Original Article

Placebo-Controlled Histamine Challenge Disproves Suspicion of Histamine Intolerance

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What is already known about this topic? Histamine intolerance (HIT) is commonly suspected in patients with unexplained gastrointestinal and allergy-like symptoms. Studies using a placebo-controlled histamine challenge are rare, and the value of serum diamine oxidase (DAO) remains inconclusive.

What does this article add to our knowledge? A single-blind placebo-controlled histamine challenge is safe and excludes HIT in the majority of patients. Histamine skin prick test wheal sizes do not discriminate HIT from non-HIT patients. Serum DAO analysis is not specific enough for diagnosis.

How does this study impact current management guidelines? High DAO levels may be determined to exclude HIT, whereas low levels are quite common and not diagnostic. Thus, a single-blind placebo-controlled histamine challenge is required to confirm the diagnosis.

BACKGROUND: Histamine intolerance (HIT) is frequently diagnosed in patients with polysymptomatic otherwise unexplained symptoms.
OBJECTIVES: To exclude HIT by a single-blind placebo-controlled histamine challenge (SBPCHC), to study clinical features of patients with positive challenge, and to examine the predictability of HIT by biomarkers.
METHODS: SBPCHC was performed in 59 patients with suspected HIT. History and clinical data, including serum diamine oxidase (DAO) and histamine skin test wheal size of patients with positive versus negative SBPCHC, were compared.
RESULTS: Patients were predominantly middle-aged women (84.7%). Three-quarters reported improvement but never resolution of symptoms during a histamine-low diet. Histamine provocation was safe; only 1 patient was treated with antihistamines. Thirty-seven patients (62.7%) displayed symptoms to placebo. HIT was excluded in 50 patients (84.7%). Objective symptoms occurred in 4 of 59 cases (6.8%) after histamine but not after placebo challenge. These were diagnosed with "plausible HIT" because reactions occurring by chance could not be excluded. Another 5 patients (8.5%) were diagnosed with "possible HIT" after case-dependent detailed analysis. Patients with plausible/possible HIT had reported more gastrointestinal symptoms ($P = .01$), but comparable diet response and equal histamine skin prick test wheal sizes to those without HIT. Serum DAO activity tended to be lower in patients with HIT ($P = .08$), but was highly variable in those without, limiting its value as a biomarker.
CONCLUSIONS: SBPCHC disproves HIT in the majority of patients. Placebo-controlled challenges are needed as placebo reactions were frequent. Gastrointestinal symptoms after food intake and reduced DAO levels are markers for HIT; however, specificity is not sufficient enough for making the diagnosis. **(J Allergy Clin Immunol Pract 2023;■:■-■)**

Key words: *Histamine intolerance; Single-blind placebo-controlled histamine challenge; Diamine oxidase; Histamine oral provocation; Gastrointestinal symptoms*

Approximately 10% to 20% of the Western population complains about possible food hypersensitivity.[1,2] In 80% to 90% of the cases, skin tests, specific IgE determination, and oral challenge tests fail to confirm this suspicion.[1,2] Patients with otherwise unexplained symptoms and their health care professionals often attribute such symptoms to be caused by histamine in the normal daily diet, leading to the assumption that they suffer from histamine intolerance (HIT). Available data on HIT are scarce, outdated, and lacking scientific reliability. A prevalence of up to 1% to 3% of the population has been proposed but never substantiated.[3]

High intravenous doses of histamine lead to objective symptoms such as gastrointestinal discomfort, flushing, bronchospasm, and hypotension in healthy subjects.[4] Scombroid poisoning with equivalent symptoms was frequently reported after the consumption of spoiled fish, where bacteria had

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Abbreviations used
CSU- Chronic spontaneous urticaria
DAO- Diamine oxidase
HIT- Histamine intolerance
HMT- Histamin-N-methyltransferase
SBPCHC- Single-blind placebo-controlled histamine challenge

converted histidine into histamine during inappropriate storage, before legislative regulations were installed.[5,6] Whereas histamine content is important for scombroid poisoning, additional biogenic amines seem to potentiate histamine toxicity.[7] It is postulated that HIT results from an imbalance between histamine accumulation from food and decreased activity of histamine-degrading enzymes.[5,6,8] Patients suspecting HIT often report gastrointestinal and other allergy-like symptoms for which no other medical explanation has been found.

Although interest in HIT has increased in recent years, scientific evidence on how to diagnose this condition is scarce.[9] Many patients and doctors diagnose HIT based solely on the history and response to a histamine-low diet. However, the list of histamine-rich food is extensive—additionally, histamine content in food varies widely depending on ripeness, storage time, and processing. Other food has been postulated to be histamine releasing based on *in vitro* results from basophils.[9,10] An average person consumes various histamine-containing foods on a daily basis, making diagnosis difficult from the patient's history. Diets are of limited help in clarifying causality because of their strong placebo effect. In addition to histamine content, other factors (eg, composition, other biogenic amines, and psychosomatic factors) may influence food tolerance and explain the beneficial effects of a specific diet. HIT is thought to result from a reduced activity of the histamine-degrading enzymes diamine oxidase (DAO) and histamine-N-methyltransferase (HMT). Serum DAO can be measured by immunoassay; however, studies on the association between DAO and HIT are controversial.[9-15] Placebo-controlled challenges are the gold standard for diagnosing food hypersensitivity. We sought to investigate the outcome and safety of a single-blind placebo-controlled histamine challenge (SBPCHC) in patients with a history of HIT, characterized patients with and without positive SBPCHC, and evaluated the validity of clinical and laboratory parameters including history, DAO levels, or histamine skin test wheal size.

METHODS

Patients

From January 2016 until December 2021, 59 patient records of the Department of Dermatology and Allergology, Technical University of Munich were included in this retrospective analysis (Table I). All patients who were suspected to have HIT, either by themselves or by the referring physician who received an SBPCHC, were included. The study was approved by the local medical ethics committee (approval number 2022-634-S-KH).

Patients' history of histamine intolerance

On presentation at our clinic, a detailed medical history was obtained from each patient, focusing on the symptoms and the type of food leading to suspecting an HIT. Furthermore, preliminary diagnostics were documented in detail, especially if a previous histamine-low diet had alleviated symptoms. In patients with gastroenterological symptoms, a colonoscopy/gastroscopy was performed and an exclusion of fructose malabsorption or lactose intolerance was guaranteed.

