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Review

More than a rabbit's tale – *Encephalitozoon* spp. in wild mammals and birds

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ABSTRACT

Within the microsporidian genus *Encephalitozoon*, three species, *Encephalitozoon cuniculi*, *Encephalitozoon hellem* and *Encephalitozoon intestinalis* have been described. Several orders of the Class Aves (Passeriformes, Psittaciformes, Apodiformes, Ciconiiformis, Gruiformes, Columbiformes, Suliformes, Podicipediformes, Anseriformes, Struthioniformes, Falconiformes) and of the Class Mammalia (Rodentia, Lagomorpha, Primates, Artyodactyla, Soricomorpha, Chiroptera, Carnivora) can become infected. Especially *E. cuniculi* has a very broad host range while *E. hellem* is mainly distributed amongst birds. *E. intestinalis* has so far been detected only sporadically in wild animals. Although genotyping allows the identification of strains with a certain host preference, recent studies have demonstrated that they have no strict host specificity. Accordingly, humans can become infected with any of the four strains of *E. cuniculi* as well as with *E. hellem* or *E. intestinalis*, the latter being the most common. Especially, but not exclusively, immunocompromised people are at risk. Environmental contamination with as well as direct transmission of *Encephalitozoon* is therefore highly relevant for public health. Moreover, endangered species might be threatened by the spread of pathogens into their habitats. In captivity, clinically overt and often fatal disease seems to occur frequently. In conclusion, *Encephalitozoon* appears to be common in wild warm-blooded animals and these hosts may present important reservoirs for environmental contamination and maintenance of the pathogens. Similar to domestic animals, asymptomatic infections seem to occur frequently but in captive wild animals severe disease has also been reported. Detailed investigations into the epidemiology and clinical relevance of these microsporidia will permit a full appraisal of their role as pathogens.

Contents

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1. Introduction

With their broad host spectrum and often poor host specificity, microsporidia receive increasing scientific attention as pathogens of humans and animals. Recent developments in molecular diagnostics and phylogenetic analyses now allow for the screening of large numbers of samples for microsporidial infections and yield detailed information on different genotypes and their relationships. This gives a clearer picture on host specificity, transmission pathways and zoonotic risks (Deplazes et al., 2000; Ghosh and Weiss, 2009).

Since the first description of clinically overt infection in human patients with AIDS (for a review see Kotler and Orenstein, 1999), microsporidia including *Encephalitozoon* spp. have been recognised as opportunistic pathogens and further research revealed infections also in non-immunocompromised humans (Cotte et al., 1999; Didier and Weiss, 2011).

Within the genus *Encephalitozoon*, three species have been described in mammals and birds (for a review see Didier, 2005; Mathis et al., 2005), *Encephalitozoon cuniculi*, *Encephalitozoon hellem* and *Encephalitozoon intestinalis*. *E. cuniculi* infections of pet rabbits and laboratory rabbits are best described (for review see (Künzel and Joachim, 2010)). However this species can also infect several other mammals (Wasson and Peper, 2000; Levkutová et al., 2004; Mathis et al., 2005; Goodwin et al., 2006; Lindsay et al., 2009; Sasaki et al., 2011; Wagnerová et al., 2012; Cray and Rivas, 2013; Meng et al., 2014).

In contrast to infections of humans and domestic animals, comparatively little is known about the situation in wild animals. As the awareness of the role of wildlife as a source of infectious agents for human and animal health is growing, so is research on this topic (Thompson, 2013). Infections of wild animals are not only considered a possible threat to human and animal health, but also an issue concerning wildlife conservation since infections with pathogens not previously encountered might be detrimental to wild animal species themselves. This is of special concern to endangered species that might become infected through the intrusion of infected hosts into their habitat (Thompson, 2013).

Until now, the sylvatic cycles of *Encephalitozoon* spp. are largely unknown, but understanding the epidemiology of these pathogens is a crucial step for controlling microsporidial infections. In this review, we want to give an overview of the occurrence of *Encephalitozoon* spp. in wildlife and discuss the possibility of cross-species (zoonotic and animal-to-animal) transmission. We focus on wild mammals and wild birds and included both non-domesticated animals living in their natural environment as well as captive animals.

2. Encephalitzoon: species, diagnosis and transmission

2.1. *Encephalitozoon* species

Spores of *Encephalitozoon* spp. are morphologically indistinguishable from each other. While *E. cuniculi* has already been described in 1923, the detection of further species of the genus *Encephalitozoon* was not made before the early 1990s when molecular analyses allowed identification and discrimination on the species level.

2.1.1. *Encephalitozoon cuniculi*

E. cuniculi can be assumed to circulate in rabbit populations worldwide and has the broadest host range, mainly among the non-human Mammalia, but also in birds and humans. Four different strains have so far been differentiated by analysis of the ITS region of ribosomal genes, although there seems to be a certain host preference in each strain this specificity is not strict (Selman et al., 2013). Strain I ("rabbit strain") is found predominantly in rabbits; strain II ("mouse strain") is found in rodents but also in blue foxes and cats; strain III ("dog strain") has been shown to cause high mortality in monkeys, steppe lemmings and dogs. The recently discovered strain IV ("human strain") has so far been found in humans, cats and dogs (Talabani et al., 2010; Nell et al., 2014, 2015).

Humans have been found to be infected with all known strains (although only rarely with strain III). It is most likely that infections with *E. cuniculi* are predominantly zoonotic (Shadduck et al., 1979; Didier, 2005; Mathis et al., 2005; Didier and Weiss, 2011; Sokolova et al., 2011).

2.1.2. *Encephalitozoon hellem*

E. hellem was first described as the cause of keratoconjunctivitis in a human AIDS patient but its broadest distribution can be found amongst birds. Monkeys, carnivore and rodents can also be infected by this species (Tables 1, 2, 4 and 5). Different genotypes can be distinguished using three different gene loci: Mathies distinguished three genotypes (named 1,2,3) using internal transcribed spacer (ITS) sequences (Mathies et al., 1999). Later Xiao et al. (2001) could further distinguish these genotypes by additionally targeting the polar tube protein gene locus and the small subunit rRNA gene: The former genotype 1 could be distinguished in 1A, 1B, 1C; genotype 2 was distinguished into 2A and 2B moreover genotype 3 was suggested to be renamed 2C. There are further intraspecies variations so that more genotype variants can be described (Haro et al., 2003). Distinguishing the genotypes could be helpful to exclude or suggest infections of a common origin (Haro et al., 2006a).