Whole Gastrointestinal Transit Time is Associated with Clinical Severity and Nutritional Status of HIV-Infected Children

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Background: *Malnutrition and malabsorption are common consequences in pediatric human immunodeficiency virus (HIV) infection. The gastrointestinal tract is a major site affected by HIV. Rapid gastrointestinal transit time may contribute to malabsorption.*
Objective: *To determine whether the whole gastrointestinal transit time (WGTT) correlates with disease stages or degrees of malnutrition in HIV-infected children.*
Material and Method: *Forty HIV-seropositive children, at various stages of disease, and thirty seronegative age-matched controls, aged between 1 mo and 3 yr, were enrolled in the present study. The body weight, length, or height and the WGTT were assessed. Then the WGTT of children in different stages of HIV disease and in different degrees of malnutrition were compared with those of the control group.*
Results: *The mean ages were 15.5 and 14.3 mo in HIV-infected and control groups respectively. A greater degree of malnutrition was found in HIV-infected children with more advances HIV clinical symptoms. Compared to controls, WGTT was most rapid in severely symptomatic acquired immunodeficiency syndrome (AIDS) patients (Category C) (14.32 $\pm$ 3.88 versus 7.22 $\pm$ 3.17 h; $p < 0.01$) but not in asymptomatic, mildly and moderately symptomatic children. Accelerated WGTT in HIV-infected children was also significantly associated with a higher degree of malnutrition.*
Conclusion: *Malnutrition is clearly related to the progression of HIV disease. Accelerated WGTT is associated with HIV seropositivity, severe clinical symptoms, and higher degrees of malnutrition.*

Keywords: *Gastrointestinal transit time, HIV Infections, Malnutrition, Nutritional status*

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Pediatric human immunodeficiency virus (HIV) infection has been recognized as one of the major health problems in Thailand. Malnutrition, characterized by a decrease in body weight compared to height, leading to changes in body composition, is a major complication of HIV infection. Poor weight gain was associated with an increased risk of death[1,2].

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In Thailand, Chearskul et al[3] reported that 46% of perinatally HIV-infected children died at the median age of 22 months (range: 2-69 months) and the most common cause of death was infection such as cause from pneumonia, diarrhea, and sepsis. Furthermore, wasting syndrome was found in 38% of class C clinically HIV-infected children. Although the problem of using an highly active antiretroviral therapy-related lipodystrophy is increasing, malnutrition and wasting syndrome still remain persistent problems in pediatric HIV infection in Thailand.

The gastrointestinal (GI) tract houses 60% of all the lymphocytes in the body, therefore, it is a major

target for human immunodeficiency virus by binding to CD4 receptors of intestinal T lymphocytes resulting in the GI tract malfunctions and finally malnutrition[4].

The aim of the present study was to determine whether the nutritional status of HIV-infected children in all clinical stages had any correlation with whole gastrointestinal transit time (WGTT).

Material and Method

Population

Children aged 1 month to 3 years admitted to Siriraj Hospital between January and December 2000 constituted the study population. The subjects were divided into two groups composed of a control group and an experimental group. The former, non-HIV infected children, were admitted with other resolved diseases and waited for discharge from the hospital. The latter, HIV-infected children, were classified into four subgroups according toclinical categories 1) N = not symptomatic, 2) A = mildly symptomatic, 3) B = moderately symptomatic, and 4) C = severely symptomatic[5]. Neither groups had gastrointestinal symptoms and were receiving any medication known to affect gut transit time. There were thirty subjects in the control group. There were forty subjects in the experimental groups, which were divided into four categories, having 10 children in each category. The authors explained the detail of the present study to the subjects' parents and they gave written informed consent.

Procedure

Demographic data such as age, sex, and anthropometric data *e.g.* weight, length, or height were collected. Anthropometric measurements were performed by an experienced dietitian. Nutritional assessment was calculated by percentages of weight-for-age (%W/A) and height-for-age (%H/A), and protein-energy malnutrition was assessed. The percentage of weight-for-age was defined as normal, 1st, 2nd, and 3rd degrees of malnutrition with values $\geq$ 90%, 75-89%, 60-74%, and < 60%, respectively. The percentage of height-for-age was also determined by using cut-off values of Waterlow's classification of normal ($\geq$ 95%), 1st degree (90-94%), 2nd (85-89%), and 3rd degree (< 85%).

Carmine, a naturally occurring bright red pigment extracted from the cochineal insect, is a water-soluble, non-absorbable powder used as an indicator of WGTT. One hundred milligrams of carmine was mixed in milk formula given to each subject. WGTT was measured from consumption of carmine-containing formula until the first appearance of red color of this marker in stool indicating the arrival of carmine at the anal level.

