

Evaluation of diagnostic examinations of lactose intolerance in children

Ocena badań diagnostycznych w nietolerancji laktozy u dzieci

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Przegląd Gastroenterologiczny 2010; 5 (2): 94–98
DOI: 10.5114/pg.2010.14037

Key words: lactase activity, hydrogen breath test, oral lactose load test with determination of glucose concentration in capillary blood.

Słowa kluczowe: aktywność laktazy, wodorowy test oddechowy, doustny test obciążenia laktozą z oceną stężenia glukozy we krwi włośniczkowej.

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Abstract

Introduction: The diagnosis of lactose intolerance is established on the basis of the clinical picture, the hydrogen breath test and/or determined concentration of glucose in the blood after the oral lactose load. The most valuable examination seems to be the determination of lactase activity in the intestinal biopsy. However, in the literature there are only a few studies comparing these diagnostic methods.

Aim: To evaluate the sensitivity and specificity of the hydrogen breath test and the evaluation of glucose concentration in the blood after lactose load in comparison with lactase activity in the intestinal biopsy.

Material and methods: In 61 children we performed the hydrogen breath test and the oral lactose load test with determination of glucose concentration in the blood, and we determined lactase activity in the intestinal biopsy.

Results: In 79% of the patients we observed compatibility between the hydrogen breath test and lactase activity, in 16.6% the hydrogen breath test gave false positive results, and in 4.4% the results were false negative. In a majority of the patients with false positive results of the hydrogen breath test, lactase levels were in the low normal range. The oral lactose load test with the determination of glucose concentration in the blood was characterized by lower sensitivity and specificity. In over 20% it showed false positive results and in 10% false negative results.

Conclusions: With regard to the large number of false positive and negative results in the hydrogen breath test and the oral lactose load test with the determination of glucose concentration in the blood, in the case of diagnostic difficulties it seems reasonable to determine lactase activity in the intestinal biopsy.

Streszczenie

Wstęp: Rozpoznanie nietolerancji laktozy ustala się na podstawie obrazu klinicznego, wyniku wodorowego testu oddechowego i/lub oznaczonego stężenia glukozy we krwi włośniczkowej po doustnym obciążeniu laktozą. Najbardziej miarodajnym badaniem wydaje się oznaczanie aktywności laktazy w biopsjach błony śluzowej jelita cienkiego. W piśmiennictwie jest jednak bardzo mało prac porównujących te metody diagnostyczne.

Cel: Ocena czułości i swoistości wodorowego testu oddechowego i oznaczenia stężenia glukozy we krwi włośniczkowej po obciążeniu laktozą w porównaniu z aktywnością laktazy w biopsjach błony śluzowej jelita cienkiego.

Materiał i metody: U 61 dzieci wykonano wodorowy test oddechowy, doustny test obciążenia laktozą z oznaczeniem stężenia glukozy we krwi włośniczkowej oraz oznaczenie aktywności laktazy w biopsjach błony śluzowej jelita cienkiego.

Wyniki: U 79% chorych stwierdzono zgodność między wynikiem wodorowego testu oddechowego i aktywnością laktazy. U 16,6% osób wodorowy test oddechowy dał wynik fałszywie dodatni, natomiast u 4,4% fałszywie ujemny. U większości pacjentów z fałszywie dodatnim wynikiem wodorowego testu oddechowego wartości laktazy były zawarte w pobliżu dolnej granicy normy. Mniejszą czułością i swoistością charakteryzował się doustny test obciążenia laktozą z oznaczeniem stężenia glukozy we krwi włośniczkowej. W ponad 20% dał on wynik fałszywie dodatni i w 10% wynik fałszywie ujemny.

Wnioski: Ze względu na dużą liczbę wyników fałszywie dodatnich i ujemnych testów nieinwazyjnych – wodorowego testu oddechowego i testu doustnego obciążenia laktozą z oznaczeniem stężenia glukozy we krwi włośniczkowej – w przypadku trudności diagnostycznych celowe wydaje się oznaczenie stężenia aktywności laktazy w biopsjach błony śluzowej jelita cienkiego.

Introduction

Lactose intolerance includes a group of clinical symptoms such as: nausea, vomiting, abdominal pain, fullness and diarrhoea, which appear after lactose intake or after a load of this disaccharide. Lactose intolerance is connected with the presence of lactose in the lumen of the large intestine and intensification of the process of fermentation caused by intestinal flora. As a result of these processes short-chained fatty acids appear and cause a change of the pH of intestinal contents, the acceleration of peristaltic movement and secondarily, diarrhoea, pain and abdominal flatulence.

