Review Article

Lactose intolerance

Yvan Vandenplas MD, PhD

Department of Pediatric Gastroenterology, Universitair Ziekenhuis Brussel, Brussels, Belgium

Lactose is the main carbohydrate in infant feeding, but its impact decreases as the child gets older and consumes less milk and dairy products. Congenital lactose intolerance is a very rare condition. However, lactase activity may be low and need to mature during the first weeks of life in many infants. However, the evidence that unabsorbed lactose is causing infantile crying and colic is contradictory. Unabsorbed lactose has a bifidogenic effect and improves calcium absorption. Lactose malabsorption may occur secondary and thus temporally to other etiologies such as infectious gastroenteritis, cow's milk allergy and celiac disease. One the cause is treated, lactase activity will gradually return to normal. The vast majority of Asian children will develop late onset congenital lactase deficiency. However, this entity only exceptionally causes symptoms before the age of 4-5 years. Symptoms are abdominal cramps, flatulence and watery, acid stools, and decrease the quality of life but lactose intolerance is not associated with "true disease". The diagnosis is made on clinical grounds and confirmed with a lactose breath test, if needed. These patients need to have a lifetime long reduced lactose intake to improve their quality of life.

Key Words: hydrogen breath test, lactose intolerance, lactase

METABOLISM OF LACTOSE

During infancy, lactose accounts for most of the dietary carbohydrates. Lactose is a disaccharide present in dairy products. The concentration of lactose in mother's milk is 7.2 mg/100 ml whereas in a cow's milk it reaches only 4.7 mg/100 ml.[1] In order to be digested and absorbed, lactose requires the presence of lactase in the small intestinal brush border. Lactose digestion in the premature neonate may be incomplete in the small intestine but partially salvaged from the colon. Lactase levels decline from a peak at birth to less than 10% of the pre-weaning infantile level in childhood. The decline in lactase in other mammals occurs even if weaning is prolonged. However, lactase activity may persist in some populations where dairy products are consumed into adulthood. The latter occurs in white Caucasians (Northern and Western Europe, USA).

In older children, starch becomes more important. Digestion of starch starts in the mouth, but not the digestion of lactose.

Disaccharides are hydrolysed to monosaccharides by specific enzymes located in the brush border of intestinal epithelial cells. The disaccharidases are mostly oligosaccharidases which hydrolyze sugars containing three or more hexose units. They are present in highest concentration at the villous tips in the jejunum and persist throughout most of the ileum but not in the colon. In normal subjects the capacity of the small intestine is such that virtually all free mono- and disaccharides present in the normal diet are completely absorbed. Unabsorbed carbohydrates may be fermented in the colon by bacteria, which leads to the production of carbon dioxide, hydrogen and methane, proprionic and butyric acids (short chain fatty acids). Butyric acid can be utilized by colonic mucosal cells as an energy source and the bulk of the absorbed proprionate is cleared by the liver.

Hydrolysis is the basic process of digestion. Carbohydrate malabsorption leads to colonic fermentation and diarrhea. Disaccharidase deficiencies cause persistence of the undigested carbohydrate along with an isotonic luminal content into the colon, where bacteria ferment up to 90 g of undigested sugar into short chain fatty acids, stimulating water and sodium absorption. This results in small volume diarrhea with low quantities of fecal electrolytes.

TYPES OF LACTOSE INTOLERANCE

The most common type of carbohydrate maldigestion and malabsoprtion is caused by intestinal lactase deficiency. Lactose malabsorption or hypolactasia is a common condition caused by a low lactase activity. Lactose intolerance occurs when the malabsorption causes symptoms.
Lactase deficiency has been described in three different conditions congenital, primary late onset and secondary.

Congenital lactase deficiency has been described but is rare, and a locus (2q21) has been identified. Symptoms occur then short after birth. In the first year of life a number of infants may display partial malabsorption of dietary carbohydrate present in human milk or formula. This

Corresponding Author: Prof Yvan Vandenplas, Department of Pediatrics, Universitair KinderZiekenhuis Brussel, Vrije Unversiteit Brussel, Laarbeeklaan, 101, 1090, Brussels, Belgium.
Tel: +32 (0)24775781; Fax +32 (0)24775783
Email: yvan.vandenplas@uzbrussel.be
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phenomenon of physiological malabsorption due to enzyme insufficiency may be cause of colic, especially given that enzyme insufficiency generally resolves at approximately three months of age which coincides with when colicky behaviour usually subsides.