Skin test and laboratory allergy diagnostics

Histamine solution (1 mg/mL) and 0.9% saline (ALK, Horsholm, Denmark) were used as positive and negative skin test controls, respectively; wheal and erythema were measured after 20 minutes. Blood samples for determining serum DAO activity were drawn before histamine SBPCHC, stored at −20°C, and determined by a DAO radio extraction assay from Immundiagnostik AG, Bensheim, Germany. According to the manufacturer, HIT was likely in serum DAO values <10 U/mL. For some patients, immediate-type allergic reactions to other food were excluded by history, prick-to-prick skin test, and/or oral challenge tests.

Single-blind placebo-controlled oral histamine provocation

Patients were hospitalized and received a histamine-low, pseudoallergen-low diet (Figure 1). Before SBPCHC, patients were instructed to come in a stable health condition and advised to follow a vegetable-based mixed diet with a restriction of biogenic amine intake, especially histamine intake. Such a diet was supposed to be followed for 10 to 14 days, as recommended by a scientific position paper on HIT, but was not individually controlled by a dietician.[9] Peppermint tea was used as placebo with 2-hourly observation intervals. Two patients received placebo testing twice due to severe reported symptoms such as dyspnea, severe headache, and abdominal cramps during the first placebo test.

For verum provocation, 5 mL, 10 mL, and 15 mL of 1% histamine hydrochloride solution, prepared in our pharmacy, were diluted in peppermint tea, corresponding to 30 mg, 60 mg, and 90 mg of histamine, respectively. The histamine amount used for testing is much higher than normally consumed by an adult eating food products in compliance with the legal limits, but lower than needed for histamine intoxication.[16,17] Immunomodulating medications and H_1-antihistamines had to be discontinued for at least 7 days before the provocation test. Physicians recorded the onset and the self-reported symptoms occurring within 24 hours of each challenge.

Group allocation and outcome definition

SBPCHCs were evaluated following the European Academy of Allergy and Clinical Immunology's guideline for food allergy testing.[18] SBPCHCs were evaluated to be positive if objective signs (flushing and diarrhea) occurred after histamine SBPCHC and no objective or subjective symptoms occurred after placebo testing ("plausible HIT," Table II). Diarrhea was defined as a discharge of watery stool and the urge to defecate, this being either confirmed by the medical staff or reported by the patient. SBPCHCs were regarded as clearly negative if no objective symptoms (flushing, diarrhea, vomiting, and rhinorrhea) occurred during a histamine challenge or if objective symptoms occurred to a similar or greater degree after a placebo than after a histamine challenge (Figure 2; Tables E1-E5, available in this article's Online Repository at www.jaci-inpractice.org).

Objective reactions to histamine with subjective symptoms to placebo and subjective symptoms only to histamine but not to placebo were regarded as questionable reactions and prompted a detailed case analysis performed by the allergy resident together with the supervisor. The diagnosis "possible HIT" was only made if

TABLE I. Baseline clinical characteristics of the total study population and in those patients with plausible/possible histamine intolerance (HIT) or excluded HIT

	Total study population (n = 59)	Plausible/possible HIT (n = 9)	No HIT (n = 50)	Plausible/possible HIT vs No HIT, *P* value
Age in years, median (IQR)	50 (14.5)	50 (9.5)	50 (15.2)	.72
Female, n (%)	50 (84.7)	8 (88.9)	42 (84.0)	.71
Previous diagnostics, n (%)				
Previous histamine-low diet reduced symptoms	44 (74.6)	8 (88.9)	36 (72.0)	.28
Previously performed colonoscopy/gastroscopy	23 (39.0)	7 (77.8)	16 (32.0)	.0095**
Exclusion of fructose/lactose intolerance	19 (32.2)	6 (66.7)	13 (26.0)	.016*
Symptoms after histamine rich food, n (%)				
Diarrhea	29 (49.2)	8 (88.9)	21 (42.0)	.009**
Abdominal pain/abdominal bloating/flatulence	30 (50.8)	8 (88.9)	22 (44.0)	.011*
Runny nose/sneezing	14 (23.7)	1 (11.1)	13 (26.0)	.33
Vomiting	21 (35.6)	3 (33.3)	18 (36.0)	.87
Flushing	21 (35.6)	3 (33.3)	18 (36.0)	.88
Tachycardia/palpitation	9 (15.3)	1 (11.1)	8 (16.0)	.71
Dyspnea/breathing difficulties	9 (15.3)	2 (22.2)	7 (14.0)	.52
Dizziness/drowsiness/faint	20 (33.9)	2 (22.2)	18 (36.0)	.42
Pruritus	20 (33.9)	1 (11.1)	19 (38.0)	.12
Itching of the face/heat sensation	14 (23.7)	2 (22.2)	12 (24.0)	.91
Headache	18 (30.5)	4 (44.4)	14 (28.0)	.32
Globus sensation	9 (15.3)	1 (11.1)	8 (16.0)	.71
Fatigue/concentration difficulties	5 (8.5)	0 (0.0)	5 (10.0)	.32
Additional symptoms: aphthous stomatitis, muscle cramps, paresis, burning urine, constipation, and hiccups	8 (13.6)	0 (0.0)	8 (16.0)	.19
Foods/drinks associated with symptoms, n (%)				
Vegetables (tomato, spinach, avocado, eggplant, and sauerkraut)/fruit	35 (59.3)	6 (66.7)	29 (58.0)	.63
Meat (ham, sausage, and salami) and fish	22 (37.3)	3 (33.3)	19 (38.0)	.79
Cheese	23 (39.0)	4 (44.4)	19 (38.0)	.72
Alcohol (beer/sparkling wine/red wine)	29 (49.2)	3 (33.3)	26 (52.0)	.30
Dark chocolate	17 (28.8)	2 (22.2)	15 (30.0)	.64
Coffee	4 (6.8)	0 (0.0)	4 (8.0)	.38

IQR, Interquartile range.
*$P < .05$.
**$P < .01$.

objective reactions significantly exceeded subjective symptoms after placebo or if subjective symptoms matched the patient's history during histamine testing, taking histamine dose dependence into account (Figure 2, Table II, and Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Histamine dose dependence was defined as higher severity of symptoms with an increasing histamine dose, whereas symptoms to a lower dose and tolerance of a higher dose precluded a reaction.

Statistics

GraphPad PRISM (GraphPad Software, Boston, Mass) was used for all analyses. Patient characteristics were noted as a median for continuous variables and as a percentage number for dichotomous variables. The Wilcoxon test for ordinal numbers was used to calculate potential differences between the groups at baseline and follow-up points of time. The characteristics of each group were compared using Mann-Whitney *U* tests for ordinal variables, the 2 independent samples *t*-test for interval and normally distributed variables, and the Pearson χ^2 test for categorical variables. Reported *P* values were considered statistically significant if $^*P < .05$ or $^{**}P < .01$.