The prevalence of lactose intolerance varies greatly between countries. Lactose intolerance is diagnosed in over 50% of adult people of South America and Africa, but is diagnosed in 15% of white people in the United States, 53% of Mexicans and 80% of black people.

Adult-type hypolactasia in Europe occurs with different rates (the least frequent in Scandinavia, 2%, the most frequent in Sicily, 70%). The incidence of lactose intolerance in adult people in Poland is about 35%, although in children aged between 7 and 15 years it is lower, about 20% [1-3].

Lactose transformation in the intestine depends not only on lactase activity but also on the frequency and amplitude of stomach emptying, intestinal passage, intestinal microflora and the response of the large intestine to the osmotic load. Several authors are of the opinion that only half of patients with lactose intolerance have clinical symptoms. There is not a uniform minimal dose of lactose which causes clinical symptoms in patients with diagnosed intolerance of this disaccharide. A majority of patients do not have clinical symptoms even after drinking two glasses of milk [1]. The symptoms of lactose intolerance may be similar to the symptoms observed in organic or functional diseases of the alimentary tract.

The diagnosis of lactose intolerance is established on the basis of the clinical picture, evaluation of pH of stool and the presence of reducing substances in it, determination of glucose concentration in the capillary blood and/or results of the hydrogen breath test after oral lactose load. However, each of these examinations may give a high percentage of both false positive and false negative results. The diagnosis of lactose intolerance may be established on the basis of elimination of milk from the diet for two weeks and remission of ailments can suggest a suspicion of lactose intolerance. According to literature, the most valuable examination seems to be evaluation of lactase activity in biopsy specimens from the small intestine mucosa; however, it is an invasive examination [4-6].

Aim

The aim of the study was to evaluate selected tests used in the diagnosis of lactose intolerance (the hydrogen breath test and oral lactose load test with determination of glucose concentration in the capillary blood) in comparison with lactase activity in the small intestine mucosa.

Material and methods

The examined group included 61 children (31 girls – 50.8%, 30 boys – 49.2%), aged from 3 to 18 years (mean age 11 years), who were patients of the Department of Gastroenterology at the Silesian Medical University in Katowice due to abdominal pain and/or body mass deficiency. The diagnostics of lactose intolerance included the clinical picture, lactase activity in the biopsy specimens from the small intestine mucosa and results of the hydrogen breath test and the oral lactose load test with evaluation of glucose concentration in the capillary blood.

We compared lactase activity in the biopsy specimens from the small intestine with the results of the hydrogen breath test and the oral lactose load test with determination of glucose concentration in the capillary blood.

Lactase activity in the biopsy specimens of the small intestine mucosa was determined using Dahlquist's method in Dyduch's modification. This method is based on the enzymatic evaluation of disaccharidase activity in a homogenised small intestine tissue sample (disaccharidase activity is expressed in μmol of decomposed disaccharide in 1 min of incubation per gram of mucous membrane homogenate) [7, 8].

As a norm we accepted the range of lactase from 1.0 to 19.0 U/1 g of tissue. During the endoscopic examination we took biopsy specimens from the descending part of the duodenum in order to determine lactase activity. The biopsy specimens were frozen at a temperature of minus 20°C in isotonic salt solution and stored until the evaluation of lactase activity, no longer than four weeks.

The endoscopic examination of the upper part of the alimentary tract, including taking biopsy specimens from the descending part of the duodenum, was performed using the Olympus endoscope (in younger children – GIV N30, GIV P140; in older children – GIV V2). An indication for the endoscopic examination was a suspicion of malabsorption syndrome and an investigation of the causes of abdominal pain.

The hydrogen breath test was performed by measuring the amount of exhaled hydrogen before and after 30, 60, 90 and 120 min of the oral lactose load in

the amount of 1.75 g/kg of body mass (max. 50 g). As a positive result indicating lactose intolerance we accepted an increase of hydrogen in exhaled air over 20 ppm after lactose load.

In all the children we evaluated glucose concentration in the capillary blood while fasting and after 30, 60 and 90 min of the oral lactose load in the amount of 1.75 g/kg (max. 50 g). As a result indicating lactose intolerance we accepted an increase of glucose concentration in blood of less than 20 mg%.

