Both Exocrine Pancreatic Insufficiency and Signs of Pancreatic Inflammation Are Prevalent in Children with Complicated Severe Acute Malnutrition: An Observational Study

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Objectives To assess whether pancreatic function is impaired in children with severe acute malnutrition, is different between edematous vs nonedematous malnutrition, and improves by nutritional rehabilitation.

Study design We followed 89 children with severe acute malnutrition admitted to Queen Elizabeth Central Hospital in Blantyre, Malawi. Stool and blood samples were taken on admission and 3 days after initial stabilization to determine exocrine pancreatic function via fecal elastase-1 (FE-1) and serum trypsinogen and amylase levels.

Results A total of 33 children (37.1%) had nonedematous severe acute malnutrition, whereas 56 (62.9%) had edematous severe acute malnutrition. On admission, 92% of patients showed evidence of pancreatic insufficiency as measured by FE-1 <200 μg/g of stool. Patients with edematous severe acute malnutrition were more likely to have low FE-1 (98% vs 82.8%, $P = .026$). FE-1 levels remained low in these individuals throughout the assessment period. Serum trypsinogen was elevated (>57 ng/mL) in 28% and amylase in 21% (>110 U/L) of children, suggesting pancreatic inflammation.

Conclusion Exocrine pancreatic insufficiency is prevalent in children with severe acute malnutrition and especially in children with edematous severe acute malnutrition. In addition, biochemical signs suggestive of pancreatitis are common in children with severe acute malnutrition. These results have implications for standard rehabilitation treatment of children with severe acute malnutrition who may benefit from pancreatic enzyme replacement therapy. *(J Pediatr 2016;174:165-70)*.

Trial registration ISRCTN.com: 13916953.

Despite a decrease during the last decade, the rates of mortality in children in general but also in those with severe acute malnutrition remain high, with up to 47% of deaths in children younger than 5 years of age occurring in Sub-Saharan Africa.[1,2] In low-income countries affected by HIV/AIDS and tuberculosis like Malawi, however, case fatality rates in children with severe acute malnutrition remain high, and tackling them is an international priority.[3] An estimated 45% of deaths worldwide are attributable to undernutrition, defined as a weight for height ≤−2 SD from the norm,[4,5] despite protocolized treatment as determined by the World Health Organization (WHO).[6-8]

Diarrhea commonly is found in children with severe acute malnutrition and is associated with increased risk of death.[9-11] The broad etiologies of diarrhea in severe acute malnutrition include enteropathy related to malabsorption leading to osmotic diarrhea and infectious secretory diarrhea.[12] Extraintestinal factors such as changes in bile acid excretion or exocrine pancreatic function have not been well studied in the etiology of diarrhea in severe acute malnutrition.

Previous studies have suggested that severely malnourished children may suffer from exocrine pancreatic insufficiency (EPI).[13-24] EPI is defined as a lack of digestive enzyme production; this in turn leads to impaired weight gain and growth as the result of protein and lipid malabsorption.[25-28] In children with cystic fibrosis (CF), pancreatic function is an important predictor of long-term survival.[29]

Nearly all studies on pancreatic (dys-) function in malnourished children were conducted in the 1940s through 1980s in small groups of children.[13-15] These studies showed that malnourished children had reduced pancreatic enzymatic output compared with reference ranges,[16,17,20] with evidence that pancreatic function recovered after refeeding.[14,16,17,30] Autopsy studies on children with malnutrition describe a combination of pancreatic atrophy and loss of zymogen-secreting pancreatic acinar cells in severe acute malnutrition.[17-20,31-33]

CF	Cystic fibrosis
EPI	Exocrine pancreatic insufficiency
FE-1	Fecal elastase-1
NRU	Nutritional Rehabilitation Unit
WHO	World Health Organization

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Since these studies, the assessment of pancreatic function has advanced and warrants reassessment.

The current diagnosis of EPI relies on "direct" or "indirect tests" of exocrine pancreatic function.[34] Direct tests are expensive and invasive, which limits their use in children and in low-resource settings or routine clinical practice.[35] More feasible tests are indirect test via the measurement of pancreatic enzymes in serum (trypsinogen, amylase), in stool (fecal elastase-1 [FE-1], fecal chymotrypsin), or the detection of C^{13}-mixed-triglyceride in a breath test.[34] FE-1 is a clinically validated marker with good specificity and sensitivity to diagnose severe EPI and currently is recommended as a screening tool of EPI.[34,36,37] The role of trypsinogen in detecting pancreatic insufficiency is valuable in the assessment of pancreatic function in patients with CF.[38,39] Both serum trypsinogen and amylase levels are released by damaged pancreatic cells and are therefore used as a marker of pancreatitis.[40,41] Their use in diagnosing EPI is limited by their low sensitivity and specificity.[34]

The aim of this study was to assess pancreatic function in children with severe acute malnutrition. We hypothesized that pancreatic function in children with severe acute malnutrition, as assessed by FE-1 and serum trypsinogen and amylase levels, is impaired, correlates to clinical outcomes of duration of hospital stay and number of days from admission to clinical stabilization, differs between edematous vs nonedematous malnutrition, and improves during nutritional rehabilitation.

