A head tilt is a common clinical sign of *E.cuniculi*

Photo: R Saunders

ENCEPHALITOZOON CUNICULI IN RABBITS

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Encephalitozoon cuniculi is a protozoan parasite of the phylum Microsporidia closely related to fungi. The main host for this parasite is the domestic rabbit, but other mammals can also be affected including monkeys, foxes, birds, dogs, cats, mice and humans.

Transmission

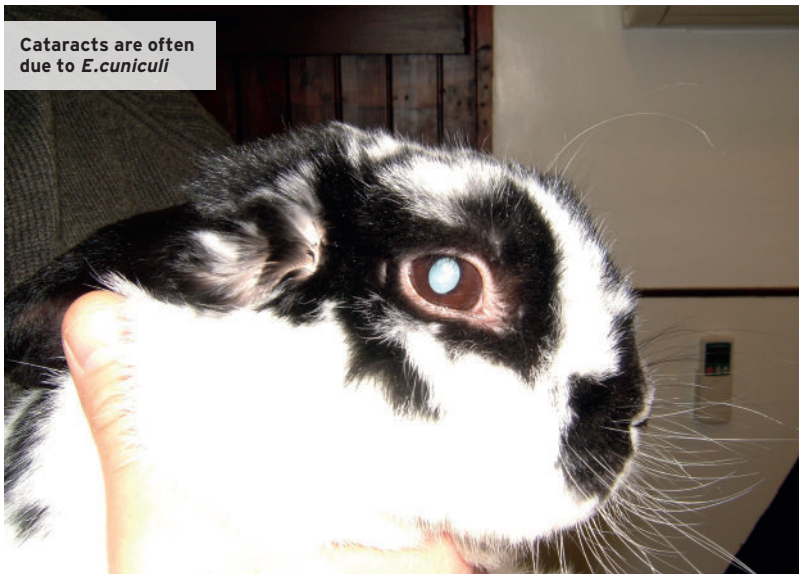
Transmission of the parasite in rabbits occurs mainly via two routes:

- **Horizontal** – between rabbits via ingestion of contaminated food/water with spores excreted in the urine of infected animals (more rarely via inhalation of spores). After eating the spores, these travel to the intestines where they multiply and then infect blood cells called macrophages to reach the liver, kidneys, central nervous system (CNS), lungs and heart via the blood stream. When they reach these organs, they cause inflammation. Spores are shed in urine intermittently from 35 days post-infection and up to 3 months or more, and so infecting other rabbits.
- **Vertical** – or transplacental from doe to kittens in utero (during pregnancy). Here the spores tend to go to the lens of the eye.

Clinical signs

Infected rabbits can show neurological signs, eye problems and kidney issues but can also be asymptomatic (not show any signs). The asymptomatic rabbits will be carriers, playing an important role in the spread of the disease.

The severity of symptoms will depend on the immune status of the patient.



Cataracts are often due to *E.cuniculi*

Photo: R Saunders

Immunocompetent rabbits can present mild or even non-existent signs (subclinical), whilst immunocompromised rabbits will present with severe signs and might even die from the disease.

Clinical signs will depend on the organ affected:

- **CNS signs** – this generally occurs in acute (rapid) cases and will present with vestibular signs including torticollis (when the head becomes persistently turned to one side, often associated with painful muscle spasms), head tilt, ataxia (lack of co-ordination), nystagmus (flickering of the eyes) paralysis, tremors and/or seizures.
- **Renal signs** – this tends to happen when the infection is chronic (longer standing) and will show as an increase in drinking, increased urination, changes in kidney values (urea and creatinine), weight loss and/or cystitis.
- **Ocular signs** – due to the parasite invading the lens of the eye during pregnancy, this can rupture and lens material releases into the anterior chamber (aqueous humor-filled space inside the eye between the iris and the cornea's innermost surface) of the eye causing inflammation (phacoclastic uveitis). Usually this happens in one eye. Secondary increase in the eye pressure (glaucoma) and cataracts can also happen.

