

Lactose Intolerance in Children with IgE-Dependent Allergy to Milk Proteins

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The aim of this study was to assess the frequency of the occurrence of lactose intolerance in children with an IgE-dependent allergy to cow's milk. The study group consisted of 48 children diagnosed with IgE-dependent allergy to cow's milk proteins (group I). The control group (group II) included 40 children, in a similar age range and with normal architecture of the mucosa of the small intestine, with excluded food allergy. All patients underwent gastroduodenoscopy with biopsy, in which the activity of lactase was determined. The average activities of lactase in the group of patients with allergy were lower than in group II and amounted to 5.6 and 8.64 U/1 g. Lactase deficiency was observed in 6/48 patients in the group of patients with allergy. In group II, lactase deficiency was observed in 20%, which corresponds to the frequency of lactase intolerance in Poland. Lower activity of lactase was statistically significantly more common in older children. A reduced activity of lactase was more frequent in children with atrophy of the intestinal villi; however, that difference was not statistically significant. Lactose intolerance was less frequent in children with a diagnosed IgE-dependent milk proteins allergy. Due to the positive role of lactose in the diet, it seems that including a lactose-free formula in patients with diagnosed IgE-dependent allergy to milk is not necessary.

Introduction

FOOD ALLERGY TO THE PROTEINS of cow's milk and lactose intolerance irrespective of their pathomechanisms are considered food intolerances, so reversible, adverse reactions to a particular food or its components. The effector mechanism of the symptoms of lactose intolerance is abnormalities triggered after lactose has been consumed, whereas the effector mechanism of food allergies is an inflammatory condition that may be activated by both allergy systemic and nonsystemic triggers.¹⁻⁴ The highest percentage of allergies to the proteins of cow's milk has been reported in toddlers and small children, 3%–5% of the population. The frequency of lactose intolerance increases with age and may affect 15%–20% of the Polish population aged 15–20.^{2,5,6} The clinical symptoms of lactose intolerance and an allergy to cow's milk may be similar. The clinical picture may be dominated by diarrhea, abdominal pains, and/or insufficient body mass. However, in the case of an allergy to cow's milk, it is necessary to completely exclude from the diet those products that contain the proteins of cow's milk.^{1,3} In lactose intolerance, the reduction in the amount of food containing this disaccharide suffices.^{3,4,7,8} Therefore, it is important to distinguish between the 2 conditions and to assess the frequency of their co-occurrence. Lactose is a source of energy, but it also has beneficial influence on the regenerative processes of the intestines, stimulates the growth of acidophilic

bacteria, and increases the absorption of calcium from the gastrointestinal tract. The literature concerning the co-occurrence of the food allergy and lactose intolerance is inconsistent. It seems that the frequency of the occurrence of allergy to the proteins of cow's milk and lactose intolerance has been on the rise. It is a common practice in children with a diagnosed allergy to the proteins of cow's milk to completely eliminate products containing lactose. The reasoning behind it seems to be wrong. The sometimes observed symptoms after the inclusion of lactose into the diet may be related to the presence of antigens to the proteins of cow's milk in lactose or an adverse reaction of a nonimmunological mechanism, for example, hypolactasia.⁹⁻¹² So, the inclusion of a completely milk-free diet in patients with the clinical symptoms resulting from lactose intolerance seems to be unfounded.

The aim of this study was the assessment of the frequency of the occurrence of lactose intolerance in children with IgE-dependent allergy to the proteins of cow's milk and the assessment of the usefulness of selected tests used in the diagnosis of lactose intolerance.

Patients and Method

The study group consisted of 88 children (43 girls and 45 boys), aged from 7 months to 15 years (the average being 6 years).

The study subjects were classified into 2 groups. Group I included 48 children with diagnosed IgE-dependent allergy to the proteins of cow's milk (based on the clinical picture—abnormalities in the physical examination and information obtained from the medical history, results of specialist tests—positive results of s-IgE for the proteins of cow's milk and the elimination and allergen provocation tests).

