Hereditary myopathy of Devon rex cats

R. Malik, K. Mepstead, F. Yang* and C. Harper*

Department of Veterinary Clinical Sciences and *Department of Pathology, The University of Sydney, Sydney, New South Wales 2006, Australia

Journal of Small Animal Practice (1993) 34, 539-546

ABSTRACT

Six closely related Devon rex cats afflicted with a congenital muscle disease were investigated over a three-year period. Physical findings included passive ventroflexion of the head and neck, dorsal protrusion of the scapulae, mega-oesophagus, generalised appendicular weakness and fatigability. Signs became evident at three to 23 weeks of age and then usually progressed slowly or remained static. Plasma levels of creatine kinase and aspartate aminotransferase were not elevated. Histological examination of tissues from affected cats showed changes indicative of a primary myopathy, with neither nerve nor spinal cord involvement. Four of the six cats died suddenly of laryngospasm after obstruction of the pharynx or larynx with food.

INTRODUCTION

In human medicine, the term 'muscular dystrophy' is applied to a number of different disorders which have in common an hereditary nature, primary involvement of striated muscle and a tendency to progress (Gardner-Medwin 1980, Sharp and others 1989). Characteristically, the distribution of muscle involvement is highly stereotyped, involving certain muscles more than others in patterns that are usually consistent within affected families. These patterns, together with the rate of progression and mode of inheritance, provide an effective basis for classifying patients (Gardner-Medwin 1980).

Since 1974 it has been recognised that some Devon rex cats suffer from an inherited disease that results in muscle weakness. This disorder has been erroneously termed 'spasticity' by breeders throughout the world, and numerous case descriptions can be found in journals such as Rex Talk, Rexchange and the Devon Rex Newsletter. The clinical syndrome has been described briefly by Lievesley and Gruffydd-Jones (1989), while detailed accounts of individual cases are available in breeders' journals. A synthesis of these descriptions is presented below.

The most obvious and consistent feature of this condition is passive ventroflexion of the head and neck (Fig 1A). This sign is also seen in some other feline diseases in which there is generalised muscle weakness, such as polymyositis (Schunk 1984), hypokalaemic polymyopathy (Dow and others 1987, Leon and
MATERIALS AND METHODS

Six Devon rex cats with hereditary myopathy were examined over a three-year period. All were related to a ‘carrier’ stud used in a test mating scheme. This cat sired cases 1 to 5, while the remaining case was sired by case 3. Routine physical and neurological examinations were performed on all the cats. Blood from four cats was collected for haematology and plasma biochemical analyses, including creatine kinase (CK), aspartate aminotransferase (AST) and electrolyte determinations. Blood typing of four cats was performed using methods described by Auer and Bell (1981).

Muscle biopsies were collected from five of the animals, either under halothane/nitrous oxide anaesthesia (two cats) or at necropsy (five cats). The long or lateral head of m. triceps brachii was examined in all cases, while a selection of appendicular muscles including m. biceps femoris and some dorsal cervical muscles (usually m. splenius or m. semispinalis capitis) were evaluated in animals examined post mortem. Fresh unfixed muscle samples from three cats were rapidly frozen by submerging small blocks of tissue immersed in isopentane cooled in liquid nitrogen. Longitudinal and transverse sections (8 μm) were cut on a cryostat and stained with haematoxylin and eosin, Gomori’s modified trichrome, oil red O, periodic acid-Schiff, and reacted for myosin adenosine triphosphatase (ATPase) preincubated at pH 9.4 or 4.6, succinic dehydrogenase and acid phosphatase. The presence of dystrophin was determined using immunofluorescence (Carpenter and others 1989). Haematoxylin and eosin stained, paraffin embedded sections of formalin-fixed muscle (7 μm) were also prepared from these three cases, and in all the cats examined post mortem. In two cases, fresh muscle was submitted for determination of mitochondrial enzyme activities. Muscles from a young adult, domestic shorthaired cat were processed simultaneously as a control for the histochemical reactions and mitochondrial enzyme determinations.