Primary late onset hypolactasia is an autosomic recessive condition that is characterized by a gradual reduction of lactase activity, but does not occur before the age of two years. Mostly, constitutional lactase deficiency manifests itself after the age of 5 to 6 years in white populations and sometimes what earlier in non-whites. In some racial groups it does not occur before adolescence. It is the normal condition for most humans. In Europe, the frequency of primary late onset lactase deficiency varies between 2% in Scandinavia to 70% in some regions of Italy.[2] The prevalence in the white population in the USA is about 20%. In Asia, the incidence of this condition is close to 100%. When the low lactase activity does not cause symptoms, it is called "lactose malabsorption". When symptoms occur, "lactose intolerance" is the preferred terminology. Mutation of a regulatory gene for lactase has been postulated to explain the delayed onset of hypo-lactasia. Continued exposure to milk can to some extend affect the expression of the regulatory gene.

Secondary hypolactasia is due to gastrointestinal disease causing (partial) atrophy of the small bowel villi such as gastroenteritis, celiac disease or inflammatory bowel disease (Crohn's disease).[3] Recovery of full function may take months, because lactase is the last disaccharidase to return to normal following injury. The presence of lactose in the colon is responsible for fluid shifts that result in osmotic diarrhea. Fermentation of a carbohydrate causes bloating and cramps.

Clinically, lactase deficiency occurs after small bowel injury, such as viral and parasitic infections. Whether it makes sense to decrease the lactose intake in infants with a severe gastroenteritis for a limited period of time (1 to 3 weeks) is heavily debated. The recommended feeding in infants is breastfeeding, which contains a high amount of lactose, and it is not recommended to stop breastfeeding because of gastroenteritis. Moreover, when lactose is fermented in the colon, it results in the growth of bifidobacteria, thus stimulating a healthy gut microbiota.

SYMPTOMS

Symptoms and nutritional history lead to the diagnosis of adult-type hypolactasia. Symptoms of adult-type hypolactasia increase with age, with many patients developing symptoms of lactose intolerance in adolescence and adulthood. They start briefly after consumption of milk. Although there is a broad heterogeneity in response among patients, symptoms are in general related to the amount of ingested lactose. Non-absorbed lactose is fermented by the gastrointestinal microbiota resulting in the production of shirt chain fatty acid but mainly hydrogen, carbon dioxide and methane.[4] The production of gas is the pathophysiologic mechanism causing symptoms such as abdominal pain, cramps, borborygmi, bloating and flatulence, watery and acid diarrhea, nausea and vomiting.[5-7]

Studies measuring breath hydrogen levels in colicky infants have produced inconsistent results. The role of lactose in infantile colic is controversial. Limited literature suggests that a transient low lactase activity can trigger excessive crying. A beneficial role of lactose-free or soy based formulae has not been consistently demonstrated in patients with infantile colic. Selection of patients is likely to be a major bias in these studies. After some initial enthusiasm about the role of lactase treatment, negative results suggest a minor role of lactase in infantile colic. Although a UK-recommendation suggests a one-week trial of lactase drops in breastfed and formula-fed infants, the evidence for this recommendation is limited. A trial with a new formula containing a stable lactase as the result of a fermentation process indicated a decreased incidence of infant crying at the age of four weeks. There is insufficient evidence to recommend a trial of lactase or reduced lactose formula in every infant presenting with infantile colic, although this is a safe intervention.

DIAGNOSIS

Laboratory assessment of this diagnosis includes, preferentially, a lactose hydrogen breath test and, exceptionally, confirmation by lactase activity of a duodenal biopsy. The diagnostic value of other procedures, such as reducing substances, which are positive in the feces of patients with lactose malabsorption are limited and depend more on the context of the patient's complaints and the results of additional laboratory evaluation. Measurement of the stool pH and/or the presence of reducing sugars in the stools are indirect indications of a carbohydrate malabsorption.

The lactose tolerance test is considered to be less sensitive than the lactose breath test. The lactose tolerance blood test measures the evolution of glucose levels in blood after a challenge with lactose. Glucose is created when lactose breaks down. For this test, several blood samples need to be taken after the intake of a liquid containing lactose. The relationship between lactase activity and the lactose breath test is not uniform. A poor correlation was found between lactase activity, lactose tolerance test and lactose hydrogen breath test in children suffering form chronic diarrhea. Lactose tolerance and hydrogen breath test must be performed after a 6 hour fast beyond infancy.

