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Research Article

REASONS FOR THE DEVELOPMENT OF LACTASE DEFICIENCY IN CHILDREN OF EARLY AGE

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ABSTRACT

This article contains analysis of modern data upon infantile lactase deficiency, diagnostics and clinical presentation. Special attention is paid to the disease treatment analysis and its dietary correction. We present clinical variants of the disorder.

KEYWORDS

Lactose, lactase deficiency, children, dietary treatment.

INTRODUCTION

Lactase deficiency (LD) is a variant of disaccharidase deficiency based on impaired lactose breakdown associated with congenital or acquired defects in the enzyme lactase [1]. The problem of LN is of greatest importance in early childhood, since lactose constitutes approximately 80-85% of breast milk carbohydrates and is found in the amount of 6-7 g/100 ml. It has now been shown that lactase activity is mainly associated with the enzyme lactase-florisinghydrolase, which is the main glycoprotein of the membrane of the brush border membrane of enterocyte microvortsins. The mentioned enzyme shows high lactase (beta-D-galactoside hydrolase) and florisinghydrolase activity (glycosyl N-

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acetylsphingosylglucose), providing the breakdown of lactose and some other glucosides, such as florisin, which regulates the absorption of monosaccharides. Lactase is synthesised as a single-chain pre-lactase precursor consisting of 1927 amino acid sequences [2].

Later, the enzyme undergoes a series of sequential changes in the endoplasmic reticulum (with the formation of a proenzyme) and the Golgi complex (with the formation of a 3-dimensional structure characteristic of a "mature" enzyme). The mature enzyme is transported to the membrane of the brush border of the enterocyte. The N-terminal end of the molecule is located outside the cell membrane and the C-terminal end is located in the cytosol. The active enzyme has 2 catalytic sites. Lactase activity is associated with the Glu-1749 site, while activity towards phlorizin is associated with the Glu-1273 site [3]. It is the mechanism of enzyme activation and expression on the membrane that has been shown to be impaired in adult-type lactase deficiency and congenital LN. In humans, lactase activity is detected from 10-12 weeks of gestation; from 24 weeks onwards, its activity begins to increase and reaches a maximum by the time of birth. From 17 to 24 weeks of gestation, lactase activity is highest in the small intestine; thereafter, activity in the proximal and distal small intestine becomes equal. By 28-34 weeks of gestation, lactase activity reaches 30% of that in a preterm infant, and by 39-40 weeks it reaches its maximum value, which is maintained throughout the first six months of the child's life [4].

Primary and secondary lactase deficiency are distinguished by origin. Primary is caused by decreased lactase activity in morphologically intact enterocytes. It includes congenital (genetically determined, familial), adult-type (constitutional) and transient LN of premature and immature newborn infants.

Congenital alactasia is a rare condition in which a mutation is identified in the LCT gene encoding lactase synthesis. The highest number of cases of congenital alactasia has been described in Finland [5].

Transient LN of prematurity is associated with morphological and functional immaturity of the small intestine in children born earlier than 34-36 weeks of gestation.

Secondary LN is a decrease in lactase activity caused by enterocyte damage, which may occur in infectious, allergic (including intolerance to cow's milk proteins) or other inflammatory processes in the intestine, as well as atrophic changes in the intestinal mucosa. They are characterised by a reduction in the pool of enterocytes (e.g. due to prolonged complete parenteral nutrition in the postoperative period, in mucosal atrophy of other genesis), or a reduction in the total length of the jejunum after its surgical resection, or in congenital short bowel syndrome.

The main link in the pathogenesis of lactase deficiency is the impaired breakdown of lactose to galactose and glucose in the small intestine. Lactose is a nutrient substrate for lactic acid bacteria (mainly lacto- and bifidobacteria), its small intake into the large intestine is necessary for acidification of the contents and formation of normal intestinal biocenosis. Lactose digestion takes place with the formation of lactic and acetic acids, as well as gases such as carbon dioxide, methane and hydrogen. Organic acids formed in the process of lactose digestion stimulate intestinal peristalsis, and the formed acidic environment prevents the reproduction of putrefactive flora. With excessive intake of lactose into the colon there is an increase in osmotic pressure, quantitative and qualitative changes in the composition of intestinal microflora with the development of clinical manifestations of diarrhoeal syndrome. The severity of

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clinical manifestations in lactase deficiency varies widely, which is due to the level of enzyme activity, the amount of incoming lactose with nutrition, individual intestinal sensitivity, and peculiarities of intestinal biocenosis. Children with lactase deficiency usually have a history of complicated pregnancy and labour (hypoxia), and their immediate relatives have adult-type LN symptoms. Clinical signs (regurgitation, flatulence, colic, diarrhoea) can occur from the moment of birth, but more often appear in the child at 3-6 weeks of life, which is associated with the increasing volume of nutrition and increasing lactose quota in the child's diet. A few minutes after the beginning of feeding, the child becomes restless, screams, refuses to eat. Meteorism, intestinal bloating and abdominal pain are caused by the formation of large amounts of gas during the fermentation of lactose by microflora. Increased intra-abdominal pressure, in turn, can cause regurgitation. Stools in children with lactase deficiency are frequent, liquid, frothy with a sour odour. Approximately 10% of children have constipation due to intestinal spasm. In severe cases, children may develop toxicosis with exicosis.