RESULTS

Study population, elicitors, and reported symptomatology

Patients were predominantly female (84.7%) with a median age of 50 ± 14.5 years (range: 17-82 years) (Table I). The majority of patients (74.6%) reported less symptoms after the elimination of histamine-rich food; however, a complete abatement of symptoms could not be reached.

Previous examinations based on patients' complaints consisted of a colonoscopy and/or gastroscopy in 23 cases (39.0%) and the exclusion of fructose malabsorption and/or lactose intolerance in 19 cases (32.2%). Symptoms occurred after the consumption of histamine-rich foods, primarily vegetables and fruit (59.3%), alcoholic beverages (49.2%), and cheese (39.0%), which lead to the suspicion of HIT (Table I). Reported symptoms were mostly gastrointestinal with abdominal pain, bloating, and flatulence in 30 cases (50.8%) and diarrhea in 29 cases (49.2%), but also consisted of a broad range of multiple symptoms such as dizziness, drowsiness, fainting, and pruritus in 20 cases (33.9%).

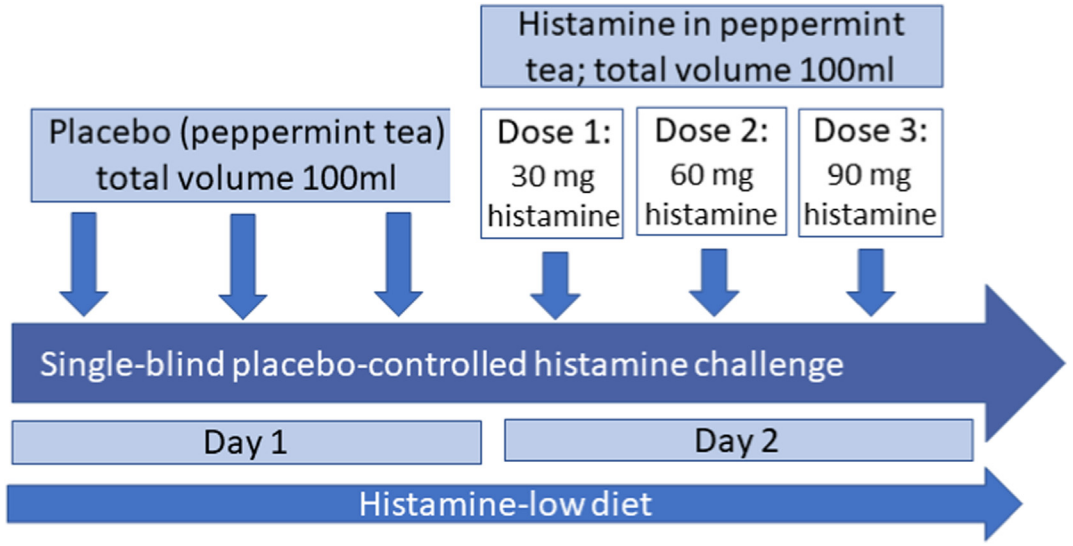

FIGURE 1. Flow diagram of the challenge procedure during the study.

Results of histamine and placebo provocation tests

Histamine provocation was safe without any severe reactions. No hypotension or reduced peripheral oxygen saturation was elicited; no patient received adrenaline. Only 1 patient with diarrhea received an antihistamine (dimetindene, n = 1, patient 1), whereas for the rest of the patients, symptoms resolved without therapy.

Objective symptoms after histamine provocation and no symptoms after placebo leading to a diagnosis of plausible HIT were found in only 4 of 59 cases (6.8%, Table II, Figure 2). In addition, "possible HIT" was diagnosed in 3 patients who had objective symptoms after histamine provocation and only mild subjective symptoms after placebo provocation and in 2 patients (3.4%) with subjective symptoms to histamine only. With these patients, symptoms/reactions corresponded to the patients' history and often increased in severity with increasing histamine dose dependently (Figure 2, Table E1, available in this article's Online Repository at www.jaci-inpractice.org). About a quarter of the patients (23.7%) showed no symptoms during the SBPCHC to either histamine or placebo. Three patients (5.1%) only reported symptoms after placebo (Table E5, available in this article's Online Repository at www.jaci-inpractice.org). A total of 16 patients (27.1%, Table E4, available in this article's Online Repository at www.jaci-inpractice.org) had the same or even more subjective symptoms after the placebo challenge compared with those after the histamine challenge, and 10 patients (16.9%, Table E3, available in this article's Online Repository at www.jaci-inpractice.org) had different subjective symptoms with comparable severity after the histamine and placebo challenge, leading to the exclusion of HIT. Another 5 patients (8.5%, Table E2, available in this article's Online Repository at www.jaci-inpractice.org) had objective symptoms with the same or even higher severity after the placebo than after the histamine challenge.

Thus, of 59 patients, plausible HIT by objective symptoms to histamine (n = 4) or possible HIT with convincing objective or subjective symptoms compatible to history and dose dependence (n = 5) was diagnosed only in altogether 9 patients (15.3%), 8 female and 1 male. In the vast majority of patients (84.7%) with self- or doctor-suspected HIT, however, the diagnosis HIT was excluded.

Comparison of patients with plausible/possible HIT to those without HIT

Patients with plausible/possible HIT had undergone significantly more previous diagnostics such as a colonoscopy/gastroscopy (77.8% vs 32.0%, $P = .0095$) and fructose malabsorption or lactose intolerance tests (66.7% vs 26.0%, $P = .016$) than those without HIT. After consuming histamine-rich food, patients with plausible/possible HIT significantly stated more gastrointestinal symptoms: diarrhea (88.9% vs 42.0%, $P = .009$) or abdominal pain, bloating, and flatulence (88.9% vs 44.0%, $P = .011$). Food categories reported to elicit symptoms did not differ significantly between the groups.

Immediate histamine and saline skin test results

Wheal size 20 minutes after skin prick test with histamine (5 ± 1.5 mm vs 6 ± 1.9 mm, $P = .43$) and physiological saline (0 ± 0.7 mm vs 1 ± 1.1 mm, $P = .35$) did not show any differences between patients with diagnosed HIT and those without, respectively (Table III).

Serum levels of diamine oxidase in patients with histamine intolerance

Serum DAO activity <10 U/mL was found in 4 patients (50%) with plausible HIT/possible HIT and 11 patients (22.9%) without HIT, indicating a poor sensitivity of 0.5 and a specificity of 77% for diagnosing HIT in our patient population (Figure 3). The low sensitivity resulted from highly heterogeneous DAO levels between 2.9 U/mL and 47.2 U/mL in patients without HIT; 10 patients (20.8%) had even lower DAO levels than patients with HIT. In contrast, patients with plausible HIT/possible HIT had uniformly low values between 9.3 and 15.6, and there was a trend ($P = .08$) toward lower activity in this patient group (Table III). Levels >16 U/mL had a negative predictive value of 100%, but a specificity of only 52%.

