COMPANION OR PET ANIMALS

Canine central nervous system neosporosis: clinical, laboratory and diagnostic imaging findings in six dogs

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SUMMARY
This report describes the clinical, neurological, laboratory and imaging findings in six dogs affected by CNS neosporosis and reviews previous publications. All dogs were born in England and never travelled outside the UK. Cerbellar and proprioceptive ataxia were the most common presenting neurological deficits. Markedly elevated creatine kinase in the serum was detected in four of the six dogs. Increased cerebrospinal fluid (CSF) protein concentration and mixed pleocytosis were present in five of the six dogs. Abnormal MRI findings were detected in five of the six dogs. The diagnosis was based on positive antibody titres on serum (1:800 or above) and positive PCR on CSF. All patients were treated with a combination of clindamycin and trimethoprim/sulfamethoxazole. The clinical signs improved in all cases. One dog developed hypothyroidism and another one died due to liver disease of unknown causes, respectively six and eight months after initial presentation.

BACKGROUND
Neosporosis is a systemic protozoal disease caused by Neospora caninum. It was first described in dogs in Norway in 1984.1 Dogs and cattle are the most frequently affected species; however, clinical neosporosis has also been reported in sheep, goats, deer, horses and in a rhinoceros.2 3 In addition, cats, mice, pigs, rats, gerbils, foxes and monkeys may be experimentally induced to be intermediate hosts. There is serological evidence of human infections with N caninum, but clinical disease has never been proven.4

Animals manifesting clinical neosporosis, including dogs, always act as intermediate hosts. In these animals, replication of the parasite occurs by asexual reproduction to produce tachyzoites and tissue cysts (bradyzoites). Both of these forms are intracellular.5 In the infected animal, tachyzoites can be found in several cell types, including neurons, macrophages, fibroblasts, vascular endothelial cells, myocytes, hepatocytes and dermal cells.5 Tissue cysts can only be observed in neural tissues (brain, spinal cord, nerves and retina).5

The sexual reproduction occurs in the intestine of the definitive host. Until recently, the only known definitive host was domestic dogs; however, recent studies have shown that coyotes, grey wolves and Australian dingo dogs can also act as definitive hosts.7

Carnivores usually become infected by ingesting tissues containing bradyzoites, whereas herbivores usually become infected by ingesting food or water contaminated by oocysts. Transplacental infection can also occur, with the transmission of tachyzoites from an infected mother to the fetus during pregnancy (this is the major route of transmission in cattle).3 10 11

N caninum can affect dogs of all ages.2 In puppies, the typical presentation includes myositis and polyradiculoneuritis, usually leading to severe paraparesis, muscle atrophy and characteristic rigid hyperextension of the pelvic limbs.12 In adult dogs, neosporosis is a recognised cause of necrotising cerebellitis and cerebellar atrophy.13–15 Diffuse CNS neosporosis in adult dogs has also been described, as well as non-neurological signs, such as myositis, dermatitis, pancreatitis, pneumonia and hepatitis.16

A limited number of published cases of CNS neosporosis are available in the literature. The aim of the present case series is therefore to describe the clinical, neurological, laboratory and MRI findings of this disease in six recently confirmed cases in the UK and to compare these findings with previous publications.

The clinical presentation, investigation findings and outcome of the six cases are summarised in table 1.

CASE PRESENTATION
The clinical database of a private referral hospital in England (Dick White Referrals) was searched for dogs diagnosed with neosporosis. The inclusion criteria for this case series were based on positive serology (1:800 or above) and positive PCR on cerebrospinal fluid (CSF). All serum samples were also tested for Toxoplasma gondii and were negative.

An immunofluorescent technique was used for the serology: the slides were coated with antigens (lysates of T gondii/N caninum tachyzoites) and incubated with the serum provided at a starting dilution at 1 in 50 for T gondii IgG/N caninum IgG and a starting dilution of 1 in 20 for T gondii IgM. (The starting 1:50 dilution of T gondii and N caninum refers to the semi-quantitative titre measurement of anti-IgG antibodies present in the serum. The same applies to the 1:20 dilution for the T gondii IgM. Anti-IgM antibodies for N caninum were not tested.) After incubation the slides were rinsed and a species-specific conjugate containing a fluorescent
An 11-year-old, female, spayed Labrador retriever was referred for cerebellar ataxia of three weeks’ duration. The dog was bright, alert and responsive on presentation. Physical examination was unremarkable. Neurological examination revealed cerebellar ataxia, normal cranial and spinal nerve reflexes, and no pain on palpation of the spine. The tentative neuroanatomical localisation of the lesion was the cerebellum.

