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Journal of Feline Medicine and Surgery (2009) **11**, 1005–1010
doi:10.1016/j.jfms.2009.02.011

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CASE REPORT
Axonal neuropathy with unusual clinical course in young Snowshoe cats

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Date accepted: 19 February 2009

Neuropathies in cats are mostly acquired. In comparison to the dog, only very few inherited forms have been described. This case report describes the clinical and diagnostic findings of a suspected inherited feline axonal neuropathy with a very unique clinical course. Two young related male Snowshoe cats were presented with an initially progressive history of recurrent pelvic limb weakness. Electrodiagnostic investigations suggested an axonopathy and muscle–nerve biopsies confirmed axonal degeneration. Over the following 2 years both cats stabilised without any specific treatment, and repeat electrodiagnostic investigations and muscle biopsy in one cat confirmed the tendency for remission.

Snowshoe cats were first introduced by a breeder in Philadelphia in the late 1960s by crossing Siamese with bicolour American Shorthair cats. Three kittens of Siamese parentage that were born with white feet formed the foundation of the breed.[1–3] The breed is established in Europe and, although it is not very common, the number of individuals is increasing. Up to date, no inherited disease in this breed has been reported. This case description presents a probably inherited axonal neuropathy with unusual clinical course in two young Snowshoe cats.

Two male Snowshoe cats, 4 and 8 months old, were presented with a history of pelvic limb weakness. The older cat (cat 1) had revealed the first obvious episode of pelvic limb weakness at 6.5 months of age. The onset was described a fairly acute with a gradual, but complete recovery of signs over 1 week. The cat relapsed with similar signs 2 weeks later. The recurrent episode was again described as rather sudden in onset, but more severe than the first episode. The cat was gradually improving, but not back to normal at the time of presentation 3 weeks later. The owner of the younger cat (cat 2) reported that obvious signs of pelvic limb weakness were noted over the last 3 weeks. The onset was described as rather insidious and the course was initially slightly progressive. Both cats were grown in different environments and have not shared the same home or owner at any point. Both cats were fed commercial cat food and kept indoors. There was no history of toxin exposure.

Clinical examination in cat 1 was unremarkable. Cat 2 revealed severe constipation with large amounts of faeces in the descending colon and rectum. In cat 1, neurological examination revealed a normal mental status and posture. The gait was both ataxic and weak in all four limbs, with the pelvic limbs much more pronounced. Paw positioning was considered as within normal limits. Deficits in hopping, hemiwalking, wheelbarrowing and extensor postural thrust became increasingly evident when testing was repeated. All four limbs were affected with reduced muscle mass, tone and spinal reflexes (withdrawal, extensor carpi radialis, cranial tibial and patella reflexes). In the younger cat, only the pelvic limbs were affected. The gait was ataxic and weak, and hopping, hemiwalking and extensor postural thrust were reduced. Muscle bulk, muscle tone and withdrawal were decreased in the pelvic limbs. Myotactic reflexes were unremarkable. Mental status and posture were normal in this cat. Nociception, panniculus, anal

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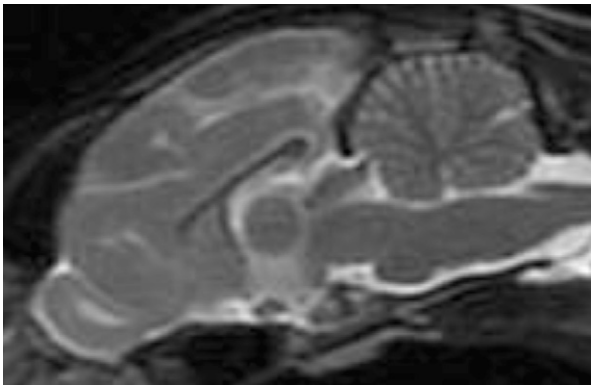

Fig 1. Sagittal T2-weighted MR image of the brain of cat 1: cerebellar sulci are slightly widened as indicated by increased amount of CSF signal in-between foliae, possibly suggesting mild cerebellar hypoplasia or atrophy.