TABLE II. History and symptoms to a placebo-controlled histamine challenge in patients with final diagnosis of plausible histamine intolerance (HIT, patients 1-4) or possible HIT (patients 5-9)

Patient no.	Age	Sex	Previous histamine-low diet reduced symptoms	Colonoscopy/gastroscopy performed	Exclusion of fructose-malabsorption/ lactose intolerance	Placebo challenge*								Histamine challenge*								Dose-dependent symptoms
						Diarrhea	Vomiting	Flushing	Running nose	Abdominal pain/ cramps	Palpitation	Heat sensation/ itching of the face	Headache	Fatigue	Diarrhea	Vomiting	Flushing	Running nose	Abdominal pain/ cramps	Palpitation	Heat sensation/ itching of the face	Headache	Fatigue	
1	47	M	Y	Y											Y								Y	
2	58	W	Y	Y	Y										Y				Y					Y
3	54	W	Y	Y	Y										Y									Y
4	48	W	Y	Y	Y												Y			Y				Y
5	58	W	Y		Y						Y					Y	Y					Y		Y
6	29	W	Y	Y	Y					Y				Y			Y		Y			Y	Y	
7	62	W										Y			Y				Y					
8	42	W	Y	Y	Y														Y					Y
9	56	W	Y	Y															Y					

*Y = Yes = having symptoms.

DISCUSSION

To our knowledge, this is the largest and most conclusive study demonstrating that the diagnosis of HIT can be excluded by SBPCHC in the majority of patients believing to suffer from HIT. These patients had undergone extensive and prolonged dietary restrictions before HIT was excluded, presumably reducing their quality of life without medical need. The high rate of placebo reactions (62.7%) is another important outcome of the study. This makes it impossible to exclude reactions that appear by chance when using only 1 verum and 1 placebo challenge and to confirm the existence of HIT in the studied patients and as a disease. Three highly resource-demanding double-blinded placebo-controlled histamine challenges would be needed to reliably exclude positive verum reactions by chance with near certainty (>99%). In this study, using SBPCHC, in 4 patients (6.8%), HIT seemed plausible because of objective reactions only to histamine, and in additional 5 cases, HIT was evaluated as possible. Histamine provocation was safe, reactions were nonsevere, and antihistamine treatment was only applied on 1 patient. Although serum DAO activity was uniformly low in plausible HIT/possible HIT, values were >10 U/mL in 50% of those patients. In those patients, the optimal cutoff of 15.6 U/mL with a 100% sensitivity had a low specificity of only 52% due to highly variable DAO levels in patients without HIT, resulting in a large overlap of low DAO values in both groups.

Diagnosing HIT is of great importance for the patients; however, making the diagnosis is challenging.[9] As SBPCHC is time-consuming and resource-intensive, other parameters for making the diagnosis of HIT were sought for, such as a compatible history together with serum DAO values <10 IU/mL[19,20] as well as an additional reduction of symptoms after a histamine-low diet.[21] Middle-aged women were predominant among patients in the present study reporting a suspicion of HIT, as has also been reported by others.[19,22,23] Interestingly, the response to a histamine-low diet in the patient's history did not differ between patients with positive versus negative SBPCHC. Patients with positive SBPCHC had undergone more excessive diagnostic investigations including endoscopy and exclusion from lactose intolerance and fructose malabsorption. Other differential diagnoses had been excluded, for example, food allergies, mastocytosis, or *Helicobacter pylori* infection.[4,9] Gastrointestinal symptoms in the patients' history, such as diarrhea, abdominal pain, bloating, or flatulence, were indicative of HIT ($P = .01$), whereas no significant differences to SBPCHC-negative patients were found for headache, nausea, and flushing. Unfortunately, as irritable bowel syndrome with gastrointestinal symptoms is common and a histamine-low diet may also lead to symptom relief in patients with this disease,[24] history alone seems to be unreliable for the diagnosis of HIT. Also, the wheal size of the histamine skin prick test after 20 minutes did not discriminate between patients reacting to histamine and those without reactions.

Decreased activity of histamine-degrading enzymes DAO and/or HMT has been proposed as a mechanism resulting in HIT. In our study, DAO activity measured by radio extraction assay was indeed uniformly lower than 15.6 U/mL in patients with HIT, although not below the postulated cutoff of 10 U/mL in half of the patients, and there was only a tendency to differ from patients without HIT ($P = .08$), because of highly variable levels in the latter patient group. Some publications reported DAO activity to

Group number	Placebo challenge	Histamine challenge	Diagnostic certainty	Final diagnosis (n)
I	-	+ objective	HIT	plausible HIT (4)
II	+ subjective	+ objective	Case analysis	possible HIT (3)
	-	+ subjective	Case analysis	possible HIT (2), no HIT (2)
III	+ objective	+ objective	HIT excluded	no HIT (48)
	+ subjective	+ subjective		
	+/-	-		

A

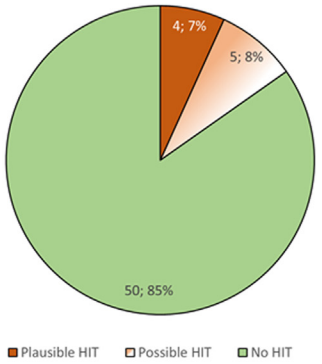

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FIGURE 2. (**A**) Patient categorization depending on the outcomes of placebo-controlled histamine challenges and detailed case analysis. Case analysis is evaluating objective and subjective symptoms, the patient's history, and dose dependence of symptoms to histamine challenge (eg, tolerance of a higher dose disproves a reaction). (**B**) Number and relative percentage of patients with plausible HIT, possible HIT, and excluded HIT in the patient population. *HIT*, Histamine intolerance.

be significantly lower in HIT.[11,12,15] A DAO activity less than 10 U/mL, measured by radio extraction[11,19,25] or enzyme immune assay,[12,15] has been suggested as an indicator for HIT. In contrast, other studies concluded that serum DAO activity has no diagnostic value, although, unlike the present study, they only used the patients' history to classify patients with HIT.[9,13,14]