Portions of the sciatic, tibial and ulnar nerves were collected at necropsy, fixed in 3 per cent glutaraldehyde or Karnovsky’s fixative, trimmed, post fixed in 1 per cent osmium tetroxide and processed for embedding in resin. Sections (1 μm) were cut and stained with toluidine blue. Samples of other tissues including spinal cord, brain, heart, stomach and oesophagus were fixed in 10 per cent buffered formalin, embedded in paraffin, cut at 7 μm and examined using conventional light microscopy.
Electromyography and motor nerve conduction studies were performed in one cat using standard techniques (van Nes 1986, Malik and Ho 1989). Oesophageal motility was assessed in four cats using videofluoroscopy following the administration of a liquid suspension of barium sulphate (100 per cent w/v).

**RESULTS**

**Physical findings**

Signs of muscle weakness were first detected by breeders when kittens were three to 23 weeks old. Affected cats showed similar manifestations of weakness, although there was considerable variation in the severity of signs and, to a lesser extent, the muscle groups most affected. Passive ventroflexion of the head and neck was most consistent abnormality (Fig 1A). In some cases it was so severe that the chin became tucked into the sternum, particularly after exertion. Appendicular weakness was present to a variable degree: one cat could exercise freely and had a near normal gait most of the time, four cats had a stiff exaggerated forelimb action, head bobbing and reduced exercise tolerance, while the most severely affected cat eventually developed such severe weakness that it could only move a few metres before fatiguing (Fig 1B). Shortening of the stride and tremor of the limbs was sometimes evident during exercise, reflecting maximal recruitment of motor units in the face of deteriorating muscle strength. Dorsal elevation of the scapulae was noted consistently during exercise, reflecting weakness of the shoulder girdle musculature.

The severity of signs in a given cat fluctuated from day to day and week to week for reasons that could not always be appreciated. Concurrent illness (typically respiratory infections), stress (such as an unfamiliar environment) and cold ambient temperature tended to accentuate the weakness. Muscle strength tended to deteriorate slowly with time, although this trend was often subtle. Some cats had little or no difficulty in prehending and swallowing food, while others suffered recurrent ‘choking’ episodes during eating, presumably because pharyngeal muscles were too weak to adequately propel boluses of ingesta through the upper oesophageal sphincter. Cats were usually fed by hand or from a raised platform to minimise the risk of asphyxiation. Despite these precautions, four animals died of generalised muscle atrophy and mitral valve dysplasia were observed at necropsy. Hereditary ri~yopatl~y of Devon rex cats

Detailed neurological testing was difficult to perform because of the strong willed personality of these cats, however there were no significant findings apart from cervical ventroflexion. Muscle tone, deep tendon and withdrawal reflexes were all within normal limits.

**Case histories**

Case 1, a male, first displayed signs at 10 weeks of age. Muscle weakness was moderate (Fig 1A) and pharyngeal dysfunction was not prominent. It was used as a stud in a test mating programme, siring one litter before being castrated at 25 months of age. The cat’s clinical status remained essentially static until death occurred suddenly at 27 months of age after choking on a large piece of meat. Laryngospasm, pulmonary oedema, megaesophagus, oesophagitis and chronic bronchitis were observed at necropsy.

Case 2, a female littermate of case 1, first displayed signs when 11 weeks old. Although appendicular weakness was only moderate, it suffered repeated ‘choking’ episodes during feeding. These episodes were so severe that on many occasions the owner would intervene to dislodge offending food material. Electrodiagnostic studies, ovariohysterectomy and muscle biopsy were performed on the kitten at nine months of age. The cat’s clinical status remained stable until it died suddenly during a choking episode when 19 months old. Laryngospasm, pulmonary oedema, megaesophagus and chronic bronchitis were noted at necropsy.