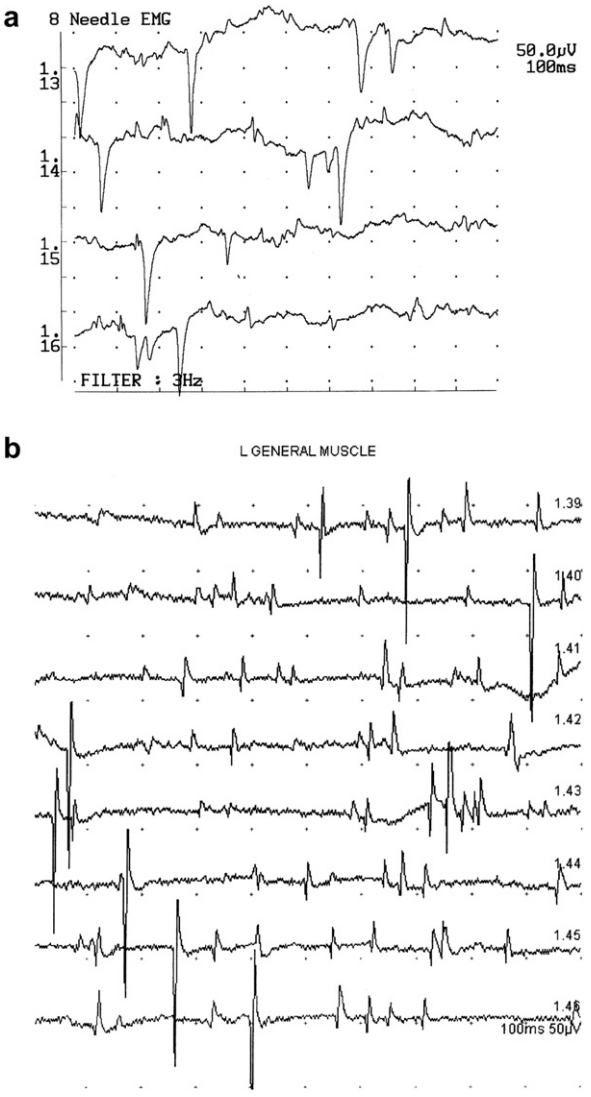

Fig 2. Positive sharp waves and fibrillation potentials were evident in all four limbs upon initial electrodiagnostic assessment (a) in cat 1 and (b) cat 2.

reflex and tail tone were unremarkable in both cats. There was no evidence of spinal pain in cat 1; cat 2 revealed some discomfort on lumbar palpation. Upon cranial nerve examination, mild vestibular/vestibulo-cerebellar disturbances were detected in both cats. Cat 1 had a pendular nystagmus that became intermittently jerky with a fast phase to the left. This cat also showed reduced menace response with normal vision and pupillary light reflexes. In cat 2, occulocephalic reflexes were absent initially, but this could not be confirmed with a repeated neurological examination the same day. The main neurolocalisation in cat 1 was neuromuscular; however, a caudal fossa neurolocalisation was considered additionally. Neurological examination in cat 2 was caudal lumbar intumescence or bilateral sciatic nerve. An additional caudal fossa neurolocalisation appeared rather unlikely in this cat, as occulocephalic reflexes were unremarkable upon repeat examination.

Haematology and blood biochemistry results, including serum creatine kinase activity, were considered as unremarkable in both cats. An acetylcholine receptor antibody titre was performed in cat 1 and was 0.06 nmol/l (reference range 0.00−0.30 nmol/l). Serology for feline leukaemia virus (FeLV) and feline immunodeficiency virus (FIV) was negative in both cats. The *Toxoplasma gondii* titre suggested exposure, but not active infection in cat 1 and was negative in cat 2. Feline coronavirus (FCoV) titres of 1:320 and 1:1280 had been found in cat 1 and cat 2, respectively.

In cat 2, magnetic resonance imaging (MRI) of the lumbar spine and brain was performed, which was unremarkable. In cat 2, MRI of the brain revealed that the cerebellar sulci were slightly widened (Fig 1), possibly indicating mild cerebellar hypoplasia or atrophy. A sample of cerebrospinal fluid (CSF) was obtained by lumbar puncture in both cats. In cat 1 the results were within reference ranges. CSF cytology was unremarkable. In cat 2, the CSF results were consistent with blood contamination (4225 red blood cells/µl, 5 nucleated cells/µl, total protein 0.42 g/l; reference range for nucleated cells <5/µl, reference range for total protein <0.40 g/l). CSF polymerase chain reaction tests for FeLV (cat 1), FIV (cat 1), FCoV, *Toxoplasma gondii* and feline herpesvirus were negative.