Our results may shed some light on the ongoing controversy. Uniformly low DAO levels were associated with HIT, but appeared insufficient and not specific enough to diagnose the disease. On the other hand, in patients with high levels, the marker might be helpful to exclude HIT without the need for SBPCHC, as a DAO activity of >16 U/mL had a negative predictive value of 100% in our population. DAO is predominantly expressed in the gut, and even if DAO levels were crucial for HIT, it has been discussed that serum DAO levels only partially reflect gut DAO levels.[26]

Thus, as the patients' history and diet response are unreliable and low DAO activity has low specificity, currently, SBPCHC is the gold standard for diagnosing HIT, although double-blinded challenges and repeat challenges would have a better accuracy. To our knowledge, there are only 2 other SBPCHC studies in HIT patients with diverging results. The first provided inconclusive results, as positive open provocations with 75 mg of histamine were not reproducible when tested in a blinded fashion and were associated with a placebo reaction rate of 64.1%.[23] The other SBPCHC study in only 14 patients recorded mostly subjective symptoms to histamine and not to placebo, but plasma histamine levels were highest in 4 healthy controls and remained stable throughout the challenge. The authors concluded that the dose of 75 mg was too low to detect an increase of histamine in plasma.[27]

In this study, HIT was excluded in the majority of patients with suspected HIT. The cause of symptoms in these patients remains unclear. The majority of the patients (62.7%) reported symptoms already to placebo, demonstrating the importance of placebo-controlled challenge tests.[23] Without those, 31 patients (52.5%) who additionally reacted positively to the histamine challenge would have been misdiagnosed as HIT. This may indicate that psychosomatic factors such as anticipation, anxiety, and stress may play an important role in the genesis of symptoms in patients suspecting HIT. Palpitations, tachycardia, hyperventilation with dyspnea, dizziness, drowsiness, and fainting reported by patients during placebo-controlled challenges are also often seen with stress or anxiety reactions.[28]

A limitation of this study is that the sequence of the challenge was always first placebo and then histamine. Although the high placebo rate in this study argues for effective blinding, a bias of the outcome cannot be excluded. Furthermore, SBPCHC can exclude HIT in approximately 85% of patients by nonreproducibility of symptoms or placebo reactions, but it cannot unequivocally prove the existence of HIT in the remainders, as reactions to challenges were frequent and could have led to reactions by pure chance. Thus, positive reactions only to histamine, but not to placebo in very few patients in this study are an argument, but no proof for the principal existence of HIT as a disorder. Individual susceptibility to histamine has also been discussed in cases of scombroid poisoning after eating contaminated fish; however, other biogenic amines than histamine may be involved and enhance histamine toxicity.[29,30] The average histamine content in food causing histamine intoxication is approximately 1110 mg/kg, and legal limits in food products have been set between 100 and 400 mg/kg.[16,17] The optimal dose for the histamine challenge is unknown: low histamine levels might lead to underdiagnosing patients,[23] whereas high dosages might have toxic effects.[9] While some studies on HIT, urticaria, and eczema used 75 mg of histamine for the oral provocation challenge,[8,31] other studies used up to 1.5 mg/kg body weight histamine for testing.[9,10] In a study with 10 healthy volunteers, SBPCHC with 75 mg of histamine already led to diarrhea, flatulence, rhinorrhea, pruritus, cephalgia, or conjunctivitis in 5 patients.[32] Conversely, in the present study, a very similar number and severity of reactions to either placebo or 90 mg of histamine argue against a pronounced toxic effect of that dose, and only in patients 5 and 7, reactions occurred to the highest histamine dose. Furthermore, no severe symptoms evolved. Thus, as this dose is clearly higher than the amount of histamine normally ingested with the normal diet, it may be used to reliably exclude HIT.

TABLE III. Comparison of test characteristics in patients with possible/plausible and without histamine intolerance

	With plausible/possible histamine intolerance* (n = 9)	Without histamine intolerance (n = 50)	*P* value
Intradermal test (mm), mean (SD)			
Wheal histamine	5 (1.5)	6 (1.9)	.43
Erythema histamine	14 (9.8)	15 (8.2)	.64
Wheal saline	0 (0.7)	0 (1.0)	.47
Erythema saline	0 (0.7)	1 (1.1)	.35
Diamine oxidase (U/mL), mean (SD)			
Serum diamine oxidase	11.25 (2.2)	17.97 (10.34)	.08
Challenge test, n (%)			
Placebo testing negative	6 (66.7)	16 (32.0)	.03*
Placebo testing positive	3 (33.3)	34 (68.0)	
Histamine testing negative	0 (0.0)	16 (32.0)	.05
Histamine testing positive	9 (100.0)	34 (68.0)	

SD, Standard deviation.
*$P < .05$.

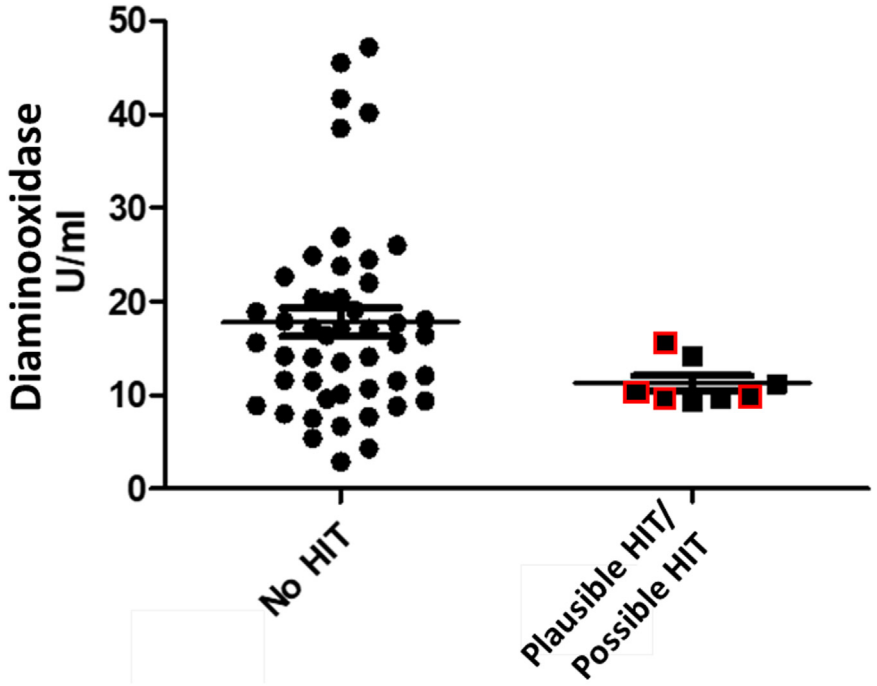

FIGURE 3. Comparison of serum diamine oxidase activity levels measured by REA (Immundiagnostik AG, Bensheim, Germany) in 8 patients with plausible/possible HIT and 48 patients after exclusion of HIT. *P* values of an unpaired *t*-test ($P = .08$). Patients with confirmed HIT by objective symptoms had DAO values of 9.7, 15.6, 9.9, and 9.8 U/mL (marked in red). *DAO*, Diamine oxidase; *HIT*, histamine intolerance.