Differential diagnoses

As we have seen, the clinical signs for encephalitozoonosis are varied and non-specific so we must make sure we make a correct diagnosis. The differential diagnosis depends on the type of signs the rabbit presents:

- **CNS signs** – other infectious causes of central vestibular disease including bacteria *(Pasteurella, Pseudomonas, Listeria)*, viruses (Herpesvirus-1 and rabies) and parasites such as *Toxoplasma*. Non-infectious causes such as tumours, lead toxicity, cerebral infarcts (areas of the brain where blood supply fails), hepatic encephalopathy (neurological signs caused by liver failure), enterotoxaemia (toxins produced by bacteria) and sepsis. Spinal disease can also present with paresis (partial paralysis) and ataxia (lack of coordination). Causes of peripheral vestibular disease such as middle ear disease, ear drum rupture, ear toxicity caused by antibiotics and idiopathic vestibular disease.
- **Renal signs** – acute and chronic renal failure.
- **Ocular signs** – old age cataracts, bacterial uveitis due to *Pasteurella multocida* (generally both eyes are affected).

With all these possible diagnoses it is imperative that your vet performs a thorough physical exam, and they are likely to recommend various diagnostic tests.

Photo: Shutterstock, Mary Swift

It is important to consider the companion when a positive rabbit is diagnosed

Diagnostic testing

Due to the variety of symptoms, diagnosing the disease in a live rabbit remains a challenge and multiple tests are generally required. The main methods include:

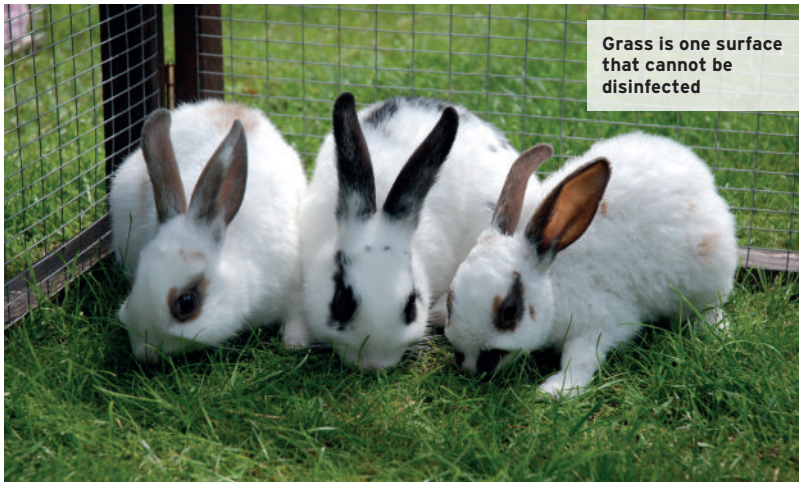
- **Histopathology** – looking for the lesions caused by the parasite and parasitic spores in tissues at post mortem, generally in brain, kidneys and eyes. The actual organism is not often found in these lesions.
- **Serology** – measuring the antibody response to *E.cuniculi* in a blood sample. Rabbits produce antibodies against *E.cuniculi*, in particular immunoglobulins M (IgM) and G (IgG). However, the severity of the clinical signs is not correlated to the levels of antibodies present and these vary depending on the stage of the disease, so interpreting this test can be difficult.

IgM indicates initial exposure and active infection. They go up 20-30 days post exposure and then levels fall over the next 8-10 days. High levels indicate early or active infection.

IgG goes up later in the disease and indicates long term exposure; they rise from 30 day post-exposure and peak around 70 days post-infection. High levels indicate a chronic or latent infection.

It is advisable to test both antibodies to help with interpretation. A negative result can generally rule out encephalitozoonosis, although it could also mean a test is performed too early in the disease, so repeated testing is required three weeks later to ensure negativity. High IgG and IgM together indicate an active infection. Measuring antibodies tells us if the patient has been exposed to the parasite but doesn't confirm that the symptoms we are seeing are caused by the parasite. Studies have shown that these antibodies don't offer enough protection against reinfection even when they persist for a long time in the rabbit's body, so a rabbit that has been treated successfully for *E.cuniculi* can develop the disease again.