Statistical analysis

WGTT was described as means $\pm$ SD and one-way ANOVA was used to determine significant differences in WGTT between HIV-infected and non-HIV infected groups, and between non-malnourished and malnourished groups. The statistical significance was defined as $p < 0.05$. All statistical analyses were performed with the use of SPSS software (version 11.5; SPSS Inc, Chicago, IL).

Results

Subjects enrolled in the present study were composed of both male and female (13 and 17 in the control group versus 22 and 18 in HIV-infected groups, respectively) (Table 1). The mean ages of subjects were 14.3 and 15.5 months old in the control and HIV-infected groups respectively.

Fig. 1A shows the nutritional status of non-HIV and HIV-infected subjects classified by the percentage of body weight-for-age. In the non-HIV-infected patients, 76.7% had normal weight and 23.3% had first degree of malnutrition. In the HIV-infected patients of subgroup C, none had a normal weight and they had the largest percentage of severe malnutrition (40%). The authors concluded that advances in clinical stages of HIV disease were to be related to a higher severity of malnutrition.

The height-for-age data are shown in similar pattern (Fig. 1B). The height-for-age index was lower in seropositive than seronegative children. Most of the non-HIV patients had normal height with 6.7% of 1st degree and 3.3% of 2nd degree stunting. However, the rate of stunt increased remarkably in the HIV-infected group associated with the more severe status of HIV. In subgroup C, none had normal height, with 1st, 2nd,

Table 1. Characteristics of subjects in this study

	HIV-seronegative group	HIV-seropositive group			
		N	A	B	C
Number	30	10	10	10	10
Sex (M/F)	13/17	4/6	7/3	6/4	5/5
Mean age (mo)	14.3	5.4	21.0	14.7	21.2

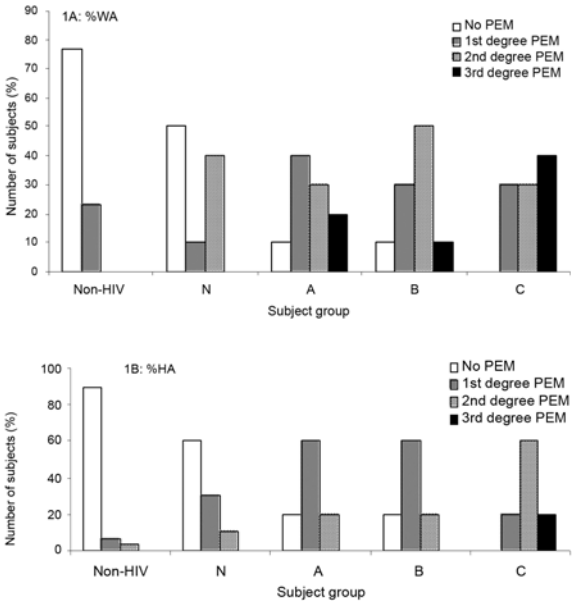

Fig. 1 Nutritional status classified by the percentage of weight-for-age (1A) and the percentage of height-for-age (1B) in non-HIV and HIV-infected groups studied. %W/A of $\geq$ 90, 75-89, 60-74, and < 60 is classified as normal, 1st, 2nd, and 3rd degrees of protein energy malnutrition %H/A of $\geq$ 95, 90-94, 85-89, and < 85 is classified as normal, 1st, 2nd, and 3rd degrees of protein energy malnutrition

and 3rd degree stunting occurring in 20, 60, and 20% of children, respectively. No children of other subgroups were classified as 3rd degree stunting.

The WGTT of HIV-infected patients were different from that of seronegative children (Table 2). Compared to a control group, the HIV-seropositive group had a statistically significant lesser average GI transit time (10.3 $\pm$ 2.1 versus 14.3 $\pm$ 3.9 h; p-value < 0.01). Moreover, the WGTT was shorter in subgroup C than in other subgroups of seropositive children, but the differences were not significant.

A reduction in average WGTT was associated with severity of malnourishment in the HIV-infected group (Table 3). The WGTT appreciably decreased from 13.2 h in HIV-infected children whose weight-for-age percentage of standard was 90% or greater, to a transit time of 6.9 h in children whose weight-for-age percentage of standard was less than 60%. This finding was in line with a significant diminishment of WGTT in HIV-infected children with 2nd degree stunting compared to those in the absence of stunting. On the other hand, the WGTT in malnourished, non-HIV subjects were not different from well-nourished controls.

