REVIEW ARTICLE

Breath Hydrogen Test in Lactose Malabsorption

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ABSTRACT Lactose is the most important source in mammalian milk. In normal children, lactose is hydrolyzed by lactase, and directly absorbed into bloodstream by an active transport mechanism. The term of lactose malabsorption is reserved to patients in whom impaired intestinal lactose hydrolysis and uptake has been proven by an appropriate test. The severity of lactose malabsorption and the extent of symptoms vary widely and are the results of several factors such as the amount of ingested lactose, gastric emptying time, intestinal transit time, and colonic flora. The diagnosis of lactose malabsortion is based on clinical finsdings and the results of appropriate tests. The breath hydrogen test has obvious advantages for pediatric population because it is painless, non-invasive, sensitive and specific. In the absence of bacterial colonization in the small intestine, the elevation of the concentration of hydrogen in the expired air implies the arrival of lactose in the colon. The increasing respiratory excretion of hydrogen is indicatve of a deficit of lactase in enterocyte brush border. This test can also be used to show the existence of bacterial growth. Dietary fiber, some drugs, preparation for colonoscopy, colonic pH, and diarrhea can influence the result of breath hydrogen test. **[Paediatr Indones 1995; 35:161-171]**

Introduction

Lactose malabsorption and lactose intolerance are two terms which have been used to describe clinical symptoms related to the ingestion of milk or the absence of lactase. The term lactose malabsorption is reserved for patients in whom impaired intestinal lactose hydrolysis and uptake has been proven by an appropriate test,[1,2] and lactose intolerance is characterized by the occurrence of symptoms after the ingestion of lactose.[3] Lactose malabsorption and lactose intolerance therefore may be not be used synonymously.

As a test, breath hydrogen measurements has obvious advantages for pediatric populations because of it's painless and noninvasive nature. The challenge of introducing this test into clinical practice

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has now been met by using both sensitive technology to measure accurately the minimal concentration of hydrogen and simple devices to gather samples from the full range of pediatric patients. The test is dependent on the generation of hydrogen from lactose that has been administered orally to free diffusible hydrogen that is ultimately excreted by the lungs.[4] This test has also been proven to be useful in establishing bacterial overgrowth and to delineate small bowel transit time.

Lactose Digestion and Absorption

Lactose is the most important carbohydrate source in mammalian milk, and occurs only in milk as a free molecule. It is synthesized by lactose synthetase, exclusively in the mammary gland during late pregnancy and lactation.[5] In normal children, lactose is hydrolyzed to glucose and galactose on the microvillous membrane of the intestinal absorptive cells by lactase (lactase-phlorizin hydrolase), and directly absorbed into the bloodstream by an active transport mechanism (the sodium-dependent glucose carrier). Lactose digestion is slow, and hydrolysis is the rate-limiting step in its absorption. Lactase is the only intestinal disaccharidase responsible for the digestion of lactose. The distribution of lactase along the crypt-villus axis is strictly programmed.[1] Maximum lactase activity is not attained until the mid villus (maximal expression at the upper villus). The delay in expression of maximal lactase activity might explain the vulnerability of this enzyme to villus injury.[6] Lactase activity is not constant throughout the length of the small intestine, but maintains a characteristic proximal to distal gradient. In mature intestine, maximal lactase activity occurs in proximal to mid jejunum, with lower activity in the duodenum and ileum.[1]

In healthy infant, the amount of ingested lactose is almost completely hydrolyzed in the small intestine, and virtually no lactose reaches the colon. Whenever the capacity of intestinal lactase to split lactose is exceeded, the sugar passes undigested into the colon. This can be due to an excess amount of lactose or the result of low or absent lactase enzyme.

Pathophysiology of Lactose Malabsorption

The severity of lactose malabsorption and the extent of symptoms varies widely and is the result of several factors.[1,3,7] Lactase activity is the critical step in lactose hydrolysis. When lactose is consumed in quantities exceeding the capacity of available lactase, malabsorption symptoms may occur. The digestion of lactose is increased by slow gastric emptying. The stomach empties lactose faster in the malabsorbers than in absorbers. This may be due to the increased sensitivity of the osmo-receptors in the intestine to unhydrolyzed lactose in the malabsorbers. The intestinal transit time decreases in parallel with the severity of the lactose intolerance symptoms. In other words there is more rapid intestinal transit time when lactose digestion is incomplete.