Lactose malabsorption is a common disorder that may well be diagnosed through the non-invasive lactose breath test (LBT). The LBT is a rapid, non-invasive test that allows measuring the content of hydrogen in the expired air. The Rome Consensus Conference did evaluate the methodology and indication of LBT in gastro-intestinal disorders and suggested a cut-off increase of hydrogen of 20 parts per million (ppm) above the baseline level to be considered as positive. The duration of the breath test should be three hours in pediatric patients, with a sample interval of at least 30 minutes, after a fasting of at least three hours in the youngest up to at least six hours in older children.[8,9] Sensitivity and specificity of hydrogen measuring LBT is evaluated at around 70-100% and 100%, respectively. [10, 11]

However, false-negative results are reported to range between 2.5% and 15% of all lactose malabsorbers.[12,13] False negative results are mainly due to a lack of gastrointestinal microbiota able to produce hydrogen. The

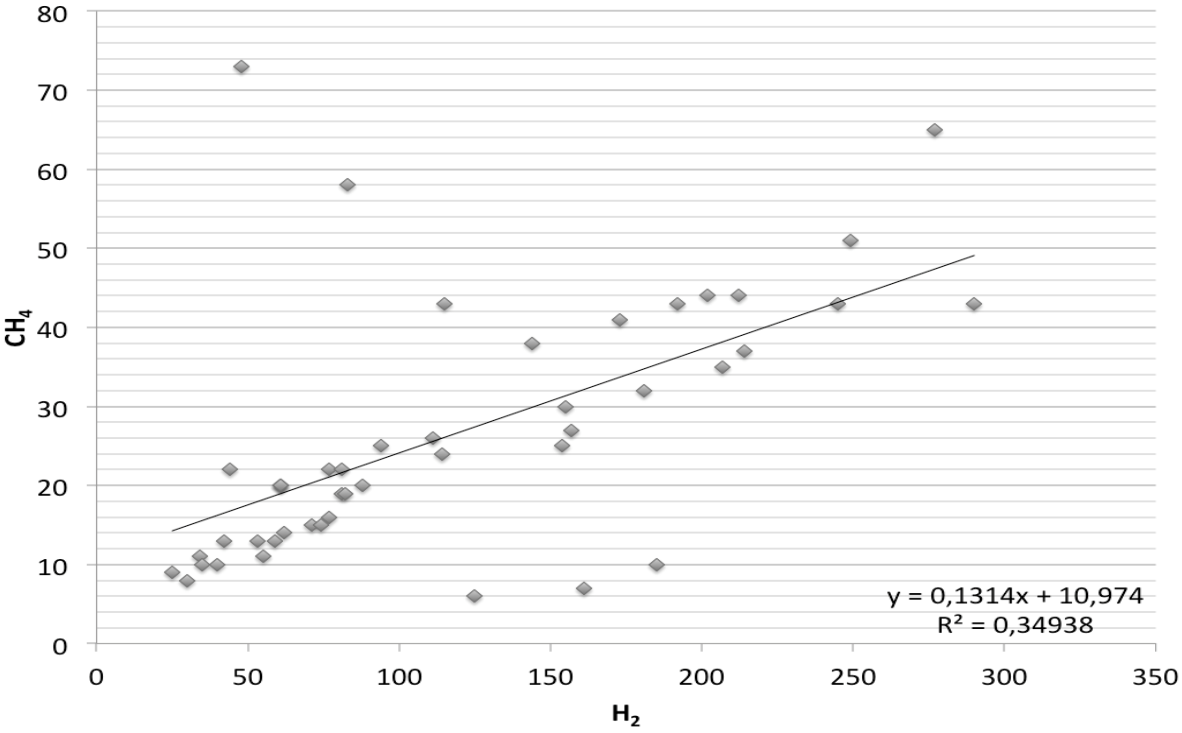

Figure 1. Relation between expired hydrogen and methane during lactose breath test

