Microsporidia and Acquired Immunodeficiency Syndrome

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Microsporidia is a common term that has been used to refer to a group of eukaryotic, obligate intracellular protozoan parasites belonging to the phylum Microspora. They are important agricultural parasites, contaminating commercial insects; they are also important by infecting laboratory rodents, rabbits and primates. Ever since the early cases found by Magarino Torres, who reported the presence of Encephalitozoon in a patient suffering of a meningoencephalomyelitis, some human pathology caused by microsporidia has been described. However, only after the acquired immunodeficiency syndrome outbreak have these organisms appeared as significant etiological agents in different pathologies. Even so, they remain underestimated. In the present article, the importance of microsporidia for the human pathology in immunocompromised host has been stressed.

Key words: microsporidia - immunocompromised host - pathology - acquired immunodeficiency syndrome-Aids

Parasites belonging to the phylum microsporidia Balbiani 1882 (Sprague & Becnel 1998) are spore-forming, small, obligate intracellular living eukaryotes with a unique morphology (Vavra & Larsson 1999). These parasites are distributed by spores which contain a characteristic polar tube apparatus which is necessary for the transfer of the "the parasite" sporoplasm, from the spore to a host cell. The mature spores are Gram positive. The spore wall is composed of a protein-rich exospore, an electron-dense surface coat, and a structure-less layer below this coat, the electron-transparent endospore which contains chitin. The internal surface of the endospore is covered by a plasma membrane which limits the cytoplasma of the spore. The life cycle of these parasites comprise three distinct phases: the infective phase, the proliferative, vegetative phase or schizogonie and the spore-forming phase or sporogony. Microsporidia are world-wide distributed in invertebrates and vertebrates including man. More than 140 genera including more than 1,000 species are known (Wittner & Weiss 1999).

The first mammalian infection was reported by Wright and Craighead (1922) in rabbits. The first human case was described by Magarinos Torres in 1927. Some years later Matsubayashi et al. (1959) described another case of a 9-year old Japanese boy with headache, recurrent fever, seizures, among other symptoms. Margileth et al. (1973) described an human case proven by autopsy of a 4-month old immunocompromised infant with thymic aplasia and disseminated nosematosis. Ashton and Wirashina (1973) mentioned a case of ocular microsporidiosis in a 11- year old boy from Sri Lanka. Pinnolis et al. (1981) described the case of an African woman with a perforated corneal ulcer. The parasite was identified as *Nosema*.

Up to the beginning of the acquired immunodeficiency syndrome (Aids) pandemie in 1981, only single cases of microsporidia infections in men and animals were reported because these microorganisms were not routinely diagnosed. Since this time, the microsporidia are increasingly recognized as cause of severe infections with a wide range of clinicopathologic findings especially in immunocompromised patients. At present, seven genera: *Enterocytozoon*, *Encephalitozoon*, *Nosema*, *Pleistophora*, *Trachipleistophora*, *Vittaforma*, *Brachiola*, with 12 species are known as pathogens in humans plus the collective group of *Microsporidium* with uncertain taxonomic status. The spores of these genera can morphologically be distinguished in regard of the combination of the number of their nuclei (one or two), the number and arrangement of the coils of the polar filament inside the spores and whether the spore is envolved by a parasitophoric vacuole or not in the cytoplasm of the host cell.

From the mentioned microsporidia, only the species *E. bieneusi*, *E. hellem*, *E. intestinalis*, *E. cuniculi*, *Pleistophora* sp., *T. hominis*, *T. anthropopthera*, *N. connori*, *B. vessicularum*, *V.*

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vesicularum were diagnosed in patients with human immunodeficiency virus (HIV) together with a *Thelohania/Pleistophora*-like parasite. From patients without HIV were described *E. cuniculi, E. intestinalis, E. bieneusi, N. ocularum, V. coneae, M. ceylonensis* and *M. africanum*. In both groups of patients special attention should be paid to ocular microsporidial infections. In patients without HIV such infections were found with *Nosema, Vittaforma* and *Microsporidium*; in patients with HIV *E. cuniculi-like, E. hellem and E. intestinalis* plus some cases without analysis of the genera and species (Kotler & Orenstein 1999).