CBC was unremarkable. Serum chemistry abnormalities included alanine aminotransferase (ALT, 277 iu/l, reference interval (RI) 13–88 iu/l), aspartate aminotransferase (AST, 202 iu/l, RI 13–60 iu/l), cholesterol (8.7 mmol/l, RI 3.8–7.0 mmol/l) and triglyceride (1.4 mmol/l, RI 0.56–1.14 mmol/l). 

MRI revealed mild cerebellar atrophy with increased T2 and T2-FLAIR hyperintensities on thalamus and brainstem. CSF analysis revealed mixed pleocytosis and increased protein concentration.

The presence of *T gondii* and *N caninum* in the CSF was detected by quantitative PCR using the Genesig *T gondii* repeat region and *N caninum* Nc5 marker genomic sequence assays (PrimerDesign, Chandler’s Ford, UK) in a Stratagene MX3005P thermocycler (Agilent Technologies, Stockport, UK), as per the manufacturer’s instructions.

#### Case 1

An 11-year-old, female, spayed Labrador retriever was referred for cerebellar ataxia of three weeks’ duration. The dog was bright, alert and responsive on presentation. Physical examination was unremarkable. Neurological examination revealed cerebellar ataxia, normal cranial and spinal nerve reflexes, and no pain on palpation of the spine. The tentative neuroanatomical localisation of the lesion was the cerebellum.

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MRI revealed mild cerebellar atrophy with increased T2 and T2-FLAIR hyperintensities on thalamus and brainstem. CSF analysis revealed mixed pleocytosis and increased protein concentration.

**Table 1** Signalment, investigation findings and outcome after treatment of six cases of confirmed CNS neosporosis

| Signalement and reason for presentation | Complete blood count and serum chemistry | *Neospora caninum* serology | MRI findings | CSF analysis | Outcome after treatment |
|----------------------------------------|----------------------------------------|-----------------------------|--------------|-------------|------------------------|
| 11-year-old, female, spayed Labrador retriever presented for cerebellar ataxia. | Mild elevation AST, ALT, cholesterol and triglyceride. Significant elevation of CK. | Positive at 1:3200. | Mild cerebellar atrophy. | Mixed pleocytosis and increased protein concentration. PCR positive for *N caninum*. | Resolution of clinical signs. |
| 2-year-old, male, neutered saluki presented for pelvic limbs ataxia. | Significant elevation of CK. | Positive at 1:800. | Unremarkable. | Mixed pleocytosis and increased protein concentration. PCR positive for *N caninum*. | Marked improvement of clinical signs. |
| 10-year-old, female, spayed lurcher presented for ambulatory tetraparesis. | Normal. | Positive at 1:800. | Cervical spinal cord: multifocal, intra-axial T2 and STIR signal intensities. Brain: increased FLAIR signal intensity on mesencephalon and cerebellum. | Mixed pleocytosis and increased protein concentration. PCR positive for *N caninum*. | Initial improvement of clinical signs. |
| 1-year-7-month-old, female, English springer spaniel cross presented for cerebellar ataxia and behavioural changes. | Normal. | Positive at 1:800. | Severe cerebellar atrophy. Heterogeneous T2 and FLAIR hyperintensities on thalamus and brainstem. | Increased protein concentration. PCR positive for *N caninum*. | Improvement of clinical signs. |
| 2-year-old, male, neutered Labrador retriever presented for cerebellar ataxia. | Significant elevation of CK. | Positive at 1:800. | Severe cerebellar atrophy. | Mixed pleocytosis and increased protein concentration. PCR positive for *N caninum*. | Improvement of clinical signs. |
| 4-year-11-month-old, male, neutered greyhound presented for ambulatory tetraparesis. | Moderate elevation of ALT and AST. Significant elevation of CK. | Positive at 1:800. | Multifocal, ill-defined T1 isointense, T2 and FLAIR hyperintense areas on right caudate nucleus, right frontal lobe, hippocampus and medulla oblongata. | Mixed pleocytosis and increased protein concentration. PCR positive for *N caninum*. | Improvement of clinical signs. |

*ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; CSF, cerebrospinal fluid; FLAIR, fluid attenuation inversion recovery; STIR, short-tau inversion recovery.*
Actevis, Barnstaple, UK; 15 mg/kg orally every 12 hours). The owner reported that the dog became much more energetic after two weeks of treatment. After eight weeks since the beginning of treatment, the serology titre decreased from 1:3200 to 1:800. The dog was kept on the same antibiotic regimen and reassessed monthly. Six months after initial presentation, the owner complained about severe lethargy and weakness. Physical and neurological examinations were normal. The previously reported cerebellar ataxia had completely resolved. Blood analysis revealed low thyroxine (T4, <6.44 nmol/l, RI 15–50 nmol/l) and elevated thyroid stimulating hormone (TSH, 5.25 ng/ml, RI 0.0–0.6 ng/ml). Although this is just a speculation, the dog was believed to have developed hypothyroidism secondary to treatment with trimethoprim/sulfamethoxazole, as T4 levels six months before were normal (24.4 nmol/l). Treatment with trimethoprim/sulfamethoxazole was stopped, thyroid hormone replacement therapy was started and immediate improvement in the general conditions was seen by the owners. Repeated blood examination after six weeks revealed normal T4 concentration. N caninum titre was stable at 1:800. At this point, treatment with clindamycin was also stopped. The patient has remained clinically stable until the time of writing (nine months after diagnosis).

Case 2
A two-year-old, male, neutered saluki was referred for progressive pelvic limb ataxia of two weeks duration. The dog was lethargic but responsive on presentation. Physical examination was unremarkable. Neurological examination revealed ambulatory paraparesis and severe pelvic limb ataxia. Sural reflexes were normal in all four limbs. The tentative neuroanatomical localisation was T3–L3 spinal cord segment.

CBC was normal. Serum chemistry analysis revealed increased CK (1494 iu/l). N caninum serology was positive at greater than 1:800. MRI of the thoracolumbar spine was unremarkable. CSF analysis showed a mixed pleocytosis (13/μl, consisting mainly of approximately 72 per cent lymphocytes of mixed sizes, 21 per cent monocytes, 8 per cent non-degenerate neutrophils and 7 per cent eosinophils) and increased protein concentration (0.85 g/l). PCR on CSF was positive for N caninum and negative for T gondii. The patient was treated with a combination of clindamycin (12.5 mg/kg orally every 12 hours) and trimethoprim/sulfamethoxazole (15 mg/kg orally every 12 hours). Serology titre decreased from 1:800 to 1:400 after two months of treatment. Marked improvement in ataxia and general condition was observed 12 weeks after initiation of therapy. At this point, the serology titre was stable at 1:400. The dog was then lost to follow-up.

Figure 2 Case 3. STIR sagittal (a) image demonstrating multifocal linear hyperintense lesions centrally in the spinal cord parenchyma at the level of caudal C3, mid-C5 and C6–C7 (white arrows). Note the susceptibility artefact from the microchip over the mid-cervical region. Postcontrast fast spine echo T1 sagittal image (b) showing focal contrast enhancement at the level of the C3 lesion (arrow). Transverse T2 FLAIR image (c) showing increased signal intensity surrounding the mesencephalon (arrows). STIR, short-tau inversion recovery; T2 FLAIR, T2-weighted fluid attenuation inversion recovery.

Case 3
A 10-year-old, female, spayed lurcher was referred for pelvic limb ataxia of four weeks duration, which recently progressed to ambulatory tetraparesis. Physical examination was unremarkable. Neurological examination revealed ambulatory tetraparesis, reduced proprioception on all four limbs (worse on the left) and increased spinal cord reflexes. The tentative neuroanatomical localisation was C1–C5 spinal cord segment.

CBC and serum chemistry were unremarkable. N caninum serology was positive at 1:800. MRI of the cervical spinal cord revealed multifocal, intra-axial, asymmetric, increased T2 and short-tau inversion recovery (STIR) signal intensities at the level of caudal C3, mid-C5 and C6–C7 (figure 2A). There was focal but marked contrast enhancement associated with the lesion at C3 (figure 2B) on T1-weighted (T1w) postcontrast images following intravenous injection of 0.1 mmol/kg of gadopentetate dimeglumine (Magnevist, Bayer). MRI of the brain revealed a rim of increased FLAIR signal intensity surrounding the mesencephalon and cerebellum (figure 2C). This rim of abnormal signal intensity also enhanced on postcontrast T2w images. CSF analysis revealed a mixed pleocytosis (46/μl, consisting mainly of approximately 72 per cent lymphocytes of mixed sizes, 21 per cent monocytes, 5 per cent plasma cells and 2 per cent non-degenerate neutrophils) and increased protein (0.85 g/l). PCR on CSF was positive for N caninum and negative for T gondii.

