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Microsporidiosis: Not just in AIDS patients

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Abstract

Purpose of review—Microsporidia emerged as causes of opportunistic infections associated with diarrhea and wasting in AIDS patients. This review describes recent reports of microsporidiosis in HIV-infected individuals and the growing awareness of microsporidiosis in non-HIV-infected populations.

Recent findings—Microsporidia were only rarely recognized as causes of disease in humans until the AIDS pandemic. Implementation of combination antiretroviral therapy (cART) to curtail HIV replication and restore immune status drastically reduced the occurrence of opportunistic infections, including those due to microsporidia, in HIV-infected individuals. In developing countries where cART is not always accessible, microsporidiosis continues to be problematic. Improvement of diagnostic methods over the previous 25 years led to identification of several new species of microsporidia, many of which disseminate from enteric to systemic sites of infection and contribute to some unexpected lesions. Among non-HIV-infected but immune suppressed individuals, microsporidia have infected organ transplant recipients, children, the elderly, and patients with malignant disease and diabetes. In otherwise healthy immune competent HIV seronegative populations, self-limiting diarrhea occurred in travelers and as a result from a foodborne outbreak associated with contaminated cucumbers. Keratitis due to microsporidosis has become problematic and a recent longitudinal evaluation demonstrated that non-HIV-infected individuals seropositive for microsporidia who had no clinical signs continued to intermittently shed organisms in feces and urine.

Summary—Greater awareness and implementation of better diagnostic methods are demonstrating that microsporidia contribute to a wide range of clinical syndromes in HIV-infected and non-HIV-infected group of people. As such, microsporidia should be considered in differential diagnoses if no other etiology can be defined.

Keywords

microsporidia; opportunistic infection; emerging infection; diarrhea

Introduction

Over the previous 150 years, microsporidia were known for their impact on commercially-important insects (e.g. silkworms, honey bees), fish (e.g. salmon), farm animals, and companion pets. During the past 25 years, opportunistic infections due to newly-identified

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species of microsporidia came to be recognized in persons with AIDS, predominantly associated with wasting and diarrhea. Microsporidiosis is being recognized in both immune-competent and immune-deficient groups of people including travelers, children, organ transplant recipients, cancer patients, diabetics, and the elderly [1].

Microsporidia are obligate intracellular unicellular eukaryotic parasitic protists related to fungi that have a unique mechanism of host cell infection. The infectious stage, or spore, contains a coiled polar tube, also called a polar filament that everts under appropriate conditions (change in pH or osmotic pressure) and essentially injects the spore cytoplasm through the polar filament into the host cell [2*]. Recent studies of the extent of gene compaction and reduction have suggested that the microsporidia are highly efficient parasites and excellent model systems for studies on evolution [3*, 4**, 5*].

Transmission is believed to occur primarily through fecal-oral routes with sources of infection including other infected humans and animals, as wells as contaminated water and food [1]. Human pathogenic microsporidia such as *E. bieneusi*, *E.hellem* and *E. intestinalis*, were recently detected in municipal wastewaters in Ireland at levels that correlated with elevated temperatures peaking in April and July [6**]. Of public health concern was the detection of spores in effluents and biosolids that are spread back into the environment to potentially infect animals and humans. Recently, a gastrointestinal foodborne outbreak due to microsporidia was attributed to contaminated cucumbers eaten by visitors to a hotel in Sweden [7**]. Microsporidiosis may also result from direct contact to broken skin or eyes, trauma, and sexual transmission [1]. Although transplacental (vertical) transmission has been reported in nonhuman primates and a wide range of other mammals, this has not yet been documented in humans.

The purpose of this review is to provide an overview with an emphasis on reports of microsporidiosis in HIV-infected and non-HIV-infected individuals published during the previous two years.