GENERA AND SPECIES

ENCEPHALITOZOON

The genus *Encephalitozoon* contains the species *E. cuniculi, E. hellem* and *E. intestinalis*. These pathogens are morphologically indistinguishable. The development of the spores takes place in the cytoplasm of the host cell inside of a parasitophorous vacuole. In the longitudinally sectioned spores, the polar filament can be seen in form of five to six coils arranged regularly in a single row. The mature spores have only one nucleus. This pathogen has a reservoir in different mammals (Canning 1998). This agent was also found in HIV patients (Deplazes et al. 1996, Didier et al. 1996a, Weber et al. 1997). Human infections with this microorganism can not be discussed without a side-glance on animal pathogenic strains. Up to now three groups have been identified: group I was originally isolated from rabbits and also described from HIV patients (Deplazes 1996). The group II was isolated from a mouse and is able to infect blue foxes but was not found in humans, until now (Didier 1995). Group III was isolated from domestic dogs and identified in Aids patients (Didier et al. 1996b). These examples demonstrate that in some cases human infections can trace back to animal reservoirs. The importance of these strain variations and whether *E. cuniculi* strains exist pathogen only for animals should furtherhin be observed.

Spores of E. cuniculi - Have been found in a patient with cytomegalovirus adrenalitis. The spores were seen in epithelium and endothelial cells of the adrenal glands. De Groote et al. (1995) described three pathogens in the soft tissue of a tongue ulcer in a patient with Aids with a disseminated *E. cuniculi* infection. These protozoa were also described by Belcher et al. (1997) as infection of the mandible of an Aids patient. Weber et al. (1997) reported that *E. cuniculi* infection in Aids patients was associated with keratoconjunctivitis, hepatitis, peritonitis, encephalititis, urinary tract infections and respiratory tract infections. A case of *E. cuniculi* infection of duodenal mucosa was described by Franzen et al. (1995). This patient has had no gastrointestinal symptoms. Franzen et al. (1996) analyzed this species as pathogen for a chronic rhinosinusitis in patients with Aids. Zender et al. (1989) mentioned a case of peritonitis in an immunocompromised patient. Experimentally infections with *E. cuniculi* and *E. hellem* could be transferred to healthy and immunocompromised rhesus monkeys *Macaca mulatta* (Didier et al. 1994).

E. hellem - This microsporidia was found in immunocompromised patients. The first isolation and characterization was made from Aids patients with keratoconjunctivitis. This pathogen was also diagnosed in cases of chronic rhinosinusitis (Eeftinck-Schattenkerk et al. 1992), disseminated microsporidiosis (Schwartz et al. 1992), keratoconjunctivitis (Schwartz et al. 1993a), bronchiolitis (Schwartz et al. 1993b), isolated out of a prostatic abcess (Schwartz et al. 1994), pulmonary and intestinal microsporidiosis (Weber et al. 1992), in an Aids patient with pulmonary colonization, microhematuria, and mild conjunctivitis (Weber et al. 1993). This pathogen could be identified in cases of superficial keratitis in Aids patients (Didier et al. 1991). Cases of ocular microsporidiosis are described by Diesenhouse et al. (1993), Rosberger et al. (1993), Schwartz et al. (1993a), Didier et al. (1996a) and Silverstein et al. (1997). Until today, *E. hellem* was found in immunocompetent humans (Weber et al. 1999) and could be transferred to *M. mulatta* (Didier et al. 1994). Furthermore, this infection was detected in wild parrot (Suter et al. 2000).

