DETECTION OF INTOLERANCE TO SUGARS (LACTOSE, FRUCTOSE) AND BACTERIAL OVERGROWTH BY BREATH TEST (H2, CH4)

Lactose is present in the milk of all mammals, in dairy products derived from it and in a wide variety of foods in the form of additives and preservatives which are regularly consumed in Western diets (pâtés, cured meats, margarine, sausages, sauces, ice creams, ready meals, medicines, etc.).

Lactase is an enzyme present on the edges of intestinal villi, mainly in the jejunum, which hydrolyses the lactose in glucose and galactose. The LCT gene which codes for Lactase maps on the long arm of chromosome 2 (2q 21).

Physiopathology:

When the activity of Lactase is inadequate, lactose reaches the colon without being hydrolysed, where the bacteria present convert it into short-chain fatty acids (SCFAs), methane gas, carbon dioxide and hydrogen (CH4, CO2 and H2). In this way, the undigested Lactose will cause osmotic diarrhoea and its colonic fermentation products will cause watery diarrhoea and gas.

Definitions:

- **NPL (Non-persistence of Lactase or adult Hypolactasia):** In the majority of humans, there is a reduction or disappearance of intestinal Lactase after weaning.
- **PL (Persistence of Lactase):** Persistence of high activity of Lactase in the adult, which will allow the absorption of large quantities of lactose.
- **MAL (Malabsorption of Lactose):** Inefficient absorption of Lactose due to NPL or following a digestive pathology (viral gastroenteritis, celiac disease, Crohn's disease, etc.) or multisystemic processes (cystic fibrosis, carcinoid syndrome, etc.).
- **ITL (Lactose Intolerance):** Symptoms following MAL, diarrhoea, tympanites, abdominal pain. Due to not being specific, they may be due to celiac disease, irritable colon, etc.

Genetics of NPL:

The kinetics of reduction/disappearance of intestinal Lactase after weaning presents great ethnic and demographic variability, depending on the cultural custom of maintaining milk as a food in the diet of the adult subject.

Adult hypolactasia affects three quarters of the global population. Over 90% of the Asian population and 60-70% of the African American population present NPL. However, in the European population, hypolactasia is only present in 30%. The latest studies in Spain have found 33% among children and 36% among adults.

NPL has an autosomal recessive character. Genotype C/C-13910 causes the NPL phenotype (Lactase of 10% compared with that present at birth). Genotype T/T-13910 determines the PL phenotype, and genotype C/T-13910 corresponds to a phenotype with intermediate lactase presence.

Clinical Manifestations:

NPL frequently manifests in adolescents or young adults, although it should be noted that the vast majority of NPL does not present any clinical symptomatology. That is; NPL and the resulting MAL do not necessarily lead to lactose intolerance (ITL).

Typical symptoms of ITL are diarrhoea, abdominal pain, tympanites, perianal redness, nausea and abdominal bloating. Its presence and intensity depend on the concentration of lactose ingested, mixed with another type of food, the individual's bacterial flora (microbiota) and individual perception of pain. The first symptoms usually appear 45 minutes after ingestion, at the maximum within 4 to 8 hours, and may last up to 12 hours.

Diagnosis:

There is no "gold standard" test for diagnosing MAL, as each one reveals different aspects of the process.

- **Intestinal biopsy:** This may be the method of reference for diagnosing primary or secondary MAL, but it has the disadvantage of cost, invasiveness and false negatives due to the "patched" appearance of lactose in the intestine.
- **Genetic test:** These have the advantage of Negative VP of 98% in the determination of CC_ 13910 in heterozygosity in the Caucasian population, although it does not correspond to ITL and it has a high cost.
- **Breath test:** Detects the exhaled H2 which comes from the fermentation of lactose by intestinal bacterial. It has a sensitivity of 76-94% and a specificity of 77-96%, both being greater than those of the oral overload of lactose for the diagnosis of MAL.

The result will be considered pathological when after ingesting 25 grams of Lactose, the elevation of H2 compared with the base level is equal to or greater than 20 ppm at one of the 7 measurement points. The appearance of symptoms during the test guarantees its validity for the diagnosis of MAL and ITL. False positives are usually due to poor preparation of the patient or the presence of bacterial overgrowth, while false negatives may be due to the presence of bacteria which does not produce H2 in the colon (10% of cases). The latter case may be suspected if the symptoms exist despite the exhaled H2 not increasing over the base level, and in these cases, a breath test may be carried out to detect CH4. The disadvantage of the breath tests is that they do not diagnose the aetiology, instead only MAL and ITL.

Nevertheless, they are currently the most used, as it has been demonstrated that patients with genotype C/C-13910 present a positive breath test in 90% of cases and symptoms during the test in 75% of cases.

Intolerance to Fructose/Sorbitol

Introduction:

Fructose is a monosaccharide which can be ingested as a pure monosaccharide, as a disaccharide, Sucrose, made up of glucose and fructose, or as fructose polymers or fructans. Fructose is present in fruit and vegetables. In the United States, it has replaced sucrose as a sweetener, having led to a 50% increase in consumption compared with the 1950s. In Europe, consumption of fructose is maintained, and sucrose (table sugar) continues to be used as the main sweetener. Therefore, in our environment, the main source of fructose in the diet is fruit and vegetables (pear, apple, onion, leeks, asparagus, lettuce, artichokes).

Sorbitol or glucitol is an alcohol which is present in leaves and fruits of the Rosaceae family (quince, pear, apple, plum, peach), used as a sweetener in dietetic products, chewing gum, juices, jelly beans and industrial pastries. It has 60% of the sweetening power of sucrose, has just over half the calories, and does not elevate blood sugar.