Microsporidiosis and the AIDS Pandemic

Prior to the AIDS pandemic, microsporidia were only rarely identified in humans. In 1985, a report was published identifying a new microsporidian, *Enterocytozoon bieneusi* in a Haitian AIDS patient with diarrhea and wasting [8] and this species is still considered the most prevalent microsporidian species infecting HIV-infected individuals. Nearly 100 genotypes of *E. bieneusi* have been identified among which some infect only humans, only animals, or both humans and animals, spurring some to suggest that these genotypes may actually represent a group of species [9]. The *Encephalitozoon* species, *E. intestinalis, E. hellem*, and *E. cuniculi,* also are commonly identified in humans (with or without concurrent HIV-infection), and a total of 14 species of microsporidia have been detected in humans (Table 1). Prevalence rates for enteric microsporidiosis in persons with HIV-infections prior to the implementation of cART ranged from 2 – 50% based on geography, method of detection, and experience of diagnostician with an overall estimate of approximately15% [10]. It is difficult to estimate the prevalence of systemic microsporidosis because clinical signs are non-specific or absent, and microsporidia are often not considered in the differential diagnoses.

Early reports of microsporidiosis in HIV-infected individuals were primarily associated with diarrhea and wasting, with *E. bieneusi* and *E. intestinalis* the predominant species infecting villus epithelial cells of the small intestine (primarily jejunum and duodenum). A cause and effect between microsporidiosis and diarrhea was reasonably well-accepted but was complicated by concerns about the direct effect of HIV itself, declining immune status, and the presence of other intestinal pathogens on the intestinal mucosa. Intestinal biopsies from

AIDS patients and microsporidia as the only detectable enteric pathogen exhibited partial villus atrophy and crypt hyperplasia whereas AIDS patients with no detectable enteric pathogens did not display these changes [11]. Similar to *Cryptosporidium*, microsporidiosis reduced mucosal surface area and contributed to malabsorption as expressed by reduced serum concentration of D-xylose after oral dose testing as well as decreased absorption of mannitol.

The *Encephalitozoon* species contribute to enteric disease but also have a propensity to disseminate [12]. Virtually all organs can be infected with *Encephalitozoon* species or the less common species described in the Table 1. Among clinical syndromes associated with disseminated microsporidiosis are encephalitis, keratoconjunctivitis, sinusitis, pneumonia, myositis, peritonitis, nephritis, and hepatitis [11].

Treatment of HIV-infected patients with cART resulted in a dramatic decline in opportunistic infections, including those due to microsporidia, in great part due to the partial restoration of cell-mediated immunity via HIV reduction. Microsporidiosis associated with diarrhea and wasting, however, continues to be problematic in areas of the world where access to cART may be limited as recently reported from Russia [13*], Malaysia [14], Thailand [15, 16], India [17], Republic of Congo [18], and West Ethiopia [19]. Children with concurrent HIV and *E. bieneusi* co-infection with diarrhea living in Uganda, exhibited lower rates of weight gain that was even more pronounced when also infected with *Cryptosporidium* [20]. An HIV-infected newborn with microsporidia and *Cryptosporidia* co-infection was presumably infected from contact with the mother who had diarrhea but who refused fecal diagnostic evaluation, so it was unclear if the microsporidia infection was transmitted from breast milk, fecal contamination, or transplacentally [21*]. In HIV-infected children living in a Thai orphanage who received cART, diarrhea due to *E. bieneusi* infection tended to be self-limiting, although re-infections were reported [22]. To date, only one case of microsporidiosis associated with immune reconstitution inflammatory syndrome (IRIS) has been described in an HIV patient presenting with diffusely distributed peritoneal and small bowel granulomatous nodules associated with *E. bieneusi* and *E. intestinalis* infection [23].

Microsporidiosis in non-HIV-infected populations

The etiologic agent in nearly 50% of diarrhea cases is undetermined, and it is likely that microsporidia may contribute since these infections are difficult to diagnose or methods to deliberately look for microsporidia are not applied. Furthermore, several species of microsporidia cause systemic infections with a broad range of clinical syndromes and often are overlooked or not considered for diagnosis. Studies in laboratory animals infected with species that naturally infect both humans and the laboratory animals under investigation (e.g. *E. cuniculi*) demonstrated that infections could occur through horizontal (fecal-oral or trauma) and vertical (mother-offspring) modes of transmission [1]. Clinical signs of disease often occurred during the acute stage of infection that resolved even though infections persisted for the life of these animals unless treated [1]. This raised questions about conditions in addition to HIV infection, under which microsporidia cause disease in humans, whether otherwise healthy individuals carry persistent infections that reactivate under conditions of immune-compromise, and whether these asymptomatic carriers also may transmit infections to those at risk. Among persons not infected with HIV, microsporidiosis is being detected world-wide, although economic status may influence incidence in specific regions. A study correlating lack of sanitation and exposure to contaminated water and infected animals demonstrated that economic wealth was protective against microsporidia infection [24*]. Microsporidia are consistently detected in drinking and recreational water sources [25*] and the recent foodborne outbreak associated with ingesting cucumbers [7**]

further support inclusion of microsporidia on the NIH/CDC biodefense category B list of pathogens of concern for water-borne and food-borne transmission.