Group II included 40 children (19 girls and 21 boys), in a similar age range and with normal architecture of the mucosa of the small intestine, with excluded food allergy, and who had undergone endoscopy of the upper section of the gastrointestinal tract due to reported abdominal pains and/or insufficient body mass.

The level of s-IgE in blood serum was assessed using the immunofluorescent method and with reactors manufactured by Hycor Biomedical GmbH. The level of IgEspec of the majority of patients matched classes 1, 2, and 3. However, all our patients were diagnosed with IgE-dependent food allergy to the proteins of cow's milk, following clinical pictures and the provocation and elimination tests. Elimination diets were then introduced for a period of 3–12 months, depending on age and clinical symptoms, followed by an open provocation challenge. The positive result justified the diagnosis of food allergy. The group of patients with IgE-dependent allergy to the proteins of cow's milk was then divided into 2 subgroups: younger children (less than 3 years old—10 children, 20.8%) and older children (more than 3 years old—38 children, 79.2%). In addition, a subgroup of children with insufficient body mass was isolated—28 children (58%). All children underwent endoscopy of the upper part of the gastrointestinal tract, using an endoscope manufactured by Olympus with the biopsy of fragments of the descending part of the duodenum for histopathological assessment. The activity of lactase was determined in the fragments, using Dahlquist's method in Dyduch's modification.¹³ The biopsy material for the assessment of the activity of lactase was frozen at -20°C in a saline solution. The activity of lactase was shown in micromoles of the broken-down disaccharide in 1 min of incubation per 1 g of the mucosa. Values between 1.0 and 19.0 U/1 g of tissue were considered normal.

The following were also considered in the diagnostic process of lactose intolerance: the clinical picture, the results of lactose hydrogen breath test (using a Bedfont gastrolyzer), and/or oral lactose tolerance test with the determination of the concentration of glucose in blood samples. The lactose hydrogen breath test was performed by measuring the amount of exhaled hydrogen before and after 30, 60, 90, and 120 min from the moment of the oral administration of lactose in the amount of 1.75 g/kg of body weight (a maximum of 50 g). A positive indicator of lactose intolerance was a value of more than 20 ppm of hydrogen in the exhaled air—with excluded bacterial overgrowth. Moreover, the oral lactose tolerance test was performed, with glucose determination in the capillary blood in the fasting state and after 30, 60, and 90 min after lactose administration. The result demonstrating lactose intolerance was an increase in capillary blood glucose of less than 1.1 mmol/L. The lactase activity was determined with regard to age, gender, the level of insufficiency in body weight, and villous atrophy in the mucosa of the small intestine. The activity of lactase was then compared with the results of the hydrogen breath test and/or oral lactose tolerance test with

the assessment of the concentration of glucose in blood. The study was conducted after obtaining the consent of the Bioethical Committee of the Silesian Medical University (NN-013-220/00).

The results were statistically analyzed with the level of significance at $p < 0.05$. The χ^2 test was used for the assessment of the frequency of the feature in study groups and the Mann–Whitney U test extended to Kruskal–Wallis's was used for intergroup comparisons of the studied parameters.

Results

The clinical symptoms in children with IgE-dependent allergy to the proteins of cow's milk most commonly involved deficiency of body mass (30/48 children—62%), abdominal pains (27/48—56.2%), and recurrent diarrhea (7/48—14.6%). In younger children, the clinical picture was dominated by deficiency of body mass (70%) and in older children—abdominal pains (62.5%). Abdominal pains (83.3%) and recurrent diarrhea (66.6%) were most often observed in patients with co-occurring IgE-dependent allergy to the proteins of cow's milk and lactose intolerance.

The average values of the activity of lactase in the group of patients with IgE-dependent allergy to the proteins of cow's milk were lower than in group II (control group) and were 5.6 versus 8.64 U/1 g of tissue, respectively (Table 1).