The patient was treated with a combination of clindamycin (12.5 mg/kg orally every 12 hours) and trimethoprim/sulfamethoxazole (15 mg/kg orally every 12 hours). The patient's ataxia and general condition improved markedly over the course of four weeks, but the serology titre was unchanged after six months of treatment. Eight months into the treatment, the dog's clinical condition suddenly deteriorated and it became anorexic. An abdominal ultrasound performed at the referring veterinarian showed a severely enlarged liver.

Treatment with fluid therapy, amoxicillin, S-adenosylmethionine and anti-inflammatory doses of prednisolone was attempted by the referring veterinarian, but no improvement was noted and the owners elected euthanasia. No postmortem examination was available.

Case 4
A one-year-seven-month-old, female English springer spaniel cross was referred for progressive cerebellar ataxia and behavioural changes (the dog started to defecate and urinate inside the house) of four weeks duration. The dog was bright, alert and responsive on presentation. Neurological examination revealed cerebellar ataxia on all four limbs. The tentative
neuroanatomical localisation was multifocal intracranial (cerebellum and forebrain).

CBC and serum chemistry were unremarkable. *N caninum* serology was positive at greater than 1:800. MRI revealed severe cerebellar atrophy (figure 3A). Additionally, heterogeneous T2 FLAIR hyperintensities were noted in the thalamus and the rostral aspect of the brainstem (figure 3B). CSF analysis revealed increased protein levels (0.39 g/l). PCR on CSF was positive for *N caninum* and negative for *T gondii*. The patient was treated with a combination of clindamycin (12.5 mg/kg orally every 12 hours) and trimethoprim/sulfamethoxazole (15 mg/kg orally every 12 hours). The behavioural changes resolved and the patient’s ataxia improved markedly after the first month of treatment; however, repeated serology titre for *N caninum* after six months of treatment was unchanged (>1:800). A phone update two years after the diagnosis revealed that the ataxia had improved. The owner declined a follow-up examination for logistical reasons.

**Case 5**

A two-year-old, male, neutered Labrador retriever was referred for progressive cerebellar ataxia of two weeks duration, more pronounced in the pelvic limbs. The dog was bright, alert and responsive on presentation. Physical examination was normal. Neurological examination revealed hypermetria, more pronounced in the pelvic limbs. The tentative neuroanatomical localisation was the cerebellum. CBC was normal. Serum chemistry analysis revealed increased CK (1169 iu/l). *N caninum* serology was positive at greater than 1:800. MRI scan of the thoraolumbar tract was unremarkable. MRI scan of the brain revealed severe cerebellar atrophy (figure 4). CSF analysis showed increased protein (84 g/l) and nucleated cell count (7/μl, consisting of approximately 56 per cent small lymphocytes, 28 per cent of non-degenerate neutrophils, 11 per cent of monocytes and 5 per cent eosinophils). PCR on CSF was positive for *N caninum* and negative for *T gondii*. The patient was treated with a combination of clindamycin (12.5 mg/kg orally every 12 hours) and trimethoprim/sulfamethoxazole (15 mg/kg orally every 12 hours).

The patient’s ataxia improved after the first two weeks of treatment, but repeated serology titre for *N caninum* after four months of treatment was unchanged (>1:800). The patient remained clinically stable and treatment was stopped after two more months. A follow-up phone call two years after the diagnosis revealed that the ataxia had improved. The owner declined a follow-up examination for logistical reasons.

**Case 6**

A four-year-11-month-old, male, neutered greyhound was referred for progressive ambulatory tetraparesis of three weeks duration. The dog was bright, alert and responsive on presentation. Physical examination was unremarkable. Neurological examination revealed ambulatory tetraparesis (more severe on both thoracic limbs), generalised (mixed vestibular and cerebellar) ataxia, hypermetria in all four limbs and postural reaction deficits in all limbs. Cranial nerve examination was unremarkable. The tentative neuroanatomical localisation was multifocal intracranial (cerebellum and centrum semiovale).