Fermentation of unhydrolyzed lactose by bacterial flora in the colon leads to the formation of short chain fatty acids as

well as gas in the form of hydrogen. The extent of utilization of gas will affect the clinical symptoms of malabsorptions. The quantity of colonic bacteria, the organisms involved and the absorption of the fermentation products, differ considerably among individuals, affecting the degree of complaints. In the normal intestine, more than 96-99% of hydrogen production is of colonic origin.[8,9] Colonic flora should be relatively constant in unlimited supply to digest all of the malabsorbed lactose. Indeed there is a large number of bacteria in stool, approximately 1×10^{11} viable bacteria per gram of wet stool weight. The predominant fecal flora mainly consists of non-spore forming anaerobe bacteria, far exceeding *Escherichia coli* lesser population.[10]

The assimilation of the lactose in a meal is improved because the delayed passage by the food allows for longer extraintestinal lactase and this account for the difference found when lactose is ingested in the form of milk compared to water.[12]

According to those factors, the pathophysiological effects of lactose malabsorption may be described. The presence of lactose in the lumen of small intestine not hydrolyzed by lactase, provides an osmotic load, resulting in an influx of water into the lumen and an increase of volume. This stimulates peristalsis of the small intestine, which in turn contributes to rapid intestinal transit,[3] and further impairing absorption. In the colon, lactose is fermented by the colonic flora, resulting in the production of short-chain fatty acids, lowering of pH, and among others in hydrogen gas. The amount of unabsorbed lactose that each individual can tolerate influences the severity of symptoms.[1,13] The gas formation leads to flatulence and cramps. The low pH stimulates colonic peristalsis, augmenting the diarrhea. The short-chain fatty acids are absorbed by colonic mucosa, and this route salvages malabsorbed lactose for energy use.[14] It also stimulate absorption of salt and water, and significantly reduces the mucosal atrophy of the bowel.[15]

Clinical Manifestations of Lactose Malabsorption

Lactose malabsorption is a prevalent clinical problem, and the clinical manifestations varies among lactose malabsorbers. The clinical manifestations often leads to nausea, vomiting, abdominal pain, cramps or distention, flatulence, and diarrhea. Borborygmi may be audible on physical examination and to the patient. The stool are usually watery, bulky, and frothy.[1,3,7,14,16]

The feeling of abdominal fullness and sometimes nausea are usually experienced within 30 minutes of ingestion of the test dose of lactose in water, while the abdominal pain, flatulence, and less frequently, diarrhea occur within 1-2 hours after consumption of lactose. There is no correlation between residual lactase levels and the threshold for lactose intolerance.

Patient who have manifestations of lactose intolerance should be evaluated in a systematic fashion and it is important to remember that lactose malabsorption may occur in patient with other disorders. The most important cause of is due to lactose intolerance in young children, such as after gastrointestinal infection.[1]

Nomenclature of Lactase Deficiency

Lactase deficiency is either a primary or secondary event. Primary lactase deficiency occurs in 3 clinical setting: (a) developmental lactase deficiency, (b) congenital lactase deficiency, and (c) genetically determined of lactase deficiency.[1,14] Secondary lactase deficiency is due to intestinal mucosal damage.

The developmental form of lactase deficiency is a consequence of gestational age. The activity of lactase increases in the third trimester of gestation to reach maximal levels around or just after birth. The decrease in activity of lactase is coupled with a decreasing ability to hydrolyze lactose.[5] It can be seen in premature babies born before 36 weeks of gestation.[1]

The congenital form is very rare, and is characterized by the total absence or sometimes very low levels of lactase. This condition was potentially lethal until lactose-free milk became available.[1]

The genetically determined lactase deficiency form is used for conditions in which lactase levels decline during weaning, and the continuing of this low levels (approximately 10% of the values at birth) throughout adulthood. Most of the children up to the age 3-5 years are able to digest lactose, because their small intestine synthesizes sufficient amounts of lactase.