Cat 2 was successfully treated for constipation. The owner reported no further progression of signs, but still evidence of pelvic limb weakness. When the cat was neurologically re-examined after 3 months, a tendency to walk with dropped hocks was found. Postural reactions were only slightly delayed in the pelvic limbs, but pelvic limb withdrawal and patella reflexes were weak. The remainder of the neurological examination was unremarkable. The neurolocalisation was lumbar intumescence or lower motor neuron.

Electrodiagnostic testing was performed upon initial presentation in cat 1, and upon the second presentation in cat 2. Fibrillation potentials, positive sharp waves (Fig 2a,b) and reduced motor nerve conduction velocity

Table 1. Motor nerve conduction velocities (m/s) of both cats upon initial electrodiagnostic assessment (investigation 1) and of cat 2 upon repeat electrodiagnostic assessment 22 months later (investigation 2)

Nerve tested	Cat 1, investigation 1	Cat 2, investigation 1	Cat 2, investigation 2	Reference range
Sciatic/tibial overall	51.7 m/s	51.7 m/s	87.95 m/s	86.4–133.2 m/s
Sciatic/tibial proximal	–	65.2 m/s	100.0 m/s	94.8–133.6 m/s
Sciatic/tibial distal	–	38.2 m/s	75.9 m/s	78–133.8 m/s
Ulnar overall	48.8 m/s	–	–	60.2–124.2 m/s

Reference ranges are for cats over 3 months of age.

(MNCV) were found (Table 1). In both cats, there was marked reduction in the amplitude of the compound muscle action potential, and evidence of dispersion (Fig 3a). Repetitive nerve stimulation showed no reduction in the amplitude of the elicited potential.

Surgical biopsies of the quadriceps femoris (cat 1) and biceps femoris and cranial tibial muscles (cat 2) as well as common peroneal nerves (both cats) were obtained. Muscle specimens revealed moderate (cat 1) and marked (cat 2) variation in myofibre size and atrophic fibres of anguloid shape affecting both fibre types, consistent with denervation (Fig 4a). Cat 2 also revealed some fibres undergoing necrosis and phagocytosis secondary to denervation. Semithin sections of the nerve fibres were within normal limits (Fig 5a,b), but teasing preparation (cat 1) revealed a mild axonopathy with secondary myelin changes (Fig 5A–F). Increased myelin sheath crenation, wrinkling and infoldings, that involved paranodes as well as internodes, indicated a mild axonal atrophy confined to large and medium-sized fibres. Further axonal changes comprised varicosities of the internodal segments and crowding of axoplasm at multiple paranodes. Consistent with a reactive Schwann cell hypertrophy, the perinuclear compartments and Schmidt–Lanterman incisures of more than 35% of teased large myelinated fibres (LMF) showed a remarkable enlargement.

Urine organic and amino acids, as well as mucopolysaccharide and oligosaccharide screening (cat 1) was unremarkable.