Among immune-suppressed individuals, opportunistic infections due to microsporidia were increasingly reported in solid organ transplant recipients during the past 2 years. In a report by Champion et al. [26**], ten renal transplant recipients with intestinal *E. bieneusi* infections presented with abdominal pain, weight loss, and afebrile diarrhea beginning 2 to 168 weeks (median = 58 weeks) after transplantation and lasing 1 to 40 weeks (median = 2 weeks). Treatment with fumagillin relieved these symptoms and reduced (or cleared) parasite shedding in feces, but reversible thrombocytopenia was observed in some cases. A disseminated infection due to a new genotype of *E. cuniculi* (type IV with five 5′GTTT-3′ repeats in the ITS region of the rDNA) also was reported in a renal transplant recipient [27*]. This patient presented with intermittent fever and evidence of microsporidia in urine, sputum, and kidney biopsy (but not in stool, CSF, duodenal biopsy or blood) by PCR and histochemical staining. Albendazole treatment resolved the fever and cleared parasite shedding in urine. Disseminated *E. cuniculi* infections were reported post-mortem in two allogeneic hematopoietic stem cell transplant (SCT) recipients, and more recently, a third report was published about an allogeneic SCT recipient who was diagnosed with *E. cuniculi* in bronchoalveolar lavage cells and successfully treated with albendazole [28*]. The first opportunistic enteric *E. bieneusi* infections in renal transplant recipients in Spain were also published that included a review of the literature highlighting the growing number of enteric and disseminated opportunistic infections in patients undergoing transplantation with kidney, liver, heart, lung, bone marrow and cornea [29**].

Opportunistic microsporidiosis also occurred in the elderly, in patients with malignant disease undergoing chemotherapy, and diabetics [30, 31*, 32**]. An unusual case of a vocal cord infection due to the microsporidian, *Anncaliia* (syn. *Nosema, Brachiola*) *algerae* was described in a 69-year-old chronic lymphocytic leukemia patient [33*]. *A. algerae* primarily infects mosquitoes and this finding suggests that vectorborne transmission of microsporidiosis is possible. A patient with diabetes and a history of myocardial infarction and hypertension was reported with a brain abscess due to *Streptococcus intermedius* and *E. cuniculi* genotype I [34*], and endocarditis associated with *E. cuniculi* was reported in a patient whose pacemaker had been replaced 3 months earlier [35]. As awareness grows and diagnostic methods are applied to deliberately examine immune compromised individuals for microsporidia, it is expected that the number of case reports of opportunistic microsporidioses in such patients will continue to increase. While it is probable that many of these infections resulted from exposure to contaminated water, food, and aerosols, a question remains whether these infections may be transmitted from the donor organ or whether reactivated chronic infections developed that were not detected prior to transplantation, immunosuppressive treatment, or onset of diabetes.

Enteric microsporidiosis was detected in young children below the age of 60 months, and particularly during the ages of 18–24 months when they engage in somewhat independent activities but have not yet developed good hygienic practices [22]. A longitudinal study in a Thai orphanage identified *E. bieneusi* in fecal specimens by PCR in 18.2% of HIV-infected given cART treatment and 13.2% of non-HIV-infected children. Diarrhea tended to be self-limiting in both groups and infections occurred with higher incidence during the rainy month season.

