference value: <11.4 μg/L) was measured by fluorescence immunoassay to determine a food allergy and a mast cell-activating disease (ImmunoCAP®, Phadia 250, Thermo Fisher Scientific Inc., Phadia GmbH, Freiburg, Germany).

2.5 | Statistical analysis

The statistical analysis was performed with R version 3.2.4.[27] Clinical and laboratory variables were summarized by absolute and relative frequencies for categorical variables and by means and standard deviations for continuous variables. 95% confidence intervals (95% CI) and boxplots are reported for histamine levels and DAO activities. Statistically significant differences between the three diagnosis groups were tested by means of the chi-square test and Kruskal-Wallis test, respectively. Wilcoxon signed-rank test and Dunn-Bonferroni post hoc testing were used to compare intergroup differences as well as observed and prescribed values. All statistics are based on 2-sided testing. *P*-values ≤.05 were considered statistically significant.

3 | RESULTS

3.1 | Group allocation

In summary, 64 patients (n = 54 female, 84.4%) with an average age of 38.3 ± 14.2 years were analysed. A total of 33 patients (n = 28 female, 84.8%) with an urgent suspicion of histamine intolerance were included in the study. In addition, 21 patients (n = 17 female, 81%) with a proven food allergy and a total of 10 (n = 9 female, 90%) healthy volunteers who had no complaints were recruited. As expected, the IgE antibodies were significantly increased in the food-allergic patients (361.2 ± 911.2 kUA/L) ($P < .001$), whereas the IgE antibodies were in the normal range in the suspected histamine-intolerants (29 ± 24.4 kUA/L) and healthy volunteers (14.3 ± 9.6 kUA/L). Correspondingly, proven food-allergic patients were tested positive for nut mixture (76.2%), wheat flour (47.6%), celery (42.9%), tomato (23.8%), rye flour (23.8%), soybean (14.3%) and milk protein (4.8%) and negative for chicken egg white, casein and salmon.

3.2 | Day profiles of histamine levels and diamine oxidase (DAO) activities

By recording the progression of histamine levels and DAO activities over time, 24% (8 of 33, all female) suspected histamine-intolerant patients featured elevated histamine levels and constantly reduced DAO activities. Despite the typical symptoms, the remaining 25 subjects (n = 20 female, 80%) did not show any changes in histamine levels or DAO activities, which would correspond to the definition of a histamine intolerance. In order to distinguish these patients from the patients with reduced DAO activities, they are hence referred to as "food-hypersensitive patients." Figure 1 and Table 1 demonstrate the day profiles of histamine levels and DAO activities of patients with suspected histamine intolerance, food-hypersensitive patients, food-allergic patients and healthy control patients. Diamine oxidase (DAO) activities were significantly lower in histamine-intolerants (see Figure 2) and tended to be within the normal range in the other groups. There were no significant differences between the groups regarding the bandwidth of histamine levels (see Figure 2).

3.3 | Food intolerances

The overall prevalence of food intolerances in symptomatic patients did not differ significantly between groups (see Figure 3). Splitting the