CBC was unremarkable. Serum chemistry abnormalities included increased activities of ALT (678 U/l), AST (471 U/l) and CK (8383 iu/l). *N caninum* serology was positive at greater than 1:800. MRI of the brain showed multifocal ill-defined T1 isoointense, T2 and FLAIR hypointense areas: one in the right caudate nucleus, one involving the cerebral cortex of the right frontal lobe, one diffuse on the left rostral aspect of the hippocampus and several ill-defined patchy lesions in the medulla oblongata (figure 5A,B). There was questionable faint contrast enhancement of the lesions within the hippocampus and medulla oblongata. CSF analysis revealed mixed pleocytosis (17/μl, consisting of approximately 50 per cent lymphocytes, 32 per cent non-degenerate neutrophils and 18 per cent monocytes) and increased protein (0.47 g/l). PCR on CSF was positive for *N caninum* and negative for *T gondii*. The patient was treated with a combination of clindamycin (12.5 mg/kg orally every 12 hours) and trimethoprim/sulfamethoxazole (15 mg/kg orally every 12 hours).

The patient’s ataxia improved after four weeks of treatment and the owner reported that the dog became much more energetic. However, repeated *N caninum* serology at eight weeks of treatment showed that the titre had increased (1:1600). CK activity was within RI. Pyrimethamine (1 mg/kg every 24 hours) and integration with folic acid (0.15 mg/kg every 24 hours) were therefore added to the treatment. Monthly repeated examinations showed progressively decreasing *N caninum* serology titre, up to 1:100 at six months from presentation, when the medications had been stopped, and had remained 1:100 four weeks later, when the dog was neurologically normal.

**DISCUSSION**

In this case series the authors describe the clinical, laboratory and MRI findings of six dogs diagnosed with CNS neosporosis.

As previously mentioned, the inclusion criteria for this case series were based on positive serology (1:800 or above) and...
positive PCR on CSF. This choice was based on the idea that positive serology titres can be found in previously exposed dogs, although titres are generally 1:800 or more in clinically affected animals. A definitive diagnosis of CNS *N caninum* infection is usually based on the presence of DNA of this agent by CSF PCR analysis, although in the literature there is no clear information on the specificity and sensitivity of this diagnostic test.

The present study showed cerebellar involvement in four out of six adult patients, confirming that cerebellar dysfunction and atrophy are a common change in adult dogs infected with *N caninum.* The reasons for the predilection for the cerebellum in adults have not been elucidated yet.

Labrador retrievers seem to be over-represented in studies reporting cerebellar dysfunction caused by *N caninum.* In three previous studies of neosporosis in dogs, three of seven, one of one, and eight of 27 affected dogs were Labrador retrievers. Of the latter eight dogs, three had sustained cerebellar dysfunction. In another study of four dogs with CNS neosporosis, two dogs were Labrador retrievers which showed evidence of cerebellar atrophy and cerebellar lesions on MRI. In the present study, two of four dogs with cerebellar atrophy/lesions detected on MRI were Labrador retrievers.

Also, four out of the six patients diagnosed with CNS neosporosis were fed (occasionally or regularly) with raw meat. This is suspicious of a relationship between this type of diet and the infection (horizontal transmission), but because the diets were not tested for *N caninum* this is speculative.

CK activity was increased significantly in four of the six dogs. The markedly increased CK activity in cases 1 and 6 and its moderately increased activity in cases 2 and 5 could reflect polymyositis, often seen in adult dogs with neosporosis. Normal CK in the other two cases could be explained by the fact that this enzyme can be normal in slowly progressive myopathies. Lack of histopathological examination precludes the differentiation between slow but progressive and absent myopathy.

Increased protein concentration and pleocytosis mixed inflammatory cells in the CSF were the most common alteration found in the CSF of the patients of this study. Typically, the CSF cytology in patients with CNS neosporosis shows pleocytosis, consisting in decreasing order of frequency, monocytes, lymphocytes, neutrophils and eosinophils. This seems to be different in the present study, where five out of six patients showed predominance of (medium and small) lymphocytes.