Physiopathology:

The intestinal absorption of Fructose is caused by facilitated diffusion, but two membrane transport proteins also intervene:

- **GLUT5**, present on the apical border of the enterocytes, whose specific function consists of transporting fructose from the intestinal lumen to the interior of the enterocyte.
- **GLUT2**, present on the lateral base end of the enterocyte, whose shared function consists of transporting glucose, galactose and fructose from the enterocyte to the bloodstream. Thus, elevated levels of glucose in the intestine, and therefore in the enterocyte, in turn promote the absorption of fructose and galactose in the blood.

Fructans, present in grains such as wheat and oats, etc., are not absorbed in the intestine of mammals, as the enterocytes do not have hydrolases for splitting the fructose-fructose links. They can only be hydrolysed by some bacteria of the intestinal microbiota (Bifidobacteria and Lactobacillus) which possess Beta fructofuranosidase.

The absorption of sorbitol is caused by passive diffusion, depending on the concentration gradient and depending on the activity of the intestinal mucosa. It has been proven that when fructose and sorbitol are ingested at the same time, the intestinal absorption of the former is impeded.

The small intestine has a very limited capacity for absorbing sorbitol; only 25% of that ingested. Thus, the ingestion of 25 grams of sorbitol will cause diarrhoea in the majority of healthy people.

The presence of Fructans, Sorbitol and fructose due to malabsorption cause short-chain fatty acids (SCFAs) (acetate, butyrate and propionate) and gases (H2, CO2, CH4) due to bacterial fermentation in the colon.

The malabsorption of Fructose and Sorbitol may be primary, caused by transfer protein deficit, or secondary to all processes which affect the integrity of intestinal villi. The incidence of this type of malabsorption is unknown; it is calculated that it may affect up to 40% of the population. However, the genetic or racial factors which affect its appearance are unknown at present.

Clinical Manifestations:

As with lactose intolerance, it presents diarrhoea, abdominal bloating, tympanites and nausea. In some cases, if the colonic bacterial flora produces methane, it can cause constipation. The symptoms vary in their appearance depending on mixing with other foods and the intestinal rhythm. Thus, they may occur from 30 minutes up to 4 hours following ingestion.

Diagnosis:

The breath test for H2 and CH4 is the best diagnostic test for this type of sugar intolerance.

Intestinal bacterial overgrowth

Introduction:

Intestinal flora (microbiota) lives in symbiosis with each individual, being a hidden “endocrine organ” with very varied functions such as production of folic acid, vitamin K, biotin, short-chain fatty acids, biotransformation of pharmaceuticals, metabolisation of oxalic acid, etc.

It remains relatively constant from weaning through the life of each subject. From studies carried out on homozygote twins, it is known that the microbiota is genetically determined. The bacteria which make up the microbiota vary in quantity and type along the intestine, so in the upper intestinal tract (stomach, duodenum and proximal jejunum) we find Gram positive flora (Corynebacterium, Lactobacillus, Enterococcus, Streptococcus and Staphylococcus), while in the middle and distal tract (middle and distal jejunum, colon) coliforms and anaerobic microorganisms live.

Intestinal Bacterial Overgrowth (IBO) is defined as presence in the upper digestive tract exceeding 10^3-10^5 CFU/ml.

The clinical finding of Gram positive bacteria in the upper tract remains unclear, but the presence of coliforms and anaerobic microorganisms is always due to deficit lightening or anatomical alterations. In the latter case, patients will suffer malabsorption, diarrhoea, weight loss and nutritional deficits.

Causes and predisposing factors of IBO:

- Failure in the gastric acid barrier: Intestinal gastritis, proton-pump inhibitors (consumers are at 3 times greater risk of suffering IBO), gastrectomy, gastric bypass due to obesity, etc.
- Failure in intestinal lightening: neuropathy, muscular dystrophy, amyloidosis, connective tissue disease, opiates, etc.
- Anatomical alteration of the ID: Duodenal or jejunal diverticulosis, fistula, stenosis, resection of the ileo-caecal valve.
- Immune deficiencies
- Other illnesses: pancreatitis, cystic fibrosis, celiac disease, hypothyroidism, etc.

Clinical:

Varies in each subject depending on the intestinal section affected and the aetiological factor. Abdominal bloating, tympanites (malabsorption of lactose), diarrhoea, megaloblastic anaemia due to vitamin B12 deficit, fat-soluble vitamin deficit (A, D and E) and weight loss may appear.

Diagnosis:

There is no reference method, as although the culture of jejunal aspirate is suggested as the gold standard, it may have false negatives due to distal IBO, patched presence of IBO, and false positives due to contamination with oropharyngeal flora.

The diagnostic test which is currently most used is the breath test (H2, CH4), based on the appearance of elevation of H2 or CH4 in the air exhaled after ingesting glucose or lactulose, above 20 ppm over the base level and in a time under 90 minutes following ingestion of these substrates.

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Breath Test (H2, CH4)

The test is based on the fact that there is no endogenous production in the human body; therefore, all H2 exhaled will come from the bacterial fermentation of sugars not absorbed in the intestine. Likewise, the CH4 present in the breath can only originate from the intestinal production by bacterial flora. Both compounds are absorbed through passive diffusion in the intestine, where they pass to the bloodstream, and from this to the alveoli where they are excreted in the air exhaled.

For the diagnosis of Lactose and Fructose intolerances and bacterial overgrowth, it is sufficient to study H2 in the breath test, except in cases where the test is negative and high suspicion remains due to symptomology (approximately 10%), in which the intolerance will have to be ruled out with a breath test for CH4.

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