Only people of Scandinavian or Caucasian genetic background continue to produce high amount of lactase throughout adulthood, whereas all others (about 75% of human population) show a decline of lactase activity during childhood to adult population resulting in the low lactase levels seen in adult population.[3] In the Japanese, the incidence of lactase deficiency gradually increases with age starting from 3 years, and about 90% of normal adults are lactase deficient.[9] In Indonesia, the incidence of lactose intolerance is about 70%,[17] while in the Netherlands the incidence is very low, varying from 0-2%.[1]

Population genetic analysis has indicated that the genetically determined low levels of lactase group is most likely an autosomal recessive inheritance, and high levels of lactase activity is inherited as an autosomal dominant trait.[3] Human lactase gene is known to be located on chromosome 2.[18]

Secondary lactase deficiency occurs after mucosal injury of the intestinal tract causing villus flattening or damage to the intestinal epithelium.[16] This disorder can be caused by acute or chronic infection, radiation, drugs or other toxic agents. Lactase seem to be vulnerable and return of enzyme activity lags behind the return of normal mucosal morphology.

The diseases that can cause damage of the epithelium include infectious gastroenteritis, bacterial overgrowth, inflammatory bowel disease, giardiasis, celiac disease, or cow's milk protein enteropathy.[1,16]

Diagnostic Procedures of Lactose Malabsorption

There are several tests to diagnose lactose malabsorption; from a non-invasive (fecal analysis, breath hydrogen test) procedures to an invasive procedures (small intestine biopsy). The diagnosis of lactose

malabsorption is based on a combination of clinical findings and the results of an appropriate test.

In fecal analysis, the presence of low fecal pH or reducing substances indicates lactose malabsorption, but this test is only valid when lactose has been ingested, intestinal transit time is rapid, stool are collected fresh and assay performed immediately, and when bacterial metabolism of colonic lactose is incomplete.[1,16] In general, confirmation of lactose malabsorption is best accomplished using more specific tests.

Breath hydrogen test can be used to indicate the presence of intestinal malabsorption of lactose. In the absence of bacterial colonization of the small intestine, the elevation of the concentration of hydrogen in the expired air implies the arrival of lactose in the colon. The increasing respiratory excretion of hydrogen is indicative of lactase deficiency in the enterocyte brush border.

The breath hydrogen test can also be used to show the existence of bacterial overgrowth. The presence of hydrogen in the expired air expresses the bacterial catabolism in the intestine.

This method has a superior sensitivity and specificity compared with the absorption test. It is simple and noninvasive, and can be performed in all ages.[1,16]

The assay of lactase activity in small intestine biopsy establishes the presence of lactase deficiency and has been used to define populations at risk for low lactase levels. However, when lactase deficiency accompanies intestinal injury, the lesion may be focal or patchy; consequently, intestinal biopsy samples may not yield an abnormal result .[1,16]

Of various methods to detect lactose malabsorption, the lactose breath hydrogen test has been shown to be the most sensitive,[2] and becomes the diagnostic method of choice for determining lactose malabsorption,[1,9] although small intestinal biopsies should be performed when mucosal diseases are suspected.[3]

Breath Hydrogen Test

As has been mentioned, hydrogen is produced in the human body exclusively by colonic origin as a consequence of fermentation of unabsorbed lactose. Eighty six percent of the hydrogen produced is eliminated via the rectum. The other 14% is absorbed by the colon, transported to the blood and excreted by the lung via in the expired air. The hydrogen disappears almost totally from the blood after the first time it passes through the lungs.

Hydrogen in the breath appears approximately 5 minutes after the arrival of lactose in the colon.[19] Thus the quantity of hydrogen expired is equal to the quantity absorbed by the intestine, and this is directly proportional to the intestinal production of hydrogen.[8,20] This method has 80% sensitivity and 100% specificity.[21]

Technique

The sensitivity of breath hydrogen test depends on rebreathing air in a closed system over a given period of time in which the CO_2 is removed and the hydrogen concentrated. Initially, samples of hydrogen expired were obtained by closed circuit recirculation procedures and the

concentration of hydrogen was measured by gas chromatography.[8,13] This technique is widely used for the estimation of expired hydrogen, but requires time and expert personnel. Then, a method for the estimation of expired hydrogen without these disadvantages has been developed, the lactoscreen breath test. The measuring system is formed by a detector which is a semi-conductor highly sensitive to the presence of hydrogen, and this emit an electric signal to a microprocessor when the sample contains hydrogen. The appliance consist of a plastic syringe, with a lateral orifice such that it is possible to fill during expiration into its interior through a mouthpiece, after which the lateral orifice is closed. The sample thus obtained corresponds to the air at the end of the expiration.