lactose breath test does not reliably predict tolerance toward lactose in infants recovering from diarrhea. This may be due after antibiotic treatment because of a strongly reduced microbiota or because of an increased production of methane by intestinal bacteria. An overwhelming production of methane can strongly reduce the concentration of hydrogen. Vernia et al used a cut-off of 10 ppm for methane and demonstrated that predominant methane production resulted in higher rates of false negative results of the hydrogen increase than low methane production.[14] However, Myo-Khin et al, using a cut-off of 2 ppm for methane, concluded that the addition of the determination of methane to hydrogen did not increase the sensitivity and specificity of the hydrogen LBT.[15] The production of one mole methane consumes four moles of hydrogen and one mole of carbon dioxide, reducing the intracolonic gas content.[16] For that reason, several authors evaluated the role of methane in expired air to improve the sensitivity of hydrogen LBT. However, literature is not conclusive and pediatric literature suggests that the measurement of methane in the expired air is of no additional value to the measurement of hydrogen alone. In a study that we performed, the level of methane increase according to the increasing of the level of hydrogen (unpublished data) (Figure 1). This can be explained as a mechanism to decrease the level of hydrogen and the presence of gas in the gut. Conditions that cause false-positive results are a slow gastric emptying rate and fast gastro-intestinal transit time.

However, others reported no consistent relation between jejunal lactase levels and the threshold of lactose to develop symptoms.

TREATMENT

Treatment is a lactose free or lactose poor diet. Lactose free is only needed in the rare infants with congenital lactase deficiency. In all the other clinical situations, some lactase activity will persist and thus "small" amounts of lactose are tolerated. Most lactose malabsorbers will tolerate small amount of lactose. Amounts of 0.5 to 7.0 g lactose have been shown to not cause symptoms. Some malabsorbers haven been shown to even tolerate 240 and up to 500 ml of milk per day. Fermented dairy products such as yoghurt are in general better tolerated as the lactose is fermented by the probiotic strains added.

The question has been raised as to whether symptomatic lactose malabsorbers have an additional gastrointestinal affection, such as irritable bowel syndrome. About 70% of patients with milk intolerance and patients with irritable bowel syndrome have a positive hydrogen breath test, and bowel transit is increased in irritable bowel syndrome. It is hypothesized that the fast intestinal transit contributes to the complaints of lactose malabsorbers.

In many countries, lactase can be administered as an "enzymatic supplement". This exists as well in powder as in liquid form, and needs to be taken just before a lactose containing meal.

CONCLUSION

Primary lactose intolerance is almost non-existent before the age of 5-6 years. If symptomatic lactose malabsorption occurs before that age, it is likely to be secondary to another disease. In the latter situation, treatment of the etiology results in recovery of the lactase activity. Slow maturation of lactase after birth may cause infantile crying and colic, but is no reason to stop breastfeeding. In this case, the lactose has a prebiotic bifidogenic effect. Late onset lactose intolerance requires a reduced lactose intake.

AUTHOR DISCLOSURES

Potential conflict of interest: none for this manuscript. YVDP is consultant for Aspen, Biocodex and United Parmcaceuticals.

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Yvan Vandenplas MD, PhD

Department of Pediatric Gastroenterology, Universitair Ziekenhuis Brussel, Brussels, Belgium

乳糖不耐症

乳糖是嬰兒主要的醣類來源，它的影響會隨著兒童年紀增長與牛奶及乳製品攝取降低而遞減。先天性乳糖不耐症是一種很罕見的情形。許多嬰兒出生的第一週，其乳糖酶活性可能較低，並需要時間逐漸成熟。然而，未被吸收的乳糖是否是引起嬰兒哭鬧及絞痛的證據仍是矛盾的。未被吸收的乳糖可作為雙岐桿菌生長之用，及促進鈣吸收。乳糖吸收不良也可能是次發性的，起因於其他暫時的病因，如腸胃道感染、對牛奶過敏或乳糜瀉。一旦疾病被治癒，乳糖酶活性會逐漸回復正常。亞洲兒童絕大多數為晚發型先天性乳糖酶缺乏症。但是，只有少部分在 4-5 歲前就有症狀。症狀為腹部絞痛、脹氣、水便或酸便及降低生活品質，但乳糖不耐症與真正的疾病並無相關。如果需要，可經臨床表現及乳糖呼吸測試確診。這些病人需要終身降低乳糖攝取，以改善他們的生活品質。

關鍵字：氫氣呼吸測試、乳糖不耐症、乳糖酶