The eye is an immunologically-privileged site and infections due to microsporidia in HIV-infected and non-HIV-infected can be manifested as punctuate keratoconjunctivitis and stromal keratitis [36*]. *Encephalitozoon* species are the more common cause of microsporidial keratoconjunctivitis in HIV-infected and non-HIV-infected individuals,

although cases due to *Vittaforma corneae* (syn. *Nosema corneum*) were recently reported [36*, 37]. Microsporidial stromal keratitis occurs less often than conjunctivitis, is typically identified in otherwise immunecompetent individuals, and has been caused by infections with *Vittaforma corneae, Nosema* species and *Trachipleistophora* species. Risk factors, in addition to HIV infection, included use of contact lenses, long-term topical corticosteroid treatment, and exposure to muddy (contaminated) water. Trauma or wounding has been associated with microsporidial stromal keratitis, and ocular infections have occurred as a consequence of systemic infection and secondary spread to the eye via contact. As reported in children, presentation with ocular infections due to microsporidia occurred more frequently during the rainy season. It has been speculated that ocular microsporidiosis probably have been overlooked because this clinical presentation mimics herpes simplex virus and adenovirus infections of the eye [37*].

Travelers to the tropics were among the first groups of individuals without concurrent HIV infection identified with enteric microsporidiosis due to *E. bieneusi* or *Encephalitozoon* species. In these otherwise healthy immune-competent patients, diarrhea tended to be self-limiting and lasting 3 – 6 weeks [1, 12]. A number of these travelers were treated symptomatically with albendazole which resolved diarrhea and cleared infections due to *Encephalitozoon* species (i.e. spore shedding in feces ceased). Albendazole treatment however, was not effective for, and did not directly clear infections due to *E. bieneusi* infection. Also, *E. bieneusi* spore shedding continued intermittently after symptoms resolved, suggesting a transient correlation between spore shedding and diarrhea such that symptoms occurred primarily during the acute stage of infection [38]. Recently, a missionary from Mozambique with abdominal pain and frequent bowel movements due to chronic microsporidiosis was reported. Metronidazole treatment for giardiasis did not completely resolve symptoms. Subsequently, microsporidia spores consistent in size for *Encephalitozoon* were later identified in fecal specimens, and albendazole treatment led to complete recovery [39*].

Unapparent microsporidia infections are also being identified. Diagnosis can be accomplished via histochemical staining of biopsies or fluids (urine, feces, sputum) using stains such as Calcofluor White, Gram, concentrated Chromotrope, Silver, Kinyoun, or various combinations [40*]. Greater sensitivity and specificity can be achieved using PCR-based methods and multiplex PCR also has been applied for detecting *E. bieneusi*, *E. intestinalis*, *Cryptosporidium* and *Cyclospora* [41*, 42*]. Serology has been used for diagnosing microsporidiosis in lab animals but has been questionable in HIV-infected patients who exhibit hypergammaglobulinemia but also are immune-deficient. Further compromising reliability of serology is the inability to culture *E. bieneusi* which limits the availability of antigen for testing. Recently, however, serological testing for *E. bieneusi* and *Encephalitozoon* species has been applied in both immune-deficient and immune-competent populations of people, and a relatively high seropositivity rate was detected in persons with occupational exposure to animals and otherwise healthy immune competent individuals with no clinical signs [43*]. A recent parasitological evaluation of fecal specimens from immune-competent Czech Republic citizens and foreign students of varying age groups identified 34 to 56 percent prevalence rates for shedding *E. bieneusi* and *Encephalitozoon* species with the highest prevalence in the group of persons 50 years of age and older [32**]. In addition, a 12-week longitudinal study on 15 asymptomatic but IFA seropositive individuals in the Czech Republic demonstrated that *E. bieneusi, E. cuniculi,* and *E. hellem* spores were shed intermittently and at irregular levels in both urine and feces [44**]. These results gave credence to the likelihood that, as demonstrated in lab animals (e.g. mice, rabbits), seropositivity in asymptomatic immune-competent people was indicative of chronic microsporidia infections that persist unless treated with drugs. Furthermore, these results suggested that among humans, several fecal specimens need to be evaluated before ruling

out microsporidial infection [32**, 43*, 44**]. The pathogenesis of microsporidiosis in otherwise healthy individuals has not been evaluated but in laboratory animals, clinical signs often were observed during the acute stages of infection that resolved, even though the microsporidia infections persisted. In addition to concerns about persistence and reactivation, these reports raise the question about whether asymptomatic carriers of infection may transmit infections to those at risk.

