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Combined lactase and trehalase deficiency as a cause of blood lose in young man

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Abstract: Trehalose is a disaccharide composed of two glucose that can be found in various plant and animal species. Mammals are not able to synthesize trehalose but it is usually easily enzymatically broken down into 2 molecules of glucose. As a structural additive, trehalose can be used in food mainly for stabilizing proteins. Low trehalase activity (primary trehalase deficiency) leading to intolerance is rare but may appear manifest as a complication of enteropathy from other causes (celiac disease, Crohn's disease, etc.). We present the case of a young 27-year-old male with repeated tenesmus followed by enterorrhagia, weight loss, and elevated markers of inflammation caused by combined lactase and trehalase deficiency. Unique exome sequencing analysis of gene *TREH* was performed to distinguish between primary and secondary trehalase deficiency.

Keywords: case report; trehalose; trehalase deficiency; enterorrhagia; *TREH*

Trehalose (α, α-trehalose) is a disaccharide composed of two molecules of glucose. The occurrence of trehalose is relatively widespread in plant and animal species, although it occurs mainly in small amounts. Mammals do not synthesize it, but usually they can enzymatically break its molecule–into glucose. Trehalose is a non-reducing very slightly reactive saccharide. Its sweetness is about half that of sucrose (Dahlqvist 1962; Canani at al. 2016; Ackerman at al. 2017).

The natural food sources of trehalose are the baker's yeast *Saccharomyces cerevisiae* (5–20% of dry matter), mushrooms, partly honey, or crustaceans (mainly shrimp). In other foods, natural trehalose is significantly less present (Dahlqvist 1962; EC 2001/721; Canani at al. 2106).

Land plants (*Embryophyta*) synthesize trehalose but are unable to accumulate it – it is thought to serve as one of the signalling molecules. A significant amount is produced by some microorganisms (mainly yeasts and bacteria) as well as by non-vascular plants. Some invertebrates can accumulate high concentrations of trehalose. In certain organisms (mosses, lichens, but also some of vertebrates), trehalose allows so-called cryptobiosis – an ametabolic state that allows them to survive even extremely adverse conditions (Dahlqvist 1962; Halford at al. 2011; Canani at al. 2016).

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Trehalose can be synthesized chemically. But currently, mainly highly efficient biotechnologies are used, which enable wide use of trehalose as a food additive. In the USA, it has the status of Generally Recognized as Safe (GRAS), in Europe, it was already included in the list of so-called Novel Foods in 2001.

As a structural additive (not as a sweetener), trehalose can be used in foods mainly for stabilizing proteins, which can be damaged by ice crystals during freezing or, conversely, by drying, resulting in loss of functional properties of the protein. Furthermore, the use of trehalose in food prevents the formation of ice crystals that damage the food, such as in ice cream production. In bakery products from a frozen semi-finished product, there are no consequential losses during the thawing of the food. Trehalose is not hygroscopic, so it is used as an anti-caking additive. In technological food processing, such as cooking, trehalose can stabilize the colour and aroma of food. In bakery products, trehalose reduces the decomposition of starch and stabilizes the aroma. For some other products, such as fruit snacks, ketchup, and mustard, it reduces water activity, stabilizes colour and aroma, and stabilizes texture.

It should be the responsibility of European food producers to declare its presence on the packaging as a novel food. But what the reality? Currently, trehalose is labelled on the package as a carbohydrate. This non-specific labelling or non-labelling of trehalose on food packaging significantly complicates adherence to diet in patients with reduced trehalase activity.

Because trehalose is non-hygroscopic, it begins to be used worldwide (but not in Europe) in a pharmaceutic industry during the production of solid dosage forms as a tableting agent, which replaces the widely used lactose, because it increases the stability of preparations.

The enzyme trehalase (α, α-trehalose-1-C glucohydrolase, EC 3.2.1.28), which allows the breakdown of trehalose into two glucose molecules, was discovered in 1893 by E. E. Bourquelot, who isolated it from a fungal species *Aspergillus niger*. Human trehalase was described in 1962 by A. Dahlqvist (1962). Enzyme activity occurs mainly in the intestinal mucosa, especially in the jejunum, (less in the ileum), on the surface of the microvilli. However, trehalase activity has also been found in other organs, such as lymphocytes, kidneys, liver, and also in bile. Low trehalase activity leading to trehalose intolerance is naturally rare (mostly occurring in the Nordic countries, estimated in 8% in Greenlanders) but it may manifest as a consequence of enteropathy (celiac disease, Crohn's disease etc.) (Madzarovova-Nohejlova 1973; Gudmand-Hoyer et al. 1988; Teramoto et al. 2008; Walmagh et al. 2015; NORD 2022).

CLINICAL CASE

We would like to present a case of a 27-year-old male university student (height 172 cm, weight 78 kg). Till now, he has had no significant disease or disorder in his anamnesis. His parents and sister are also healthy. There were no intolerances or allergies in past. He does not use any regular medication.

He had fever over 39 °C lasting for two days (using paracetamol as a treatment), suffering from mild pressure in the epigastrium. There was no stool, flatulence was reduced.

Third day after onset of symptoms, he got collapsed. He was examined in an emergency ambulance of the department of general internal medicine, the acute abdomen was excluded by native X-ray of the abdomen and by abdominal sonography. Higher marker of inflammation (C-reactive protein 200 $mg \cdot l^{-1}$, reference range 0–5 $mg \cdot l^{-1}$) was detected. The diagnosis considered was 'Gastroenteritis with high inflammatory markers and fever, probably of infectious etiology'. The patient was sent to the outpatient department of the infectious disease clinic to undergo further examination to investigate the infectious etiology.

