



Distal polyneuropathy in an adult Birman cat with toxoplasmosis

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Abstract

Case summary A 6-year-old female spayed Birman cat presented with a history of weight loss, stiff and short-strided gait in the pelvic limbs and reluctance to jump, progressing to non-ambulatory tetraparesis over 6 weeks. Poor body condition, dehydration and generalised muscle wastage were evident on general examination. Neurological examination revealed mildly depressed mental status, non-ambulatory flaccid tetraparesis and severely decreased proprioception and spinal reflexes in all four limbs. The neuroanatomical localisation was to the peripheral nervous system. Haematology, feline immunodeficiency virus/feline leukaemia virus serology, serum biochemistry, including creatine kinase and thyroxine, thoracic radiographs and abdominal ultrasound did not reveal significant abnormalities. Electromyography revealed fibrillation potentials and positive sharp waves in axial and appendicular muscles. Decreased motor conduction velocities and compound muscle action potential amplitudes were detected in ulnar and sciatic–tibial nerves. Residual latency was increased in the sciatic–tibial nerve. Histologically, several intramuscular nerve branches were depleted of myelinated fibres and a few showed mononuclear infiltrations. *Toxoplasma gondii* serology titres were compatible with active toxoplasmosis. Four days after treatment initiation with oral clindamycin the cat recovered the ability to walk. *T gondii* serology titres and neurological examination were normal after 11 and 16 weeks, respectively. Clindamycin was discontinued after 16 weeks. One year after presentation the cat showed mild relapse of clinical signs and seroconversion, which again resolved following treatment with clindamycin.

Relevance and novel information To our knowledge, this is the first report of distal polyneuropathy associated with toxoplasmosis in a cat. This case suggests the inclusion of toxoplasmosis as a possible differential diagnosis for acquired polyneuropathies in cats.

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Introduction

Toxoplasmosis is a parasitosis caused by the obligate intracellular protozoan *Toxoplasma gondii*. *T gondii* can potentially affect all warm-blooded animals, including humans, with cats and other felidae being definitive hosts. Congenital infection and ingestion of infected tissue from intermediate hosts or of food and water contaminated with sporulated oocysts are the primary modes of transmission in cats.¹ Neurological signs in cats with serologically or histologically confirmed toxoplasmosis are rare, with reports of 1/15 and 7/100 cases.^{2,3} However, in one study *T gondii* was identified in 44/55 analysed brains.³ Non-suppurative myelitis/meningomyelitis and intracranial granuloma with histological identification of *T gondii* or *Toxoplasma*-like parasites have been previously documented in cats with neurological signs including seizures, circling, altered

behaviour, blindness, anisocoria, ataxia, para-/hemi-/tetraparesis or paraplegia.^{3–9} Considering the association between toxoplasmosis and polyradiculoneuritis in dogs,^{10–12} the potential for *T gondii* to affect the peripheral nervous system in cats has always been suspected; however, to our knowledge, no clinical report confirming this hypothesis has been published previously.

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Herein we describe clinical, serological, electrodiagnostic, histological findings and treatment in an adult Birman cat presented for progressive neuromuscular signs associated with distal polyneuropathy and serologically confirmed toxoplasmosis.

Case description

A 6-year-old spayed female Birman cat presented with a history of weight loss, stiff and short-strided gait in the pelvic limbs and reluctance to jump, progressing to non-ambulatory tetraparesis over 6 weeks. The cat had always lived in the UK and was rehomed 2 months before the onset of neurological signs. It lived indoors and was fed commercial cat food. When initially presented to the primary veterinarian, lumbosacral pain was suspected and 0.1 mg/kg meloxicam (Metacam; Boehringer Ingelheim) PO q24h was initiated. The treatment was discontinued after 48 h because of vomiting, diarrhoea and lack of clinical improvement. The neurological signs slowly progressed for 5 weeks then rapidly deteriorated 1 week before referral, when the cat became non-ambulatory paraparetic and, finally, non-ambulatory tetraparetic. At that stage diarrhoea also recurred. The owner reported a weight loss of 600 g, despite the cat having a normal appetite.