A decreased activity of lactase was observed in 6/48 patients (12.5%) with IgE-dependent allergy to the proteins of cow's milk. In group II (without organic diseases of the gastrointestinal tract), decreased activity of lactase was concluded in 8/40 patients (20%), which corresponds with the population frequency of the occurrence of the lactose intolerance in Poland. A lower activity of lactase was statistically more significant in older children. Lactase deficit was not reported in any of the children younger than 3 years old, with diagnosed IgE-dependent food allergy. No statistically significant differences in the activity of lactase were observed in the group of patients with IgE-dependent allergy to the proteins of cow's milk with regard to their gender and the level of nutrition. However, the average values were the lowest in children with significant body mass deficiency, and the highest in those whose level of nutrition was normal (Table 1).

TABLE 1. THE ACTIVITY OF LACTASE IN THE STUDIED GROUPS

The activity of lactase	Patients with IgE-dependent allergy to the proteins of cow's milk (group I)	Control group (group II)	State of nutrition	
			Body mass deficiency	Normal level of nutrition
Average	5.6	8.64	4.85	6.92
Median	2.7	4.31	2.6	1.81
Standard deviation	9.7	15.37	5.9	12.7
MIN	0	0	0	0
MAX	46.37	76.85	21.2	46.37
Number	48	40	30	18
P	0.32			

TABLE 2. THE ASSESSMENT OF THE CONFORMITY OF THE LACTOSE HYDROGEN BREATH TEST AND THE ORAL LACTOSE TOLERANCE TEST WITH THE ASSESSMENT OF THE CONCENTRATION OF GLUCOSE IN THE CAPILLARY BLOOD COMPARED WITH THE ACTIVITY OF LACTASE IN THE BIOPTATES OF THE MUCOSA OF THE SMALL INTESTINE

	<i>Hydrogen breath test (%)</i>	<i>Oral lactose tolerance test with the assessment of the concentration of glucose in the capillary blood (%)</i>
Consistent results	79.5	69.3
False positive results	15.9	20.5
False negative results	4.6	10.2
Sensitivity/specificity	94/45	85/30
Reliability of positive/ negative results	78/71	74/47

A lower activity of lactase was reported to have been more frequent in children with villous atrophy, but the difference was not statistically significant (6.06% vs. 20%). However, the average activities of lactase in biopsies of the intestinal mucosa were not significantly statistically different in those subgroups (5.7 vs. 5.1 U/1 g of tissue).

The assessment of the usefulness of lactose intolerance diagnostic tests

The conformity between the results of the lactose hydrogen breath test and lactase activity was confirmed in 70/88 patients (79.5%). In 14/88 patients (15.9%), the lactose hydrogen breath test gave positive results with normal lactase activities in the bioptates of intestinal mucosa; however, those values were closer to the lower limits of the norm in the majority of patients. False negative results were noted in 4 patients (4.5%). The oral lactose test with the assessment of the concentration of glucose in the blood was found to be less sensitive and specific (it gave false positive results in more than 20% and false negative in 10%). The sensitivity, specificity, and reliability of positive and negative results of lactose hydrogen breath test and of oral lactose tolerance test with the assessment of the concentration of glucose in the blood serum were determined based on the Youden test. The sensitivity of the lactose hydrogen breath test was 94% and the reliability of positive and negative results was 78% and 71%, respectively. The oral lactose tolerance test with the assessment of the concentration of glucose in blood serum was found to be less sensitive—85%—and the reliability of the negative result amounted only to 47% (Table 2).

