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Association Between Steatorrhea, Growth, and Immunologic Status in Children With Perinatally Acquired HIV Infection

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Objective: To examine the prevalence of steatorrhea and exocrine pancreatic insufficiency (EPI) and their association with growth and immune status variables in children with perinatally acquired human immunodeficiency virus (HIV) infection.

Design: Cross-sectional study.

Setting: Tertiary care HIV subspecialty practice.

Participants: Children with perinatally acquired HIV infection. Exclusion criteria included being younger than 1 year and receiving mineral oil as a medication.

Methods: Weight, height, and upper arm anthropometric variables were measured. Spot stool samples were analyzed for steatorrhea using the Sudan III qualitative test and for EPI using fecal elastase-1 enzyme assay. Hormone-stimulated pancreatic function testing and 72-hour stool and dietary fat sample collection were performed when fecal elastase-1 enzyme was in the range of EPI, defined as less than 200 µg/g. HIV RNA viral load, CD4 status, type of antiretroviral therapy, and biochemical evidence of hepatobiliary disease were measured within 3 months of stool sample collection. *z* Scores were computed for height, weight, triceps skinfold, and upper arm muscle area.

Results: We enrolled 44 patients (23 girls [52%]) with a mean ± SD age of 7.4 ± 3.1 years. None had hepatobiliary disease. The prevalence of steatorrhea was 39% (95% confidence interval, 23%-56%). The prevalence of EPI was 0% (95% confidence interval, 0%-9%). There were no associations between steatorrhea and EPI, growth, HIV RNA viral load, CD4 status, or type of antiretroviral therapy. Older children had decreased *z* scores for height ($r = -0.42$; $P = .006$).

Conclusions: The clinical significance of steatorrhea in children with HIV infection is unclear. Furthermore, its evaluation should focus on nonpancreas-based conditions. Continual close monitoring of growth is essential in children with HIV infection.

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STEATORRHEA, defined as malabsorbed fat in feces, is prevalent in adults with human immunodeficiency virus (HIV) infection even in the absence of gastrointestinal tract symptoms.[1] The prevalence and impact of steatorrhea on growth and nutritional status in children with perinatally acquired HIV infection is not well defined. Impaired growth in HIV infection has multifactorial origins ranging from inadequate energy (caloric) intake to nutrient malabsorption, inefficient utilization, and increased losses.[2] Because a goal of nutritional care in children with HIV infection is to achieve a positive energy balance and normal growth, knowledge of the prevalence of steatorrhea and its growth-related abnormalities can lead to optimized care. Pancreatic dysfunction has been suggested in children and adults with HIV infection.[3-8] The aim of this study was to examine the prevalence of steatorrhea and exocrine pancreatic insufficiency (EPI) in children with perinatally acquired HIV infection. The hypothesis was that a significant proportion of children with HIV infection and steatorrhea has EPI. If true, this would merit consideration of pancreatic enzyme therapy.

RESULTS

Of 65 children within the age range of interest, 44 (23 girls [52%]) enrolled in the study. Participants were aged 7.4 ± 3.1 years, and their growth characteristics were as follows: HAZ, −0.70 ± 1.36; WAZ, −0.40 ± 1.20; WHZ, −0.17 ± 1.34; TSFZ, −0.19 ± 0.65; and UAMAZ, −0.05 ± 1.23. None of the study patients had hepatobiliary disease. Reasons for nonparticipation included disinterest in the study (n = 14) and foster care (n = 7). Nonparticipants were aged 6.7 ± 4.0 years, and

PATIENTS AND METHODS

Patients were enrolled between June 1, 1998, and December 31, 1998, from the outpatient HIV subspecialty office practice or while hospitalized at The Children's Hospital of Philadelphia (Pa). Patients with perinatally acquired HIV infection[9] were eligible for enrollment. Exclusion criteria included (1) being younger than 1 year because of the normal infancy-related higher loss of dietary fat[10] and (2) receiving therapy with mineral oil stool softeners because of interference with interpretation of steatorrhea test results. Children in foster care were also excluded because of no immediately available guardian authorized to provide consent. Current antiretroviral therapy with nelfinavir (Agouron, La Jolla, Calif), a protease inhibitor associated with diarrhea, or didanosine (Bristol-Myers Squib, Princeton, NJ), a nucleoside analog associated with pancreatitis, or both was determined by reviewing the medical record. HIV RNA viral load, CD4 status, and biochemical evidence of hepatobiliary disease (defined as liver enzyme or bilirubin levels greater than the reference range) within 3 months of stool sample collection were documented from medical chart review and confirmed with the primary care team.