Case 3, a male sibling of cases 1 and 2, first developed definitive signs at 23 weeks of age, although regurgitation was observed prior to this. Its condition deteriorated over several months, the cat developing a slow deliberate crouching gait with protrusion of the scapulae and low head carriage (Fig 1B). Although it could only walk short distances before fatiguing, cervical ventroflexion was not particularly prominent. The cat sired two litters before disabling myopathic weakness prevented mating. The cat suffered post prandial colic, referable to reflux oesophagitis, which responded to varying combinations of ranitidine, metoclopramide and cisapride. Muscle strength continued to deteriorate, particularly after a respiratory infection acquired at 18 months of age. Although eventually responding to antibiotics, the cat never fully regained its original level of strength or activity and oesophagitis became refractory to therapy. It was euthanased at two years of age. Megaesophagus (Fig 2A), severe chronic reflux oesophagitis (Fig 2B), mild generalised muscle atrophy and mitral valve dysplasia were observed at necropsy.

Case 4, a male, developed typical signs when six weeks old. Although weakness was moderate, episodes of ‘choking’ during meals were encountered from an early age and laryngeal obstruction
FIG 2. Megaoesophagus in a Devon rex with severe hereditary myopathy (case 3). (A) Although the entire oesophagus was affected, dilatation was most prominent in the caudal thoracic region (long arrows) and at the thoracic inlet (short arrows). (B) Chronic ulcerative reflux oesophagitis was present resulting in death at six months of age.

Case 5, a male (Fig 1C), developed signs at seven weeks of age. Muscle weakness was moderate but worsened during winter. Episodes of laryngeal obstruction were problematic, although feeding from a raised platform reduced their frequency. Weakness was markedly exacerbated following the intravenous administration of edrophonium (0.1 mg/kg). Muscle biopsies were obtained at nine months of age when the cat was castrated and 11 months later after it died of upper airway obstruction. Laryngospasm, pulmonary oedema, forelimb muscle atrophy and megaoesophagus were observed at necropsy.

Case 6, a female, developed typical signs at four weeks of age, although more subtle weakness was detected one week earlier. This cat was only mildly affected, with near normal exercise tolerance and no swallowing difficulties. It was 20 months of age at the time of writing, with only slight deterioration in motor performance.

Laboratory findings

Routine haematology and plasma biochemistries were within reference ranges in all four cats tested. In particular, there was no elevation in CK or AST activity and electrolyte concentrations including potassium were normal. All four cats tested were of blood group B. The activities of a range of mitochondrial enzymes in fresh muscle samples from cases 2, 5 and a control cat were similar, and within the human reference range.

Radiological findings

Oesophageal hypomotility and megaoesophagus were observed in all four cats examined. In each case a U-shaped diverticular dilatation of the oesophagus was present at the thoracic inlet (Figs 3A and B). Although ventral deviation of the oesophagus at the thoracic inlet may represent normal anatomical variation (Thrall 1980, Stickle and others 1992), the changes seen in these cats were pathological. In cases 1, 2 and 6 oesophageal dilatation and hypomotility were mild to moderate, with primary contractions adequate to clear the oesophagus of liquid barium. However, case 3 had marked oesophageal hypomotility with prominent dilatation of the cranial and caudal portions of the thoracic oesophagus (Fig 3B). Dilatation and hypomotility of the stomach was also present in this cat (Fig 3C) and poor lower oesophageal sphincter function allowed
severe gastroesophageal reflux of barium during contractions of the fundus.

**Neurophysiological findings**

Only case 2 was examined electrodagnostically. Sparse fibrillation potentials and positive sharp waves were detected in the m. triceps brachii and dorsal cervical muscles using a concentric needle electrode. Myotonic or bizarre high frequency discharges were not encountered. Conduction velocity of motor axons in the tibial and ulnar nerves and the response to repetitive supramaximal nerve stimulation were within normal ranges (Malik and Ho 1989).

**Pathology**

In each instance, skeletal muscle appeared grossly normal at biopsy and necropsy. Similar histological changes were observed in all muscles examined, although the extent and severity of changes varied from case to case and from muscle to muscle in a given individual. There was a tendency for dorsal cervical and proximal forelimb muscles to be affected more than proximal hindlimb and distal limb muscles. Histological changes were positively correlated with both the severity of signs and age at time of biopsy.

Pathology was subtle in mildly affected individuals, especially if specimens were collected when cats were young. A proportion of muscle fibres had larger cross sectional areas than those observed in normal cats and tended to be more rounded and less polygonal than usual (Fig 4B). There were also small angular fibres, both singly and in small groups. These two features resulted in an increased variation in the size of muscle fibres. Occasional degenerating fibres were observed, with numerous histiocytes in and around them (Fig 4B). The number of subsarcolemmal nuclei was increased and some fibre regeneration was evident.