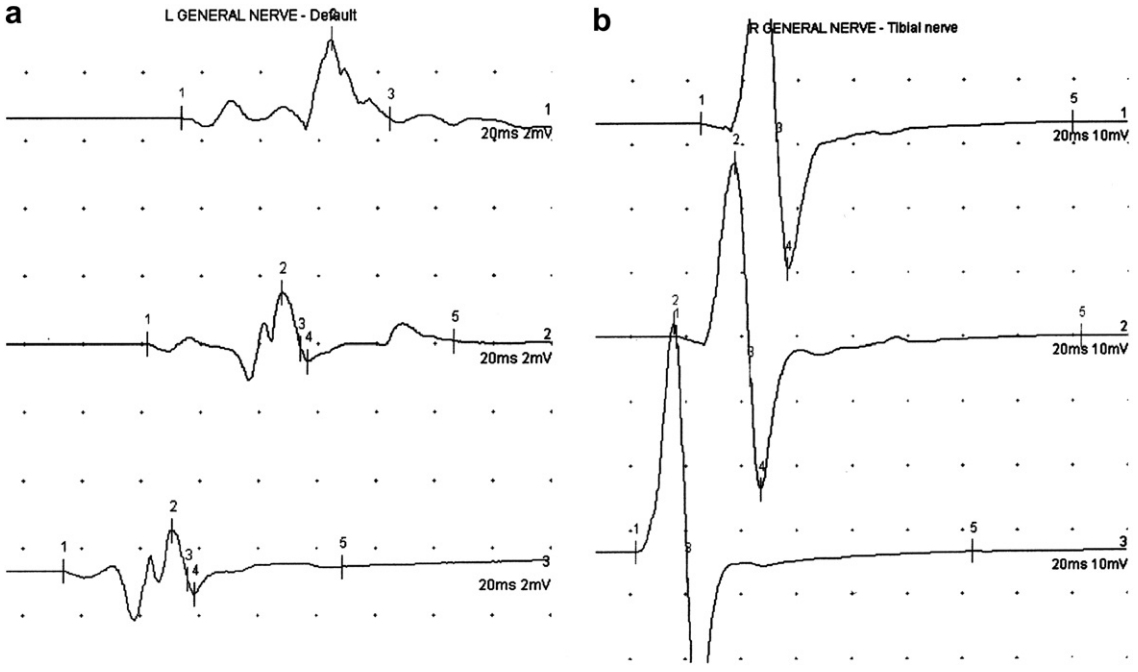

Fig 3. Motor nerve conduction velocity (MNCV) and compound muscle action potentials (CMAP) of the right sciatic/tibial nerve in cat 2 (a) upon initial electrodiagnostic assessment and (b) 22 months later. Note the delay in MNCV (also see Table 1) and dispersion of CMAP with reduction in amplitude upon initial assessment (a) compared with markedly improved values 22 months later (b); Site 1: sciatic notch, Site 2: level of stifle, Site 3: level of tarsus; Latency (ms): Site 1: 7.30 (a) and 4.50 (b), Site 2: 6.15 (a) and 3.65 (b), Site 3: 3.40 (a) and 2.20 (b); Amplitude (mV): Site 1: 2.3 (a) and 23.2 (b), Site 2: 1.5 (a) and 27.4 (b), Site 3: 1.2 (a) and 35.5 (b); Duration (ms): Site 1: 7.10 (a) and 2.75 (b), Site 2: 5.25 (a) and 2.65 (b), Site 3: 4.20 (a) and 1.85 (b).

