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**UPDATE ON NEUROLOGICAL DISEASE IN THE RABBIT**

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Signs of neurological disease, such as head tilt and hindlimb paresis or paralysis, are a commonly encountered in pet rabbits, and localisation of lesions and establishment of a definitive diagnosis can be challenging. Although a full neurological assessment should always be attempted, findings should be interpreted with care as reactions can be variable and different to those anticipated due to the stress response and the fact rabbits are a prey species. For example, rabbits have no menace reflex. With spinal cord injuries, absence of deep pain sensation carries a poor prognosis, however this test is not always reliable in rabbits since they conceal signs of pain. Rabbits have no cauda equina and the spinal cord runs within the entire length of the spinal column.

### Differential diagnoses for clinical signs of neurological disease in rabbits:

<table>
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<tr>
<th>Clinical Sign</th>
<th>Differential Diagnoses</th>
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| Head tilt (vestibular dysfunction) | Central vestibular disease (cerebellum, medulla oblongata)  
Bacterial infection  
Encephalitozoonosis  
Toxoplasmosis  
Herpesvirus (Herpes simplex 1) encephalitis  
Cerebrovascular accident  
Degenerative changes  
Visceral larva migrans  
Trauma  
Toxins  
Neoplasia  
(Rabbits) |
| Peripheral vestibular disease (CN VIII, inner ear) | Bacterial otitis media/interna  
Toxins  
?idiopathic vestibular syndrome  
Neoplasia |

**Encephalitozoon cuniculi**

*Encephalitozoon cuniculi* can cause a wide variety of neurological signs in rabbits and is a major differential diagnosis for any rabbit presenting with any neurological signs, including urinary incontinence. Although fairly well studied in experimental laboratory rabbits, our understanding of this parasite in pet rabbits is still poor.
and establishment of a definitive diagnosis is difficult. There has been limited research into the therapy of this disease in pet rabbits, and with fenbendazole currently being marketed specifically for prophylactic treatment of this disease in rabbits, it is important to understand what we do and don't know about the disease and its treatment.

*E. cuniculi* is a mammalian protozoal parasite which belongs to the phylum *Microsporidia*. This is a diverse group of single-celled obligate intracellular protozoa with a unique organelle, the polar filament. It is a spore-forming parasite with a wide host distribution. Infection has been recognised since the 1920s in laboratory rabbits. There is one report of infection in wild rabbits in the UK (1979) and it is present in wild rabbits in France and Australia. It has however only recently been found to be widespread in the pet rabbit population in the United Kingdom, with a seroprevalence of 52% in clinically healthy pet rabbits (Keeble and Shaw 2006). Infection has also been described in rodents (guinea pigs, rats, mice, hamsters), dogs, cats, foxes, goats, sheep, pigs, cows, horses, exotic carnivores and non-human primates. *E. cuniculi* is also emerging as a significant opportunistic pathogen in immunocompromised humans and was first reported in 1995 in an HIV-positive patient causing chronic sinusitis, rhinitis and keratoconjunctivitis. More typically in humans this organism affects the brain and kidneys. Three strains have been identified: Type I from dogs, Type II from rodents and Type III from rabbits. There have been no reports of direct transmission from pet rabbits to man, but human infections have been shown to be the same strain that infects rabbits (Deplazes et al 1996). Although disease transfer has been shown to occur from humans to rabbits, a direct zoonotic link has yet to be established. Close contact between owners and susceptible pet species may lead to an increase in human exposure.

Spores are shed in the urine and transmission occurs via ingestion or inhalation. Vertical transmission also occurs and the developing lens is one target site. The spores are relatively resistant in the environment and are known to survive for at least 4 weeks at 22°C. However, they are easily killed by boiling, autoclaving and most routine disinfectants. Host cells are infected following polar tube extrusion from the spore and injection of the sporoplasm into the host cell, or by phagocytosis. The host cell eventually ruptures releasing spores into the extracellular space and resulting in chronic inflammation and granuloma formation. Infection is thus spread to surrounding cells and via the circulation. It is the inflammatory response to the spores that is the cause of clinical signs.

Serum antibody levels rise 17-21 days post infection and peak at about 70 days (Kunsty et al 1986). Spores are shed in the urine from approximately day 30 after infection and lasts for approximately 9 weeks. Early infection (30 days post infection) is confined to target organs such as the lung, kidney and liver, with more chronic infection (100 days post infection) affecting the heart, brain and kidney. In many rabbits exposure to this organism results in a subclinical asymptomatic infection and carrier status occurs, but in some a variety of neurological and renal signs can develop.