CONCLUSIONS

The suspicion of HIT was disproven by SBPCHC in the vast majority of patients (84.7%) of our study population, who may suffer from somatoform reactions often also elicited by placebo or from other diagnoses like irritable bowel disease. Gastrointestinal symptoms and low DAO activity, but not dietary response, were indicative, although insufficiently specific for diagnosing HIT; thus, the placebo-controlled histamine challenge remains the gold standard for excluding HIT. However, placebo reactions are very common in patients with suspected HIT. Thus, the results of verum and placebo challenges have to be interpreted carefully together with the patient's history. There is a need for studies using double-blind challenges and repeat challenges. All patients with plausible/possible HIT and those without HIT should receive diet counseling. Because of the expenditure, challenges should only be performed after a histamine-low diet of 10 to 14 days (vegetable-based mixed diet with the restriction of biogenic amine intake, especially histamine intake) has led to a significant

resolution of symptoms and other differential diagnoses have been excluded, for example, intestinal malabsorptions, mastocytosis, food allergies, or *H. pylori* infection.[4,9] Furthermore, because challenges appear safe, performing the procedure in the outpatient setting could be discussed to reduce expenditures.

Acknowledgments

All retrospective data analyzed were collected as part of routine diagnosis and treatment. The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy restrictions.

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TABLE E1. History, symptoms to placebo and histamine challenge, dose dependence, reasons for diagnosis, and final diagnosis in those 7 patients with either objective reaction only to histamine but also subjective reaction to placebo (*) or in patients with only subjective reaction to histamine but not to placebo (**) in whom the diagnosis was based on case-dependent analysis

No.	Age	Sex	Previous histamine-low diet reduced symptoms	Colonoscopy/ gastroscopy performed	Exclusion of fructose/lactose intolerance	History/test	Diarrhea	Vomiting	Flushing	Running nose	Dyspnea/ hyperventilation	Chest pressure/pain	Abdominal pain/cramps	Palpitation	Heat sensation/itching of face	Pruritus	Globus sensation	Headache	Fatigue	Concentration difficulty	Drowsiness	Dose dependent	Reason for diagnosis	Final diagnosis
5*	58	W	Y		Y	Anamnestic symptoms	Y	Y					Y		Y		Y	Y					Vomiting after histamine ingestion, only after the highest dose	Possible HIT
						Placebo OC								Y										
						Histamine OC		Y	Y									Y				Y		
6*	29	W	Y	Y	Y	Anamnestic symptoms			Y				Y					Y					Flushing after 2 and 3 doses of histamine, abdominal pain and headache only after the highest dose	Possible HIT
						Placebo OC							Y						Y					
						Histamine OC			Y				Y					Y	Y					
7*	61	W				Anamnestic symptoms	Y	Y	Y				Y					Y					Diarrhea and abdominal pain only after the highest dose of histamine	Possible HIT
						Placebo OC									Y									
						Histamine OC	Y						Y											
8**	42	W	Y	Y	Y	Anamnestic symptoms	Y			Y			Y										Abdominal pain only after histamine, not after placebo, compatible with patient history and getting worse with higher histamine dose	Possible HIT
						Placebo OC																		
						Histamine OC							Y									Y		

(continued)

TABLE E1. *(Continued)*

No.	Age	Sex	Previous histamine-low diet reduced symptoms	Colonoscopy/ gastroscopy performed	Exclusion of fructose/lactose intolerance	History/test	Diarrhea	Vomiting	Flushing	Running nose	Dyspnea/ hyperventilation	Chest pressure/pain	Abdominal pain/cramps	Palpitation	Heat sensation/itching of face	Pruritus	Globus sensation	Headache	Fatigue	Concentration difficulty	Drowsiness	Dose dependent	Reason for diagnosis	Final diagnosis
9**	55	W	Y	Y		Anamnestic symptoms	Y	Y			Y		Y								Y		Abdominal pain only after histamine, not after placebo, compatible with patients history	Possible HIT
						Placebo OC																		
						Histamine OC							Y											
10	42	W	Y	Y	Y	Anamnestic symptoms	Y	Y			Y		Y				Y						Hyperventilation = anxiety reaction, patient-tolerated higher histamine dose without symptoms	No HIT
						Placebo OC																		
						Histamine OC					Y													
11	34	W	Y			Anamnestic symptoms				Y	Y					Y	Y	Y			Y		Light itching of the face, not previously described, anamnestic symptoms described as more severe, no increase of symptom with higher histamine dose	No HIT
						Placebo OC																		
						Histamine OC									Y									

HIT, Histamine intolerance; *OC*, oral challenge; *Y*, yes = having symptoms.

TABLE E2. Symptoms/manifestations of a placebo-controlled histamine challenge in patients with no histamine intolerance (HIT) having objective symptoms of the same or higher severity after placebo compared with histamine challenge (n = 5)

No.	Age	Sex	Previous histamine-low diet reduced symptoms	Colonoscopy/ gastroscopy performed	Exclusion of fructose/ lactose intolerance	History/test	Diarrhea	Vomiting	Flushing	Running nose	Dyspnea/ hyperventilation	chest pressure/pain	Abdominal pain/cramps	Palpitation	Heat sensation/itching of the face	Pruritus	Globus sensation	Headache	Fatigue	Concentration difficulty	Drowsiness	Dose dependent	Reason for diagnosis	Final diagnosis
12	51	W	Y			Anamnestic symptoms	Y		Y	Y			Y		Y	Y			Y				Patient with an anxiety disorder, diarrhea, flushing and runny nose = anxiety reaction, they also happened to placebo	No HIT
						Placebo OC	Y		Y	Y			Y		Y	Y		Y						
						Histamine OC	Y		Y	Y			Y			Y		Y						
13	76	M	Y	Y		Placebo OC	Y	Y															Diarrhea occurred to placebo and it only occurred after the first and second histamine dose, not with the highest histamine dose	No HIT
						Histamine OC	Y																	
						Placebo OC	Y																	
14	41	M	Y	Y	Y	Histamine OC	Y			Y			Y		Y		Y	Y	Y	Y			Diarrhea occurred to placebo and histamine, reactions had a similar severity	No HIT
						Placebo OC	Y						Y					Y		Y				
						Histamine OC	Y						Y					Y		Y	Y			
15	83	W				Placebo OC				Y								Y					Rhinorrhea to the same amount after placebo and histamine provocation	No HIT
						Histamine OC				Y					Y									
						Placebo OC				Y					Y									
16	62	W	Y		Y	Histamine OC							Y					Y			Y		Severity of flush was comparable with placebo and histamine	No HIT
						Placebo OC			Y							Y								
						Histamine OC			Y															

OC, Oral challenge; *Y*, yes = having symptoms.

