Primary Lactase Deficiency among Malnourished Children with Persistent Diarrhea in Tbilisi, Georgia

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Abstract

Persistent diarrhea became the major cause for diarrheal mortality in children from developing countries. This study was therefore designed to establish the prevalence of primary lactase deficiency and associated factors among mild malnourished children with persistent diarrhea. This was a prospective cohort study. The study population consisted of mild malnourished children with persistent diarrhea aged 3–24 months admitted between October 2014 and September 2015. The Gomez classification of malnutrition was used. A mild malnourished child was whose weight-for-height was less than 75%–90% of the median National Centre for Health Statistics (NCHS)/WHO reference median. The study included 78 malnourished children with persistent diarrhea 3–24 months of age. The prevalence of primary lactase deficiency among the study children was 41.0%. The reasons of persistent diarrhea in lactose tolerant group were: Rotavirus infection – 33.3%, Bacterial gastroenteritis –20.5% (Enteropathogenic E.coli (EPEC) – 7.7%, Shigella – 6.4%, Yersinia enterocolitica – 3.8%, Salmonella – 2.6 %) and Gastroenteritis of unknown etiology – 5.1%. Only 4 children had Rotavirus infection in lactose intolerant group. The relationship between diarrhea and malnutrition is bidirectional: diarrhea leads to malnutrition while malnutrition aggravates the course of diarrhea. Lactose intolerance is a relatively common cause of persistent diarrhea. The most common cause of primary lactase deficiency is lactase enzyme non-persistence.

Keywords

- primary lactase deficiency
- persistent diarrhea

Introduction

Around the world, diarrhea is the second leading cause of death in children under the age of 5 years, taking the lives of 760,000 children each year, according to the World Health Organization (WHO, 2013). The great majority of diarrhea episodes last less than 1 week. When diarrhea persists for more than 14 days, it is called persistent or chronic diarrhea. In resource-limited (developing) countries, persistent diarrhea (PD) is most common in children younger than 2 years of age, and especially in children under 1 year,[1] but can also occur in older children. In the developing world, chronic diarrhea is typically associated with serial enteric infections and malnutrition. In developed countries, chronic diarrhea is more likely to be induced by underlying disease-causing malabsorption or maldigestion. These prolonged episodes are important not only because of the discomfort of having diarrhea but also because of the association with malnutrition and increased risk of death.[2] As a result, diarrhea is a major cause of malnutrition, and malnourished children are more likely to fall ill from diarrhea. Lactose intolerance is a common complication of diarrhea in infants with malnutrition and a cause of treatment failure.[3] Malnourished children commonly have a reduced activity of intestinal lactase, the enzyme responsible for the digestion of lactose,[4] and it has been suggested that feeding them this disaccharide can retard nutritional recovery. A large proportion of children with PD are seen in the wake of lactation failure and following the introduction of animal milk

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feeds.[5] The most common clinical problem encountered in dietary selection is possible lactose intolerance. The consequence of lactose malabsorption and continued milk feeding include osmotic diarrhea and increased stool output. Reduced intake of nutrients, maldigestion, and malabsorption increase nutrient losses, and the effects of the inflammatory response also contribute to adverse outcomes. Given the propensity of PD in the younger age group, it is natural that milk forms a major part of the dietary intake in these children. However, some of these children may be lactose intolerant, possibly contributing to the high rate of unfavorable treatment outcomes. Genetically regulated reduction of lactase enzyme activity or lactase nonpersistence is determined by racial or ethnic factors and is the underlying mechanism of lactose malabsorption in healthy individuals. Lactase nonpersistence is most frequent in Asian and African populations; in contrast, the majority of Caucasians, particularly of northern European background, maintain elevated lactase activity into adulthood.

Aim

This study was therefore designed to establish the prevalence of primary lactase deficiency and associated factors among mildly malnourished children with PD.

Methods

This was a prospective cohort study. The study population consisted of mildly malnourished children with PD aged 3 to 24 months admitted to Globalmed Pediatric Clinic between October 2014 and September 2015. The Gomez classification of malnutrition was used. A mildly malnourished child was one whose weight-for-height was less than 75 to 90% of the National Centre for Health Statistics/WHO reference median. The study included 78 malnourished children with PD aged 3 to 24 months. The study population was divided into two age groups: 3 to 12 months age group and 13 to 24 months age group. Fifty children were in the age group of 3 to 12 months and 28 children were in the age group of 13 to 24 months. Forty-three children in the study group were females and 35 were males (►**Table 1**).