At presentation, the cat's body weight was 2.05 kg and body condition score was 3/9. Dehydration and generalised muscle wastage were evident. The neurological examination revealed mildly obtunded mental status, non-ambulatory flaccid tetraparesis (almost plegia in the pelvic limbs) and severely decreased to absent general proprioception and spinal reflexes in all four limbs. The cutaneous trunci reflex could not be elicited whereas perineal reflexes were preserved. Nociception was normal in all four limbs. Cranial nerve examination was unremarkable and head and neck posture were normal. No hyperalgesia was elicited on spinal or muscle palpation. The neuroanatomical localisation was to the peripheral nervous system. The mild obtundation was

considered the result of dehydration. Differential diagnoses included infectious, immune-mediated, metabolic, idiopathic, neoplastic, paraneoplastic and degenerative polyneuropathies.

Haematology and serum biochemistry revealed signs of mild dehydration. Serum creatine kinase and total thyroxine were within normal limits. Serology for feline immunodeficiency virus (FIV) and feline leukaemia virus was negative. Fluid therapy with Hartmann's solution (Aquapharm 11; Animalcare) was initiated. Twelve hours after presentation, the cat was sedated with 0.2 mg/kg butorphanol (Alvegesic Vet; Dechra) IV and 0.25 mg/kg midazolam (Hypnovel; Roche) IV. Anaesthesia was induced with propofol (Vetofol; Norbrook) to effect and maintained with isoflurane in oxygen. Thoracic radiographs and abdominal ultrasound were unremarkable. Electromyography revealed fibrillation potentials and positive sharp waves in axial and appendicular muscles (Figure 1). The motor nerve conduction study is summarised in Table 1 (Figure 2a,b). Biopsies were obtained from the right biceps femoris and tibialis cranialis muscles and from the right common peroneal nerve.

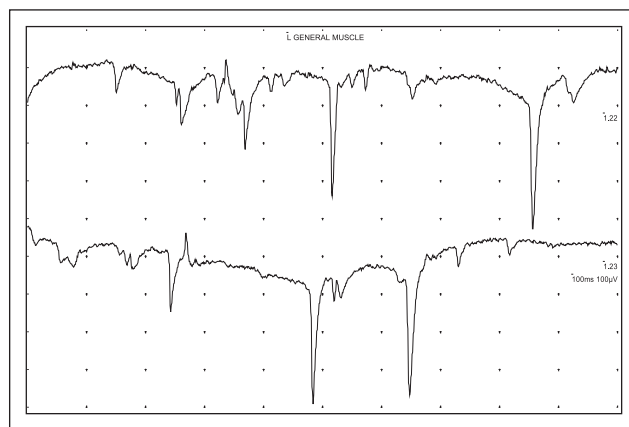


Figure 1 Electromyography of the left biceps femoris muscle showing fibrillation potentials and positive sharp waves

Table 1 Motor nerves conduction study

	Ulnar nerve	Sciatic-tibial nerve
MNCV (reference interval)¹³		
Proximal–distal (m/s)	51.3 (88.3 ± 17.8)	66.0 (101.4 ± 12.9)
Intermediate–distal (m/s)		55.4 (97.4 ± 14.8)
Residual latency (m/s)	1.21 (1.30 ± 0.30)	2.47 (1.9 ± 0.4)
CMAP amplitude (reference interval)¹³		
Proximal stimulation (mV)	1.0 (15.7 ± 4.8)	0.2 (15.6 ± 4.0)
Intermediate stimulation (mV)		0.2 (18.4 ± 3.3)
Distal stimulation (mV)	1.0 (18.8 ± 4.7)	0.2 (20.9 ± 3.4)
Morphology	Temporal dispersion and polyphasia	
Body temperature (°C)	36.9	