TABLE E3. Symptoms/manifestations of placebo-controlled histamine challenge in patients with no histamine intolerance (HIT) having different subjective symptoms during the histamine challenge and placebo challenge of comparable severity (n = 10)

No.	Age	Sex	Previous histamine-low diet reduced symptoms	Colonoscopy/ gastroscopy performed	Exclusion of fructose/ lactose intolerance	History/test	Diarrhea	Vomiting	Flushing	Running nose	Dyspnea/ hyperventilation	Chest pressure/pain	Abdominal pain/cramps	Palpitation	Heat sensation/ itching of the face	Pruritus	Globus sensation	Headache	Fatigue	Concentration difficulty	Drowsiness	Dose dependent	Reason for diagnosis	Final diagnosis
17	53	W	Y			Anamnestic symptoms	Y	Y	Y						Y	Y	Y						Heat sensations after histamine, fatigue after placebo, severity of fatigue and heat sensation comparable, less severe than anamnestic symptoms, no dose dependence,	No HIT
						Placebo OC													Y					
						Histamine OC									Y									
18	54	W	Y		Y	Anamnestic symptoms			Y						Y	Y					Y		Same symptoms (abdominal pain, heat sensation) with ASS and celebrex OC, no dose dependence, multiple placebo symptoms same severity than histamine symptoms	No HIT
						Placebo OC								Y					Y		Y			
						Histamine OC							Y		Y									
19	53	W	Y		Y	Anamnestic symptoms			Y	Y	Y			Y			Y	Y			Y		Heat sensation not previously described, multiple placebo symptoms more severe than reaction to histamine	No HIT
						Placebo OC					Y					Y					Y			
						Histamine OC									Y									
20	44	W	Y	Y	Y	Anamnestic symptoms	Y		Y				Y			Y		Y	Y				Headache was the main complain, equally severe at placebo and histamine OC, heat sensation minor complain, not dose dependent	No HIT

						Placebo OC											Y						
						Histamine OC								Y			Y						
21	46	W	Y		Y	Anamnestic symptoms	Y	Y	Y	Y			Y				Y				Y	Headache getting better when the dose of histamine was increased	No HIT
						Placebo OC						Y											
						Histamine OC											Y						
22	40	M	Y		Y	Anamnestic symptoms	Y	Y														Globus sensation not previously described, no dose dependence, globus sensation /drowsiness/ abdominal pain comparable	No HIT
						Placebo OC							Y								Y		
						Histamine OC										Y					Y		
23	24	W	Y			Anamnestic symptoms	Y	Y	Y				Y	Y		Y	Y					Abdominal pain not after last histamine dose, fatigue not previously described, heat sensation same severity at both OC days	No HIT
						Placebo OC								Y									
						Histamine OC							Y	Y				Y					
24	74	W				Anamnestic symptoms			Y						Y		Y					Previous diet did not reduce symptoms, severity of headache and heat sensation were comparable	No HIT
						Placebo OC											Y						
						Histamine OC									Y								
25	53	W	Y		Y	Anamnestic symptoms		Y	Y					Y	Y	Y	Y	Y	Y		Y	Globus sensation also happened with placebo, multiple symptoms with placebo, both OC (placebo/ histamine) were similar terrible	No HIT
						Placebo OC										Y		Y			Y		
						Histamine OC								Y		Y							

(continued)

TABLE E3. *(Continued)*

No.	Age	Sex	Previous histamine-low diet reduced symptoms	Colonoscopy/ gastroscopy performed	Exclusion of fructose/ lactose intolerance	History/test	Diarrhea	Vomiting	Flushing	Running nose	Dyspnea/ hyperventilation	Chest pressure/pain	Abdominal pain/cramps	Palpitation	Heat sensation/ itching of the face	Pruritus	Globus sensation	Headache	Fatigue	Concentration difficulty	Drowsiness	Dose dependent	Reason for diagnosis	Final diagnosis
26	43	W	Y			Anamnestic symptoms				Y													Symptoms not previously described, symptoms only occurred after the first histamine dose	No HIT
						Placebo OC											Y							
						Histamine OC					Y		Y											

OC, Oral challenge; *Y*, yes = having symptoms.

TABLE E4. Symptoms/manifestations of a placebo-controlled histamine challenge in patients with no histamine intolerance (HIT) having the same subjective symptom after placebo with the same or higher severity compared with the histamine challenge (n = 16)

No.	Age	Sex	Previous histamine-low diet reduced symptoms	Colonoscopy/ gastroscopy performed	Exclusion of fructose/ lactose intolerance	History/test	Diarrhea	Vomiting	Flushing	Running nose	Dyspnea/ hyperventilation	chest pressure/pain	Abdominal pain/cramps	Palpitation	Heat sensation/ itching of the face	Pruritus	Globus sensation	Headache	Fatigue	Concentration difficulty	Drowsiness	Dose dependent	Reason for diagnosis	Final diagnosis
27	36	W	Y			Anamnestic symptoms									Y						Y		Palpitation as an anxiety reaction, comparable for histamine and placebo in severity	No HIT
						Placebo OC								Y										
						Histamine OC								Y										
28	69	W	Y			Anamnestic symptoms							Y			Y		Y					Pruritus and drowsiness each after the last dose of histamine and placebo, fatigue additionally after the second testing day	No HIT
						Placebo OC										Y					Y			
						Histamine OC										Y			Y		Y			
29	46	W	Y			Anamnestic symptoms	Y	Y					Y		Y	Y		Y			Y		Dyspnea comparable in severity with histamine and placebo OC, fatigue at each end of the OC	No HIT
						Placebo OC					Y								Y					
						Histamine OC					Y								Y					
30	40	M	Y			Anamnestic symptoms			Y					Y	Y	Y			Y		Y		Drowsiness and headache comparable during histamine and placebo testing	No HIT
						Placebo OC												Y			Y			
						Histamine OC												Y			Y			
31	60	W	Y	Y	Y	Anamnestic symptoms	Y				Y			Y	Y	Y				Y	Y		Pruritus comparable in severity with histamine and placebo OC, multiple symptoms during placebo testing	No HIT
						Placebo OC					Y				Y	Y	Y				Y			
						Histamine OC										Y								