Samples stored in the collection syringes over an 8 hour period demonstrated no change in hydrogen concentration, but deterioration does occur over a period of days.[4] Gas gradually diffuses through the body of plastic syringes, a tendency effectively diminished by keeping the syringes in freezing condition.[13] Furthermore, because the lightweight field instruments are available, storage of breath samples is not needed anymore.

Recently, the new lactometer breath hydrogen test is increasingly replacing the lactoscreen test. The lactometer breath hydrogen test uses as its principle of detection a sealed electrochemical sensor which is specific to hydrogen. The sensor is of the micro fuel cell type designed to be maintenance free and stable over long periods of time. Because of the unique diffusion barrier, the sensor has a very low temperature coefficient and has a linear response to H2 concentration relatively unaffected by pressure. The oxygen requirement being automatically supplied from the ambient air by controlled diffusion. Operation is straight forward. A T-piece sampling system enables end-expired breath to be sampled easily and hygienically, using disposable cardboard tube mouthpieces.

During the examination, the patient should take a breath, hold this for a period of about 10 seconds and then breathe out gently through the mouthpiece. The most important aspect of sampling is to exhale as completely as possible, as this provides the most representative sample. On the display, the reading obtained corresponds to the hydrogen concentration in parts per million of the patient's breath. A modified sampling technique enables children and infants to be sampled with a minimum of fuss, while neonates in incubators can be monitored simply by linking the lactometer to expiratory limb ventilator.[22] Before carrying out another test, the hydrogen trapped in the sensor should be removed by removing the sampling system from the sensor part and allowing ambient air to diffuse into the sensor. The apparatus has a very low weight (500 g) and is fully portable with its own power source, so that it can be easily carried anywhere.

Substrate Selection

Flexibility of substrate selection, substrate form, and dosage is characteristic of breath hydrogen testing. Lactose is most commonly selected as a substrate for breath hydrogen test because lactase activity is rate-limiting for absorption and

the enzyme is vulnerable. Conventionally, 2 gram of lactose per kilogram up to a maximum of 50 gram in a 20 percent aqueous solution is the test dosage.[15,23,24] This dosage was adapted from the standard lactose tolerance test using blood glucose as the measured response.[9] The osmolality of the solution may need to be modified in patients younger than 6 months of age, and commonly one uses a 10 percent solution in this age group.[4] Lactose in water remains the most readily available substrate. Also glucose, fructose, and lactulose can be used in a breath hydrogen test in the evaluation of the handling of these compounds.

Interpretation of Data

Results are most commonly expressed as the concentration of hydrogen excreted in parts per million (ppm) above baseline. To assure low baseline values, the breath hydrogen test must be conducted after an adequate overnight fast. In toddlers and infants, fasting may be reduced to 8 and 4 hours respectively.[13] Hydrogen concentrations are generally performed by obtaining samples of expired air before and at 30 minute intervals for 3 hour following administration of aqueous lactose solutions, which represent the test substrate. Hydrogen concentrations tend to decline during the fasting state, and the baseline value can therefore be defined as the lowest value of hydrogen obtained at any sampling time. Such a 3 hour monitoring period detects lactose malabsorption, with more than 90% of malabsorbers exhibiting hydrogen excretion curves consistent with a positive response by 2 hours following lactose ingestion.[4,13] A two-hour lactose breath hydrogen test has been described in which expired air analysis at 0 and 120 minute was found to be sufficient to document lactose malabsorption.[25]

An increment of 20 ppm of hydrogen over the baseline or the lowest recorded value, is accepted as a positive response.[26,27] Increment values between 10 and 20 ppm are considered intermediate unless accompanied by symptoms, and increment value of 10 ppm or less is considered normal.[14] In addition, an early rise in hydrogen concentration in the first 60 minutes following substrate ingestion may be consistent with small bowel bacterial overgrowth,[1] especially if accompanied by a subsequent second peak in expired hydrogen. The latter is thought to be consistent with the bolus of the substrate reaching the colon. Unfortunately, the second peak does not commonly occur in practice, and one must therefore rely on either the early rise in breath hydrogen or the elevation of the fasting hydrogen as an indicator of bacterial overgrowth.[4] In children less than five years of age, an abnormal lactose breath hydrogen test should alert the clinician to the possibility of intestinal mucosal disease, which usually needs further definition with a small intestinal biopsy.[28]