E. intestinalis (formerly *Septata intestinalis*) - this pathogen was first described by Cali et al. (1991b) found in patients with chronic diarrhea, by Orenstein et al. (1992) in a case of disseminated microsporidiosis and from humans infecting enterocytes, macrophages and associated with diarrhea in an Aids patient. This result was underlined by the analysis of Baker et al. (1995) who suggest that *S. intestinalis* should be designated as *E. intestinalis* on the basis of the phylogenetic analysis of the small subunit ribosomal DNA. This parasite was found associated with chronic diarrhea and dissemination in Aids patients (Cali et al. 1993), small intestinal microsporidiosis (Field et al. 1993). Orenstein et al. (1993) reported about four cases of *S. intestinalis* infection in Aids patients with intestinal and disseminated microsporidiosis. This microsporidia species was not only found in immunocompromised persons but also in immunocompetent humans. Enriquez et al. (1997) described such infections in children and adults with diarrhea and in travelers with chronic diarrhea (Raynaud et al. 1998). This pathogen was found in dogs, pigs,

cows, goats and donkeys (Bornay-Llinares et al. 1998) and SCID mice could be infected (Achbaron et al. 1996, Enriquez et al. 1997). Therefore, it can not be excluded that by an oral-fecal infection these pathogens can be transferred from animals to humans. Patients with *E. intestinalis* infection have the tendency to develop disseminated infection (Molina et al. 1995). A consequence of *E. intestinalis* infection can be the break-down of the renal function. The infection of the kidneys can result in urethritis (Corcoran et al. 1996, Soule et al. 1997). *E. intestinalis* can infect the biliary tract (Schwartz & Bryan 1997). Ocular infections with *E. intestinalis* were reported by Lowder et al. (1990).

E. bieneusi - this pathogen was first described by Desportes Livage et al. (1985). It is found in enterocytes of the small intestine of HIV patients with chronic diarrhea (Orenstein et al. 1997). Furtherhin this agent was identified, in pulmonary and intestinal microsporidiosis (Weber et al. 1992), and in the biliary tree, gall bladder the biliary tract and nonparachymal liver cells (Beangerie et al. 1992, Pol et al. 1992). The spores and their electron microscopical morphology can be distinguished from the spores and their morphology of the species of the genus *Encephalitozoon*. The spores of *E. bieneusi* are formed in direct contact with the cytoplasma of the host cell and not enveloped by a parasitophoric vacuole. The mature spores have one nucleus and the polar filament has five to six coils forming two rows (Vavra & Larsson 1999). *E. bieneusi* was found as cause of self-limited diarrhea in immunonocompetent persons (Weber et al. 1994, Bryan et al. 1997). Bertange et al. (1993) described that this microsporidia was found in 1% of African children with diarrhea. Furtherhin it was found that this opportunistic protozoa was diagnosed in patients with bone-marrow, liver, and heart-lung transplantation (Weber et al. 1994, Rabodonirina et al. 1996).

E. bieneusi was first described as animal infection in a pig by Deplazes et al. (1996). This microsporidia species could also be detected in macaques which had been experimentally infected with simian immunodeficiency virus (SIV) (Mansfield et al. 1998), in contrast to human infections where these pathogens were found in the small intestine, in the macaques the parasites were found in the gallbladder. Carville et al. (1997) have found this agent in immunocompetent macaques which were not infected by SIV.

Tzipori et al. (1997) were successful to transfer an infection of *E. bieneusi* from an Aids patient to SIV infected macaques.

PLEISTOPHORA TRACHIPLEISTOPHORA

Pleistophora spp. was found in three immunodeficient patients: first in an immunodeficient but HIV negative man, then in Aids patients (Ledford et al. 1985, Macher et al. 1988, Grau et al. 1996) suffering in myositis. These microsporidia are serious muscle parasites of fishes (Canning & Lom 1986, Lom & Dykova 1992). These are the only publications of these microsporidia species in mammals.

