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Natural History of Intestinal Microsporidiosis among Patients Infected with Human Immunodeficiency Virus

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A chart review of 73 human immunodeficiency virus (HIV)-infected patients with enteric microsporidiosis was conducted to define the natural history of microsporidiosis. A substantial proportion of patients remained symptomatic after 6 months (54.8% with persistent diarrhea and 51.2% with weight loss). Predictors for persistent diarrhea included high HIV RNA viral load and no initiation of protease inhibitor therapy.

Two microsporidia (*Enterocytozoon bieneusi* and *Encephalitozoon intestinalis*) have been identified as possible causes of diarrheal illness in human immunodeficiency virus (HIV)-infected patients. However, despite numerous clinical descriptions of patients with symptomatic gastrointestinal disease attributed to enteric microsporidiosis, studies have concluded that enteric microsporidia have limited pathogenicity (2, 6, 7). To better describe the presentation and clinical course of patients with enteric microsporidiosis, a retrospective chart review of patients with enteric microsporidiosis was conducted through a nationwide survey of the National Institutes of Health-sponsored AIDS Clinical Trials Group sites.

HIV-infected patients with a stool specimen positive for microsporidia between 29 January 1993 and 8 August 1997 at the Medical Center of Louisiana at New Orleans (MCLNO) ($n = 47$), San Francisco General Hospital (San Francisco, California) ($n = 15$), Cook County General Hospital (Chicago, Illinois) ($n = 8$), or State University of New York (Buffalo, New York) ($n = 3$) were eligible for this study. Stool specimens were examined for microsporidia at the clinical laboratory of each hospital, using a modified trichrome (chromotrope 2R) stain. Routine ova and parasite examinations to evaluate for other parasitic infections and screening for enteric infections caused by bacteria such as *Aeromonas*, *Plesiomonas*, *Campylobacter*, *Yersinia*, *Salmonella*, and *Shigella* were performed at all sites. In addition, bloody stools were tested for *Escherichia coli* O15H7 at the MCLNO and San Francisco sites. Specimens submitted to MCLNO were transported to the Tulane Regional Primate Research Center for secondary identification of microsporidia, using a fluorescent stain (Calcofluor 2MR white) to screen for microsporidia, followed by a modified trichrome stain for corroboration (3). Species identification was unavailable for all specimens.

Medical records of eligible patients were retrospectively abstracted 6 weeks after the first positive stool specimen (baseline data) and 6 months after the index stool specimen until death or study termination. Persistent diarrhea was defined as continued or worsening diarrhea within 6 months after initial diagnosis, as per the provider's progress notes. Weight loss was defined as a loss of ≥10% of baseline body weight within 6 months of primary diagnosis. Statistical testing for categorical variables included Fisher's exact test and chi-square analysis. Nonparametric median testing and analysis of variance were utilized for continuous variables.

The cohort was predominantly male (89.1%), between the ages of 30 and 40 years (57.1%), and of Caucasian or African American origin (42.5 and 46.5%, respectively). Most (57.4%) had a CD4 cell count at diagnosis of less than 50 cells/dl and a viral load of greater than 10,000 copies/ml (79.1%). Nine patients had stool specimens positive for other pathogens during follow-up. These pathogens included *Cryptosporidium* spp., *Giardia lamblia*, *Campylobacter*, *Entamoeba histolytica* or *Entamoeba dispar*, and *Blastocystis hominus*. Testing to distinguish between *E. histolytica* and *E. dispar* was not performed. Three patients had microsporidia identified from additional specimens (conjunctival swab, sinus aspirate, or clean-catch urine specimen). These patients also had positive stool specimens.

Forty-three (58.9%) of the 73 patients had 6 months of follow-up. There were no significant baseline demographic or clinical differences between the patients with 6 months of fol-

TABLE 1. Clinical characteristics associated with persistent diarrhea after 6 months of follow-up

Clinical characteristic	Persistent diarrhea after 6 mo ($n = 23$)	No diarrhea after 6 mo ($n = 19$)
Mean no. of stools/day at diagnosis (SE)	5.6 (±1.0)	3.6 (±0.6)
Mean no. of stool specimens submitted after diagnosis (SE)	2.4 (±0.3)	1.2 (±0.5)
CD4 cell count of ≤50 cells/dl	60.0%	60.0%
Median viral load (no. of copies/ml)	63,863	9,360[d]
History of opportunistic process	60.9%	66.7%
ARV[a] use at diagnosis	52.2%	63.2%
ARV use after diagnosis	73.9%	84.2%
PI[b] use after diagnosis	21.7%	52.6%[d]
Albendazole use at diagnosis	8.7%	10.5%
Antidiarrheal use at diagnosis	78.3%	47.4%
Morphine use at diagnosis	8.7%	15.8%
Narcotic[c] use at diagnosis	17.4%	26.3%

[a] ARV, antiretroviral therapy (includes protease inhibitor and non-protease inhibitor regimens).
[b] PI, protease inhibitor therapy.
[c] Not inclusive of morphine or antidiarrheal agents described in the text.
[d] Statistically significantly different from the values for persistent diarrhea ($P < 0.05$ by Fisher's exact test or by the nonparametric median test).