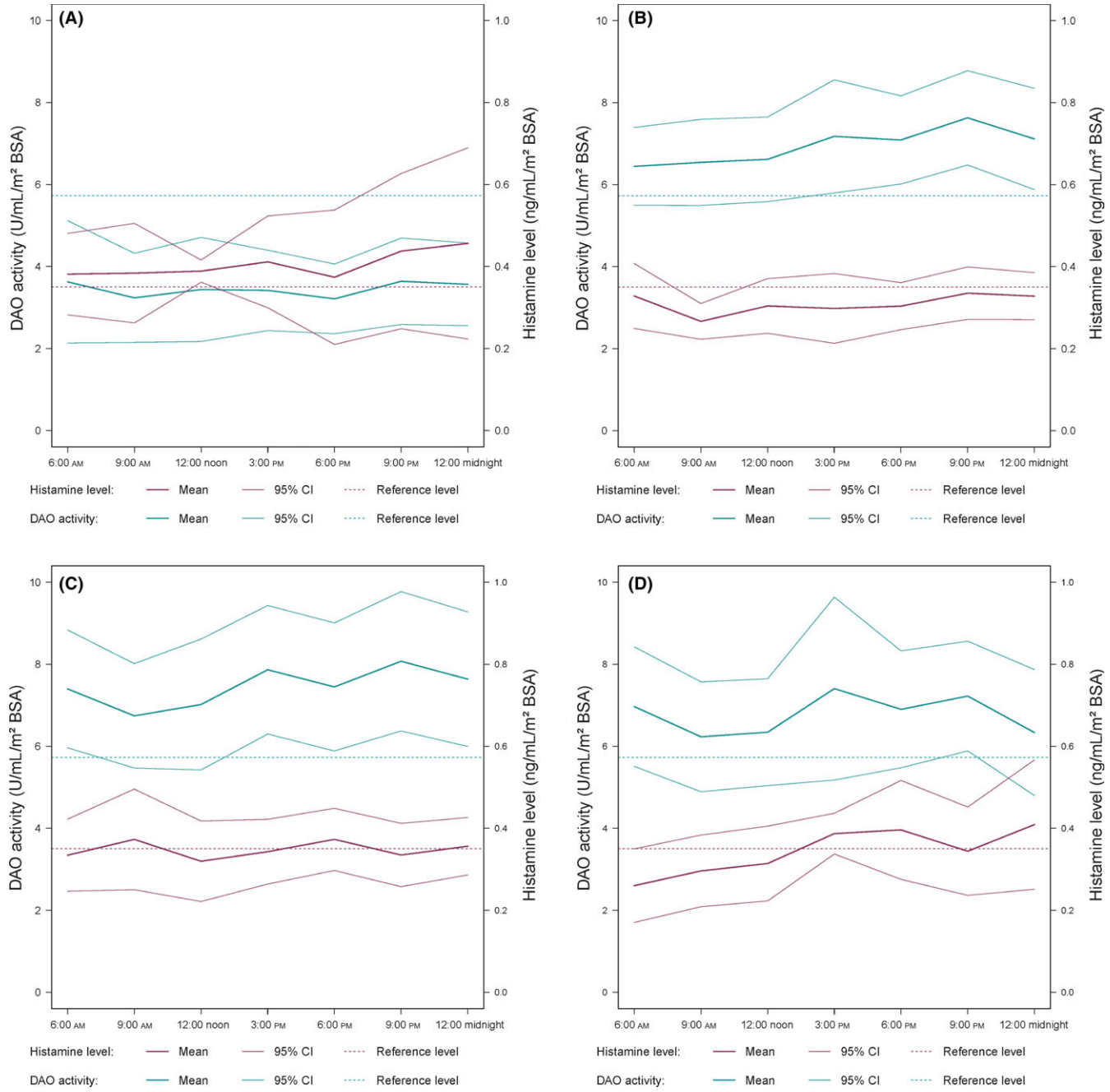

FIGURE 1 Day profiles of histamine plasma levels and diamine oxidase serum activities. For both histamine plasma levels and DAO serum activities, mean values, 95% confidence intervals and reference levels to be regarded as healthy (maximum histamine level: 0.35 ng/mL/m² BSA; minimum DAO activity: 5.73 U/mL/m² BSA) are illustrated. A, Histamine-intolerant patients, B, food-hypersensitive patients, C, food-allergic patients and D, healthy control patients. DAO, diamine oxidase; BSA, body surface area; 95% CI, 95% confidence intervals [Colour figure can be viewed at wileyonlinelibrary.com]

food intolerances against fructose, lactose and sorbitol into single and multiple intolerances revealed an intriguing result: histamine intolerance was exclusively associated with single food intolerances, whereas food-hypersensitive and food-allergic patients showed similar percentages of single and multiple food intolerances (see Figure 3).

3.4 | Variety and diversity of clinical symptoms

To assess the health status, clinical symptoms were recorded in categories: allergic rhinitis including oral allergy syndrome, skin changes, gastrointestinal alterations as well as asthmatic symptoms and headache (see Table 2). In general, histamine-intolerant, food-hypersensitive and food-allergic patients presented a wide variety of symptoms. No differences between these groups were seen in the prevalence of symptoms (see Table 2). Further self-reported disorders, for example palpitations, flush, heartburn, nervousness, fatigue, increased sweating, muscle and joint pain, were infrequent (<15% each), except for flatulence (histamine-intolerant patients: 12.5%; food-hypersensitive patients: 25%; food-allergic patients: 19%). Likewise, their prevalence did not vary between the groups ($P > .05$, not reported in Table 2).