**Clinical Signs associated with encephalitozoonosis:**
- Head Tilt
- Torticolis
- Hind limb paresis
- Paralysis
- Retarded growth
- Collapse
- Tremors
- Seizures
- Urinary incontinence (may be the only presenting sign)
- Renal failure (PU/PD)
- Cataracts and lens-induced uveitis
- Death

**Main differential diagnoses**
- Otitis media / interna
- Spinal fracture, trauma, abscess
- Bacterial central abscess
- Splay leg and other inherited abnormalities
- Lead toxicity
- Toxoplasmosis
- Listeriosis

**Diagnosis**

*Encephalitozoon cuniculi* antibody assays are available. Enzyme-linked immunosorbent assay (ELISA) tests measure serum IgG levels to the parasite. A single negative result in a healthy animal does not rule out recent infection and can be followed by a repeat test 4 weeks later to rule out the possibility of early infection prior to seroconversion. However, in animals with neurological signs a single negative result rules out *E. cuniculi* as a cause of clinical disease, as the parasite takes 100 days to reach the CNS. To diagnose an active infection, paired rising antibody titres need to be demonstrated over a period of time. However, this is rarely practical when dealing with a clinical case as treatment is usually initiated after a first positive test, and it is not known how specific treatment affects antibody titres. A PCR test has recently become available which can detect the antigen in urine. A positive result confirms active shedding of the parasite. On post mortem examination there may be gross changes to the kidneys with pitting and scarring of the renal cortex. Histological examination of the brain will show microgranulomata. Identification of parasites...
is possible on histopathological examination of infected tissues, where they appear as gram-positive, rod-shaped, refractile, intracytoplasmic structures. Endoscopic kidney biopsy could be performed in the live rabbit to diagnose this infection on histopathology. It is known that immunodeficient animals do not mount a reliable immune response. Recent research has indicated that phagocytosis of spores is the primary method of cell infection, rather than extrusion of the polar tube. Some of these spores then extrude their polar tube and germinate, but others are digested. In an individual animal the immune response to this infection will therefore depend on the relative balance between parasite multiplication and the host immune response. Where these are matched infection will remain latent and asymptomatic. The host-parasite relationship has yet to be fully understood, however it is thought that immunosuppression is a major factor in the development of clinical disease post exposure.

Other Diagnostic Tests (less commonly used)
Intradermal skin tests are not very sensitive and therefore these are no longer used. Culture of spores from urine or tissue samples on rabbit fibroblast monolayers. Urine samples can be centrifuged and examined for spores using modified trichrome stains or immunofluorescence.

Treatment
Response to treatment varies, with successful treatment depending on whether the infection is acute or chronic. Chronic cases usually present with central nervous system signs and in these cases, where cell damage is severe, treatment may not be successful. In acute cases clinical signs may be treated with fenbendazole at 20 mg/kg orally q24h for 28 days, and in some cases this can prove very effective. There has only been one small study on the use of fenbendazole in rabbits (Suter et al 2001) and our current dosing regimes are based solely on this. However, although found to be effective, the dosages and lengths of treatment given are not well justified, and more work needs to be done to see if shorter treatment courses can be as effective, especially as the current 28 day recommendation can be difficult for owners to comply with. Fenbendazole is also marketed in the UK for prophylactic treatment at 20 mg/kg q24h for 9 days. This was based on a small trial where rabbits were treated for 7 days before and 2 days after experimental infection with E. cuniculi, so again it may not be the optimum regime. Fenbendazole has no residual effect and so the rabbit is only protected from exposure on the days when it is receiving the drug, so it has limited use in situations where risk of prolonged exposure is high.

Glucocorticoids, such as dexamethasone or prednisolone, may also be given to reduce inflammation, although they should be used with care and for a short time only in rabbits, as they are immunosuppressive.

Traditionally Microsporidia have been considered protozoal organisms, however more recent research has indicated that they may be more closely related to fungi, since they contain chitin and trehalose. Treatment of E. cuniculi infection in humans is with albendazole, however more recent in vitro work has shown polyoxin D and nikkomycin Z, which inhibit chitin synthetase enzymes, may also be effective.

Prevention
Prevention of infection may not be possible since the parasite is widespread in the pet rabbit population. Many rabbits are likely to have been exposed at the time of purchase, either in uterus or from conspecifics, so there is an argument for treating all newly acquired pet rabbits once to eliminate the parasite if it is present in the body. This should only need to be done once if the rabbit is not going to be exposed further to environmental spores. Serocconversion precedes renal shedding, so contact rabbits should be serologically screened to identify infected animals before the parasite is excreted, in an outbreak. These animals may be isolated and treated with fenbendazole. When a case is diagnosed, infection of in-contact rabbits may be prevented by prophylactic administration of fenbendazole, or they can be treated on presumption of infection in order to prevent the development of clinical signs at a later date. Strict hygiene practices are vital; minimisation of urine contamination of food and water supplies by use of water bottles, hay racks etc. and routine disinfection to kill spores.

References and further reading