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Microsporidiosis: An emerging and opportunistic infection in humans and animals

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Abstract

Microsporidia have emerged as causes of infectious diseases in AIDS patients, organ transplant recipients, children, travelers, contact lens wearers, and the elderly. These organisms are small single-celled, obligate intracellular parasites that were considered to be early eukaryotic protozoa but were recently reclassified with the fungi. Of the 14 species of microsporidia currently known to infect humans, *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis* are the most common causes of human infections and are associated with diarrhea and systemic disease. Species of microsporidia infecting humans have been identified in water sources as well as in wild, domestic, and food-producing farm animals, raising concerns for waterborne, foodborne, and zoonotic transmission. Current therapies for microsporidiosis include albendazole which is a benzimidazole that inhibits microtubule assembly and is effective against several microsporidia, including the *Encephalitozoon species*, but is less effective against *E. bieneusi*. Fumagillin, an antibiotic and anti-angiogenic compound produced by *Aspergillus fumigatus*, is more broadly effective against *Encephalitozoon* spp. and *Enterocytozoon bieneusi* but is toxic when administered systemically to mammals. Gene target studies have focused on methionine aminopeptidase 2 (MetAP2) for characterizing the mechanism of action and for identifying more effective, less toxic fumagillin-related drugs. Polyamine analogues have shown promise in demonstrating anti-microsporidial activity in culture and in animal models, and a gene encoding topoisomerase IV was identified in *Vittaforma corneae*, raising prospects for studies on fluoroquinolone efficacy against microsporidia.

Keywords: Encephalitozoon; Enterocytozoon; Opportunistic infection; Emerging infection; Zoonosis

1. Introduction

Microsporidia were first identified as the cause of pébrine disease of silkworms in 1857 (Nägeli, 1857). Since then, over 1200 species of microsporidia have been identified as causes of infection in a wide range

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of invertebrate and vertebrate hosts (Wittner, 1999). Microsporidia were only sporadically identified in humans prior to 1985 and then emerged as causes of opportunistic infections associated with diarrhea and systemic disease in persons with AIDS. As diagnostic methods improved and awareness increased, microsporidiosis also is being detected in organ transplant recipients, children, travelers, contact lens wearers, and the elderly (Bryan and Schwartz, 1999; Schwartz and Bryan, 1999; Deplazes et al., 2000; Didier et al., 2004).

2. Organism

Microsporidia are nucleated, single-celled, obligately intracellular parasites that were considered to be early-branching eukaryotic organisms based on the presence of prokaryote-like ribosomes, and the apparent absence of true Golgi, peroxisomes, and mitochondria (Vossbrinck et al., 1987; Vavra and Larsson, 1999; Desportes-Livage, 2000). The microsporidia, however, were recently reclassified with the fungi based on observations that include the presence of chitin in the spore wall, identification of a mitochondrial HSP70 gene, and phylogenetic analyses of genes encoding beta tubulin, large subunit RNA polymerase II, TATA box binding protein, translocation elongation factors EF-1α and EF-2, and glutamyl synthase (Edlind et al., 1996; Germot et al., 1997; Hirt et al., 1997, 1999; Cavalier-Smith, 1998, Fast et al., 1999; Weiss and Vossbrinck, 1999; Weiss et al., 1999; Keeling et al., 2000; Weiss, 2000; Keeling and Fast, 2002; Williams et al., 2002; Vossbrinck et al., 2004). In addition, the microsporidian genome has been found to be highly reduced and compact, and mature organisms now appear to possess mitochondrion-derived organelles, or mitosomes (Biderre et al., 1995, 1999; Katinka et al., 2001; Vivarès et al., 2002; Williams et al., 2002; Slamovits et al., 2004; Vivarès and Méténier, 2004). Golgi-like membranes also have been identified in association with polar filament formation, and the posterior vacuole has been postulated to function as a peroxisome (Takvorian and Cali, 1994; Sokolova et al., 2001; Weidner and Findley, 2002, 2003).

The mature and infectious spores of the microsporidia species that infect mammals are relatively small, measuring 1.0–3.0 μM $\times$ 1.5–4.0 μM (Vavra and Larsson, 1999; Desportes-Livage, 2000; Canning and Vavra, 2000). Microsporidian spores are relatively resistant in the environment and are surrounded by an outer electron-dense glycoprotein layer and an electron-lucent endospore layer composed primarily of chitin. A plasma membrane encloses the cytoplasm which contains an anterior anchoring disc, membranous Golgi-like apparatus, membrane-bound nucleus, posterior vacuole, and polar filament that originates at the anterior end and coils in the posterior region of the spore. The polar filament distinguishes the microsporidia from other single-celled organisms and is used for infecting the host cell (Cali and Takvorian, 1999; Keohane and Weiss, 1999). A change in osmotic pressure or pH results in swelling of the posterior vacuole due to an influx of water, or possibly, the generation of water, and the ensuing pressure leads to the propulsion of the nucleus and cytoplasmic contents through the everting polar filament into the host cell (Fig. 1; Weidner, 1972; Undeen, 1990; Keohane and Weiss, 1999). Organisms then undergo merogony, during which nuclear division occurs, followed by sporogony, during which differentiation and maturation occur (Cali and Takvorian, 1999; Desportes-Livage, 2000). Cytokinesis occurs after either merogony (e.g. *Encephalitozoon* species) or sporogony (e.g. *Enterocytozoon bieneusi*).

3. Disease associated with infection

Clinical symptoms and disease associated with microsporidiosis vary with the species causing the infection and the status of the host's immune system. *E. bieneusi* infections are believed to result most commonly through ingestion of spores with the primary site of infection developing in the epithelial cells (enterocytes) lining the duodenum and jejunum of the small intestine (Fig. 1). Persistent diarrhea, abdominal pain, and weight loss are common clinical symptoms associated with *E. bieneusi* infection in immunodeficient individuals, such as persons with AIDS with $\leq$ 100 CD4+ T cells per microliter blood (Kotler and Orenstein, 1998, 1999). On rare occasions, *E. bieneusi* caused pulmonary infections or infected the bile ducts to cause cholecystitis and cholangitis. In otherwise healthy individuals such as travelers, *E. bieneusi* infection has resulted in self-limiting diarrhea of approximately one