INCIDENCE AND RISK FACTORS FOR CARBOHYDRATE INTOLERANCE IN THAI INFANTS WITH ACUTE DIARRHEA : AN OUTPATIENT-BASED STUDY

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Abstract. Until recently, information concerning carbohydrate intolerance complicating acute infantile diarrhea of outpatients in Thailand has been lacking. This prospective study was undertaken to determine the incidence and risk factors of secondary carbohydrate intolerance in outpatients. Of 197 well-nourished infants with acute diarrhea who were seen at the outpatient department of Songklanagarind Hospital between July 1991 and June 1992, 62 infants (31.3%) had carbohydrate intolerance, and 7 of the 62 (3.5%) also had acquired monosaccharide intolerance. The clinical characteristics that predicted infants with carbohydrate intolerance were : a low bodyweight relative to the length, dehydration (OR 4.55, 95% CI 1.15-17.9), the presence of mucus in diarrheal stools (OR 2.79, 95% CI 1.23-6.32) and rotavirus infection (OR 3.49, 95% CI 1.20-10.18).

INTRODUCTION

Carbohydrate intolerance (CI) is a well-recognised complication of diarrhea in infants and is frequently specific for lactose (Chandrasekaran *et al*, 1975; Davidson *et al*, 1984; Varavithya *et al*, 1971). Recently, acquired monosaccharide intolerance (AMI) has also been increasingly recognised as an important complication of acute gastroenteritis of infancy, and features in some infants with protracted diarrhea (Khoshoo *et al*, 1989; Lifshitz *et al* 1970 ; Manual *et al*, 1984). However those studies of secondary CI in infants have mostly focused on hospitalized patients in whom severe diarrhea, malnutrition, or prolonged diarrhea were underlined.

To date information concerning secondary CI of outpatients has not been adequately emphasised even though acute infantile diarrhea is common in the everyday practice of ambulatory pediatrics. We believe, therefore, that such information is important to ambulatory management of acute diarrhea, since the early recognition of CI at outpatient departments and exclusion of offending sugar when necessary may hasten the rehabilitation from acute diarrhea, which will ultimately lead to decreased hospital admissions.

The aims of the present study were (1) to determine the incidence of CI, in particular AMI, in outpatient infantile acute diarrhea and (2) to provide data on risk factors associated with CI.

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MATERIALS AND METHODS

A prospective descriptive study of all infants with acute diarrhea (duration < 7 days) attending the pediatric outpatient department of Songklanagarind Hospital from July 1991 to June 1992 was conducted. Infants with underlying gastrointestinal disease were excluded. Data collected from each infant included :

- age, sex,
- duration and frequency of diarrheal stools,
- degree of dehydration by clinical assessment following WHO (1984) criteria
- Z scores of weight for age and length for age, with reference to the National Center of Health Statistics (NCHS); to avoid the effect of dehydration, the exact weight was calculated by (wt × 100) / (100-% of dehydration)

- etologic agents including bacterial pathogens and rotavirus (ELISA method, Dakopatts, Dako Laboratories, Denmark) ;
- stool examination (characteristics, microscopic findings, reducing substances, glucose, pH).

Reducing substances in the feces were determined by Clinitest tablet (Miles Australia), and stool glucose and pH by Labstix (Miles Australia). The tests described were performed immediately after stools were taken. Daily stool specimens from each infant were tested during the follow-up period until the diarrheal symptoms resolved.

Criteria to diagnose CI

The presence of more than 0.5% (+1) reducing substance in stool (Kerry and Anderson, 1964), with or without a pH less than 6. In infant who had stool glucose of more than +1 together with the presence of more than 0.5% reducing substance, AMI was also diagnosed.

Infants who were bottle-fed and considered to have CI were then put on lactose-free formula after 4 to 6 hours rehydration with oral glucose electrolyte solution (WHO/UNICEF). For AMI infants, dilute lactose-free formula was initially introduced in frequent and small amounts, then both feeding volume and concentration were gradually increased when their diarrhea settled. Indications for hospital admission were severe dehydration and vomiting that required intravenous fluid.

Data analysis

Statistical analyses were done with STATA software. Association between CI and the various clinical and stool characteristics together with etiologic agents was analysed using logistic regression. In the first set of analyses each variable was modelled separately yielding crude odds ratios for each association. In the second set of analyses all candidate predictor variables were first included and the model was then simplified using stepwise removal of predictors which did not make a significant contribution to the log-likelihood ratio.

RESULTS

From July 1991 to June 1992, 244 infants with acute diarrhea were seen at the outpatient department. Forty-seven infants were excluded: 39 were excluded because their stools could not be collected, and 8 had equivocal diagnosis of CI due to being fed with lactose free-formula before study. Therefore 197 infants were enrolled in this study. The clinical characteristics of the 197 infants are summarized in Table 1. In general, subjects in our study were well-nourished infants, and had mild diarrhea. Diarrheal pathogens were isolated in stools of a minority of the infants. Rotavirus was most often seen during the period January to April. Thirty-six infants (18%) needed intravenous rehydration in the hospital because of vomiting and severe dehydration.