TABLE 1 Day profiles of histamine plasma levels and diamine oxidase serum activities

	6:00 AM	9:00 AM	12:00 noon	3:00 PM	6:00 PM	9:00 PM	12:00 midnight
Histamine plasma levels (ng/mL/m^2 BSA)							
Histamine-intolerant patients	**0.38**	**0.38**	**0.39**	**0.41**	**0.37**	**0.44**	**0.46**
Food-hypersensitive patients	0.33	0.27	0.3	0.3	0.3	0.34	0.33
Food-allergic patients	0.33	**0.37**	0.32	0.34	**0.37**	0.33	**0.36**
Healthy control patients	0.26	0.3	0.31	**0.39**	**0.4**	0.34	**0.41**
DAO serum activity (U/mL/m^2 BSA)							
Histamine-intolerant patients	**3.62**	**3.23**	**3.44**	**3.42**	**3.21**	**3.64**	**3.56**
Food-hypersensitive patients	6.44	6.54	6.62	7.18	7.09	7.63	7.11
Food-allergic patients	7.4	6.74	7.02	7.87	7.45	8.07	7.64
Healthy control patients	6.97	6.23	6.34	7.41	6.9	7.22	6.33

DAO, diamine oxidase; BSA, body surface area.
Mean values are reported. Values outside the reference levels to be regarded as healthy (maximum histamine level: 0.35 ng/mL/m² BSA; minimum DAO activity: 5.73 U/mL/m² BSA) are bold.

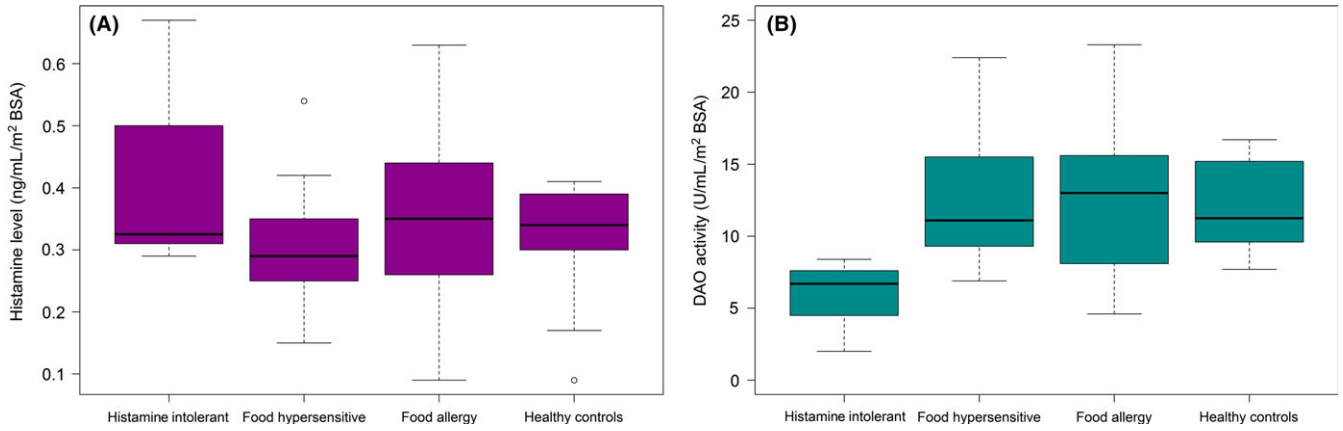

FIGURE 2 Comparison of histamine plasma levels and diamine oxidase serum activities. *P*-values of Wilcoxon signed-rank test for (A) histamine plasma levels: n.s., and (B) diamine oxidase serum activities: histamine-intolerant patients – food-hypersensitive patients: $P = .002$; histamine-intolerant patients – food-allergic patients: $P < .001$; histamine-intolerant patients – healthy control patients: $P < .001$. DAO, diamine oxidase; BSA, body surface area [Colour figure can be viewed at wileyonlinelibrary.com]