- **Molecular genetic testing** – with these we look for parasitic DNA in samples. Urine, faeces, cerebrospinal fluid (CSF) and organs collected at post mortem can be tested. These tests are called polymerase chain reaction or PCR. These tests are problematic in faeces and urine as the spores get excreted intermittently and for a short period of time so we can get false negative cases.
- **Additional testing** – these are ancillary tests that might help determining the severity of the disease and prognosis, as well as ruling out other possible differential diagnoses. They include blood testing to evaluate kidney function and look for inflammatory markers such as C-reactive protein or increased white blood cells. Imaging such as ultrasound to assess the kidneys or computed tomography (CT) to check for brain lesions or exclude other causes of CNS signs such as ear disease.



Grass is one surface that cannot be disinfected

Photo: D Cordell

Treatment

Treatment can also be challenging as no specific cure is available and acute cases in immunocompromised animals are generally fatal. The parasite can be treated but the damage to the cells cannot be reversed, so a full recovery might not occur. Rabbits that are successfully treated can still develop the disease later, especially in periods of stress or immunosuppression. The treatment is two-fold, by directly attacking the parasite to reduce spore proliferation and migration, and by indirectly treating the inflammation that the spores cause and manage severe neurological signs and concurrent disease.

- **Direct treatment** – the anti-parasitic of choice is fenbendazole and is recommended for treatment as well as prevention. It is used at 20mg/kg body weight once daily for 28 days.
- **Indirect treatment:** Anti-inflammatories such as steroids have shown promising results in severe cases but their use is controversial due to their immunosuppressive effect. Most veterinarians will use non-steroidal anti-inflamammatories but care must be taken as this can have renal side effects.

Anticonvulsive and sedative drugs are indicated in cases with severe neurological signs.

Anti-sickness medications can help in cases of severe torticollis/head tilt.

Antibiotics might be indicated in acute cases.

Ocular medications can be used in cases of uveitis. Although in persisting cases, surgical removal of the lens might be required.

Antifungals – as this organism is part parasite, part fungus, antifungals have been trialled in laboratory studies, but their clinical use has not been fully evaluated.

Other supportive care including fluids, assisted feeding, treatment for gut stasis etc. might also be required in acute cases.

It is important to consider the companion rabbits when a positive rabbit is diagnosed. It is generally advisable to treat them with fenbendazole for 28 days, as well, and ensure the litter trays are cleaned regularly, to avoid contact with infected urine for the companion rabbit, as well as to avoid re-infection during treatment.

Prevention

As with everything related to this disease, prevention can be challenging.

Prophylactic use of fenbendazole for 28 days for any newly acquired rabbits before introducing them to other rabbits can help to reduce the spread of the disease; however, this will not guarantee that future infections will not happen. Reducing contact with other rabbits and wildlife, thorough disinfection, good hand washing routines and raising food and water bowls to reduce urine contamination can also help.

Serological testing of rabbits before introducing them to a group is also useful. If two negative tests occur then they can be assumed to be negative and ideally not mixed with a known positive companion. If they have both previously been exposed to *E.cuniculi* a 28 day course of fenbendazole should be used.

Regular short prophylactic courses of fenbendazole (9 days every 3 months) have been suggested to reduce excretion and thus limit infection in exposed rabbits, and might be considered at times of stress or boarding, but is not required routinely.

E.cuniculi is a very resistant parasite in the environment and so appropriate disinfectants need to be used. These include 0.1% bleach with a 10 minute contact time or ethanol (70%) with a 30 second contact time. Sodium hydroxide (1%), formaldehyde (0.3%) and hydrogen peroxide (1%) with a contact time of 30 minutes are other options to kill spores.

The spores survive on most surfaces for four to six weeks, so this will need to be considered before introducing rabbits into an environment that cannot be disinfected, such as grass in the garden.