Severe dystrophic changes were present in muscles collected from older, more severely affected cats (Figs 4A and 5B and C). Variation in fibre cross sectional areas was more extreme. Increased numbers of nuclei, internal nucleation and fibre splitting were conspicuous (Figs 4A and 5B and C). Necrotic fibres and regenerating fibres were present, histiocytes were evident around blood vessels and surrounding fibres undergoing segmental necrosis and increased quantities of interfascicular connective tissue were present. There was a tendency for abnormal fibres to be grouped in fascicles (Fig 5B). There was no lymphocytic or plasmacytic infiltrate or vasculitis in any muscles examined.

Sections reacted for myosin ATPase showed the normal predominance of fast twitch (type II) fibres observed in feline muscle (Collatos and others 1977). Large rounded fibres and small angular fibres were comprised of both fibre types and fibre type grouping was not seen (Fig 5D). The presence of dystrophin was confirmed using immunofluorescence.

Peripheral nerve samples from cases 2, 3 and 4 showed no evidence of axonal degeneration, demyelination or cellular infiltration. Spinal cords (cases 1, 2 and 5) and brains (cases 1 and 5) were grossly and histologically normal.

**DISCUSSION**

There is compelling evidence that the inherited disease which afflicts Devon rex cats is a congenital myopathy. Characteristic clinical signs, including ventroflexion of the head and neck, protrusion of the scapulae and oesophageal weakness all reflect dysfunction of striated muscle, while skeletal muscle pathology is suggestive of a muscular dystrophy. The neurological findings,
FIG 5. Histology of skeletal muscle from (A) a normal cat and (B to D) a Devon rex cat with hereditary myopathy. Haematoxylin and eosin (H and E) stained frozen sections from the m. triceps brachii of a healthy young adult cat are shown in (A). Muscle fibres are polygonal, their shortest diameter ranging from 30 to 80 μm. (B) H and E stained frozen sections from the m. triceps brachii of a severely affected cat (case 3), which includes an especially badly affected fascicle (shown at higher magnification in Fig 4A). Note the extreme variation in fibre size with rounded hypertrophic fibres (up to 120 μm), groups of small angular fibres (typically less than 20 μm), necrotic fibres and regenerating fibres. Increased numbers of nuclei, internal nucleation and fibre splitting are prominent. (C) Similar changes are present in the H and E stained sections from the dorsal cervical muscles, but fibre size variation is even more extreme, diameters ranging from 10 to 160 μm. The star denotes a rounded hypertrophic fibre. (D) Myosin ATPase reacted sections of the m. triceps pre-incubated at pH 4.6; representative type I and type I1 fibres are labelled. The usual predominance of fast twitch (type II) fibres observed in normal cat muscle is preserved, with large rounded fibres and small angular fibres comprised of both fibre types. Fibre type grouping is not present. Scale bar 100 μm

particularly the persistence of deep tendon reflexes, and normal nerve histology ruled out peripheral neuropathy, while the possibility of motor neuron disease was excluded by normal spinal cord histology, and absence of neurogenic features in muscle biopsies (Gardner-Medwin 1980, Bethlem and Knobbout 1987).

Central cores, nemaline rods, ragged red fibres and increased stores of glycogen or lipid were not evident in muscle from affected cats, and mitochondrial enzyme activities were normal in the cats tested. Thus histological features of central core disease, nemaline myopathy, mitochondrial myopathies and storage myopathies were absent (Gardner-Medwin 1980, Bethlem and Knobbout 1987). Congenital myasthenia gravis was excluded on the basis of the normal response to repetitive nerve stimulation (case 2), exacerbation of weakness following anticholinesterase dosing (case 5), and the skeletal muscle pathology.