3.5 | Nutritional behaviour, alcohol and nicotine consumption

Regarding the daily intake of calories, histamine-intolerants consumed 2431.2 ± 362.3 kcal per day and food-hypersensitive patients 2873.3 ± 1218.1 kcal per day. The energy intake of food-allergic patients was 2862.9 ± 1552.8 kcal per day and 2081.7 ± 818.6 kcal per day in healthy volunteers. Thus, food-hypersensitive patients consumed significantly more calories per day compared to controls ($P = .02$). A tendency to higher calorie intake per day was also determined for food-allergic patients in comparison with controls ($P = .06$). The detailed analysis of the percentage of daily intake of macronutrients revealed no differences with regard to protein (histamine-intolerants: 14.5% ± 2.8%/d; food-hypersensitive patients: 16.6% ± 4.1%/d; food-allergic patients: 16% ± 3.5%/d; controls: 15.3% ± 3.1%/d; $P = .53$), fat (histamine-intolerants: 31.8% ± 4.7%/d; food-hypersensitive patients: 38.4% ± 6.1%/d; food-allergic patients: 37.1% ± 5.5%/d; controls: 37.6% ± 8.5%/d; $P = .09$) and carbohydrates (histamine-intolerants: 50.4% ± 6.1%/d; food-hypersensitive patients: 40.9% ± 8.3%/d; food-allergic patients: 42.1% ± 8.8%/d; controls: 44.5% ± 8.8%/d; $P = .07$).

71.9% of the study population consumed alcohol and 14.1% nicotine on a regular basis. No statistical significant intergroup differences were observed for both alcohol (histamine-intolerants: n = 6, 75%; food-hypersensitive patients: n = 15, 60%; food-allergic patients: n = 17, 81%; controls: n = 8, 80%; $P = .40$) and nicotine consumption (histamine-intolerants: n = 1, 12.5%; food-hypersensitive patients: n = 2, 8%; food-allergic patients: n = 3, 14.3%; controls: n = 3, 30%; $P = .41$).

3.6 | Irritable bowel syndrome and primary diseases

Figure 4 illustrates the distribution of IBS subtypes based on the Rome III criteria in histamine-intolerant, food-hypersensitive and food-allergic patients. Food hypersensitivity was associated with an increased risk for IBS with diarrhoea (IBS-D) in comparison with histamine intolerance. The food-allergic patients could rarely be categorized in IBS.