MNCV = motor nerve conduction velocity; CMAP = compound muscle action potential

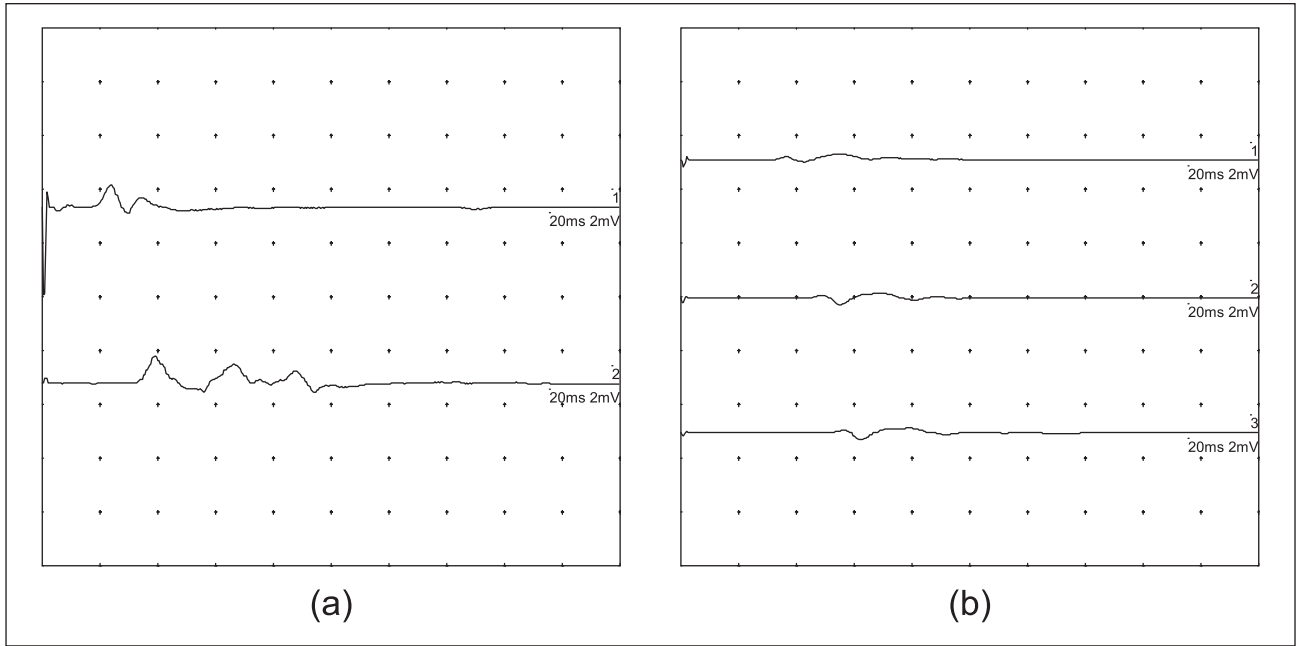


Figure 2 (a) Ulnar nerve conduction study showing decreased amplitude, temporal dispersion and polyphasia. (b) Sciatic-tibial nerve conduction study showing decreased amplitude and temporal dispersion