Incidence of secondary CI

Of the 197 infants, 62 (31.5%) had secondary CI and 7 (3.5%) of the 62 also fulfilled the criteria for diagnosis of AMI. Fifteen carbohydrate intolerant

Table 1

Clinical characteristics of 197 infants with acute diarrhea.

Mean age (months)	6.23±3[a]
Sex[b]	
male	129(65.5)
female	68(34.6)
Z wt/age	-0.038±0.96[a]
Z ht/age	-0.383±0.93[a]
Dehydration status[b]	
No dehydration	29(14.7)
Mild degree	142(72.1)
Moderate/severe degree	26(13.2)
Duration of diarrhea before study[b]	
1-3 days	151(76.6)
4-7 days	46(23.4)
Diarrheal stools frequency[b] (stools/day)	
Less than 5	50 (25.4)
5-10	106(53.8)
More than 10	41(20.8)
Stool characteristic[b]	
Watery	32(16.2)
Presence of mucus	93(47.2)
Others(runny, mushy, soft)	72(36.5)
Etiologic pathogen[b]	
Rotavirus	30/184(16.3)
Enteropathogenic bacteria[c]	56/197(28.4)

[a]Mean±SD
[b]Number of patients(%) are shown
[c]Not including stool culture for *Campylobacter*

infants were hospitalized for intravenous rehydration. Secondary CI was found in 53% (16/30) of infants with rotavirus infection. Among the 7 infants with AMI, rotavirus was identified in 3, and 4 of the 7 had severe dehydration.

Follow-up studies were possible in 50% of the total, and it was found that no infant went on to develop protracted diarrhea. The mean durations of diarrhea in secondary CI, AMI and acute diarrhea without CI were 4.0 ± 4.4, 3.3 ± 2.2, and 3.3 ± 1.7 days, respectively. No infants with AMI required parenteral nutrition or elimination of carbohydrate in their diet, and their diarrhea settled quickly while they were still being fed with lactose-free formula.

Risk factors associated with secondary CI

The multivariate analysis suggested that standardized body length for age and weight for age, after adjustment for each other and other variables, had opposite associations with CI (Table 2). Length was positively associated, whereas weight was negatively associated. This can be interpreted as meaning that infants who were relatively longer for their weight were more likely to be carbohydrate intolerant. In addition, dehydration, the presence of mucus in diarrheal stools, and rotavirus infection were found to be significantly associated with CI. A dose-response relationship between CI and increasing severity of dehydration could not be demonstrated in this study (data not shown), probably due to the small sample size of infants with moderate/severe dehydration (N=26, Table 1). Although crude analysis suggests that duration of diarrhea was a positive predictor in carbohydrate intolerance (crude OR 2.3, 95% CI 1.18-4.46), which was only observed in diarrheal duration of more than 1 day, after adjustment of other variables such association was marginally significant. To confirm our results, a further analysis using stepwise elimination of variables which did not make a significant contribution to the log-likelihood ratio was performed. It was found that the positive and negative predictors noted in Table 2 remained unequivocally associated with CI.

Table 2

Clinical comparison between infants with CI and those without.

Predictor	CI (N=62) No.(%)	Non-CI (N=135) No.(%)	Crude odds ratio (95% Conf interval)	Adjusted odds ratio (95% Conf interval)
Age(months)				
1-3	14(22.5)	24(17.7)	-	-
4-6	24(38.7)	43(31.8)	1.55(0.56-4.27)	1.75(0.49-6.19)
7-9	15(24.1)	44(32.5)	1.48(0.59-3.71)	2.16(0.69-6.69)
10-12	9(14.5)	24(17.7)	0.90(0.34-2.38)	1.25(0.39-3.95)
Sex(M/F)	39/23(62.9/37)	90/45(66.7/33.3)	0.84(0.45-1.58)	1.03(0.47-2.26)
Z(Wt/age;mean)	-0.16	0.01	0.82(0.59-1.12)	0.53(0.33-0.85)
Z(Ht/age:mean)	-0.30	-0.41	1.17(0.81-1.70)	1.83(1.08-3.10)
Dehydration status				
No	3(4.8)	26(19.2)	-	-
dehydrated (all degree)	59(95.2)	109(80.8)	4.69(1.36-16.15)	4.55(1.15-17.97)
Duration of diarrhea before study				
1 day	16(25.8)	60(44.4)	-	-
more than 1 day	46(74.2)	75(55.6)	2.3(1.18-4.46)	2.04(0.94-4.45)
Diarrheal stool frequency(stools/day)				
less than 5	10(16.1)	40(29.6)	-	-
5-10	36(58.1)	70(51.8)	2.05(0.92-4.58)	1.65(0.65-4.16)
more than 10	16(25.8)	25(18.5)	2.56(1.00-6.51)	2.3(0.72-7.36)
Watery stool	14(22.6)	18(13.3)	1.89(0.87-4.11)	1.83(0.67-4.99)
Stool with mucus	34(54.8)	59(43.7)	1.56(0.85-2.86)	2.79(1.23-6.32)
Rotavirus	16(25.8)	14(10.3)	3.14(1.41-7.01)	3.49(1.20-10.18)
Enteropathogenic bacteria	8(12.9)	48(35.5)	0.26(0.11-0.61)	0.22(0.08-0.57)