Qualitative steatorrhea was measured using the Sudan III qualitative fecal fat test, as described by Drumey et al,[11] on a sample of at least 5 g of stool. Screening for EPI was conducted using stool sample analysis with the fecal elastase-1 enzyme (FE-1) assay.[12-14] Patients with FE-1 levels in the range for EPI, defined as less than 200 µg/g, had confirmatory testing for EPI using the 72-hour stool and dietary fat sample collection[15] for quantitative steatorrhea and the hormone-stimulated pancreatic function test.[16] Informed consent was obtained before the study from the parent(s) or guardian(s), and assent was obtained from patients older than 6 years. The institutional review board at The Children's Hospital of Philadelphia approved the study.

CD4 STATUS AND HIV RNA VIRAL LOAD

CD4 counts obtained as part of routine outpatient clinical care visits were used for the analysis and were categorized as normal (≥25% of normal), moderately suppressed (15%-24% of normal), or severely suppressed (<15% of normal) based on reference ranges of age-specific CD4 counts.[17] HIV RNA viral load from blood samples obtained within 3 months of the date of stool sample collection was used for the analysis. Plasma HIV RNA levels were measured using the method of branched DNA signal amplification (r-nasba; Organon, Durham, NC).[18]

GROWTH ASSESSMENT

Height was measured using a stadiometer accurate to 0.1 cm (Holtain, Crymych, England). Weight was measured using a digital scale accurate to 0.1 kg (Scaltronix, White Plains, NJ). All measurements were taken with children in light clothing and shoeless. Middle upper arm circumference was measured using a nonstretchable plastic measuring tape. Triceps skinfold was measured using a skinfold caliper (Holtain). Both measurements were performed in triplicate on the right upper arm by one of us (T.A.S.) using a standard technique,[19] and the mean was used for analysis. Total upper arm muscle area was calculated from upper arm muscle circumference and triceps skinfold measurements.[20]

their growth characteristics were as follows: HAZ, −0.36 ± 1.28; WAZ, 0.08 ± 1.54; and WHZ, 0.23 ± 1.23 (not statistically significantly different from study patients). Two patients had chronic (>2 weeks) pathogen-negative diarrhea at the time of stool sample collection. One patient had *Mycobacterium avium-intracellulare* infection complicated by acute pancreatitis at the time of stool sample collection. Levels of HIV RNA ranged from less than 40 to 900 000 copies/mL. There were 11 patients with HIV RNA viral loads in the tertile range of less than 40 to 3000 copies/mL and 10 each with HIV RNA viral loads in the tertile ranges of 3001 to 30 000 and greater than 30 000 copies/mL. The CD4 status was normal in 17 patients (55%), moderately suppressed in 11 (35%), and severely suppressed in 3 (10%).

Thirty-three patients provided fecal specimens for analysis, and their clinical characteristics are shown in **Table 1**. The prevalence of steatorrhea by Sudan III qualitative stain was 39% (95% CI, 23%-56%). There were no significant associations between presence of steatorrhea and any of the growth variables (HAZ, WAZ, WHZ, TSFZ, and UAMAZ), HIV RNA viral load, and CD4 status (Table 1). No patient had both steatorrhea and decreased FE-1 levels in the range for EPI. Only 2 patients had FE-1 levels in the range for EPI. One was a 9-year-old girl with chronic pathogen-negative diarrhea (negative for *Giardia, Clostridium difficile, Cryptosporidium, Salmonella, Shigella, Yersinia, Campylobacter, Plesiomonas,* and *Aeromonas*), impaired growth (HAZ, −4.06; WAZ, −2.50; and WHZ, 0.38), and an FE-1 level of 174 µg/g. Her %CoA was 96% (normal, ≥93%). The hormone-stimulated pancreatic test results showed normal pancreatic enzyme and electrolyte output, and, therefore, EPI was excluded. The second patient was an 8-year-old boy with *Mycobacterium avium-intracellulare* infection complicated by acute pancreatitis with an FE-1 level of 170 µg/g. His FE-1 level after recovery from the *Mycobacterium avium-intracellulare* infection was normal (593 µg/g), and further testing for EPI was not performed. Therefore, in this sample of children with perinatally acquired HIV infection, the prevalence of EPI was 0% (95% CI, 0%-9%).