Here the patient developed tenesmus followed by enterorrhagia, without defecation. Intravenous antibiotics treatment (ceftriaxone, a third-generation cephalosporin antibiotic) was given during hospitalization. Stool cultivation was performed with a negative result. In blood, cultures found *Streptococcus intermedius* (however, it was considered a false-positive result, the patient had not stayed in the tropic areas). The diagnosis of acute enterocolitis and streptococcal sepsis was established.

The patient responded well to the antibiotics treatment, his health condition became better. The body temperature dropped to normal, the inflammatory markers decreased, defecation was gradually restored, and also the pressures in the epigastrium disappeared. From the beginning of hospitalization, the patient ate a fat-free, protective diet, with a predominance of starch component (light pastry, white rice, mashed potatoes without milk, pasta, Viennese dumplings, gnocchi from batter), with meat, with suitable fruit and vegetables mechanically processed (grated apple, apple snack, stewed spinach puree, carrot puree, to-

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mato puree), without milk. The diet was well tolerated by the patient. The hospitalization took 12 days in total, the patient lost weight by 7 kg. Then he was discharged to the home treatment and instructed about the gradual disengagement of the diet. Sigmoidoscopy was recommended. The realimentation process ran well in home condition.

Approximately 14 days later the patient discovered blood in his stool after iterant defecation. The patient was referred to the gastroenterologist. Colonoscopy was performed, slight post-inflammatory changes after previous enterocolitis were described, rectal prolapse was also detected. The patient was still on the GIT protective diet. The realimentation was successful, without any complications. After the month he was able to consume almost each kind of meal corresponding to the principles of proper nutrition.

Six months later, the patient developed feelings of virosis, higher temperatures around 38 °C. Home-performed C reactive protein examination showed 'highest field', the hospital one measured CRP 100, examination showed suspicion of appendicitis. Our patient was hospitalized, and the next day underwent an appendectomy. During the surgery, the inflammation in the terminal ileum was found, also adhesions with the omentum and the abdominal wall were discovered. Our patient got an antibiotics treatment, following a standard dietary measures after appendectomy – rice, biscuits, apple puree, mashed potatoes. The diet was well tolerated. The realimentation was again without complication, the patient gradually switched to nutrition according to his previous habits.

One month after appendectomy, diarrhoea reappeared several times a day, without fever, enterorrhea, probably after consumption two flavoured sweetened cheese desserts, several bananas, several fruit snacks, biscuits, baguettes from the frozen semi-finished products etc. in last 2 days. The patient was treated with Smecta (a medication against diarrhea – diosmectitum). He had a strict, mostly starch, diet without milk and dairy products, such as rice soup, flake soup, grated apple, mashed potatoes, boiled lean meat, sugar-free black tea. The patient's health condition stabilized, stool consistency slowly improved.

During the next month, celiac disease, Crohn's disease, and the presence of amoebae were excluded by the gastroenterological examination. Furthermore, a gastroscopy was performed, and samples were taken from the distal duodenum. Lactase activity was determined by immunohistochemical examination with a result of 0%, sucrase activity 60%, and trehalase activity 40%.

Primary trehalase deficiency is caused by genetic changes in the *TREH* gene (NORD 2022). Unique exome sequencing analysis of gene *TREH* was performed to distinguish in between primary and secondary trehalase deficiency (patient signed informal consent with genetic examination) (NORD 2022). Sequencing of this gene was performed as part of the SSELXT HS Human All Exon V8+NCV (Agilent) sequencing on the NextSeq DX-550 (Illumina) high-capacity sequencer. Because of the length of the gene (15 exons), there was not a possibility to perform Sanger sequencing. Molecular genetic examination did not reveal the presence of a causal sequence variant in the *TREH* gene leading to diagnosis of primary trehalase deficiency.

RESULTS AND DISCUSSION

Therefore, the patient had to start following a lactose free diet – gradually he added dairy products with almost zero lactose content, such as hard cheeses – emmental, edam, gouda, or cheddar. From the other dairy products, he consumes only lactose-free products (of which there is relatively wide range on the market). Furthermore, in the diet he adequately reduces sucrose and trehalose, he practically does not consume industrially made products and processed foods due to either the declared high amount of mostly sucrose, or the expected content of trehalose, respectively both. He chooses fruits with lower sucrose content, such as apples, pears, blueberries, strawberries. He also restricts foods with a larger amount of crude fibre – a combination of vegetables with legumes, seeds, etc. – which, if are used in greater amount, causes feeling of indigestion and bloating to him. He prefers more gentle technological preparation of dishes such as stewing, steaming, baking in foil, etc.

During the next month, a control colonoscopy was performed with the result within the norm, with a clinical picture of the disappearing colitis. Intermittent rectal prolapse cannot be ruled out. The patient is currently feeling well, following the dietary recommendations described above. Occasionally, approximately one time per 3 months, following defecation of formed solid stool or, conversely, repeated defecation of runny stool, a small amount of fresh blood appears transiently, practically once, due to local mechanical disruption of the rectum.

Although low trehalase activity leading to trehalose intolerance is naturally rare, it can manifest as a complication of enteropathy. Therefore, trehalase deficiency

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should be included in the differential diagnosis of enteropathy of unknown origin. Unfortunately, trehalose is still classified on food packaging as a saccharide. This non-specific labelling or non-labeling of trehalose on food packaging significantly complicates diet in patients with reduced trehalase activity.

CONCLUSION

Patients with trehalase deficiency (depending on the degree of deficiency) should be aware of possible intake of foods with a potential trehalose content, such as frozen creams, ice creams, and dairy desserts (they usually also contain significant amounts of sucrose and/or lactose), fruit snacks, pastries and bread from a frozen semi-finished product, or even instant soups. They can be excluded from a patient's diet because they are not necessarily part of an individual's diet.

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