Discussion

The present study shows that a higher severity of malnutrition was found in HIV-infected children with more advanced stages of HIV clinical symptoms. Accelerated WGTT is associated with HIV seropositivity, severe clinical symptoms, and severely deteriorated nutritional status.

The causes of malnutrition in HIV-infected patients are multifactorial such as intrauterine growth retardation, inadequate intake, poor nutrient absorption, increased tissue catabolism, and excessive cytokine production from tissue catabolism[6,7]. Perinatally HIV-infected infants had significantly lower birth weights and lengths, regardless of HIV status of the infants compared to non-infected infants[8,9]. Anorexia often found in HIV-infected children, who have both infections of gastrointestinal and non-gastrointestinal systems, results in decreased food intake[10]. HIV-seropositive children receiving enteral tube feeding showed favorable weight gain[11,12]. Moreover, reduced energy intake superimposed on malabsorption, contributed to weight loss[13]. Proximal and distal small intestinal malabsorption in HIV-associated enteropathy were reported by using d-xylose test and Schilling's test for cobalamin[14]. In addition, reduction in disaccharidase activity was found to be correlated with an advanced stage of disease in HIV-infected patients[15]. Decreased jejunal villus height-

Table 2. Whole gastrointestinal transit time of non-HIV and HIV-infected subjects[1]

Group	No.	WGTT
Non-HIV	30	14.3 $\pm$ 3.9
HIV-infected	40	10.3 $\pm$ 2.1*
Subgroup N	10	11.8 $\pm$ 4.9
Subgroup A	10	11.1 $\pm$ 4.1[2]
Subgroup B	10	11.1 $\pm$ 4.6[2,3]
Subgroup C	10	7.2 $\pm$ 3.2*[,2,3,4]

[1] All values are means $\pm$ SEM, n = 30, 40 in non-HIV and HIV-infected groups (10 in each subgroup N, A, B, C), respectively

* Significantly different from the non-HIV-infected group, p-value < 0.01

[2] Non-significantly different from the subgroup N

[3] Non-significantly different from the subgroup A

[4] Non-significantly different from the subgroup B

Table 3. Whole gastrointestinal transit time of non-HIV and HIV-infected subjects classified by nutritional status[1]

	Non-HIV-infected group (n = 30)		HIV-infected group (n = 40)	
	Whole GI transit time (h)	p-value	Whole GI transit time (h)	p-value
Weight-for-age				
No PEM	13.9 ± 3.7		13.2 ± 2.1	
1st degree PEM	15.8 ± 3.8	NS	13.6 ± 2.2	NS
2nd degree PEM	-	-	10.1 ± 2.1	NS
3rd degree PEM	-	-	6.9 ± 1.2	<0.01
Height-for-age				
No PEM	14.3 ± 4.0		13.8 ± 2.1	
1st degree PEM	15.5 ± 3.6	NS	11.2 ± 3.0	NS
2nd degree PEM	12.3 ± 3.0	NS	8.4 ± 1.3	<0.05
3rd degree PEM	-	-	9.6 ± 3.8	NS

[1] All values are means ± SEM

crypt depth ratio was described as well. Lactose malabsorption was found in either 40% of young HIV-infected children without an enteric infection or in the presence of small intestinal pathogens[16,17]. As a result, symptomatic lactose malabsorption occurs. Malabsorption also correlated significantly with the degree of immune suppression and with body mass index[18]. Proinflammatory cytokines, which are TNF-α, IFN-γ, IL-1, and IL-6, may be associated with anorexia. Studies of cytokine suppressors had been carried out, but were inconclusive[19-25].

The appearance of carmine in the stool provided a measure of WGTT (oro-anal) of milk formula and was significantly rapid in malnourished, severely clinical HIV-seropositive children. Subjects enrolled in the present study did not have any gastrointestinal symptoms and were not receiving any medication known to affect WGTT, thus this represents the effect of HIV disease and the nutritional status on the whole guts transit time. The GI tract is a major target for HIV by binding of the virus to CD4 receptors of intestinal T lymphocytes[4]. The gastric emptying time and small bowel transit were not apparently separated in the study implementation. On the contrary, Sharpstone et al[26] revealed that gastric emptying, by measuring serum 3-O-methyl-D-glucose after ingestion, was delayed in all AIDS subgroups not only in asymptomatic, wasting, and pathogen-negative diarrhea, but also in protozoal diarrhea. They also found rapid jejuno-caecal transit time, with the use of serum sulphapyridine following sulphasalazine ingestion as a measure, in HIV patients, but this did not correlate significantly with reduced absorptive capacity.