In another case of myositis of an Aids patient, biopsy material from the skeletmuscle was transferred to tissue culture and athymic mice (Hollister et al. 1996). This patient has had an additional infection in the corneal epithelium. The development and ultrastructure of these parasites differ from the genus *Pleistophora* and give rise to nomination of the genus and species *T. hominis.* Field et al. (1996) reported about a second case of human Aids with myositis and infection with *T. hominis*. Vavra et al. (1998) described the second species *T. anthropopthera* found in the brain of one and in the kidneys, brain, heart, liver, spleen, lymph nodes bone marrow, pancreas, thyroid and parathyroid of a second Aids patient. Both species differ in their development.

The mature spores of *Pleistophora* and *Trachipleistophora* have 9 to 12 coils, only one nucleus and develop inside of a parasitophoric vacuole. *Pleistophora* spp. form in merogonic and sporogonic proliferation multinucleate plasmidia while *Trachipleistophora* spp. has division of meronts and sporonts by a binary fission.

VITTAFORMA

Davis et al. (1990) have given a case report about a corneal microsporidiosis. This pathogen was named *N. corneum* by Shadduck et al. (1990). The investigation of the ultrastructure of the developmental forms in athymic mice (Silveira & Canning 1995) gave rise to the denomination of this agent as *V. corneae*. Later, this microsporidia was found in the urinary tract of an Aids patient (Deplazes et al. 1997). The mature spores are diplokaryotic with a polar filament of six coils. The development of the parasite takes place in direct contact with host cell cytoplasma. The mature spore is enclosed in several membranous layers (Vavra & Larsson 1999). An animal host of this parasite is not known.

BRACHIOLA

The species *B. vesicularum* was found in a patient with Aids associated with myositis (Cali et al. 1998). In the mature spores of the diplokaryotic *B. vesicularum*, the polar tube forms two rows of coils, each row with 8 to 10 coils, but they can also be arranged in single and triple rows of coils. This pathogen seems only to be infective for muscle cells. The development of the spores takes place in direct contact with the cytoplasm of the host cell.

The formerly described *B. connori* (Sprague 1974) is a synonym for *N. connoris* (Sprague 1974, Cali et al. 1998).

MICROSPORIDIUM

The collective group of microsporidium includes microsporidia species of which the genetic position is unclear, the developmental cycle unknown. Two human pathogenic microsporidia are placed in this group: *M. ceylonensis* and *M. africanum*. Ashton and Wirasinha (1973) described the case of an 11-year old Tamil boy with a corneal ulcera. Sprague (1977) described this parasite as *Nosema* sp. Canning and Lom (1986) transferred this pathogen to the collective group of microsporidium and denominated this agent as *M. ceylonensis*. Pinnolis et al. (1981) presented a second case of a 36 year old woman from Botswana with a perforated corneal ulcer. This parasite was identified as *Nosema* sp. Canning and Lom (1986) transferred this agent to the collective group of microsporidum and named it *M. africanum*.

NOSEMA

Microsporidia of the genus *Nosema* normally parasites in invertebrates. One case of a disseminated infection with this pathogen was found in a athymic infant (Margileth et al. 1973, Canning & Lom 1986). This microorganism was described as *N. connori*. In a second case, ocular microsporidiosis was diagnosed in a patient without immunodeficiency with keratitis. The parasite was named *N. ocularum* (Cali et al. 1991a). The development of these protozoa occur in direct contact with the host cell cytoplasma. The mature spore has paired nuclei and contain a polar filament with 11 coils.

The clinical manifestations of human microsporidial infections include systemic, intestinal, muscular and ocular diseases in immunocompromised and immunocompetent humans. Not all mentioned microsporidia species have been found in both groups of patients. The question can not be answered whether microsporidia species exist which are able to infect only one of both patient groups. We do not know how many of these opportunistic protozoa are pathogens for humans. But the clinical manifestations are so manifold and so grave, especially for immunocompromised patients, that these microorganisms should be included in the routine diagnosis of such patients.

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