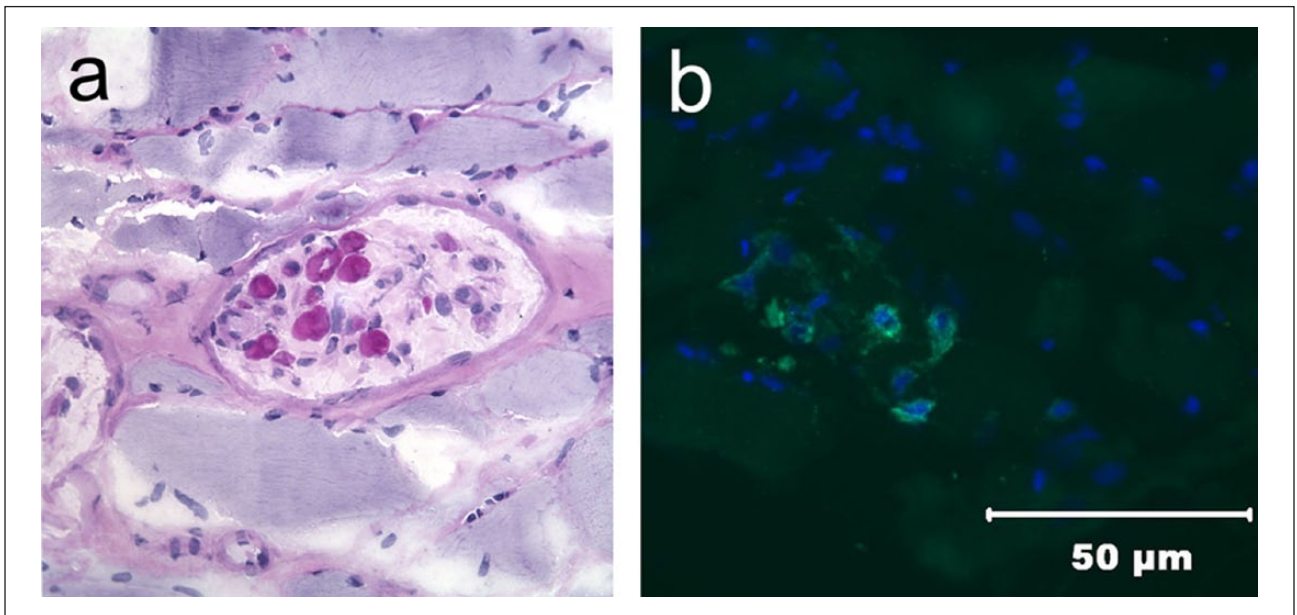


Figure 3 (a) Periodic acid–Schiff (PAS) stain of a cryosection from the cranial tibial muscle showing an intramuscular nerve branch with partial depletion of myelinated fibres and mild mononuclear cell infiltrations. With the PAS stain, myelin stains dark purple. (b) Immunofluorescence staining of cryosections from the cranial tibial muscle using an antibody against feline major histocompatibility complex II. A small cluster of mononuclear cells are highlighted in green with this antibody. (a,b) Scale bar = 50 µm

Stains employed included haematoxylin and eosin, modified Gomori trichrome, periodic acid–Schiff, myofibrillar adenosine triphosphatases at pH 9.8 and pH 4.3, esterase, nicotinamide adenine dinucleotide tetrazolium reductase, acid phosphatase, alkaline phosphatase, oil red O and staphylococcal protein A conjugated to horseradish

peroxidase. Unfixed muscle biopsies were evaluated in frozen sections. Both muscles were similar in appearance. There was a marked variability in myofibre size with numerous large and small groups of atrophic fibres having an angular-to-anguloid shape. Fibre-type grouping was not observed. Several intramuscular nerve branches

were variably depleted of myelinated fibres and contained myelin ovoids. A few of the depleted nerve branches showed an excessive mononuclear cellularity (Figure 3a,b). A fixed biopsy from the right common peroneal nerve was plastic embedded and evaluated in 1 µm sections. The density of myelinated fibres was subjectively appropriate without obvious axonal degeneration, demyelination or abnormalities of the supporting structures.

After obtaining the surgical biopsies, clindamycin (Clindacyl; Vetoquinol) was started at 18.3 mg/kg orally q12h. Meloxicam 0.1 mg/kg PO q24h was added for 3 days. The cat started improving within 24 h and was ambulatory, with occasional plantigrade posture, 4 days after treatment initiation. IgG and IgM *T gondii* serology titres measured with indirect immunofluorescence were 1:200 and 1:160, respectively. The cat was discharged 7 days after presentation. Proprioception and spinal reflexes were still markedly decreased in all four limbs.

The cat re-presented 2 weeks after discharge because of clinical deterioration. The owner reported that the cat had been inappetent during the previous week and clindamycin administration was challenging. On neurological examination the cat was again non-ambulatory tetraparetic; however, when adequately supported, the motor function was greater than at initial presentation. Repeated *T gondii* serology titres revealed 1:50 IgG and 1:40 IgM. After 3 days of appropriate administration of clindamycin the cat was again ambulatory but only for short distances, with occasional plantigrade posture.