All those examined were informed about the method and the aim of the examination. We obtained the written consent of parents, and the consent of children if they were over 16 years old, to take additional biopsy specimens of the mucosa of the duodenum.

We obtained the consent of the Committee of Bioethics of the Silesian Medical University (NN-013-220/00).

For the evaluation of sensitivity and specificity of the tests used in lactose intolerance the Youden index (J) was used.

Results

In the clinical picture of examined children abdominal pain and body mass deficiency dominated. Clinical symptoms observed in examined children are presented in Table I.

In 10 patients decreased lactase concentration in biopsy specimens from the small intestine mucosa was detected. In anamnesis these patients reported chronic diarrhoea, abdominal pain, flatulence and vomiting.

In all patients with decreased lactase activity in small intestine mucosa specimens and positive results

of the hydrogen breath test, lactose administration was followed by positive results of the clinical test: abdominal pain, flatulence, diarrhoea and/or vomiting.

Among patients with positive results of the hydrogen breath test and values of lactase in small intestine mucosa specimens at the lower limit of normal, in 70% clinical symptoms appeared after lactose administration in the provocation test.

In the diagnosis of lactose intolerance we performed the evaluation of lactase activity in biopsy specimens from the small intestine mucosa, the hydrogen breath test and the oral lactose load test with determination of glucose concentration in the capillary blood. We compared the compatibility of the results obtained in the hydrogen breath test and the oral lactose load test with determination of glucose concentration in the capillary blood in relation to the results of lactase activity in the biopsy specimens of the small intestine mucosa. Decreased lactase activity was found in 10 children (16.4%) (Table II).

In 36 patients (59%) we observed normal results of the hydrogen breath test and the oral lactose load with determination of glucose concentration in the capillary blood and normal lactase activity in the biopsy specimens from the small intestine mucosa. In 48 patients (79%) we observed compatibility between the hydrogen breath test and lactase activity. In 10 patients (16.6%) the hydrogen breath test gave false positive results and in 3 children (4.4%) false negative results.

In a majority of patients with false positive results of the hydrogen breath test the levels of lactase were in the low normal range; these patients may develop full symptomatic lactose intolerance in the future.

Table I. Clinical symptoms in examined patients

Tabela I. Objawy kliniczne u badanych pacjentów

	Abdominal pain	Body mass deficiency	Recurrent vomiting	Chronic diarrhoea	Constipation
Examined group (n = 61)	62.5% n = 38	52.5% n = 32	35% n = 21	17.5% n = 11	5% n = 3

Table II. Lactase activity in examined children

Tabela II. Aktywność laktazy u badanych dzieci

	Lactase activity			Total
	Decreased	Normal	Increased	
Examined group	16.4%	75.5%	8.1%	100%
N = 61	N = 10	N = 46	N = 5	N = 61
Min. activity	0.0	1.3	21.6	0.0
Max. activity	0.98	17.56	76.85	76.85
Mean activity	0.56	4.5	46.8	7.32

The oral lactose load test with determination of glucose concentration in the capillary blood was characterized by lower sensitivity and specificity. In 13 children (23%) this test gave false positive results and in 6 children (10%) false negative results (Table III).

On the basis of the Youden index we evaluated sensitivity, specificity and reliability of positive and negative results of the hydrogen breath test and the oral lactose load test with determination of glucose concentration in the capillary blood.

Hydrogen breath test

- sensitivity – 94%
- specificity – 45%
- reliability of positive results – 78%
- reliability of negative results – 71%

Oral lactose test with determination of glucose concentration

- sensitivity – 85%
- specificity – 30%
- reliability of positive results – 74%
- reliability of negative results – 47%

Discussion

The evaluation of lactase activity in biopsy specimens from the small intestine mucosa is considered to be one of the most authoritative examinations used in the diagnosis of lactose intolerance. However, it is an invasive examination which requires taking a biopsy specimen from the small intestine during the endoscopy or using a Crosby capsule, most frequently in the state of general anaesthesia.

In several studies the authors attempted to compare sensitivity and specificity of non-invasive tests used in diagnosing hypolactasia with an invasive test such as evaluation of lactase activity in biopsy specimens from the mucosa of the alimentary tract [9-11]. The oral lactose load tests are useful because of the simplicity of performance and small invasiveness. However, these tests may give both false positive and false negative results.