Discussion

Congenital metabolic disorders, especially those concerning the defects of the enzymes participating in the digestive process, facilitate the penetration of larger particles of proteins and glycoproteins, and the lingering of disaccharides in the lumen of the gastrointestinal tract, which may contribute to the development of a food allergy. At the same time, diarrhea that is common in carbohydrate intol-

erance causes an increase in the osmotic pressure in the lumen of the intestine and is destructive for enterocytes. This may lead to the development or worsening of the atrophic lesions in the intestinal villi and may also intensify the penetration of food antigens. The decrease in the activity of lactase as a result of the damaging effect of the food allergen on the mucosa of the small intestine has been described in the literature, but the data concerning the frequency of its occurrence are insufficient.^{7,9,12,14}

Among our patients with diagnosed IgE-dependent allergy to the proteins of cow's milk, lactose intolerance occurred in 12.5%. This frequency was lower than the populational frequency. In group II—without organic disorders of the gastrointestinal tract, it corresponded with the frequency characteristic for the Polish population of children and amounted to 20%. In Silesian children, the frequency of occurrence of lactose intolerance is about 17%–20%.⁶ Fiocchi examined 24 children with diagnosed food allergy to the proteins of cow's milk, and no adverse symptoms were reported in any of the children after the inclusion of lactose to their diet.⁴ It seems that the routine inclusion of a completely lactose-free diet in patients with IgE-dependent allergy to the cow's milk protein is not advisable.

The clinical picture of our patients with diagnosed allergy to the proteins of cow's milk and lactose intolerance was dominated by abdominal pains, insufficient body weight, and/or chronic diarrhea. In his study, Gupta did not find a correlation between lactase insufficiency and the clinical symptoms.¹⁵ Karnsakul, however, believes that the symptom that best correlates with lactose intolerance is vomiting, which was very infrequent in our patients.¹⁶ Wang and Harvey think that the activity of lactase is "programmed for life" in every individual.¹⁷ In our study, the activity of lactase in relation to age was determined. We did not observe its deficiency in any of our patients aged less than 3 with diagnosed IgE-dependent food allergy. In the control group—without organic lesions within the gastrointestinal tract—we observed statistically significantly more frequent lactase deficiency in older children, above 3 years of age. When assessing the activity of disaccharides in children more than the age of 5, hospitalized in the department of gastroenterology due to various disorders of the gastrointestinal tract, Welsh observed that a high activity of lactase and its insufficiency occurred only above that age.¹⁸ Lebenthal, having assessed the activity of disaccharides in 172 patients, aged from 8 weeks to 50 years, concluded a statistically significant lower activity in children more than 5 years old, compared with younger children. All examined patients below the age of 5 showed normal activity of lactase, whereas in those more than the age of 5, decreased lactase activity was observed in 24.6% of patients.¹⁹ There are available data confirming the effect of malnutrition on a lowered activity of lactase.^{20–23} The authors have linked this abnormality to insufficiency in protein as the substrate for the production of enzymes. In our study, we also observed that the lowest average activities of lactase happened in patients with deficiency of body weight (Cole's index below 85) compared with patients of a normal level of nutrition. This difference, however, was not statistically significant (4.84 vs. 6.92). In the majority of the observed patients, despite the reported body mass insufficiency, the levels of protein were within the norm. Nichols observed a reduction in the mRNA of lactase to 32% in undernourished patients,

and the values of the mRNA of lactase were inversely proportional to the level of undernourishment.²²

There are studies that describe lactase insufficiency related to the syndrome of malabsorption.^{24–26} Among our young patients with IgE-dependent allergy to the proteins of cow's milk, a lowered activity of lactase occurred more frequently in patients with villous atrophy, but the difference was not statistically significant. However, the average activities of lactase in the biopsies of the mucosa of the small intestine were not statistically different in both subgroups (5.7 vs. 5.1 U/l g of tissue). In the course of food allergy, villous atrophy may affect only a certain part of the small intestine, while a larger part of the mucosa remains unchanged.²⁷ In children allergic to the proteins of cow's milk, the histopathological data reported patchy lesions, which would confirm our observations.²⁸