The diagnosis of "Lactase deficiency" is made on the basis of a characteristic clinical picture, including a decrease in dyspeptic symptoms with a decrease in the amount of lactose in the child's diet, the results of laboratory and instrumental methods. Most often in paediatric practice determine the content of carbohydrates in the faeces, which reflects the overall ability to digest carbohydrates. In infants, the content of carbohydrates in the faeces should not exceed 0.25%, and in children over 1 year of age, they should be absent. An indirect sign of LN is a decrease in stool pH below 5.5 in coprological examination. The method of determining the content of hydrogen, methane or 14C-labelled CO_2 in exhaled air [6] and lactose loading methods [6, 7] are also used to diagnose lactase deficiency.

The most accurate method for diagnosing LN is the determination of lactase activity in biopsy specimens of the small intestinal mucosa. However, the invasive nature of the method limits its use in young children. It is important to know that morphological examination of the small intestinal mucosa does not provide information regarding LN, as there are no specific morphological markers for this disease.

The diagnosis of "Primary lactase deficiency of adult type" is established by genetic study (genes C/T -13910 and C/T -22018, located on chromosome 2q21).

The basis of LN treatment in children is the restriction of lactose-containing foods in the diet [8]. In adult-type lactase deficiency in older children and adults, the amount of lactose in the diet can be reduced by restricting or eliminating milk consumption. In diseases leading to secondary LN, the main attention should be paid to the treatment of the underlying disease; in secondary (against the background of intestinal infections) - consumption of low-lactose products (fermented milk products, butter, hard cheeses) is recommended. The possible reduction of calcium intake with a dairy-free diet should be taken into account.

In the treatment of newborns, the most rational tactic is the tactic of individual step-by-step selection of the amount of lactose in the diet. Lactose should not be completely eliminated from the newborn's diet, as it is a prebiotic and a source of galactose. If the baby is naturally fed, the best way to reduce lactose intake is to use lactase preparations (Lactazar, Pharmstandart-Leksredstva OJSC, Russia), which are mixed with decanted breast milk or formula before feeding. The use of lactase preparations is an alternative to the

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selection of a mixed feeding regimen using lactose-free mixtures, requires less time to obtain clinical effect and allows to increase the volume of nutrition and the corresponding lactose intake. The use of lactase preparations is also possible during artificial feeding of children with lactose-containing starter adapted milk mixtures.

The preparation Lactazar is administered at each feeding (700 units of lactase or 1 capsule for every 100 ml of milk). Feeding of the child starts with a portion of lactose-containing decanted milk and then the child is supplemented from the breast. The duration of enzyme therapy in infants depends on the severity of clinical symptoms of lactase deficiency and is determined strictly individually. The use of lactase enzyme preparations in the therapy of LN allows to manage the symptoms of the disease rather quickly, while preserving the possibility of breastfeeding [7, 9, 10]. Only when the severity of the enzyme defect is pronounced and the effectiveness of the lactase preparations used is low, the question of partial reduction of the volume of mother's milk and its replacement with lactose-free formula can be raised (Table 1). The amount of lactose in breast milk does not depend on the mother's diet, so it is not advisable to reduce the amount of lactose in the mother's diet. It should only be recommended to limit the use of foods with a high content of whole cow's milk protein to prevent allergy to cow's milk protein and the formation of secondary lactase deficiency [9].

Table 1.

Composition and energy value of specialised lactose-free infant formulae (per 100 ml of formula)

Title	Manufacturing company manufacturer	Ingredients g.				Calories, kcal
		proteins	fats	carbohydrates		
				total	lactose	
Babushkino Lukoshko from birth lactose-free		1,7	3.4	7.6	0	67,4
Nutrilac lactose-free	Nutribio	1,5	3.4	7.4	0	66
Nutrilon lactose-free	Nutritech	1,46	3.61	7.22	0	67,2
Lactose-free NAS	Nutricia	1,7	3.3	7.6	0	67
Enfamil 0-Lac	Nestlé	1,42	3.7	7.2	<0,01	68

Babies who are artificially or mixed-fed should be fed a diet with a lactose content that does not cause clinical symptoms and an increase in faecal carbohydrates. Table 2 shows the composition of modern low-lactose formulae.