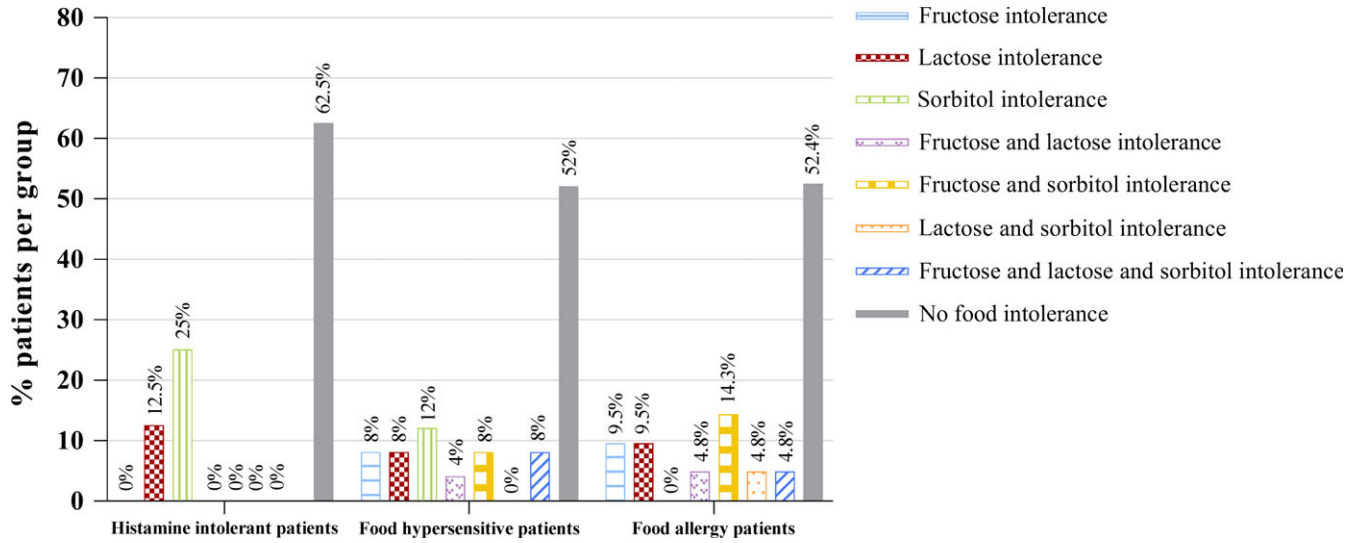

FIGURE 3 Prevalence of food intolerances. Relative frequencies of single and multiple food intolerances against fructose, lactose and sorbitol are shown [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Spectrum of histamine and allergy-related clinical symptoms

	Histamine-intolerant patients	Food-hypersensitive patients	Food-allergic patients	*P*-values
Allergic rhinitis				
Runny nose	3 (37.5%)	11 (44%)	10 (47.6%)	.89
Stuffy nose	3 (37.5%)	7 (28%)	9 (42.9%)	.57
Itchy nose	3 (37.5%)	6 (24%)	9 (42.9%)	.39
Red eyes and swollen eyelids	4 (50%)	9 (36%)	8 (38.1%)	.78
Watery eyes	3 (37.5%)	4 (16%)	6 (28.6%)	.38
Sneezing	3 (37.5%)	7 (28%)	10 (47.6%)	.39
Swollen airways	3 (37.5%)	5 (20%)	9 (42.9%)	.23
Oral allergy syndrome	4 (50%)	10 (40%)	13 (61.9%)	.33
Skin changes				
Itchy skin	5 (62.5%)	13 (52%)	7 (33.3%)	.27
Urticaria	3 (37.5%)	5 (20%)	4 (19.1%)	.53
Skin rash	3 (37.5%)	10 (40%)	7 (33.3%)	.90
Gastrointestinal alterations				
Nausea and vomiting	5 (62.5%)	12 (48%)	9 (42.9%)	.64
Stomach pain	3 (37.5%)	18 (72%)	11 (52.4%)	.16
Diarrhoea	4 (50%)	18 (72%)	16 (76.2%)	.37
Asthmatic symptoms				
Cough	0 (0%)	4 (16%)	5 (23.8%)	.30
Shortness of breath	2 (25%)	6 (24%)	5 (23.8%)	1.00
Wheezing	0 (0%)	1 (4%)	4 (19.1%)	.13
Headache	4 (50%)	14 (56%)	10 (47.6%)	.85

Absolute and relative frequencies and *P*-values of chi-square test are reported.

We found similar frequencies of primary diseases (hypothyroidism, asthma, atopic dermatitis, depression, gastrointestinal and cardiovascular diseases, endometriosis, fibromyalgia) in the symptomatic groups ($P > .05$, data not shown). Migraine exclusively appeared in food-hypersensitive patients (8%).

3.7 | Laboratory values

Differential blood count, vitamin B6, magnesium and zinc were within the normal range in all groups. Serum tryptase levels were below 20 μg/L in the entire study population (histamine-intolerants:

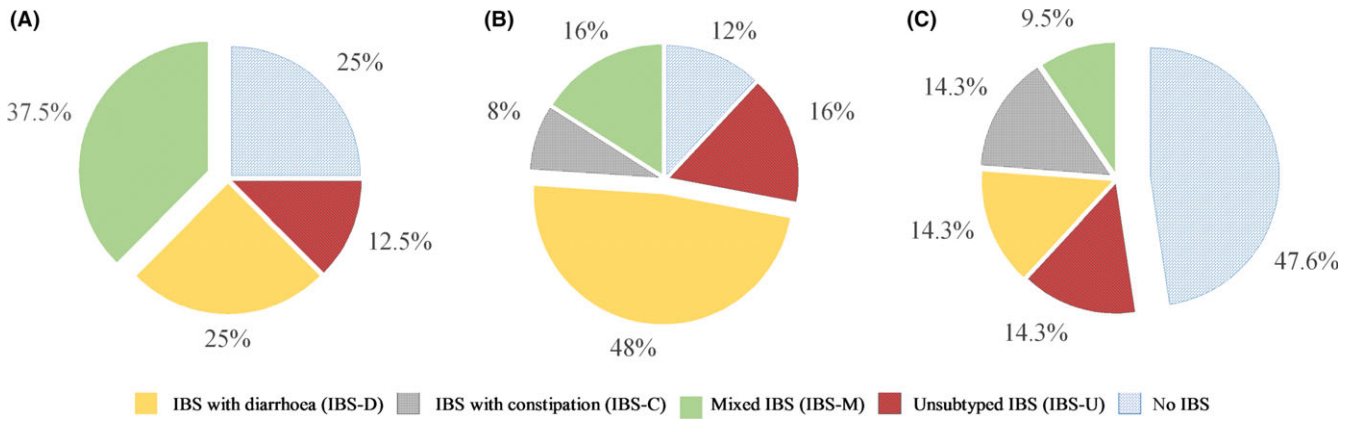

FIGURE 4 Subtype distribution of irritable bowel syndrome based on the Rome III criteria. Proportions of patients are displayed. A, histamine-intolerant patients, B, food-hypersensitive patients and C, food-allergic patients. IBS, irritable bowel syndrome [Colour figure can be viewed at wileyonlinelibrary.com]

4.58 ± 2.86 μg/L; food-hypersensitive patients: 6.57 ± 8.91 μg/L; food-allergic patients: 4.65 ± 1.69 μg/L; controls: 6.66 ± 3.46 μg/L) except for one food-hypersensitive patient (46.1 μg/L).

4 | DISCUSSION

A plethora of symptoms has been reported in patients after consuming histamine-rich and histamine-releasing foodstuffs due to histamine accumulation based on reduced activity of DAO, the main enzyme in histamine metabolism.[8,10,28,29] But is there reliable evidence that histamine intolerance exists? No diagnosis was as critically discussed as the presence of histamine intolerance. To address this issue, we determined day profiles of histamine plasma levels and DAO serum activities in patients with urgent suspicion of histamine intolerance compared to patients with proven food allergy and healthy volunteers.

For the first time, we were able to demonstrate that there are patients who can be classified as histamine-intolerants according to the definition.[9-12] In 24% (8 of 33) suspected histamine-intolerants, constantly and significantly reduced DAO activities triggered elevated histamine levels throughout the day. We observed that the most common clinical symptoms of histamine intolerance are diarrhoea, nausea and vomiting, headache, itchy skin, oral allergy syndrome as well as red eyes and swollen eyelids (≥50%). These findings appear to be consistent with literature data as gastrointestinal, skin and respiratory problems as well as headache have been described to be characteristic for histamine intolerance.[4,8,28] Like other work groups,[30] we could not find any differences in the complexity of the symptoms between patients with histamine intolerance, food hypersensitivity or food allergies. This is probably due to the nonspecific pathology, great variability and individual complaints of the patients. Unfortunately, we could not observe any correlations between subjective complaints and measured histamine parameters. Our current results show that it is difficult to differentiate between histamine intolerance and other food intolerances by clinical presentation alone. Additional laboratory chemical examinations are necessary.

In patients with a proven food allergy, increased histamine levels are expected compared to healthy controls, which was not the case in our study. Immunologically mediated food allergy is based on significantly increased serum levels of IgE antibodies against food antigens that cause the immediate reactions (type I hypersensitivity) via mediator release, for example histamine, from mast cells.[30,31] However, we did not ask the patients to consume allergenic food components and thus trigger an allergic reaction with histamine release from ethical point of view.

Based on our repeated determination, we could demonstrate that histamine plasma levels are subjected to constant fluctuations between normal and pathologic values during the day in our healthy controls. This great variety most likely depends on the quantity of the ingested histamine-rich food. In accordance with previous studies,[10,28] our healthy subjects showed normal DAO activities. Fluctuations in histamine levels do not seem to be of any clinical relevance as long as sufficient DAO activity is available. We suspect that an individual histamine sensitivity is responsible for the patient's discomfort. Even though no significant differences in the histamine levels between the groups could be detected, the patients with a laboratory-based suspicion of histamine intolerance presented persistently increased histamine values over the course of the day. This is probably due to the significantly reduced DAO activities. The intraday fluctuations emphasize the difficulties in diagnosis of histamine intolerance as single-point values might be interpreted incorrectly (false high or low). Repeated determination of histamine levels and DAO activities on several days therefore could be further pursued in the clinical course. In our study, a clear demarcation of histamine intolerance appeared best at noon so that this time point might be recommended for the blood samplings. An arithmetic mean could possibly be standardized.

