Histamine Intolerance

The clinical pattern of histamine intolerance (HIT) is defined as the exceeding of the individual histamine tolerance limit. Usually, this is caused by a lack of the histamine-degrading enzyme diamine oxidase (DAO). A decrease in activity of the second histamine-degrading enzyme histamine N-methyltransferase (HNMT) may lead to a worsening of symptoms. HIT may also manifest clinically if the organism is currently exposed to more histamine than it can degrade, despite normal DAO activity. Both a lack of DAO and an excessive exposure to histamine, can be detected with the help of laboratory diagnostic measures. In the case of proven lack of DAO, DNA testing is used to differentiate between primary and secondary causes. Furthermore, an activity-decreasing genetic HNMT variant can be detected.

Histamine – the most important vasoactive mediator

Histamine is a biogenic amine, which is released by activated mast cells. Being a vasoactive mediator, it plays a dominating role in allergic diseases, such as Rhinitis allergica (hay fever), allergic bronchial asthma and urticaria (hives). Moreover, histamine is released in cases of pseudoallergies in conjunction with drugs or food additives, inter alia. In addition to endogenously released histamine, histamine is ingested with food.

There are two histamine-degrading enzymes

Diamine oxidase (DAO) is histamine's most important degrading enzyme. DAO breaks down extracellular (free) histamine and is primarily produced by intestinal epithelial cells. If the activity of DAO is inhibited, histamine will accumulate in the blood. Histamine N-methyltransferase (HNMT), the second histamine-degrading enzyme, in contrast only breaks down intracellular histamine (primarily in liver, kidneys, bronchial mucosa and central nervous system). Due to this spatial and functional separation, a lack of these enzymes may lead to various symptoms or clinical pictures.

HIT Symptoms vary

Since histamine receptors can be found throughout the entire body's organ systems, HIT symptoms are very heterogeneous. Generally speaking, a histaminosis is caused by a lack of DAO. DAO breaks down both histamine originating from food and histamine occurring during allergic reactions intermittently. This explains why, next to the main symptoms nausea, headache, hot flushes, and shortness of breath, primarily diarrhoea also occurs. Furthermore, eczema, rhinitis, episodes of urticaria, hypertension, colitis, and asthma have been observed. A lack of HNMT, on the contrary, rather has an impact on the breakdown of the comparably constant occurrence of intracellular endogenous histamine. Hence, a lack of HNMT leads rather to chronic forms of HIT, often affecting the nervous system. Main symptoms would be unrest, myoclonic twitches, insomnia, fatigue, vertigo, and states of anxiety.

HIT can induce food intolerances

Histamine in food is formed primarily due to bacterial enzymes transforming histidine to histamine. Therefore, the longer the storage period, the higher the histamine concentration. Because of its stability, histamine can be destroyed through neither freezing nor heating. Due to bacteria being responsible for histamine formation, large concentrations of histamine can be found in microbially produced or fermented foods (cheese, sauerkraut, wine), as well as in protein-rich foods such as fish and meat, depending on the respective storage period. In the case of a decreased DAO activity, the consumption of foods that contain high concentrations of histamine can lead to the aforementioned intestinal and systemic reactions.

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Test	Result	Unit	Reference range
Diamine oxidase (DAO) activity i.s.	1.8	IU/ml	14 - 33
Histamine (tot.) i. hep. blood	176	ng/ml	< 75

The results support the clinical suspicion of histamine intolerance (HIT).

DAO activity and histamine concentration in blood are measurable

DAO is continuously released into the bloodstream, and hence the activity of DAO in blood serum is a suitable marker for HIT diagnoses. Measuring the intracellular HNMT, which occurs primarily in the liver, is, on the contrary, not possible. Here, the detection of an activity-decreasing genetic HNMT variant is available. HIT is nevertheless not only caused by the insufficient breakdown of histamine. It may also manifest clinically when there is a histamine surplus that is currently not broken down sufficiently, even under normal DOA activity. Allergic diseases, such as hay fever, sensitisation towards mould, and elevated levels of mast cell activity are sources of additional histamine that accumulates with ingested histamine. In order to diagnose this type of transgression of the individual histamine tolerance limit, DAO activity should be analysed together with the histamine total in blood.

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Genetic testing differs between primary and secondary lack of DAO

In order to avoid unnecessary lifelong dieting, whether the existing lack of DAO is caused by a genetic primary, or a secondary condition, must be analysed. The result will then have an impact on the treatment. A **primary lack of DAO** is accompanied by decreased DAO activity, due to genetic variations (polymorphisms). Patients with proven decreased DAO activity in blood and corresponding clinical symptoms ought to receive genetic screening, in order to differentiate between a genetic or secondary, and therefore causally treatable and reversible, form of histamine intolerance.