To the best of the authors’ knowledge, there are only three other papers in the veterinary literature describing the MRI findings of patients with CNS neosporosis, and only one of them reports MRI findings of spinal lesions in two dogs. MRI of the cervical spine of case 3 revealed multifocal, intra-axial, asymmetric T2 and STIR hyperintense and strongly contrast-enhancing lesions. These changes are compatible with the findings described by Parzefall and others, with the difference being that (minimal) contrast enhancement was detected just in one of the two spinal cases described in this previous study. The intracranial lesions detected on the MRI of the patients of the present study are similar to the ones described by Garosi and others in 2010, although in the present cases no loss of contrast between grey and white matter was detected, as opposed to three of seven showing this feature on FLAIR and T2-weighted images in their study. It is important to note that in case 3, although intracranial involvement was not suspected, MRI of the brain showed diffuse increased FLAIR signal intensity around the mesencephalon and cerebellum. It is therefore impossible to know if case 2 (which did not have a brain scan) also had intracranial involvement.

Contrast enhancement of the affected meninges was detected in cases 3 and 4 herein, in agreement with Garosi and others, who reported similar abnormalities in two of seven dogs with neosporosis. This finding was also detected by Gaitero and others, who also described a large left parietotemporal lesion, consistent with a secondary infarct. Additionally, Garosi and others described three dogs having mild or marked T2-weighted hyperintensities and contrast enhancement of the temporalis and masseter musculature and one dog having bilaterally symmetrical T2-weighted and FLAIR hyperintensities in the corona radiata of the occipital lobes. Neither of these findings were detected in the present study. On the other hand, some of the locations of the lesions seen in case 6 (right caudate nucleus, hippocampus) have not been previously described. Despite not having described any MRI lesions at the level of the hippocampus, Gaitero and others described histopathological changes detected in the hippocampus.

Clindamycin has classically been the main treatment for canine neosporosis; however, it has been proven to be effective just in suppressing the replication and dissemination of tachyzoites and does not seem to have any major effects on the encysted bradyzoites. Trimethoprim-sulfamethoxazole and pyrimethamine are warranted in case of neurological involvement, as these drugs have a better penetration of the CNS. It is worth noting that all of the six patients showed initial satisfactory clinical improvement following treatment with clindamycin and trimethoprim/sulfamethoxazole, but only two of them showed complete resolution of the neurological clinical signs. Additionally, case 6 showed an initial increase in serology titre despite the improvement in its neurological status. (It is important to mention that all the samples were processed by the same lab and that every follow-up sample was always analysed in conjunction with the original one; therefore, a clear explanation for this increased titre was not found.)

The lack of complete resolution of clinical signs in most of the patients is likely to reflect the inflammation and necrosis in response to the parasite rather than the presence of cysts in the affected tissues, as postulated by Parzefall and others. Garosi and others described one dog having complete resolution of clinical signs (repeated CSF analysis was normal and repeated PCR on CSF was negative) after nine weeks of treatment; however, no long-term follow-up was provided for this case.

The veterinary literature lacks data about the recommended duration of treatment for canine neosporosis. In a previous study, it was stated that a period of several months proved to be effective for improvement and stabilisation of clinical signs. In the authors’ experience, treatment should be continued for at least four to six months. Improvement or resolution of the clinical signs and monitoring of CK (in cases where this is elevated at the time of first presentation) should be used as markers of effectiveness of the therapy. Given the long-term treatment, regular blood analysis is

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**Figure 5** Case 6. T2 FLAIR transverse (a) and fast spin echo sagittal T2 image (b). The brainstem is heterogeneous with patchy increased T2 signal intensities in both planes (arrows). T2 FLAIR, T2-weighted fluid attenuation inversion recovery.

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also recommended in order to monitor possible side effects related to medications. The authors also recommend periodic serum T4 measurements during therapy with trimethoprim/sulfamethoxazole, as case 1 developed hypothyroidism after six months of treatment. In this patient T4 was completely normal at the time of presentation; therefore, the diagnosed hypothyroidism was believed to be secondary to treatment with trimethoprim/sulfamethoxazole, as previously reported by Gookin and others and Torres and others.24 25 Other adverse effects that may occur after long-term treatment with trimethoprim/sulfamethoxazole include skin eruptions, blood dyscrasias, keratoconjunctivitis sicca, arthropathy and hepatotoxicity.26 In case 3, severe hepatopathy was diagnosed by the referring veterinarian. Given the lack of postmortem examination, the nature of this remains unknown, but a correlation with the long-term use of trimethoprim/sulfamethoxazole is possible.

One of the main limitations of the present study is the lack of histopathology, which precludes establishing the exact nature of changes detected with MRI. Another limitation is the lack of long-term serological follow-up (>7 months) and the fact that the long-term clinical follow-up in cases 4 and 5 was obtained over the phone and was therefore subjective data provided by a non-medically trained person.

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