The prevalence of lactose intolerance in the study population was explored on the basis of a precoded and pretested structured questionnaire and a genetic test for primary lactose malabsorption. Characteristics that were explored during the study period were each child's anthropometric measurements, birth order, duration of breastfeeding, immunization status, diarrhea episodes in the previous 3 months, abdominal distention, vomiting, previous problems with cow's milk, average frequency of stool in 24 hour, watery stool, antibiotic use during diarrhea, and dehydration. EDTA (ethylenediaminetetraacetic acid) blood samples, 2 mL, were obtained and posted to laboratory to undergo a genetic test for primary lactose malabsorption. Two *LCT* gene mutations are associated with lactase expression, C −13910 (C at position -13910 upstream of the *LCT* gene) and G −22018 (G at position-22018), are related to lactase nonpersistence, whereas T −13910 and A −22018 are related to lactase persistence. The CC genotype is associated with physiological loss of lactase activity. The test was considered positive if (examination of polymorphism – 13910C > T [relative to *LCT* gene]) homozygous CC genotype was consistent with primary lactase deficiency. Bacteriological studies of stool samples were performed to identify major diarrheagenic bacteria, including *Salmonella* spp, *Shigella* spp, *Yersinia enterocolitica*, *Campylobacter*, *Clostridium difficile*, and enteropathogenic *Escherichia coli* (EPEC). Quick Stripe Adeno/Rota rapid test (Savyon Diagnostics Ltd.) were performed for determination of rotaviruses and/or adenoviruses in stool samples. Data were coded and entered into a computerized database. All data collected were checked for completeness and accuracy and were cleaned before analysis. The analysis was performed using the Statistical Package for Social Sciences (SPSS 22; SPSS Inc.) software. Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as frequencies. The analysis of continuous variables was performed using Student's *t*-test and that of categorical variables was performed using Fisher's exact test. Voluntary informed consent was obtained from the parents/caretakers before participating in the study. Confidentiality was maintained throughout the study. Correlation analysis was performed by Spearman rank correlation. Results were summarized in texts and ►**Table 2**.

Table 1 Distribution by age and sex

3–12 mo age group (50 children)	13–24 mo age group (28 children)
31 females	12 females
19 males	16 males

Results

The prevalence of primary lactase deficiency among the study children was 41% (►**Figs. 1–3**).

The reasons for PD in the lactose tolerant group were rotavirus infection (33.3%), bacterial gastroenteritis (20.5%; EPEC, 7.7%; *Shigella*, 6.4%; *Y. enterocolitica*, 3.8%; *Salmonella*, 2.6%), and gastroenteritis of unknown etiology (5.1%). Only four children had rotavirus infection in the lactose intolerant group (►**Figs. 4** and **5**).

Diarrhea episodes in the previous 3 months, abdominal distention, vomiting, previous problems with cow's milk, and higher frequency of stool in 24 hours were significantly associated with primary lactase deficiency. The correlation analysis demonstrated that primary lactase deficiency had a significant positive correlation with the number of diarrhea episodes in the previous 3 months ($r = 0.556$; $p = 0.0000$), abdominal distention ($r = 0.490$; $p = 0.0000$), previous problems with cow's milk ($r = 0.331$; $p = 0.0076$), and vomiting ($r = 0.294$; $p = 0.0091$).

Discussion

The 41% prevalence of primary lactase deficiency in the 78 mildly malnourished children with PD was higher and was not

Table 2 Correlation of CC genotype with clinical symptoms of lactose intolerance

	Lactase persistence			Lactase nonpersistence			*F*	*p*-Value
	ABS	Mean	Standard deviation	ABS	Mean	Standard deviation		
≥2 diarrhea episodes in the previous 3 mo	12	0.32	0.471	24	0.92	0.272	35.10	0.0000
Abdominal distention	22	0.58	0.500	26	1	0.000	18.32	0.0001
Previous problems with cow's milk	20	0.53	0.506	22	0.85	0.368	7.61	0.0076
Vomiting	21	0.55	0.504	24	0.92	0.272	11.68	0.0011
Frequency of stool ≥8 motions in 24 h		5.29	1.088		9	0.849	$T = -16.193$	0.000

Abbreviation: ABS, Absolute value.

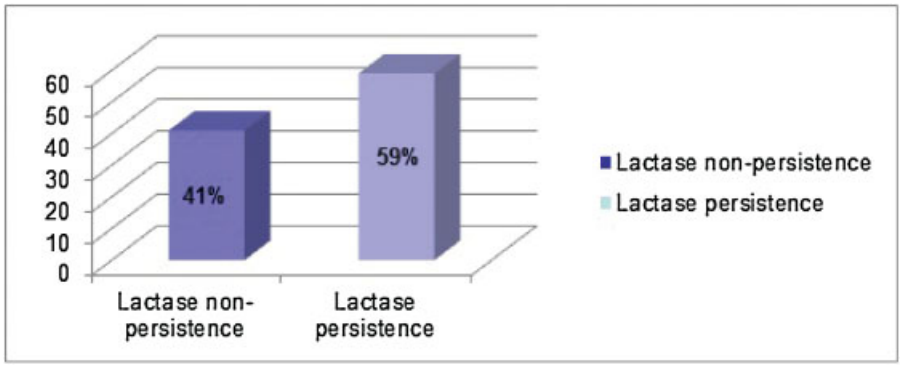

Fig. 1 The prevalence of primary lactase deficiency among the study children.

