Clinical Signs, Diagnosis, and Treatment of *Encephalitozoon cuniculi* Infection in Rabbits

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KEYWORDS

• Encephalitozoonosis • *Encephalitozoon cuniculi* • Neurologic disorders
• Vestibular dysfunction • Clinical signs • Diagnosis • Rabbit • Microsporidia

KEY POINTS

- Central vestibular dysfunction caused by *Encephalitozoon cuniculi* frequently mimics the condition of a peripheral disorder.
- A negative antibody titer rules out *E cuniculi* as the cause of present clinical signs.
- Cerebrospinal fluid analysis including polymerase chain reaction is considered an inappropriate diagnostic method for in vivo diagnosis of encephalitozoonosis.
- The usefulness of glucocorticoid anti-inflammatories in the treatment of encephalitozoonosis is called into question.
- Encouraging activity early in the course of disease and adding in therapeutic exercise may represent the most important part of therapy in rabbits with vestibular dysfunction associated with encephalitozoonosis.

INTRODUCTION/BIOLOGY OF *ENCEPHALITOZOON CUNICULI*

Classification and Cell Structure

Encephalitozoon cuniculi is a mammalian microsporidian pathogen with worldwide distribution that may infect various species of mammals, including humans. The phylogenetic origin of microsporidia has been a consistent matter of debate because they possess many unique features that make them difficult to compare with other organisms. Microsporidia were originally thought to lack mitochondria and thus considered

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to be very basic eukaryotes. However, small and highly reduced mitochondria, known as mitosomes, have been identified at the cell organelle level and are now considered to be an important differentiating characteristic of the microsporidia. The discovery of a gene for this mitochondrial-type chaperone combined with phylogenetic analysis of multiple gene sequences supports a relationship between the microsporida and atypical fungi with extreme host cell dependency.[1–3] In addition, microsporidial spores retain fungal elements, including fungal proteins, such as tubulins, trehalose, and chitin.[3] The exact branching position within the fungal tree has not been completely clarified; however, gene sequencing supports a relationship with the ascomycete and basidiomycete clade.[1]

Microsporidia produce environmentally resistant spores and survive only by living in other cells. Microsporidia possess a unique method of infecting other cells that involves a specialized extrusion apparatus known as the polar tube or filament. This coiled tube is joined to an anchoring disc at the apical part of the spore and is a key diagnostic structure used for identification. The polar tube serves as a sporal invasive apparatus whereby a change in pH or osmotic pressure results in an explosive uncoiling of the polar tube with subsequent discharge of infectious sporoplasm either directly into the host cell or after spore phagocytosis by the host cell. In the first method of infection, polar tube uncoiling results in direct invagination of the host cell plasma membrane giving rise to transfer of sporoplasm via creation of a parasitophorous vacuole (PV) where *E cuniculi* spends its entire intracellular life cycle.[3] Alternatively, this transfer of nucleus-containing sporoplasm may occur after host cell phagocytosis and subsequent polar tube discharge and uptake of sporoplasm by host-cell phagosomes.[4] It has been suggested that germination out of phagosomes is limited and does not significantly contribute to *E cuniculi* infection.[3]

Life Cycle and Pathogenesis

E cuniculi has a direct life cycle with both horizontal and vertical (transplacental) transmission. In rabbits, postnatal transmission often occurs within 6 weeks from an infected dam or contact with other infected animals.[5] Spores, measuring 1.5 $\times$ 2.5 μm, are either ingested or inhaled as the infectious stage of *E cuniculi,* with oral ingestion of spores from infected rabbit urine being the most common source of infection. Spores can be found in the urine 1 month after infection and are excreted in large numbers up to 2 months after infection.[6] *E cuniculi* spores can survive outside the host for up to 6 weeks at 72°F (22°C). Shedding of spores is essentially terminated by 3 months after infection with very intermittent shedding of small amounts of spores by the infected rabbit thereafter. Following germination via the polar tube extrusion process described above, the microsporidia undergo a proliferative phase during merogony. Morphologically simple structured cells (meronts) replicate by binary or multiple division within host cell parasitophorous vacuoles, where they are found attached and closely aligned with the PV membrane. Initial target organs for infection include those with high blood flow such as the lungs, liver, and kidney, with infection of nervous tissue occurring later in the course of the disease.[7] Further differentiation of meronts into sporonts and later into mature spores (sporogony) results in the development of the distinctive polar filament and a rigid spore wall. With time, the PV or pseudocyst becomes overcrowded and ruptures, resulting in spore release. Cell rupture is associated with an inflammatory response, and most immunocompetent rabbits develop chronic, subclinical infections in a balanced host-parasite relationship associated with granulomatous lesions primarily affecting the brain, kidney, or eyes. A wide range of tissues may show morphologic lesions; however, in general, these histologic alterations are not associated with clinical disease.