The diet can be customised by combining a lactose-free product with a standard adapted formula in a 2:1, 1:1 or 1:2 ratio.

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With a pronounced deficiency of lactase, no effect when reducing the amount of lactose to 1/3, it is recommended to use lactose-free mixtures as the main food.

In the absence of allergy to cow's milk proteins, lactose-free mixtures based on cow's milk protein are used, in the presence of allergy to cow's milk proteins - mixtures based on complete protein hydrolysate (Table 3).

In premature infants, if breastfeeding is not possible, the use of specialised lactose-reduced preformulas is recommended (Table 4)

Table 2.

Composition and energy value of specialised low-lactose infant formulae (per 100 ml of formula)

Title	Manufacturer	Ingredients, g				Калорийность, ккал
		proteins	fats	углеводы		
				всего	лактоза	
Nutrilac low lactose	Nutritech	1,6	3.5	7.3	0,9	66,3
Humana-LP	Humana	1,8	2,1	9,1	1,5	62
Humana-LP + SCT	Humana	1,9	2,0	8,9	0,5	61

Таблица 3. Состав и энергетическая ценность смесей на основе гидролизатов белка (на 100 мл готовой смеси)

Название	Фирма производитель	Ингредиенты, г			Калорийность, ккал
		белки	жиры	углеводы	
Нутрилак Пептиди СЦТ	Нутритек	1,9	3,5	6,7	66
Алфаре	Нестле	2,2	3,3	7,0	65
Нутрилон Пепти ТСЦ	Нутриция	1,8	3,6	6,9	67
Прегестимил	Мид Джонсон	1,9	3,8	6,9	68
Нутрамиген	Мид Джонсон	1,9	3,7	7,5	68
Фрисопеп АС	Фрисо	1,5	3,5	7,2	65

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Таблица 4.

Состав специализированных смесей для недоношенных детей (в 100 мл)

Название	Фирма производитель	Ингредиенты, г				Калорийность, ккал
		белки	жиры	углеводы		
				всего	лактоза	
Нутрилак Пре	Нутритек	2,0	3,9	7,8	5	75
Пре Нутрилон	Нутриция	2,2	4,4	8,0	5,9	80
Пре НАН	Нестле	2,03	3,6	7,5	1,1	70
Фрисопре	Фризленд Фудс	2,2	4,3	8,2	5,9	80
Хумана ГА 0	Хумана ГмбХ	2,2	4,2	8,2	5,6	80

The complementary food for children of the first year of life with lactase deficiency should be prepared on the formula (low- or lactose-free) that the child receives. The first main complementary food (from 4.5-5 months of age) should be porridge (rice, corn, buckwheat) or puree of vegetables with coarse vegetable fibre (cauliflower, courgette, pumpkin, carrots) with the addition of vegetable oil. After 2 weeks introduce mashed meat. Fruit juices and fruit purees are introduced into the diet of such children later, usually in the second half of life. In children of the second half of the year, it is possible to use dairy products, where the content of lactose is insignificant - cottage cheese (washed from whey), butter, hard cheese.

In primary (constitutional) lactase insufficiency, a low-lactose diet is prescribed for life. In secondary hypolactasia symptoms of LN are transient. Therefore, after achieving remission of the underlying disease in 1-3 months, the diet should be gradually expanded according to tolerability under the control of clinical symptoms (diarrhoea, flatulence). If it is necessary to prescribe probiotics in connection with the identified disorders of intestinal biocenosis in children with lactase deficiency, it is necessary to take into account the presence of excipients in their composition, since most probiotics on the Russian pharmaceutical market contain lactose as an excipient. These probiotics should not be used in children with LN.

CLINICAL CASE ANALYSIS

Clinical case № 1

The mother of a 1-month-old girl came to a gastroenterologist with complaints of restlessness of the child, frequent watery frothy stools 5-7 times a day. From the family history it is known that the mother "does not like" milk. The child has been breastfed since birth. During and after feeding, restlessness is noted. When examining the child, abdominal bloating was noted. The following changes were noted in the coprogram: odor - sour, consistency - liquid, pH of feces - 5.0, some mucus. The child was diagnosed with a preliminary diagnosis of "Lactase deficiency". Subsequent examination confirmed the diagnosis

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(feces for carbohydrates - 1.0%). When lactase was administered at a dose of 700 IU in 1/2 capsule at each feeding, a weakly positive effect was noted. When the dose was increased to 1 capsule per feeding, there was a significant improvement of clinical symptoms: sleep became calm, stools were mushy, without foam, 4 times a day.