A study including 439 patients with unclear abdominal discomfort identified fructose (5.2%) and primarily lactose (11.8%) intolerance as a frequent concomitant in histamine intolerance.[32] In conformity with this study, we also demonstrated that carbohydrate intolerances are frequently associated with histamine intolerance. Interestingly, there was a frequent co-occurrence of histamine and sorbitol intolerance (25%).

A histamine-free diet is the method of choice in the explorative diagnosis and therapy of histamine intolerance.[10,22,23] In addition, a new diet low on FODMAPs has gained increasing popularity in recent years. The acronym FODMAP—Fermentable Oligo-, Di-, Monosaccharides And Polyols—refers to the carbohydrates fructose, lactose, fructans and galactans as well as sugar alcohols, such as sorbitol and mannitol, which are ingredients of numerous foodstuffs.[33,34] They are thought to trigger gastrointestinal disorders, in particular diarrhoea and flatulence, due to the induction of luminal distension and increased intestinal permeability.[33,34] Thus, a low FODMAP diet is considered highly effective in the treatment of functional gut symptoms and IBS, respectively.[33,34] In our study, the 25 patients without serological indication of histamine intolerance had multiple proven food intolerances against fructose, lactose or sorbitol and possibly other, yet unknown, food hypersensitivities. According to the Rome III criteria, most of them matched the subtype IBS with diarrhoea. These patients would possibly benefit more from a low FODMAP diet.

The mere presence of gastrointestinal complaints does not allow conclusions about the genesis of the disease, although the diagnosis of an IBS is very frequently.[2,7,30] The prevalence of IBS is significantly higher in women than in men.[35] There was also a high rate of symptomatic young and middle-aged (18-65 years) women in our study population (83.3%) who were assigned to the IBS category according to the Rome III criteria.[25,26] Evidence suggests associations between a histamine-rich diet and IBS.[2] That is why symptom relief under histamine-poor diet is not highly specific for histamine intolerance, but may also occur in IBS. One of our food-hypersensitive patients showed increased tryptase activity, hinting towards that other, for example mast cell-activated diseases, could be present in this patient.[36] In clinical practice, frequent and known differential diagnoses for histamine intolerance should be investigated at an early stage.

To compare the patients' nutritional status, we analysed the daily intake of macronutrients and calories. The DACH reference values for the supply of nutrients, which were elaborated by expert associations from Germany, Austria and Switzerland, recommend an optimal distribution of >50% carbohydrates, 15% protein and 30% fat in daily nutrition.[37] Female patients at the age of 25-50 years with mild physical activity should consume about 2100 calories per day.[37] Our findings suggest that histamine-intolerant patients comply with the recommended optimal nutrition in all aspects ($P > .05$). In contrast, our so-called food-hypersensitive and food-allergic patients had a normal protein uptake ($P = .08$; $P = .22$), but a significantly higher caloric ($P = .001$; $P = .004$) and fat ($P < .001$; $P < .001$), and lower carb uptake ($P < .001$; $P = .001$). Systematic studies investigating nutritional differences between patients with histamine intolerance and patients with other food intolerances or allergies are currently lacking.

We did not find any noticeable deviations of micronutrients including vitamin B6, magnesium and zinc in histamine-intolerant patients, and there seems to be no association between the concentration of micronutrients and DAO activities.

5 | CONCLUSIONS

We conclude from our data that: (i) a more differential diagnosis of histamine intolerance is possible, (ii) there is no correlation between subjective complaints and serologically detectable histamine parameters, (iii) the multifaceted clinical symptoms of histamine intolerance resemble other food intolerances or allergies, and (iv) repeated determination of histamine levels and DAO activities on several days should have a greater clinical value in diagnostic investigation than the measurement at only one single time point.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest

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