Methods

This observational study was completed within the framework of a nutrient prospective intervention trial (ISRCTN 13916953). This "TranSAM Study" was conducted at the MOYO Nutritional Rehabilitation Unit (NRU) of the Pediatric Department at Queen Elizabeth Central Hospital in Blantyre, Malawi. Sample size calculations were originally based on numbers needed to assess the primary outcome of the TranSAM study (carbohydrate malabsorption). The TranSAM study aimed to determine whether the use of transition-phase diets with different carbohydrate contents affected fecal pH, duration of stay in the hospital, and other clinical outcomes in severely malnourished children. For the TranSAM study, children were assigned randomly to treatment with either F75 + ready-to-use therapeutic foods, ready-to-use therapeutic foods only, or F100 after "clinical stabilization" (absence of acute life-threatening conditions, return of appetite, improvement of gastrointestinal losses and edema, and absence of WHO "danger signs", eg, severe respiratory distress, severe dehydration, and convulsions). Accounting for contingencies, we aimed to recruit a total of 108 patients to detect a 20% difference in primary outcome with $\alpha = 0.05$ and 80% power based on previous findings.[42] The study was approved by the Malawi College of Medicine Research and Ethics Committee and carried out according to Good Clinical Practice guidelines which are based on the Declaration of Helsinki.[43]

Children with severe acute malnutrition admitted to the NRU (n = 509) were screened for recruitment. Informed consent was obtained from parents or guardians by verbal and printed explanations in Chichewa, the main local language in Malawi, or English with witnessed consent by signature or by thumbprint for those unable to write.

Inclusion criteria were as follows: children aged 6-60 months admitted with a diagnosis of severe acute malnutrition as defined by WHO by a weight-for-height of less than –3 SD and/or a mid-upper arm circumference of less than 115 mm (nonedematous malnutrition) and/or presence of bilateral edema (edematous malnutrition).[44] Both HIV-positive and -negative children were included. We excluded children who were previously admitted to the NRU within the year or presented with severe hemodynamic instability, a hematocrit level of ≤15%, or severe neurological symptoms. After admission, children were treated according to guidelines established by WHO.[6]

All children admitted to the MOYO NRU had a thick blood film examined for parasitemia (malaria) and a hematocrit count performed. HIV antibody test was offered with appropriate pre- and postcounseling. After initial anthropometry, the following clinical data were collected daily: weight, stool frequency and consistency, number of days until clinical stabilization, and duration of hospital stay. Blood was collected at admission and stool collected on admission and three days after initial clinical stabilization. On collection, stool samples were immediately homogenized and frozen at −80°C until further analysis.

Diarrhea was defined according to WHO standards (3 or more loose or watery stools in the past 24 hours).[45] Severe diarrhea was defined as 10 or more loose or watery stools in the past 24 hours. Information about stool frequency, consistency, and (severe) diarrhea was obtained from the mother or guardian through verbal recall.

Laboratory Analyses

FE-1 levels were determined with the use of an enzyme-linked immune assay at the clinical laboratory of the University Medical Center Groningen, the Netherlands. The same procedures were applied to watery and nonwatery stool. In accordance with standard practice, EPI was defined as FE-1 levels below 200 μg/g of stool and severe EPI as FE-1 levels below 100 μg/g of stool.[36,46] Serum trypsinogen concentrations were determined in a random subset of patients (n = 39) by the clinical laboratory of the Hospital for Sick Children, Toronto, Canada, with the use of a radioimmunoassay as described previously.[47] For this study, reference values for normal trypsinogen levels were 10-57 ng/mL (Hospital for Sick Children, Toronto, Canada). Serum pancreatic amylase concentrations were determined in 80 patients by enzyme-linked immune assay (Abcam, Cambridge, United Kingdom). The upper limit of normal was set at 110 U/l.

Statistical Analyses

Data were collected on standardized forms and analyzed with IBM SPSS Statistics Version 22.0.0.0 Software (IBM