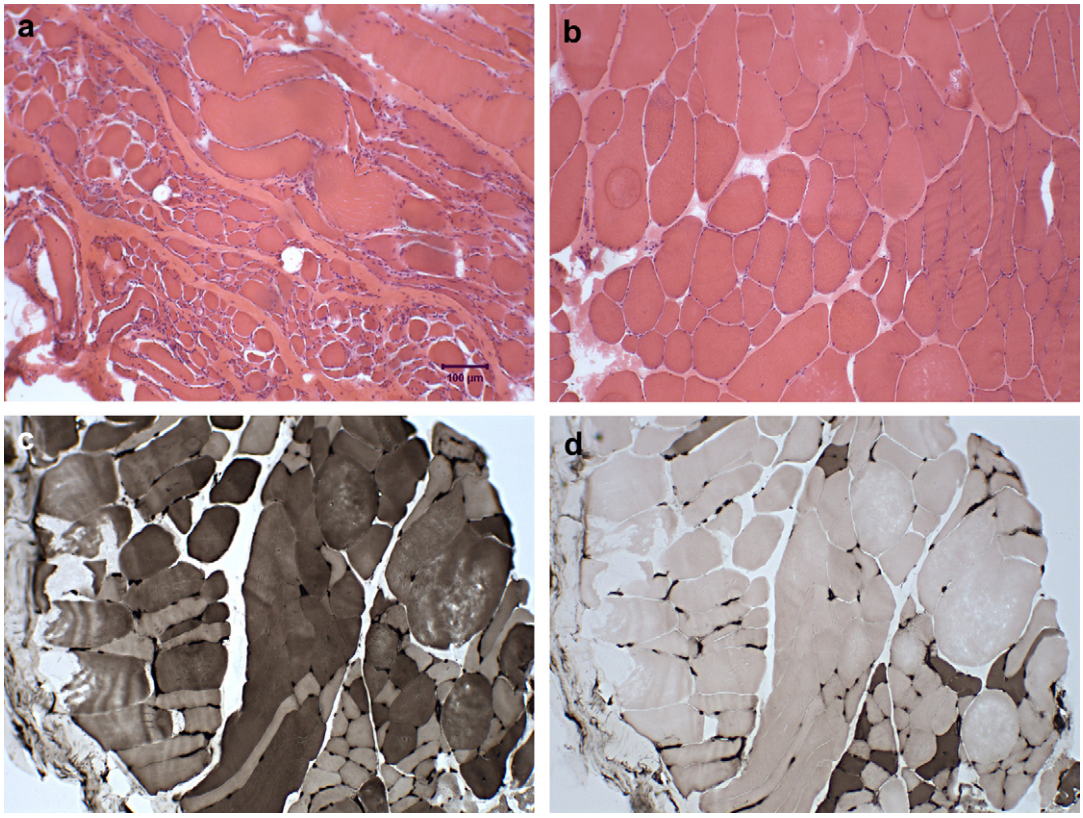

Fig 4. Biopsies of the cranial tibial muscle of cat 2: (a) upon initial assessment (HE stain) and (b,c,d) 22 months later (b, HE stain; c, ATPase ph 9.8; d, ATPase ph 4.3). There is marked variation in myofibre size with atrophic anguloid fibers in the initial biopsy (a) indicating denervation. The follow up biopsy (b,c,d) still reveals variation in myofibre size but fibre type grouping is now evident, indicating reinnervation.

Cat 1 reportedly returned to a complete normal neurological function without any treatment and there was no further evidence of pelvic limb weakness over the next few months. Seven months after the initial presentation though, there was a transient, but milder relapse of signs, from which the cat completely recovered. About 4 months later, the cat suffered a further episode, at which time it had received a single injection of corticosteroids. Since then this cat was supplemented long-term with the Chinese herb Bu Zhong Yi Qi San. Over the following year the cat has reportedly stabilised and no further deterioration was observed. All this information was retrieved by telephone conversation with the owner and referring veterinarian. In a further telephone conversation 1 year later the referring veterinarian stated that the cat seemed overall stable, even though it still could have widespread episodes of about 2−3 weeks duration were the pelvic limbs appeared slightly weaker.

Cat 2 had stabilised over the following months without any specific treatment, was however readmitted almost 22 months later as the owner felt the cat's neurological condition was deteriorating again. She had noted a behavioural change, sporadic body tremors and occasionally misjudging distances. Upon neurological examination mental status and behaviour were unremarkable. A pelvic limb tremor was evident. Postural reactions, spinal reflexes and nociception were considered normal. Bilateral mydriasis with poor pupillary light reflexes due to bilateral iris atrophy was found. The remainder of the neurological examination was unremarkable. Follow-up electrodiagnostic studies were performed and only showed mild spontaneous muscle activity. MNCV and compound muscle action potentials (CMAP) had markedly improved (Fig 3b, Table 1). A muscle biopsy from the cranial tibial muscle (Fig 4b−d) was taken and showed continued variability in myofibre size with small groups of atrophic fibres; however, there was loss of the normal mosaic pattern of muscle fibre types (fibre type grouping), indicating that reinnervation was now apparent.

Pedigree analysis revealed that the paternal grandfather of one cat was the maternal grandfather of the other, and vice versa.

Reported peripheral neuropathies in cats are most commonly acquired.[4] Inherited peripheral neuropathies have only rarely been documented[5] and often primary clinical signs may be referable to more generalised central nervous system disease with concurrent