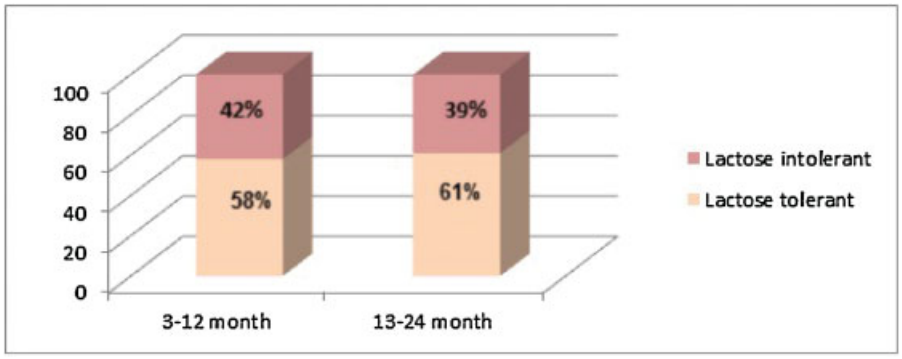

Fig. 2 Age distribution by primary lactase deficiency.

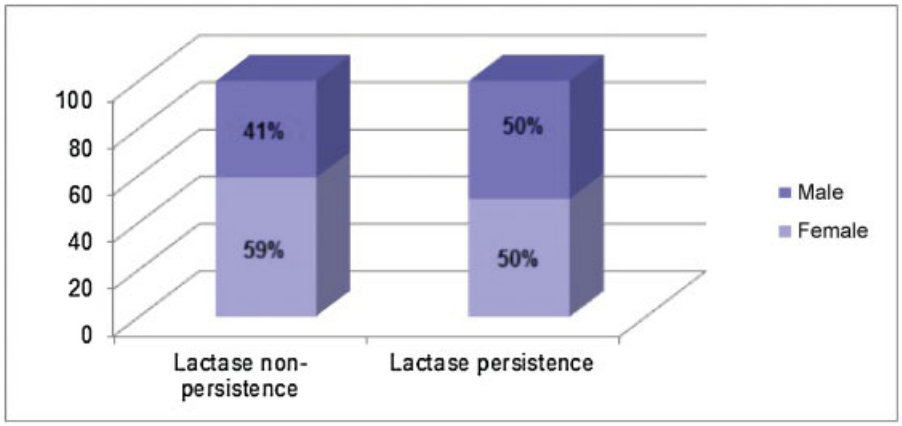

Fig. 3 Sex distribution by primary lactase deficiency.

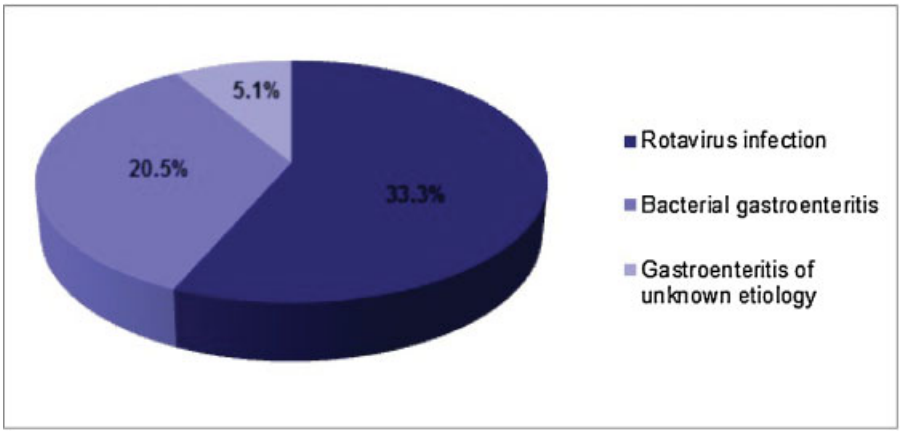

Fig. 4 Causative factors of persistent diarrhea in lactase persistent group.