From 5.5 months the girl began to receive dairy-free porridge. When milk was introduced at 10 months of age, restlessness, increased gas formation, and diarrhea were noted. The girl was prescribed a preparation of lactase 1 capsule in milk, against the background of which clinical improvement was noted. Due to the revealed changes in intestinal microbiocenosis (decrease in the total number of lacto- and bifidobacteria), the girl received lactose-free probiotics (see commentary).

Comment. Taking into account the genealogical anamnesis, clinical symptoms, changes in coprogram and the result of fecal analysis for carbohydrate excretion, the diagnosis of "Lactase deficiency" is reasonable. The weakly positive effect when taking 1/2 capsule (350 units) of lactase at each feeding is due to its insufficient dose, as the volume of one feeding of a child aged 1 month averages 120 ml, which required increasing the dose to 700 units per 1 feeding. It is important to note that the administration of probiotics in patients with LN allows to reduce the symptoms of lactose breakdown disorder. This is due to the fact that the utilization of lactose by lacto- and bifidobacteria does not significantly increase gas formation. In addition, organic acids inhibit the growth of opportunistic flora, thus reducing the risk of fermentative dyspepsia [7]. However, in case of lactase deficiency, lactose-free probiotics are indicated.

Clinical Case No. 2

The mother of a child 1 year 2 months old went to the pediatrician with complaints of flatulence, liquid stools with a sour odor up to 4-5 times a day. From anamnesis it is known that the child is from the first pregnancy, which proceeded physiologically. The labor was term independent. Birth weight 3 190 g, length 52 cm. Apgar score 8/9 points. The baby was put to the breast in the first 24 hours, immunized according to the calendar, complementary food was introduced according to age, and the mother retained breastfeeding.

The child first fell ill at the age of 1 year: fever up to 38.8°C, vomiting 3-4 times a day, frothy watery stools with mucus up to 6-7 times a day, marked flatulence. The patient was hospitalized in an infectious disease hospital with the diagnosis of "Acute gastroenteritis". At examination: feces for intestinal group was negative, rotavirus infection was detected (rotavirus antigen was isolated by ELISA method in feces). In hospital, the child received a dairy-free diet, oral rehydration, sorbents, enzymes, probiotics, and infusion therapy. The child was discharged with recovery after 10 days. After discharge, the mother resumed milk feeding of the child (breastfeeding 2 times a day, porridge on milk, cottage cheese). Against the background of nutrition, the child had restlessness, bloating and flatulence 30-40 minutes after meals, stool disorder: liquid, frothy with sour odor, 4-5 times a day. On examination, abdominal bloating, rumbling along the intestinal tract were noticed. In general blood and urine analysis - without pathology, in coprogram: pH - acidic, undigested fiber ++, mucus ++. At ultrasound of the abdominal cavity: flatulence of the intestine, no signs of changes in the pancreas. The child was diagnosed with "Secondary LN after rotavirus infection".

Advice was given to continue breastfeeding. Lactase preparation was recommended, which was

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administered before each breastfeeding. The drug in a dose of 700 units was added to pre-digested milk (20 ml), which was given to the child 20 min after the addition of lactase, then the child was supplemented with breastfeeding.

It was recommended to use mashed meat, vegetable puree on water with vegetable oil, dairy-free porridge or porridge on milk, adding 700 units of lactase to 100 ml of milk porridge. In 3 days after correction of nutrition and prescription of lactase preparation improvement of the condition was noted: including absence of flatulence and intestinal syndrome, normalized sleep. Lactase therapy was continued for 1 month.

Comment. Secondary lactase deficiency is a frequent complication of enteritis of both bacterial and viral etiology. The development of secondary LN is particularly characteristic of intestinal infection caused by rotavirus, which penetrates the epitheliocytes of the duodenum and small intestine. Damage to epitheliocytes is accompanied by their detachment from villi, accelerated movement of cells from the base of villi to the apex and incomplete differentiation process.

CONCLUSION

Lactase deficiency is often found in infants and young children. Tactics of treatment of this form of pathology depends on its cause, severity of clinical symptoms and is determined individually. The use of lactase preparations, such as Lactazar, both in primary and secondary LN is pathogenetically justified and allows for a short time to eliminate the main clinical manifestations of LN, while preserving the possibility of breastfeeding. The duration of enzyme therapy in infants is established individually. In case of impossibility to use lactase preparations in breastfed children, as well as in case of artificial feeding, the question of using low-lactose mixtures is solved.

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