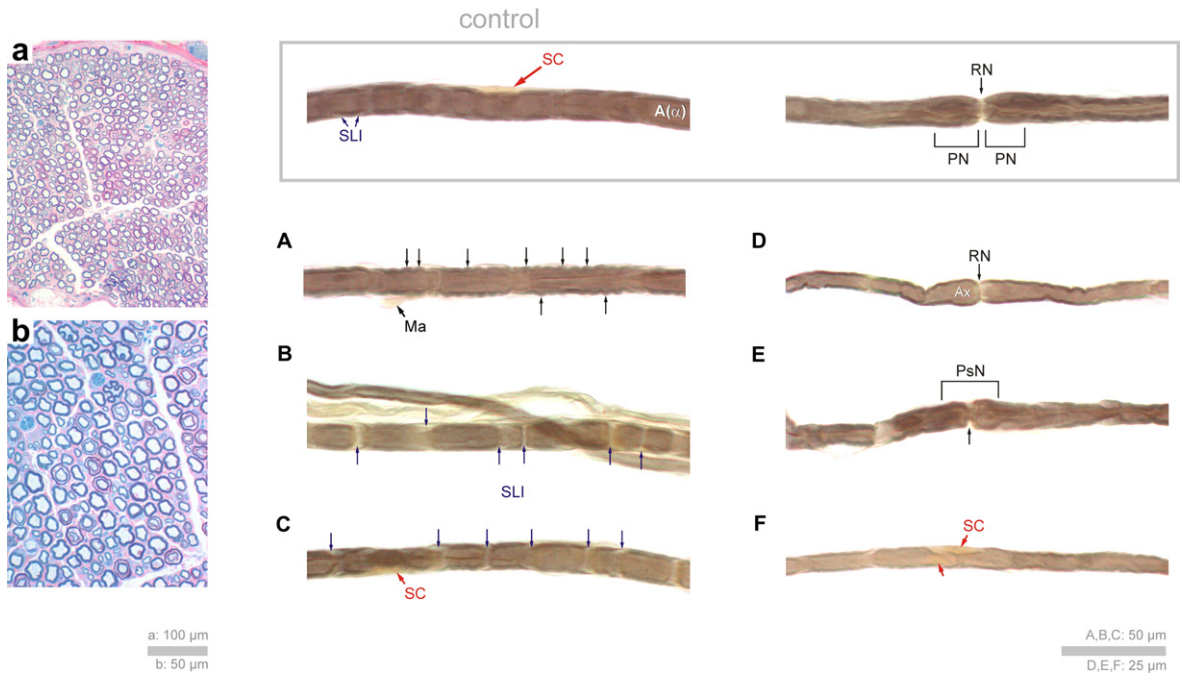

Fig 5. Biopsy of the peroneal nerve of cat 1 upon initial assessment revealing axonal degeneration: Histology (a,b; Azurblue Safranin) does not show any conclusive changes. Teasing preparation (A–F) reveals many large myelinated fibres (LMF) with changes to the internodal myelin sheath contour (A: black arrows) and a significant widening of the Schmidt-Lanterman incisures (B, C: SLI, blue arrows). Paranodal axonal swellings were observed in several large and medium-sized fibres (D: Ax). Many LMF undergoing axonal atrophy show pseudonodes (E: PsN). Throughout all fibre types the perinuclear Schwann cell cytoplasm is quite prominent (F: SC). Several fibres also display a Schwann cell hyperplasia (F: lower red arrow) and a mildly increased number of attaching macrophages (A: Ma). SC: Schwann cell; SLI: Schmidt-Lanterman incisures; RN: node of Ranvier; PN: paranode; PsN: pseudonode; Ma: macrophage/histiocyte.

changes in peripheral nerves. A central-peripheral distal axonopathy has been described in female Birman cats,[6] characterised by loss of myelinated and unmyelinated fibres in peripheral nerves in addition to fibre loss in the central nervous system. Onset of clinical signs in these cats is between 8–10 weeks, and the course is slowly progressive. One of our cats showed consistent clinical evidence of vestibulo–cerebellar signs and MRI of the brain revealed slightly widened sulci of the cerebellum. Whether this could reflect a more generalised neurological syndrome also including the central nervous system, or was an unrelated finding must, however, remain open. Signs associated with vestibulo–cerebellar disturbance did not progress and were not worse during the repeat episodes of neuromuscular weakness. We, therefore, consider the clinical syndrome in both Snowshoe cats as primarily neuromuscular.

Inborn errors of metabolism that clinically primarily reflect peripheral neuropathies have been described in cats and include primary hyperoxaluria[7] and storage disorders such as Niemann-pick disease type A.[8] With primary hyperoxaluria axons are swollen due to accumulation of neurofilaments and Wallerian degeneration occurs. Affected cats usually succumb to acute renal failure.[7] A phenotypic variant of Niemann-pick disease type A has been reported in Siamese cats, demonstrating a primary demyelinating peripheral polyneuropathy with the presence of metachromatic granules. The course of this disease is progressive, and death usually occurs by about 10 months of age.[8] Neither the clinical course, nor clinicopathological findings in our cats were consistent with a metabolic disease.