DISCUSSION

We believe that secondary CI complicating acute diarrhea is still common in Thai infants as we found in one-third of outpatient infants with acute diarrhea in this study. Our data is in contrast to some studies from Western countries, showing that lactose intolerance post-gastroenteritis might be uncommon. (Anonymous, 1987; Trounce and Walker-Smith, 1985).

Although our subjects were well-nourished, a difference in nutritional index between infants with secondary CI and those without was revealed in this study. The multivariate analysis showed that the mean body length of infants with secondary CI was significantly longer than the non CI group, whereas a lower body weight was observed in the former. This may reflect more acute weight loss occurring in infants with CI, probably due to lower caloric intake caused by carbohydrate malabsorption. In addition to the nutritional factor, other clinical features significantly associated with secondary CI in this study were dehydration, diarrheal stools with mucus, and rotavirus infection. Our data is in agreement with that of Chandrasekaran *et al* (1975) and Manual *et al* (1984), who reported that dehydration was a predominant feature in CI complicating infantile diarrhea. The relationship between CI and dehydration can clearly be explained by the fact that the unabsorbed carbohydrate and its fermentative products contribute as osmotic diarrhea to the already existing intestinal mucosal damage caused by acute enteritis, and the effect of this allows further fluid and electrolyte loss in stools. Typically, CI of all types is clinically characterized by watery, sour-smelling diarrheal stools and physicians are generally less concerned about diarrhea presenting with mucous stools.

However, it is surprising that the presence of mucus in diarrheal stool was a significant clinical characteristic in our infants with secondary CI. Perhaps this was caused by the irritative effect of high intraluminal osmotic pressure created by unabsorbed carbohydrate and its fermentative products on the colonic mucosa (Neutra and Forstner, 1987). Our results also support the concept that, among the diarrheal pathogens, rotavirus is a leading cause of secondary CI (Davidson *et al*, 1984 ; Hyams *et al*, 1981). We demonstrated that infants with rotavirus infection were 3 times more likely to be carbohydrate intolerant, while bacterial infection had a negative association. To our knowledge, a prolonged duration of diarrhea and malnutrition are well-recognised as important factors in developing CI (Lee, 1984). What happens is that the prolonged diarrhea may aggravate the malnutrition, producing intestinal mucosal atrophy and lactase deficiency, which is followed by malabsorption, further diarrhea, and more severe malnutrition. A vicious cycle may develop. Nevertheless, our findings indicate that in well-nourished infants who had acute diarrhea for not more than 7 days, the longer diarrheal duration and the more frequent diarrhea stools per day did not increase the risk of CI.

Recently, AMI complicating infantile diarrhea has been of wide concern as it may pose the most therapeutic problems, since it may require elimination of carbohydrate in the diet and prolonged intravenous alimentation. Previous studies showed that AMI occurred in 4-9% of infants hospitalized for prolonged diarrhea (Khoshoo *et al*, 1989; Manual *et al*, 1984; Nichols *et al*, 1989). Our study therefore provides more information concerning the occurrence of AMI particularly in well-nourished infants attending the outpatient department with acute diarrhea: the incidence was 3.5%.

Infants with AMI can be categorized into two groups according to their clinical course. The first group, which was well described in early studies (Burke and Danks, 1966; Lifshitz *et al*, 1970), are typically young infants who have AMI associated with protracted diarrhea, PEM, and in some cases complicated by hypoglycemia. The illness is, in general, severe and difficult to manage. There is evidence suggesting that severe villous atrophy is responsible for monosaccharide malabsorption in this group (Klish *et al*, 1978). The second group have relatively mild transient AMI, which probably occurs in healthy infants with acute gastroenteritis, in particular that caused by rotavirus (Manual *et al*, 1984). The pathogenesis of AMI is unclear for this group, but it is likely that rotavirus infection results in a high proportion of the villous enterocytes being immature and therefore having a reduced ability to absorb sodium and glucose (Hamilton, 1988). The clinical features of AMI in our study were similar to the latter group. Rotavirus was found in a half of the AMI infants, but the disorder was a minor problem not requiring sophisticated management. However, it seems that severe dehydration is also

common in AMI as it was found in a half of our patients.

In summary, the incidence of secondary CI in well-nourished Thai infants with acute diarrhea at the outpatient department was 31.3%, and 3.5% of these infants also had AMI. Of various clinical characteristics, a low body weight relative to the length, dehydration, the presence of mucus in stools, and rotavirus infection were significantly associated with CI.

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