The cat gradually recovered body weight and strength in all four limbs. General proprioception and myotactic spinal reflexes were normal 6 weeks after treatment initiation. Muscle size and withdrawal reflexes returned to normal in all four limbs 11 and 16 weeks after treatment initiation, respectively. *T gondii* serology titres were negative after 11 weeks of treatment. Clindamycin was discontinued after 16 weeks of treatment, when the cat recovered the ability to jump onto house furniture.

One year after initial presentation, the owner noticed that the cat again became reluctant to jump. At that stage, the neurological examination was unremarkable and *T gondii* serology titres were negative. Clindamycin was restarted at the same total dose (at that stage equivalent to 14.4 mg/kg) with improvement and normalisation of the ability to jump within 1 and 3 weeks, respectively. *T gondii* serology titres were rechecked 2 and 4 weeks after the suspected relapse and revealed negative IgG with IgM 1:40, and IgG 1:200 with IgM 1:40, respectively. Two months after the relapse, the serology titres showed again negative IgG and 1:40 IgM. Clindamycin was then discontinued and the cat has remained clinically normal for the 4 months until the time of writing of this report.

Discussion

Differential diagnoses for acquired polyneuropathies in cats include infectious, immune-mediated, traumatic, toxic, metabolic, nutritional, idiopathic, neoplastic and degenerative diseases.^{14–17} Reports that associate specific infectious agents with neuropathies in cats are limited to an experimentally induced polyneuropathy/polymyopathy in a cat inoculated with FIV,¹⁸ one case of mycobacterial neuritis,¹⁹ and one case of polyneuritis/polymyositis with associated fever, anaemia and icterus in which numerous intramuscular *Sarcosporidia* species were detected.²⁰ In our case, the clinical presentation, diagnostic investigations and outcome were suggestive of *T gondii* as the possible causative agent of the polyneuropathy. The current guidelines for ante-mortem diagnosis of toxoplasmosis include: (1) serum IgM titres >1:64 or four-fold increase in IgG titres over 2–3 weeks; (2) presence of appropriate clinical signs; (c) exclusion of other possible causes; and (d) positive response to appropriate medications.¹ The case we reported fulfilled at least three of the above criteria. Regarding the presence of appropriate clinical signs, as no other case of polyneuropathy associated with toxoplasmosis in cats was previously described it may be difficult to support the fulfilling of this criterion; however, as reported above, toxoplasmosis is a recognised differential diagnosis of polyneuropathy in dogs,^{10–12} and it has been previously discussed by other authors as a possible cause of similar signs in cats.¹⁴ Despite the absence of direct parasite identification on histopathology, a causal relation between *T gondii* and the clinical signs in this case is suggested by the serology titres compatible with active infection at both initial presentation and relapse (significant increase of IgG in 4 weeks from clinical recurrence) and by the rapid response to clindamycin in three different occasions. Further tests to detect the presence of *T gondii* in the muscle samples, including PCR, could have been performed; however, a positive result would have not necessarily supported the causal relation between the parasite and the clinical signs as detectable parasitic DNA does not necessarily differentiate between chronic and acute forms of the disease.²¹ Considering the lack of exposing factors after being rehomed, reactivation of a previous infection was hypothesised.

The electrodiagnostic findings were suggestive of an axonopathy with a demyelinating component, similar to findings reported in Bengal and other young cats with recurrent demyelinating–remyelinating polyneuropathy (RDRP).^{22,23} A distal localisation of the disease was suspected based on the mildly increased residual latency in the sciatic–tibial nerve.²⁴ A limitation in this report is that F-wave, sensory nerve conduction and repetitive nerve stimulation studies were not performed, which could have further characterised the distribution of the disease.^{23,25} Cerebrospinal fluid analysis would also have

helped in excluding a radicular and/or central involvement; however, it was declined by the owner. Nevertheless, even if not confirmed with electrodiagnostic investigations, the clinically preserved sensory function together with the severely affected motor function suggested a predominantly motor polyneuropathy, and the normal histological appearance of the nerve biopsy with associated significant distal pathology made the concurrent possibility of a radicular component of the disease unlikely.