(continued)

TABLE E4. *(Continued)*

No.	Age	Sex	Previous histamine-low diet reduced symptoms	Colonoscopy/ gastroscopy performed	Exclusion of fructose/ lactose intolerance	History/test	Diarrhea	Vomiting	Flushing	Running nose	Dyspnea/ hyperventilation	chest pressure/pain	Abdominal pain/cramps	Palpitation	Heat sensation/ itching of the face	Pruritus	Globus sensation	Headache	Fatigue	Concentration difficulty	Drowsiness	Dose dependent	Reason for diagnosis	Final diagnosis
32	25	W		Y	Y	Anamnestic symptoms	Y	Y					Y										Abdominal pain comparable in severity with histamine and placebo OC	No HIT
						Placebo OC							Y											
						Histamine OC							Y											
33	31	W	Y	Y	Y	Anamnestic symptoms	Y	Y					Y						Y		Y		Abdominal pain comparable in severity with histamine and placebo OC	No HIT
						Placebo OC							Y											
						Histamine OC							Y											
34	18	W	Y			Anamnestic symptoms		Y	Y				Y						Y		Y		Dyspnea, itching of the face, and headache comparable in severity with histamine and placebo OC	No HIT
						Placebo OC					Y				Y		Y							
						Histamine OC					Y				Y		Y							
35	27	W	Y	Y		Anamnestic symptoms	Y		Y	Y	Y		Y	Y	Y	Y	Y	Y		Y	Y		Heat sensation and palpitation similar during placebo and histamine testing	No HIT
						Placebo OC								Y	Y									
						Histamine OC								Y	Y									
36	44	W	Y			Anamnestic symptoms	Y	Y					Y			Y					Y		Itching of the face and body comparable during histamine and placebo testing	No HIT
						Placebo OC									Y	Y								
						Histamine OC									Y	Y								
37	56	W	Y			Anamnestic symptoms	Y						Y					Y					Abdominal pain, itching of the face, and headache comparable in severity with histamine and placebo OC	No HIT
						Placebo OC							Y		Y		Y							
						Histamine OC							Y		Y		Y							

38	72	W	Y			Anamnestic symptoms									Y		Y			Y			Y	Itching of the face and body and headache comparable during histamine and placebo testing	No HIT
						Placebo OC										Y	Y		Y						
						Histamine OC										Y	Y		Y						
39	59	W	Y	Y		Anamnestic symptoms	Y	Y			Y							Y		Y				Abdominal pain and palpitation more severe during placebo testing	No HIT
						Placebo OC						Y	Y	Y											
						Histamine OC							Y	Y											
40	72	W		Y		Anamnestic symptoms	Y	Y					Y			Y				Y	Y	Y		Abdominal pain, heat sensation, and headache comparable with histamine and placebo OC	No HIT
						Placebo OC							Y			Y			Y						
						Histamine OC							Y			Y			Y						
41	56	W				Anamnestic symptoms	Y	Y					Y				Y							Palpitation and headache more severe with placebo testing	No HIT
						Placebo OC								Y					Y						
						Histamine OC													Y						
42	54	W	Y			Anamnestic symptoms	Y		Y	Y				Y			Y		Y					Multiple symptoms even more severe when testing placebo than histamine	No HIT
						Placebo OC							Y			Y	Y	Y			Y	Y			
						Histamine OC							Y			Y		Y							

OC, Oral challenge; *Y*, yes = having symptoms.

TABLE E5. Symptoms/manifestations of a placebo-controlled histamine challenge in patients with no histamine intolerance (HIT) having negative (n = 14) or positive (n = 3) placebo and negative histamine challenge

No.	Age	Sex	Previous histamine-low diet reduced symptoms	Colonoscopy/ gastroscopy performed	Exclusion of fructose/ lactose intolerance	History/test	Diarrhea	Vomiting	Flushing	Running nose	Dyspnea/ hyperventilation	Chest pressure/ pain	Abdominal pain/cramps	Palpitation	Heat sensation/ itching of the face	Pruritus	Globus sensation	Headache	Fatigue	Concentration difficulty	Drowsiness	Final diagnosis
43	33	W	Y			Anamnestic symptoms	Y	Y					Y		Y	Y						No HIT
						Placebo OC																
						Histamine OC																
44	54	W	Y			Anamnestic symptoms			Y	Y						Y						No HIT
						Placebo OC																
						Histamine OC																
45	44	W				Anamnestic symptoms			Y	Y						Y		Y				No HIT
						Placebo OC																
						Histamine OC																
46	65	W	Y			Anamnestic symptoms		Y	Y				Y									No HIT
						Placebo OC																
						Histamine OC																
47	58	M				Anamnestic symptoms					Y			Y			Y					No HIT
						Placebo OC																
						Histamine OC																
48	52	M	Y		Y	Anamnestic symptoms	Y	Y					Y									No HIT
						Placebo OC																
						Histamine OC																
49	71	M				Anamnestic symptoms			Y						Y	Y					Y	No HIT
						Placebo OC																
						Histamine OC																
50	47	W				Anamnestic symptoms										Y		Y				No HIT
						Placebo OC																
						Histamine OC																
51	60	M	Y			Anamnestic symptoms			Y	Y	Y						Y					No HIT
						Placebo OC																
						Histamine OC																
52	46	W	Y	Y		Anamnestic symptoms	Y	Y					Y						Y		Y	No HIT
						Placebo OC																
						Histamine OC																
53	37	W				Anamnestic symptoms				Y												No HIT
						Placebo OC																
						Histamine OC																
54	45	W				Anamnestic symptoms			Y	Y	Y						Y					No HIT
						Placebo OC																
						Histamine OC																
55	46	W				Anamnestic symptoms															Y	No HIT

							Placebo OC																						
							Histamine OC																						
56	68	W					Anamnestic symptoms																					Y	No HIT
							Placebo OC																						
							Histamine OC																						
57	40	W	Y				Anamnestic symptoms		Y	Y					Y		Y	Y			Y			Y		Y	No HIT
							Placebo OC					Y	Y	Y											Y			
							Histamine OC																						
58	28	W		Y		Y	Anamnestic symptoms		Y					Y														No HIT
							Placebo OC							Y														
							Histamine OC																						
59	79	W	Y	Y		Y	Anamnestic symptoms	Y		Y	Y			Y	Y				Y									No HIT
							Placebo OC									Y										Y		
							Histamine OC																						

OC, Oral challenge; *Y*, yes = having symptoms.