The time of appearance of increased breath hydrogen after ingestion of a non absorbable carbohydrate (lactulose) is a physiological measurement of transit time from mouth to cecum.[7]

Because overnight fasting cannot be carried out in early infancy except in infant who are receiving intravenous therapy, standard breath hydrogen test in

this group becomes difficult. Utility of spot breath hydrogen measurements should be emphasized that do not carry the same implications. An elevated spot hydrogen in the continuously fed infant cannot be taken to imply bacterial overgrowth.[13]

In children with lactose malabsorption with clinical symptoms, the increase in expired hydrogen tends to occur earlier and higher after lactose ingestion than in children with malabsorption without clinical symptoms.[29,30]

Limitations

Several limitations in using breath hydrogen test has been described. A small percentage of population do not excrete hydrogen in the breath after ingestion of lactose indicating that hydrogen producing organisms are absent. The number varies between 2 to 9%.[8,31] A wide variety of broad spectrum antibiotics have an effect against the hydrogen producing organisms.[32] The maximal breath hydrogen concentration and the total hydrogen excretion were significantly increased after giving acetylsalicylic acid.[33] The hydrogen production was very markedly depressed after preparation for colonoscopy. Mechanical cleansing with enemas and laxatives will quantitatively decreases the bacterial load and the production of hydrogen. These may cause false results when using the breath hydrogen test to evaluate lactose absorption.[34]

The breath hydrogen response to malabsorbed carbohydrate is affected by colonic pH. It appears that the efficiency of bacterial carbohydrate metabolism in the colon is pH dependent.[35] Hydrogen production after exposure of carbohydrate to fecal flora is maximal at neutral pH and is strongly inhibited at acid pH. Carbohydrate disappearance and hydrogen production were highly correlated at pH varying from 5,5-7,6.[36]

Fermentation of ingested lactose by oropharyngeal bacteria can contribute significantly to measured breath hydrogen values soon after meal ingestion, and may introduce avoidable error into the interpretation of serial breath hydrogen data.[37,38] Prior bactericidal mouth-wash abolished the carbohydrate associated rise, suggesting that the hydrogen was the result of fermentation by oropharyngeal bacteria.[39]

Dietary fiber can decrease apparent nutrient absorption and increase transit time in the upper gastrointestinal tract without affecting apparent glucose absorption.[40] Fasting breath hydrogen concentrations were significantly lower after a low-fibre diet[34] A red meat and rice meal with no source of carbohydrate other than the rice should be ingested the night before a morning breath test if breath hydrogen is to be reliably used as a screening test for stasis and bacterial overgrowth.

In diarrhea patients, breath hydrogen test is one of the possible ways used to elucidate the cause of diarrhea, which is the most evident symptom of lactose malabsorption. Failure to assimilate lactose causes diarrhea in such common childhood illnesses as enteric infection, protein allergy, and malnutrition. Testing for lactose malabsorption is valid, because continued administration of lactose in the face of chronic diarrhea increases

losses of nitrogen and fat as well as carbohydrate calories.[41] Children with acute infectious enteritis have a high incidence of false negative breath hydrogen test results.[42] There are a number of possible explanations for the poor results.

Quantitative or qualitative changes in fecal flora during diarrhea could reduce the critical mass of appropriate bacteria necessary for fermentation of the carbohydrate substrate. Change in colonic motility during active diarrhea could change the partition of colonic hydrogen excretion between breath and flatus with proportionately greater amount of intestinal hydrogen being excreted by rectum.[43] Thus, breath hydrogen test in acute diarrhea is of limited value. Although the true extent of lactose malabsorption in acute diarrhea needs further research. In patient with chronic diarrhea, fasting breath hydrogen rarely exceeded normal values unless condition associated with bacterial overgrowth.[43] In chronic diarrhea the use of breath hydrogen test is very important to establish the existence of lactose malabsorption.

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