A limitation of the present study was the small sample size of HIV-seropositive subjects, which may limit association between either 2nd degree weight-for-age or severe stunting and GI transit time to be statistically significant despite more rapid transit time compared to normal nutritional status groups.

Early nutrition intervention, including individual tailor-made formula composed of being lactose-free and calorie-dense with lipids, should be instituted in severely immunocompromised HIV-seropositive children. For the clinical implications, the authors suggest that a special formula should have low osmolality in order to delay GI transit time resulting in getting more time for nutrient absorption in HIV-infected patients or supplement with exogenous lactase. N dekha et al[27] showed that malnourished, HIV-infected children benefited from home-based therapy with ready to use therapeutic food, which was energy-dense lipid paste, with more rapid weight gain and reaching targeted weight-for-height. Restoration of intestinal absorption and increase in $CD4^+$ lymphocyte count by nutritional rehabilitation were reported[28]. More data of the mechanisms for prolonged WGTT in HIV-infected children will be required in the future research.

In conclusion, severe malnutrition in HIV-infected children was found with more advanced stage of HIV clinical symptoms. Accelerated WGTT is associated with HIV seropositivity, severe clinical symptoms and severe malnutrition. The future direction of research is to study absorption and retention of nutrients of a tailor-made formula in a metabolic balanced study in order to find a suitable composition for the HIV-positive children.

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ความสัมพันธ์ระหว่างระยะเวลาที่อาหารเคลื่อนที่ผ่านระบบทางเดินอาหาร และความรุนแรงของโรค รวมทั้งภาวะโภชนาการในเด็กที่ติดเชื้อเอชไอวี

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***ภูมิหลัง**: ภาวะทุพโภชนาการและการดูดซึมสารอาหารที่ผิดปกติเป็นปัญหาที่พบได้บ่อยในเด็กที่ติดเชื้อไวรัสเอชไอวี ระบบทางเดินอาหารเป็นตำแหน่งที่สำคัญของการก่อโรคของเชื้อไวรัสเอชไอวี ซึ่งจะทำให้มีความผิดปกติของ whole gastrointestinal transit time (WGTT)*

***วัตถุประสงค์**: เพื่อศึกษา WGTT ในเด็กที่ติดเชื้อไวรัสเอชไอวีระยะต่างๆที่มีภาวะโภชนาการแตกต่างกัน*

***วัสดุและวิธีการ**: ศึกษาในเด็กอายุระหว่าง 1 เดือนถึง 3 ปี กลุ่มทดลองคือผู้ที่ติดเชื้อไวรัสเอชไอวี โดยแบ่งตามระยะความรุนแรงของโรค ส่วนกลุ่มควบคุมคือที่ไม่ติดเชื้อไวรัสดังกล่าว มีการตรวจวัดน้ำหนักตัว ความยาวหรือความสูง และประเมิน WGTT ในเด็กทั้งสองกลุ่ม หลังจากนั้นจึงเปรียบเทียบค่า WGTT ในเด็กทั้งสองกลุ่มโดยแบ่งตามความรุนแรงของโรค (Category N, A, B และ C) และระดับภาวะโภชนาการ*

***ผลการศึกษา**: อายุเฉลี่ยของเด็กในกลุ่มทดลอง และกลุ่มควบคุมมีค่าเท่ากับ 15.5 และ 14.3 เดือน ตามลำดับ เด็กที่ติดเชื้อไวรัสเอชไอวีที่มีความรุนแรงของโรคมากกว่า จะมีภาวะทุพโภชนาการรุนแรงกว่า เมื่อเปรียบเทียบกับกลุ่มควบคุมพบว่าเด็กที่ติดเชื้อไวรัสเอชไอวีที่มีความรุนแรงของโรคใน Category C มี WGTT สั้นกว่าอย่างมีนัยสำคัญทางสถิติ (14.32 $\pm$ 3.88 และ 7.22 $\pm$ 3.17 ชม. ในกลุ่มควบคุม และกลุ่มทดลอง Category C ตามลำดับ) อย่างไรก็ตามไม่พบความแตกต่างทางสถิติระหว่างเด็กในกลุ่มควบคุมและกลุ่มทดลอง Category N, A หรือ B นอกจากนั้นยังพบว่าเด็กที่ติดเชื้อเอชไอวีที่มีภาวะทุพโภชนาการรุนแรงจะมี WGTT สั้น*

***สรุป**: ภาวะทุพโภชนาการมีความสัมพันธ์กับความรุนแรงของโรคเอดส์ เด็กที่ติดเชื้อไวรัสเอชไอวีที่มีอาการของโรคและภาวะทุพโภชนาการรุนแรงจะมี WGTT สั้นกว่า*