Muscle histology in affected cats demonstrated many features of a dystrophy, including increased variability in muscle fibre size, hypertrophy and atrophy of fibres, rounded and split fibres, internal nucleation, individual myofibre necrosis, regeneration and fibrosis. Although these changes allow the disorder to be classified as a muscular dystrophy, they are unhelpful in categorising the type of dystrophy present in relation to entities so far defined in man and animals.

The muscular dystrophies have traditionally been separated into nosological entities according to phenotypic characteristics such as the age of onset, distribution of muscle involvement, rate of progression, associated features, laboratory findings and mode of inheritance (Gardner-Medwin 1980, Specht 1992). With respect to these criteria, clinical and pathological features observed in affected cats resembled those seen in the human congenital muscular dystrophies, although signs in affected children are much more severe compared with those in cats described in the present report (Zellweger and
others 1967, Gardner-Medwin 1980). These disorders are not ‘typical muscular dystrophies’ because although dystrophic pathology is present and associated with generalised weakness, there is little or no progression over time.

Signs of weakness and fatigability in affected cats were detected as early as three weeks of age, suggesting the myopathy was congenital. Generalised weakness was present, although the distribution and extent of muscle involvement was variable. Cats deteriorated up until six to nine months of age, after which the disease became stable or only slowly progressive. Contractures, hypertrophy and pseudohypertrophy were not observed, but mild atrophy developed in some cases. Dilatation of the caudal thoracic oesophagus suggested smooth muscle involvement (Bremmer and others 1970), as did gastroparesis in case 3.

The natural course of the disease depended on the severity of the myopathy and particularly the extent of pharyngeal involvement, as ingestion induced laryngospasm was usually the cause of death. Laboratory investigations were unhelpful in establishing a diagnosis, apart from excluding diseases such as hypokalaemic polymyopathy from the differential diagnosis. The consistently normal plasma levels of muscle leakage enzymes was surprising given the pathology present, but paralleled the situation in human congenital muscular dystrophy. Confirmation of the diagnosis was dependent on pedigree analysis, characteristic clinical signs and the procurement of muscle biopsies. Pathological changes were most obvious in the m. triceps brachii and dorsal cervical muscles and these muscles are recommended for biopsy.

It was possible to exclude other inherited primary myopathies of cats from the differential diagnosis on the basis of physical findings and laboratory results. Cats with X-linked muscular dystrophy with dystrophin deficiency do not have prominent cervical ventroflexion, and signs of appendicular weakness are milder and accompanied by muscular hypertrophy and markedly elevated plasma CK levels (Vos and others 1986, Carpenter and others 1989). Although cats with nemaline myopathy have appendicular weakness, their most conspicuous clinical feature is tremor. Furthermore, deep tendon reflexes are absent, CK levels are elevated and there is no ventroflexion of the head and neck (Cooper and others 1986). Although the clinical features of hypokalaemic polymyopathy (Eger and others 1983, Baxter and others 1986, Dow and others 1987, Mason 1988) are virtually indistinguishable from those encountered in affected Devon rex cats, the presence of lowered potassium levels and increased CK activity in plasma rapidly differentiates these disorders.

Finally, hereditary myopathy of Devon rex cats has certain similarities with the myopathy of labrador retriever dogs that has been studied in the UK and North America (McKerrell and Braund 1986, 1987). These dogs also show signs of muscle weakness and fatigability, low head carriage, megaoesophagus and histological changes suggestive of myopathy, but differ from affected cats in having diminished deep tendon reflexes.

ACKNOWLEDGEMENTS

The authors wish to thank Dr Peter Stewart of the Royal Prince Alfred Hospital for mitochondrial enzyme activity determinations, Dr Kevin Bell of the Australian Equine Blood Typing Research Laboratory for blood typing and Julia Bavestock for expert technical assistance. Contrast radiology was performed and interpreted by Dr Graeme Allan, while Dr Paul Canfield provided general assistance with pathology. The study would not have been possible without the cooperation and detailed observations concerning ‘Grumps’, ‘Timmy’, ‘Chinco’, ‘Heinz’, ‘Munchkin’ and ‘Beetle Brows’ provided by Sybil Drummond, Margaret Welsh and Lee Wright. The study was supported financially by the Sydney University Veterinary Teaching Hospital.

REFERENCES