The correlation between the activity of disaccharides and atrophic lesions in the histopathological test in Hetlinger's study occurred only when the mucosa was significantly damaged.²⁶ Gupta, however, concluded that in older children, even small villous atrophy caused a reduction in the activity of lactase.¹⁵ Basso proved that the frequency of the occurrence of C/T (-13910) and G/A (-22018) polymorphisms with diagnosed celiac disease is the same as in the healthy Italian population. Therefore, he concluded that the more frequent occurrence of lactose intolerance in patients with diagnosed celiac disease was caused by secondary lesions within the intestinal villi.²⁴ Ojetti, however, believes that the positive result of the lactose hydrogen test and the clinical symptoms of lactose intolerance may be the first and the only symptoms of celiac disease. He also suggests that all patients with a positive result of the lactose hydrogen test should undergo serological tests toward celiac disease.²⁷ Phillips observes that in the case of secondary disaccharide insufficiency, abnormalities in the architectonics and surface of microvilli have been reported.²⁹ Whether it is the allergy that causes lesions in the microvilli—secondary insufficiency in disaccharides—or the opposite—insufficiency in disaccharides with accompanying lesions in microvilli that causes an increased penetration of food antigens and the development of food allergy—is yet to be decided.

A number of studies have attempted to compare the sensitivity and specificity of noninvasive tests used in the diagnostics of hypolactasia with the invasive test, so the assessment of the activity of lactase in the biopsies of the mucosa of the small intestine.^{30–32} Oral lactose tests are helpful due to their simplicity in performance and minor invasiveness. However, those tests can give both falsely positive and falsely negative results. In our study, in 79.5% of patients, the conformity between the results obtained from lactose hydrogen breath tests and the activity of lactase was confirmed. In 15.9% of patients, the lactose hydrogen breath test gave positive results with the normal activities of lactase in the biopsies of the mucosa of the small intestine; however, in the majority of those patients those activities were at the bottom range of the norm. In 4 patients (4.5%), the result was falsely negative. Bergoz confirmed that the positive result of the oral lactose test with the assessment of the concentration of glucose in the blood correlates with a very low activity of lactase in the intestinal villi—when its activity is less than 5 U/l g of protein.³¹ The lactose oral test with the assessment of the concentration of glucose in blood serum proved to be less sensitive and specific (it gave a

falsely positive result in more than 20% of cases and falsely negative in 10% of cases). Also Lember stressed a better sensitivity and specificity of lactose hydrogen breath test over oral lactose test with the assessment of the concentration of glucose in blood.³⁰ However, the lactose hydrogen breath test has its limitations and it may give falsely negative results in patients after antibiotic therapy, colon resection, in the disorders of gastric emptying, and chronic use of salicylates. Falsely positive results may be observed in patients with small intestinal bacterial overgrowth, active smokers, and in those with dental decay. To increase the sensitivity of the lactose hydrogen breath test, Di Stefano suggests extending the test time to 3 h and reducing the diagnostic criteria of the concentration of hydrogen in the exhaled air to more than 6 ppm.³² Pfefferkorn determined the sensitivity and specificity of the lactose hydrogen breath test to close to 100% in adults and only 75%–77% in children.³³

Conclusions

1. Due to the positive role of lactose in the daily diet, it does not seem necessary to introduce a lactose-free formula to patients with IgE-dependent allergy to the proteins of cow's milk. In children with diagnosed IgE-dependent allergy to the proteins of cow's milk, lactose intolerance occurred less frequently than in the population group.
2. In the assessment of lactose intolerance, it is recommended to perform the lactose hydrogen breath test, as it is more sensitive and specific.

Acknowledgment

This study was conducted after obtaining the consent of the Bioethical Committee of the Silesian Medical University in Katowice (NN-013-220/00).

Authors' Contribution

S.W. collected materials, participated in the sequence alignment, and drafted the article. H.W. conceived the study and participated in its design and coordination and helped to draft the article. U.G.C. conceived of the study, participated in its design and coordination, and helped to draft the article. All authors read and approved the final article.

Author Disclosure Statement

No competing financial interests exist.

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