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TABLE 2. Clinical characteristics associated with weight loss of ≥10% of body weight among patients with microsporidiosis

Clinical characteristic	Wt loss of ≥10% of body wt after 6 mo (n = 10)	Wt loss of <10% of body wt after 6 mo (n = 33)
Mean no. of stool specimens submitted after diagnosis (SE)	3.3 (±0.9)	0.9 (±0.2)[c]
Diarrhea after 6 mo of follow-up	66.7%	51.5%
CD4 cell count of ≤50 cells/dl	87.5%	53.6%
Median viral load	15,214	28,198
History of opportunistic process	40.0%	34.4%
ARV[a] use at diagnosis	30.0%	66.7%[c]
ARV use after diagnosis	60.0%	84.8%
PI[b] use after diagnosis	30.0%	39.4%
Albendazole use at diagnosis	10.5%	9.1%
Antidiarrheal use at diagnosis	80.0%	60.6%
Narcotic use at diagnosis (probable use, diarrhea)	30.0%	6.1%
Narcotic use at diagnosis (probable use, pain)	30.0%	18.2%

[a] ARV, antiretroviral therapy (includes protease inhibitor and non-protease inhibitor regimens).
[b] PI, protease inhibitor therapy.
[c] Statistically significantly different from the values for weight loss of ≥10% ($P < 0.05$ by Fisher's exact test or by analysis of variance).

low-up and those with 6 weeks of follow-up. Twelve of the 43 patients followed died during follow-up.

The most commonly reported symptoms at diagnosis were anorexia (52.2%), cramping (56.5%), and diarrhea (100%), with a mean of 6.2 stools per day (standard error, ±1.2). After 6 months of follow-up, fewer patients reported diarrhea (54.8%) and cramping (35.5%) ($P < 0.15$). Despite the significant reduction in reporting of diarrhea at 6 months, a relatively high proportion of patients reported continued or worsening diarrhea and the median number of stools at 6 months for the 43 patients was 5 (standard error, ±0.9). Seven of the nine patients with concomitant infection experienced chronic diarrhea.

Patients with persistent diarrhea had a higher median HIV RNA viral load ($P < 0.05$) (Table 1). Patients with chronic diarrhea were also significantly less likely to have received a protease inhibitor as a part of their antiretroviral therapy ($P < 0.05$) (Table 1). Of those receiving a protease inhibitor, 15 patients initiated protease inhibitor therapy within 2 months after initial diagnosis. Of these, five (33.3%) reported persistent diarrhea. Four patients received albendazole therapy at the time of diagnosis of microsporidiosis. Of these four patients, two reported no further diarrhea and two reported persisting diarrhea (Table 1).

Twenty-two (51.2%) of the 43 patients monitored for 6 months experienced weight loss between 1 and 12 kg. Ten (23.3%) of these patients experienced weight loss of ≥10% of baseline body weight. Patients experiencing weight loss were more likely to have a CD4 cell count of ≤50 cells/dl (Table 2). Although there was a similar pattern of usage of protease inhibitor therapy, patients experiencing weight loss were less likely to have had any antiretroviral therapy prescribed at diagnosis or during follow-up ($P < 0.10$) (Table 2).

Several caveats to this study should be noted. There was not a control cohort. Additionally, study patients were not tested for all causes of diarrhea. Information is limited to that which is reported in the patient's chart. Also, the small sample size (n = 43) limited the power to test statistical associations. Finally, only those who survived for 6 months of follow-up could be included in the analysis.

Although other factors, including a concurrent enteric infection may have contributed to the diarrhea and weight loss, this study confirms that patients with enteric microsporidiosis can have symptoms and have persistent symptoms. Patients infected with microsporidia at highest risk for poor outcomes are those with uncontrolled HIV viremia and low CD4 cell counts.

Protease inhibitor therapy use was significantly associated with no persistent diarrhea (Table 1). In other prior studies, most patients with chronic enteric microsporidiosis who were initiated on potent antiretroviral therapy reported no further diarrhea (1, 4, 5). It is probable that administration of potent therapy may be effective in controlling HIV viremia, allowing immune restoration and resolution of intestinal infection. With the lack of an effective treatment against *Enterocytozoon bieneusi*, clinicians should be strongly encouraged to optimize antiretroviral therapy to avoid a poor outcome.

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