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medical report

Test	Result	Unit	Reference range
Diamine oxidase (DAO) activity i.s.	3.9	IU/ml	14 - 33

Verification of reduced activity of histamine-degrading enzyme diamine oxidase.

DAO / genetics

rs2052129	G/T	(DAO gene region)	TT
rs2268999	A/T	(DAO gene)	TT
rs10156191	C/T	(DAO gene)	TT
rs1049742	C/T	(DAO gene)	TT

Assessment

In this case, a genetic predisposition for decreased DOA activity is proven. Molecular genetic testing of the Diamine oxidase (DAO) gene showed the existence of all four sequence variants in homozygously modified form. Since each of the aforementioned sequence variants is independently associated with decreased DAO activity and considering that the patient is carrier of four modified sequence variants, the genetic constellation in question is accompanied by a decreased DAO activity. Therefore, it is probable that the decreased DAO activity in this case is primary, and thus genetically caused.

A common cause for a **secondary lack of DAO** are inflammatory or degenerative bowel diseases, because more than 90 % of DAO is produced in the intestinal epithelium. But also cases in which drugs, alcohol or toxins decrease the activity of DAO, are considered secondary forms. Drugs that have a proven record of decreasing DAO activity are mentioned below. Another possible cause for decreased DAO activity may be a copper deficiency, since copper constitutes DAO's central atom and is hence vital for its performance.

Therapeutic consequences of reduced DAO activity

When decreased DAO activity or significantly elevated histamine levels are proven, foods rich in histamine have to be avoided. In the case of a secondary HIT, meaning a decreased DAO activity despite normal genetic makeup, the cause has to be identified (chronic inflammatory bowel disease? copper deficiency? prescription drug and alcohol history?), since secondary histamine intolerance is, unlike primary histamine intolerance, in most cases reversible. In patients with decreased DAO activity, copper levels should be monitored, in order to avoid an additional deterioration of the residual DAO activity due to copper deficiency. Simultaneously, zinc levels should be monitored, since zinc inhibits intestinal copper absorption. A merely symptomatic therapy through the prescription of H1 receptor antagonists should only be a temporary measure.

Known DAO-inhibiting drugs:

- Acetylcysteine
- Alcuronium
- Alprenolol
- Ambroxol
- Amiloride
- Aminophylline
- Amitriptyline
- Cefotiam
- Cefuroxime
- Chloroquine
- Cimetidine
- Clavulanic acid
- Cyclophosphamide
- Dihydralazine
- Dobutamine
- Isoniazid
- Metamizole
- Metoclopramide
- Metronidazole
- Morphine
- Pancuroniumbromide
- Pentamidine
- Pethidine
- Prilocaine
- Propafenone
- Thiopental
- Thiamine
- Verapamil

HNMT can have genetic causes or show decreased activity due to environmental exposures

While symptoms of a lack of DAO are often periodical, symptoms of HNMT deficiency occur immediately after meals, for example. In the case of dysfunctional HNMT, especially the brain, bronchial mucosa and liver are affected. Patients with normal DAO levels, who experience only slow deterioration (days) of symptoms after dietary errors and in which after dieting properly symptoms abate only slowly, may suffer from HNMT deficiency. Testing the activity of this intracellular enzyme is not possible. Diagnostics are done via testing for a genetic variant (C314T) that decreases HNMT activity by 30-50 %. This genetic variant is associated with histamine-related diseases, such as asthma and atopic dermatitis. Additionally, drugs are known to be HNMT inhibitors. Amodiaquine, Metoprine, Tacrine and Diphenhydramine (H1-antihistamine!) block HNMT's histamine binding sites. Carriers of C314T-polymorphisms should hence avoid HNMT blockers as well as histamine liberators.

Material

DAO activity: 2 ml serum
Total histamine in blood: 10 ml heparin blood
For both tests, a sample receipt within 24 hrs has to be ensured. The sample should be stored and transported at room temperature. Within the Berlin city area, we offer a courier service (+49 (0)30 7701- 250). For collections beyond Berlin, please contact our complimentary courier service (+49 (0)30 77001-450).

DAO genetic testing and/or HNMT genetic testing:
2 ml EDTA blood
Transport to the laboratory is not time-sensitive and can be sent by mail.

Invoicing

DAO activity testing: 28.86 €

Total histamine testing: 33.22 €

DAO and/or HNMT genetic testing: 238.96 €

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