Our histological findings indeed revealed a moderately severe neuropathy characterised by distal nerve fibre loss and mononuclear infiltrates. The pathogenic mechanism causing distal nerve fibre depletion and inflammation in the absence of direct identification of *T gondii* remains unclear; however, it is possible that parasitic cysts were present in other areas of the sampled muscles or in unsampled muscles. An immune-mediated process triggered by the protozoal infection could not be excluded; however, the clinical response to clindamycin was considered too rapid to be compatible with this option. The possibility of the positive serology being an incidental/unrelated finding and the response to antibiotic therapy coincidental owing to a self-limiting disease was also considered; however, this was deemed improbable considering the serology titres suggestive of active infection at both presentation and recurrence of clinical signs and the consistently rapid response to clindamycin.

Similar histological findings affecting the distal nerve fibres were previously described in young Bengal cats with self-resolving RDRP.²² However, in adjunction to the different signalment, in our case no pathological changes were present in the nerve biopsy that would suggest demyelination or remyelination.

History and histopathological findings in our cat also differ from previously reported cases of self-resolving acute idiopathic polyneuropathy that were characterised by acute onset, rapid progression and moderate-to-severe axonal degeneration and demyelination in ventral nerve roots and nerves.²⁶

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an adult-onset, chronic, slowly progressive inflammatory polyneuropathy with some clinical similarities to the case we described. However, histological findings in CIDP differs from our case as characterised by primary paranodal demyelination and mononuclear endoneurial infiltrates sparing the intramuscular nerve branches.^{27,28} In addition, 88% cats with CIDP have been reported to improve following steroid treatment, which was not administered to our cat.

A steroid-responsive chronic, slowly progressive neuropathy has also been reported in two cats with pronounced depletion of intramuscular nerve fibres but in the absence of inflammatory infiltrates.^{24,29}

In Birman cats, a peripheral and central distal axonopathy of suspected inherited origin has been described. This condition is characterised by an onset of signs at 8–10 weeks of age, slow deterioration and histopathological findings of axonal degeneration,³⁰ and therefore was considered an unlikely differential diagnosis in this Birman cat.

Clindamycin has been described as the drug of choice in the treatment of toxoplasmosis.^{1,2} Of the cats with previously reported neurological toxoplasmosis, two cases with myelitis received clindamycin with no clinical improvement,^{6,7} and two cases with encephalic granuloma underwent decompressive surgery and clindamycin treatment with recurrence of clinical signs at 8 and 21 months, respectively.^{8,9} In our case, the initial response to clindamycin was extremely rapid; however, 4 months were required to obtain clinical remission. Considering the severity of the clinical signs, the immediate relapse associated with inappropriate treatment administration and the absence of previously described successfully treated similar cases, we elected to continue the antiprotozoal therapy until resolution of the clinical signs. Apart from the possibly related inappetence that developed after 2 weeks of treatment, the drug was well tolerated. It is possible that prolonging the treatment until clinical remission was an unnecessary precaution as the active infection may have already subsided, with the persistent clinical signs being simply associated with gradual recovery of anatomical and functional integrity of the affected structures; however, this cannot be proven. Given the absence of direct association between serology titres and clinical signs,¹ basing the duration of treatment on normalisation of the titres was not recommended. The episode of suspected relapse was supported by repeated serology showing positive IgM, significant increase of the IgG within 4 weeks (therefore compatible with active toxoplasmosis according to the reported guidelines)¹ and again rapid clinical response to clindamycin.

Conclusions

Here we describe a case of serologically confirmed toxoplasmosis in a cat with distal polyneuropathy characterised by intramuscular nerve fibre depletion and mononuclear infiltrates. Long-term treatment with clindamycin was efficacious in achieving remission of the clinical signs. An episode of mild relapse occurred 1 year after diagnosis and responded to reintroduction of the treatment. This case suggests the inclusion of toxoplasmosis as a possible differential diagnosis for acquired polyneuropathies in cats.

Conflict of Interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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