Older patients had significantly lower HAZ than younger patients (**Figure**). There was a significant trend for HAZ to decline with advancing chronological age ($r = -0.42$; $P = .006$). No similar trend was observed with the other growth variables: WAZ, $P = .2$; WHZ, $P = .3$; TSFZ, $P = .8$; and UAMAZ, $P = .5$.

COMMENT

In this sample of children with perinatally acquired HIV infection, steatorrhea was prevalent but had no consistent association with EPI, growth variables, HIV RNA vi-

STOOL STUDIES AND HORMONE-STIMULATED PANCREATIC FUNCTION TEST

Spot fecal specimens were collected, aliqouted, and stored at −70°C before measurement of qualitative steatorrhea and FE-1 analysis. Qualitative steatorrhea was assessed using the Sudan III qualitative stain[11] (Mayo Clinic Laboratories, Rochester, Minn), which is specific for detecting triglycerides and fatty acids in the stool matrix[21] and reliable for excluding steatorrhea.[22] The FE-1 content of the spot stool specimen was measured using enzyme-linked immunosorbent assay (ScheBo-Tech, Wettenberg, Germany). After age 1 month, normal FE-1 levels are greater than 200 µg/g. Thereafter, levels of 100 to 200 µg/g indicate moderate EPI. Levels less than 100 µg/g indicate severe EPI.[23,24] Fecal elastase-1 enzyme has high stability at room and cold storage temperatures[23] and has demonstrated high specificity (96%) and sensitivity (100%) for the detection of EPI in children with cystic fibrosis.[24]

Patients were admitted to the inpatient General Clinical Research Center at The Children's Hospital of Philadelphia for the 72-hour stool and dietary fat sample collections, which were performed while the patient consumed a diet containing 3 g of fat per kilogram of body weight (maximum, 100 g). Percent coefficient of fat absorption (%CoA) was calculated according to the following formula:

%CoA = [(Fat Intake [g] − Stool Fat [g]) / (Fat Intake [g])] × 100.

The normal range of %CoA is 93% or greater.[10] The stool analysis was conducted using the method of Jeejeebhoy et al[15] (Mayo Clinic Laboratories).

The hormone-stimulated pancreatic test was performed using a modified technique. After a 6-hour fast, a double-lumen nasoduodenal tube was inserted through the nose and positioned in the duodenum with fluoroscopic guidance. Pancreatic and duodenal secretions mixed with infused marker was aspirated by low-pressure suction before, during, and after infusing intravenous secretin and cholecystokinin at doses known to cause maximal pancreatic secretion (secretin, 0.033 µg/kg per dose, and cholecystokinin, 0.2 µg/kg per dose). No sedation was required.

STATISTICAL ANALYSIS

To compare growth of children of different sexes and ages, the weight, height, and upper arm anthropometry data are expressed in mean ± SD z scores. z Scores for height for age (HAZ), weight for age (WAZ), and weight for height (WHZ) were computed using an anthropometric software program (version 3.1; Division of Nutrition, Centers for Disease Control and Prevention, Atlanta, Ga). z Scores for triceps skinfold (TSFZ) and upper arm muscle area (UAMAZ) were computed using US reference data.[20] Patients were grouped according to HIV RNA viral load tertile ranges of less than 40 to 3000, 3001 to 30 000, and greater than 30 000 copies/mL. A descriptive analysis was performed to assess the prevalence and 95% confidence intervals (CIs) of steatorrhea and EPI. Differences in growth variables (WAZ, HAZ, WHZ, TSFZ, and UAMAZ) between patients with and without steatorrhea were examined using the t test. The χ^2 test was used to test associations between steatorrhea and HIV RNA viral load tertile and CD4 status (normal, moderately suppressed, and severely suppressed). Pearson correlation was used to examine associations between age and growth variables. Statistical significance was defined as $P \leq .05$. All analyses were performed using statistical software (Stata 5.0; Stata Corp, College Station, Tex).

ral load, CD4 status, or type of antiretroviral therapy. These findings suggest that steatorrhea, although prevalent in our sample, was of unclear clinical significance.