In our study the oral lactose load test with determination of glucose concentration in the capillary blood was characterized by quite high sensitivity, about 85%, but low specificity. We found that the reliability of positive results was 74%, but the reliability of negative results was only 47%.

Harrison criticized the importance of the oral lactose load test with determination of glucose concentration in the capillary blood in diagnosis of hypolactasia; he did not find a correlation between a flat curve of lactose load, clinical symptoms and lactase activity. The oral lactose

Table III. Evaluation of the hydrogen breath test and the oral lactose load test with determination of glucose concentration in the capillary blood in comparison with lactase activity in the biopsy specimens from the small intestine mucosa

Tabela III. Ocena wyników wodorowego testu oddechowego i doustnego testu obciążenia laktozą z oceną stężenia glukozy we krwi włośniczkowej w porównaniu z aktywnością laktazy w bioptatach błony śluzowej jelita cienkiego

	Hydrogen breath test	Oral lactose load test with determination of glucose concentration in the capillary blood
Compatible results [%]	79	67
False positive results [%]	16.6	23
False negative results [%]	4.4	10

load test gave both false positive and false negative results in a large percentage. Moreover, he claims that a physiological flat sugar curve occurs in 30% of people [12].

Bode discovered compatibility between lactase activity and the results of the oral lactose load test with determination of glucose concentration in the capillary blood only in 76% of patients [13].

In our study the hydrogen breath test proved to be a much better examination; its sensitivity was 94%, the reliability of positive results was 78%, and the reliability of negative results was 71%. We found a strict correlation between the intensification of ailments and the maximum increase of hydrogen in the exhaled air.

Lember also emphasizes better sensitivity and specificity of the hydrogen breath test in comparison with the determination of glucose concentration in the capillary blood after lactose load [14].

Socha claims that the sensitivity of the hydrogen breath test reaches 79-100% and its specificity 92-100% [15]. Our results were slightly worse. The hydrogen breath test may give false negative results in patients after taking antibiotics and long-term treatment with salicylates, after resection of the large intestine and in patients with disorders of stomach emptying. On the other hand, false positive results may be observed in patients with bacterial hypertrophy of the small intestine, in active smokers, in patients receiving bicarbonates and in people with dental caries [6].

Di Stefano is of the opinion that a prolongation of the time of examination until 3 h and decreased diagnostic criteria (hydrogen concentration in exhaled air > 6 ppm) can increase the sensitivity of the hydrogen breath test

[16]. Arola evaluates specificity of the hydrogen breath test as 89-100% and its sensitivity as 69-100% [17].

Pfefferkorn evaluates sensitivity and specificity of the hydrogen breath test as nearly 100% in adults, and in children as only 75-77% [18]. The excretion of hydrogen during the oral lactose load test is much lower than in patients over 70 years old. Therefore, it is suggested that this test may have limited use in elderly people [1, 6].

It is also possible that the evaluation of lactase activity in biopsy specimens from the small intestine mucosa is not a very reliable method, because it only shows the activity in the place of the biopsy. It is reliable in the case of extensive changes, but in the case of focal changes it can lead to false conclusions.

Lower values of disaccharidase activity taken by endoscopic method than by Crosby's capsule were also found by Kappler. It can be explained by higher localization of taken biopsates or different proportion of villi to interstitial [19].

Perhaps in the future genetic examinations will play a crucial role in diagnostics of lactose intolerance. At present the molecular studies aimed at this problem (detection of mutation C/T-13910) evaluate the sensitivity of this examination as 93% and its specificity as 100% [20, 21].

Lopes compared molecular studies with the hydrogen breath test. All patients with positive results of the hydrogen breath test had the positive genotype C/T 13910. There was no patient who had a positive result of the hydrogen breath test with an accompanying negative result of the molecular examination. However, in 3 patients with a positive molecular examination there were negative results of the hydrogen breath test. It is possible that the symptoms of lactose intolerance will appear in these patients later on or these patients belong to so-called "non-excreters" [22].

With regard to the large number of false positive and false negative results of the hydrogen breath test and the evaluation of glucose concentration in the capillary blood after lactose load (in the case of diagnostic difficulties), it seems reasonable to determine lactase activity in biopsy specimens from the small intestine, and in the future to perform genetic examinations.

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