There are few reports of motor neuron disease in cats,[9–12] and a juvenile onset of autosomal inherited motor neuron disease has been described as a model of spinal muscular atrophy.[10] Depletion of motor neurons in the spinal cord leads to muscle denervation and mild changes in peripheral axons may be evident. The clinical course is progressive.[9–12]

Our case report describes an axonal neuropathy in two male, related, young Snowshoe cats. An acquired disease seems very unlikely based on signalment, history, course of the disease and findings of clinicopathological investigations. This probably inherited neuromuscular syndrome described here is very unusual in respect to; (1) its intermittent occurrence of clinically apparent weakness, and (2) initial progressive character with long-term stabilisation and tendency for remission. In cat 1, the intermittent course was more pronounced, however, the overall follow-up of this cat was longer (over 3 years, compared to the other cat that had a follow-up just under 2 years).

We consider the pelvic limb tremor observed in cat 2 after 22 months as mild residual or recurrent clinical sign of pelvic limb weakness. In both cases, the neurological condition clinically stabilised at a level where they had a very good quality of life according to the owners, and repeat electrodiagnostic investigations and muscle biopsy in cat 2 confirmed remission of the disease. One retrospective study investigating muscle and nerve biopsies in 138 cats found that early age of onset appears to be associated with recovery from peripheral neuropathies.[13] However, whether the underlying cause of axonal degeneration in these two cats is a primary peripheral motor neuropathy or a motor neuron disease remains to be clarified.

References

1. Sayer A, Loxton H. Encyclopaedia of the cat. San Diego: Thunder Bay Press, 1999.
2. Canin Royal. The royal canin cat encyclopaedia. Paris: Aniwa Publishing, 2000.
3. Snowshoe Cat Association. http://www.snowshoecatassociation.co.uk/snowscat.php; 2008.
4. Dickinson PJ, LeCouteur RA. Feline neuromuscular disorders. In: Shelton GD, ed. Veterinary clinics of North America small animal practice, neuromuscular disease II. Philadelphia: Elsevier Saunders, 2004: 1307–60.
5. Coates JR, O'Brien DP. Inherited peripheral neuropathies in dogs and cats. In: Shelton GD, ed. Veterinary clinics of North America, small animal practice, neuromuscular disease II. Philadelphia: Elsevier Saunders, 2004: 1361–402.
6. Moreau PM, Vallat JM, Hugon J, Leboutet MJ, Vandevelde M. Peripheral and central distal axonopathy of suspected inherited origin in Birman cats. *Acta Neuropathol (Berl)* 1991; **82**: 143–6.
7. McKerrell RE, Blakemore WF, Heath MF, et al. Primary hyperoxaluria (L-glyceric aciduria) in the cat: a newly recognised inherited disease. *Vet Rec* 1989; **125**: 31–4.
8. Cuddon PA, Higgins RJ, Duncan ID, Miller SP, Parent JM, Moser A. Polyneuropathy in feline Niemann-Pick disease. *Brain* 1989; **112**: 1429–43.
9. Summers BA, Cummings JF, de Lahunta A. Veterinary neuropathology. St Louis: Mosby, 1995.
10. He Q, Lowrie C, Shelton GD, Menotti-Raymond M, Murphy W, Fyfe J. Inherited motor neuron disease in domestic cats: a model of spinal muscular atrophy. *Pediatr Res* 2005; **57**: 324–30.
11. Vandevelde M, Greene CE, Hoff RJ. Lower motor neuron disease with accumulation of neurofilaments in a cat. *Vet Pathol* 1976; **13**: 428–35.
12. Shelton GD, Hopkins AL, Ginn PE, et al. Adult-onset motor neuron disease in three cats. *J Am Vet Med Assoc* 1998; **212**: 1271–5.
13. Pettigrew R, Kent M, Berry WL, Shelton GD. Muscle and nerve biopsies in 138 cats: diagnosis and outcome. *J Vet Intern Med* 2005; **19**: 422.