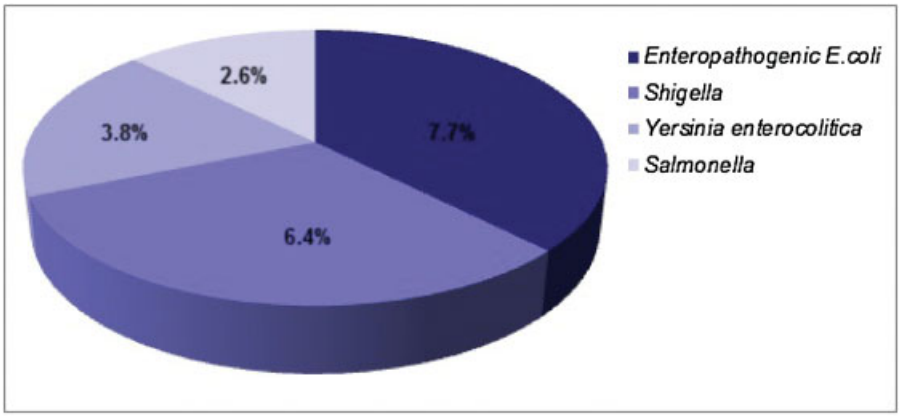

Fig. 5 Pathogens associated with bacterial gastroenteritis.

significantly different in children's age groups (3–12 months and above 12 months) in contrast to other studies.[6] This might be explained by the difference in sample size and study population. Children with primary lactase deficiency had a higher mean stool frequency (≥8 motions in a 24-hour period; $p = 0.000$), a finding consistent with one published by Ozmert et al in Turkey.[7] High prevalence of primary lactase deficiency among children having had two or more diarrhea episodes in the previous 3 months ($p = 0.000$), as found in this study, has also been reported elsewhere.[6] Recurrent episodes of diarrhea result in repeated disruption of the intestinal villi with shortened regeneration and maturation time, predisposing an individual to intestinal lactase deficiency. Conversely, lactose intolerance prolongs and increases the severity of diarrhea.[8]

Conclusion

The 41% prevalence of primary lactase deficiency in mildly malnourished children with PD is relatively high. Clinical predictors of primary lactase deficiency in mildly malnourished children include higher mean stool frequency (≥8 motions in one 24-hour period [$p = 0.000$], having ≥2 diarrhea episodes in the previous 3 months [$p = 0.0000$], abdominal distention [$p = 0.0001$], vomiting [$p = 0.0011$], previous problems with cow's milk [$p = 0.000$; $t = -16.193$].

PD has become the major cause for diarrheal mortality in children from developing countries. The relationship between diarrhea and malnutrition is bidirectional: diarrhea leads to malnutrition, while malnutrition aggravates the course of diarrhea. Lactose intolerance is a relatively common cause of PD. The most common cause of primary lactase deficiency is lactase enzyme nonpersistence. Genetic testing is a new tool for the diagnosis of lactase persistence. Prevalence of primary lactase deficiency among malnourished children with PD in different regions of Georgia is the main topic of our investigation and further studies.

References

1 Moore SR, Lima NL, Soares AM, et al. Prolonged episodes of acute diarrhea reduce growth and increase risk of persistent diarrhea in children. Gastroenterology 2010;139(04):1156–1164
2 Andrade JA, Fagundes-Neto U. Persistent diarrhea: still an important challenge for the pediatrician. J Pediatr (Rio J) 2011; 87(03):199–205

3 Suchy FJ, Brannon PM, Carpenter TO, et al. National Institutes of Health Consensus Development Conference: lactose intolerance and health. Ann Intern Med 2010;152(12):792–796
4 Klish WJ, Udall JN, Calvin RT, Nichols BL. The effect of intestinal solute load on water secretion in infants with acquired monosaccharide intolerance. Pediatr Res 1980;14(12):1343–1346
5 Yang J, Deng Y, Chu H, et al. Prevalence and presentation of lactose intolerance and effects on dairy product intake in healthy subjects and patients with irritable bowel syndrome. Clin Gastroenterol Hepatol 2013;11(03):262–268.e1
6 Nyeko R, Kalyesubula I, Mworozi E, Bachou H. Lactose intolerance among severely malnourished children with diarrhoea admitted to the nutrition unit, Mulago hospital, Uganda. BMC Pediatr 2010; 10:31. Doi: 10.1186/1471-2431-10-31
7 Ozmert E, Yurdakök K, Aslan D, Yalçin SS, Yardim M. Clinical characteristics of transient glucose intolerance during acute diarrhoea. Acta Paediatr 1999;88(10):1071–1073
8 Rao C, Tomar A, Hegde R, Anand VC. Thin layer chromatography in children with sugar intolerance in acute diarrhea. Indian J Gastroenterol 2006;25(02):102–103