Conclusion

The pathogenesis of enteric microsporidiosis, especially in non-HIV-infected individuals, needs to be better characterized to ascertain if clinical signs are common during acute stages of infection and then resolve. Unapparent infections are being verified in seropositive individuals, raising questions about whether these infections reactivate under conditions of immune compromise or stress. Since microsporidia infections contribute to wide ranging clinical signs, they should be considered when an etiology cannot be determined. Treatment with albendazole is effective for disseminating species of microsporidia. Fumagillin is effective for treatment of *E. bieneusi,* the most prevalent species causing enteric infections, but has toxic side effects, so better drugs are needed.

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41*. Lee SH, Joung M, Yoon S, et al. Multiplex PCR detection of waterborne intestinal protozoa: microsporidia, Cyclospora, and Cryptosporidium. Korean J Parasitol. 2010; 48:297–301. Multiplex PCR diagnostics methods can now be applied to identify microsporidia among other species of waterborne parasites. [PubMed: 21234231]

42*. Tuli L, Singh DK, Gulati AK, et al. A multiattribute utility evaluation of different methods for the detection of enteric protozoa causing diarrhea in AIDS patients. BMC Microbiol. 2010; 10:11. doi:10:1186/1471-2180-10-11. Results of this study suggest that at least three procedures need to be applied before ruling out the presence of enteric pathogens, including microsporidia, in AIDS patients. [PubMed: 20078872]

43*. Sak B, Kucerova Z, Kvac M, et al. Seropositivity for *Enterocytozoon bieneusi*, Czech Republic. Emerg Infect Dis. 2010; 16:335–337. Seroprevalence rates of 20% and 33% were identified in HIV-infected persons and non-HIV-infected persons with occupational exposure to animals, respectively. [PubMed: 20113575]

44**. Sak B, Kvac M, Kucerova Z, et al. Latent microsporidial infection in immunocompetent individuals - a longitudinal study. PLoS Negl Trop Dis. 2011; 5:e1162. This longitudinal study supports the use of serological testing for microsporidiosis. Seropositive individuals were evaluated for the presence of microsporidia over 12 weeks and demonstrated intermittent and irregular shedding of *E. bieneusi*, *E. hellem* and *E. cuniculi* in feces and urine. This supports the growing evidence that microsporidia cause unapparent infections in humans and raises concerns about reactivation of infection. [PubMed: 21629721]

Key points

- Microsporidia are probably underdiagnosed infectious agents in HIV-infected and non-HIV-infected groups of people because they are difficult to detect and often disseminate to produce varied clinical signs.
- Deliberate diagnostic testing for microsporidia is increasingly revealing enteric and systemic infections in HIV-infected and non-HIV-infected individuals such as travelers, children, the elderly, and immunosuppressed patients such as organ transplant recipients and patients with malignancies or diabetes.
- Studies on the pathogenesis of microsporidiosis in humans are needed to further evaluate the range of clinical syndromes and whether asymptomatic infections reactivate during conditions of immune compromise.

Table 1

Microsporidia species identified in humans

Species	Site(s) of Infection	Other Hosts
Anncaliia (syns. *Nosema* and *Brachiola*) *algerae*	Eye, skeletal muscle, skin	Mosquito
Anncaliia (syns. *Nosema* and *Brachiola*) *connori*	Systemic	Unknown
Anncaliia (syns. *Nosema*-like and *Brachiola*) *vesicularum*	Skeletal muscle	Unknown
Encephalitozoon (syn. *Nosema*) *cuniculi*	Systemic, eye, respiratory tract, urinary tract, liver, peritoneum, brain, intestine	Mammals
Encephalitozoon hellem	Systemic, eye, respiratory tract, urinary tract, intestine	Birds, fruit bats
Encephalitozoon (syn. *Septata*) *intestinalis*	Systemic, intestine, biliary tract, respiratory tract, bone, skin	Mammals
Enterocytozoon bieneusi	Intestine, biliary tract, respiratory tract, urinary tract	Mammals, birds
Microsporidium africanum (syn. *Nosema* sp.)	Eye	Unknown
Microsporidium ceylonensis (syn. *Nosema* sp.)	Eye	Unknown
Nosema ocularum	Eye	Unknown
Pleistophora ronneafiei (syn. *Pleistophora* sp.)	Muscle	Unknown
Trachipleistophora anthropopthera	Systemic, eye, brain	Unknown
Trachipleistophora hominis	Systemic, muscle, eye	Unknown
Vittaforma corneae (syn. *Nosema corneum*)	Eye, urinary tract	Unknown