Steatorrhea from EPI occurs when pancreatic lipase output is less than 10% of normal.[25,26] Kapembwa et al[3] and Carroccio et al[5] independently reported an association among HIV infection, fat malabsorption, and pancreatic function. Using the ^{14}C-triolein breath test, Kapembwa et al[3] detected fat malabsorption in 48% of 25 adults with HIV infection. Further evaluation with the tyrosyl–*p*-aminobenzoic acid test (PABA) revealed that 3 patients (12%) had mild pancreatic insufficiency.[3] One of the 3 patients also had cryptosporidial enteritis, which may be associated with PABA malabsorption and therefore a false-positive test result for EPI. In the study by Carroccio et al,[5] 47 children with HIV infection were evaluated for steatorrhea and pancreatic function using the acid steatocrit test and the FE-1 and fecal chymotrypsin tests, respectively. Steatorrhea was detected in 25% of their sample, and the severity was inversely correlated with FE-1 levels (levels >200 µg/g inclusive). They found no correlation among FE-1 levels, clinical symptoms, immunologic variables, or nutritional status. In our study, confirmatory testing was pursued when FE-1 levels were in the range for EPI (**Table 2**). These findings suggested that in children with perinatally acquired HIV infection, FE-1 less than 200 µg/g without further confirmatory testing is inadequate for making the diagnosis of EPI.

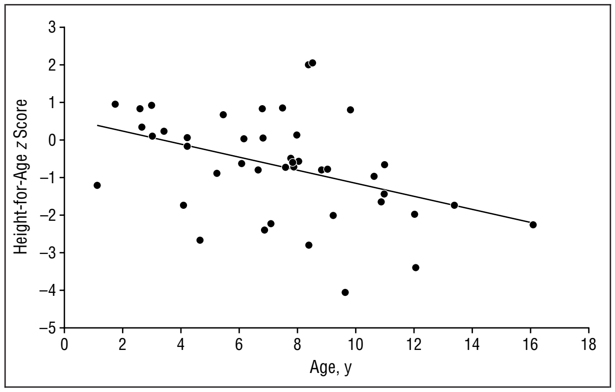
The Sudan qualitative fecal fat test is reliable for detecting quantitative steatorrhea in the range of 35 mmol or more (approximately 10 g) per 24 hours of stool,[22] and when the %CoA is less than 94%[11] (normal, ≥93%).[10] The absence of EPI and hepatobiliary disease in our sample of children with HIV infection implied that the qualitative steatorrhea had other causes, eg, small-bowel enteropathy and bacterial overgrowth. There is also the possibility that the qualitative test may have falsely classified some fecal samples as positive for steatorrhea.[11] Nonetheless, numerous investigators have similarly detected evidence of fat malabsorption in patients with HIV infection using the qualitative fecal fat test,[1,8] quantitative fecal fat test,[1,4] acid steatocrit test,[4,5,27] serum carotene level,[28] tyrosyl-PABA test,[3] and triolein breath test.[3,5] Partial jejunal villous atrophy can occur at any clinical stage of HIV infection and has been associated with fat malabsorption.[29] Altered lipid transport across the duodenal mucosa leading to fat malabsorption also has been reported with HIV infection.[30] The HIV itself is a primary enteric pathogen and may cause histological inflammation in the absence of other enteric pathogens.[31,32]

Fat malabsorption in HIV infection might not always be accompanied by clinical symptoms.[1,27] There was no consistent association between steatorrhea and im-

Table 1. Clinical Characteristics of 33 Patients Who Provided Fecal Specimens for Analysis*

	Qualitative Steatorrhea	
	Present (n = 14)	Absent (n = 19)
Age, mean ± SD, y	7.8 ± 3.1	7.7 ± 3.0
FE-1, mean ± SD, µg/g	631 ± 167	533 ± 170
CD4 status (n = 31)		
Normal	8	9
Moderate suppression	4	7
Severe suppression	2	1
HIV RNA viral load, copies/mL (n = 31)		
<40-3000	5	6
3001-30 000	5	5
>30 000	4	6
z Score, mean ± SD (n = 33)		
Height	–0.47 ± 1.04	–0.81 ± 1.63
Weight	–0.43 ± 0.86	–0.58 ± 1.27
Weight for height	–0.08 ± 1.01	–0.10 ± 1.06
Triceps skinfold	–0.38 ± 0.66	–0.02 ± 0.61
Upper arm muscle area	–0.11 ± 0.86	0.11 ± 1.62

Data are given as number of patients except where indicated otherwise. FE-1 indicates fecal elastase-1 enzyme; HIV, human immunodeficiency virus. No comparisons reached statistical significance.



Correlation between height-for-age z *score and age in children with perinatally acquired human immunodeficiency virus infection (*r *= –0.42,* P *= .006).*

Table 2. Test Results in 33 Patients Who Provided Fecal Specimens for Analysis*

	Patients, No. (%)
Negative FE-1 and negative qualitative fecal fat	18 (55)
Negative FE-1 and positive qualitative fecal fat	14 (42)
Positive FE-1 and negative qualitative fecal fat	1 (3)
Positive FE-1 and positive qualitative fecal fat	0
Pancreatic stimulation test and quantitative steatorrhea	1 (3)

FE-1 indicates fecal elastase-1 enzyme.

paired growth in our sample of children with HIV infection. Mean *z* scores for height and weight were less than zero, thereby documenting that growth was generally impaired compared with the National Center for Health Statistics reference population.[33] There was a significant trend of declining HAZ with advancing chronological age, but a similar trend was not observed with WAZ, WHZ, TSFZ, and UAMAZ. The decline in HAZ with advancing chronological age in study patients was not explained by delayed pubertal growth because most patients (>90%) were younger than the average age for progression into puberty. Two possible explanations for this significant trend are (1) a direct impact of chronic HIV infection on growth, leading to a cumulative decline in HAZ as infected children get older, or (2) unavailability of highly active antiretroviral therapy (HAART) during infancy and early childhood in patients born before 1996.[34] In general, patients with decreased HAZ were older children born before HAART become widely available.[34] Therefore, less effective control of HIV viral load during the critical growth periods of infancy and early childhood may have contributed to stunted growth patterns. Conversely, better control of HIV viral load using HAART initiated early in infancy may have led to a decreased impact of the disease on the linear growth patterns of patients born after 1996. Therefore, availability and use of HAART may be heralding a positive change from the impaired growth patterns and devastating clinical manifestations previously commonly observed in children with perinatally acquired HIV infection.

The main limitations of this study are related to its cross-sectional design. The duration and impact of steatorrhea on individual growth patterns was not specifically examined. The degree of steatorrhea was also not quantified; however, a positive Sudan III qualitative fecal fat test result generally corresponds to a %CoA of less than 94%[11] and quantitative steatorrhea in the range of 4 or more to 10 g of stool fat per 24 hours.[22] These data suggest that although the Sudan III qualitative test provides convenient, rapid, and noninvasive screening, a positive result represents broad ranges of quantitative steatorrhea. Therefore, the wide sensitivity range of the Sudan III qualitative test may have limited our ability to detect any associations between steatorrhea and growth patterns in this sample of children with perinatally acquired HIV infection. Finally, inferring a trend of impaired linear growth with advancing chronological age using cross-sectional data, and in the absence of information about genetic input to linear growth (biological parental heights) has limitations. Nonetheless, comparisons with the National Center for Health Statistics reference data indicated that the linear growth in this sample of children with perinatally acquired HIV infection was decreased.

In conclusion, in this sample of children with perinatally acquired HIV infection, there was a high prevalence of steatorrhea (39%) that was neither secondary to EPI nor consistently associated with impaired growth, HIV RNA viral load, CD4 status, or type of antiretroviral therapy. Therefore, the clinical significance of steatorrhea in children with HIV infection is unclear. Furthermore, its evaluation should focus on nonpancreatic-based causes. Even with improved HAART, continual close monitoring of growth is essential for optimal care of children with HIV infection.

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