'Continuous muscle fibre activity' in six dogs with episodic myokymia, stiffness and collapse

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Continuous muscle fibre activity was observed in a crossbred dog, a Yorkshire terrier, a border collie and three Jack Russell terriers. The clinical signs consisted of episodes of generalised myokymia which developed into muscle stiffness and delayed muscle relaxation and generally led to the dogs collapsing into lateral recumbency. These episodes were preceded by intense facial rubbing in three of the dogs, and were associated with severe hyperthermia in five of them. All three Jack Russell terriers showed continuous ataxia. The dogs had above normal activities of aspartate aminotransferase, alanine aminotransferase and creatine kinase, but their cerebrospinal fluid was normal. Myokymic discharges were observed by electromyography in two of the dogs. Two of them were treated with membrane-stabilising agents, with variable results.

IN human medicine, the phrase 'continuous muscle fibre activity' (CMFA) has been applied to a heterogeneous group of hereditary and acquired conditions that share the feature of sustained involuntary muscle contractions of peripheral nerve origin, conditions which must be differentiated from central disorders and primary muscle disorders (Auger and others 1984, Auger 1991, 1994). In conditions of peripheral nerve origin, the CMFA is due to the hyperactivity of peripheral nerve motor axons. These conditions do not stem from a single disease process but are the result of the response of peripheral nerves to several different insults, each of which affects nerve function and induces the spontaneous activity of motor axons. As a result, they vary in their clinical signs, associated electrophysiological abnormalities and morphological findings. However, they share the feature of sustained involuntary muscle contraction (Auger 1991, 1994, Odabasi and others 1996). Terms used to describe related syndromes include neuromyotonia (Mertens and Zschocke 1965), Isaacs' syndrome (Isaacs 1961), Isaacs-Merton syndrome (Coërs and others 1981), quantal squander syndrome (Isaacs 1967), generalised myokymia (Harman and Richardson 1954), pseudomyotonia (Coërs and others 1981) and neurotonia (Warmolts and Mendell 1980). A striking feature in patients with these syndromes is myokymia (Auger and others 1984, Jamieson and Katirji 1994), a contraction of independent small bands of muscle fibres which induce an undulating, vermiform movement of the overlying skin (Walton 1988). Myokymia is associated with muscle stiffness, cramps, delayed relaxation and weakness in many of the syndromes mentioned above (Kimura 1983, Jamieson and Katirji 1994, Layzer 1995, Shillito and others 1995, Engel 1996). Other associated phenomena can include the absence of tendon reflexes (Isaacs 1961, Lance and others 1979), muscle hypertrophy (Valilescu and others 1984, Sinha and others 1991), action or percussion myotonia (Isaacs 1967, Lance and others 1979, Valilescu and others 1984), excessive sweating (Isaacs 1961, Auger and others 1984) and high activities of creatine kinase (CK) (Kimura 1983, Odabasi and others 1996). In veterinary medicine, only one case of suspected myokymia has been reported, in a Yorkshire terrier (Reading and McKerrell 1993), in which it was also associated with muscle stiffness, leading to collapse into lateral recumbency and delayed muscle relaxation.

This paper describes six more dogs with myokymia associated with muscle stiffness and delayed muscle relaxation. Because the myokymia was associated with other clinical signs, the more generalised term CMFA has been used to describe the cases.

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CASE REPORTS

Case 1: crossbred dog

In 1992, an eight-month-old male crossbred dog had a series of episodes in which it collapsed into lateral recumbency without losing consciousness; the episodes were triggered by exercise and lasted for 10 minutes to two hours, during which the dog was unable to rise and developed stiffness in its hindlimbs. A blood sample taken by the referring veterinarian showed slightly high activities of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). The dog was treated with barbiturates for one week, apparently without effect; it was said to be clinically normal between episodes.

The results of clinical and neurological examinations were initially normal. A complete blood count was normal, but a biochemical examination revealed the following abnormalities: AST 102·1 iu/litre (reference range 15·0 to 35·0 iu/litre), ALT 177·6 iu/litre (24·0 to 54·0 iu/litre) and CK 1629·7 iu/litre (60·0 to 110·0 iu/litre) (Table 1). The dog was hospitalised for further examination, and while in hospital it had several episodes of rhythmic, undulating muscle movements that induced a vermicular movement of the overlying skin. These contractions were most clearly visible on the limbs, but were also present on the body. The episodes were generally preceded by a period during which the dog rubbed its nose intensely with its forelimbs for several minutes, and they were often followed by a collapse into lateral recumbency, with moderate forelimb and severe hindlimb extensor rigidity. During such a collapse, the dog panted rapidly and developed hyperthermia (40 to 40·5°C) and mild cyanosis. It did not lose consciousness. The collapses lasted between 10 and 30 minutes, after which the dog's condition gradually improved. After each collapse, the dog's gait was abnormal for several hours; it was stiff, making fluid movements impossible, and rotated both fore- and hindlimbs mildly outward when moving, holding its elbows and knees in a semi-flexed position. The episodes of involuntary muscle movements were generally precipitated by stressful situations.

An analysis of cerebrospinal fluid (CSF) was normal, and an electrophysiological examination, made when the dog was normal, revealed no abnormalities.

The dog was discharged on diazepam (Valium; Roche) at 0·5 mg/kg orally, three times a day, which had no effect. It continued to have episodes of rhythmic, undulating muscle movements, occasionally leading to its collapse into lateral

TABLE 1: Results of clinical, neurological, blood, cerebrospinal fluid (CSF) and electromyographic examinations in the six dogs with episodic myokymia

Dog	Clinical examination	Neurology	Blood (reference range)	CSF	EMG
1	Facial rubbing, rhythmic, undulating muscle contractions, collapse with extensor rigidity, hyperthermia	Normal	AST 102·1 iu/litre (15·0-35·0 iu/litre) ALT 177·6 iu/litre (24·0-54·0 iu/litre) CK 1629·7 iu/litre (60·0-110·0 iu/litre)	Normal	Normal
2	Rhythmic, undulating muscle contractions, muscle hypertrophy	Normal	Lymphocytes 25 x 10^8/litre ($7-14 \times 10^8$/litre) AST 44·0 iu/litre ALT 109·0 iu/litre AP 47·0 iu/litre (60·0-120·0 iu/litre) CK 322·6 iu/litre	ND	Normal
3	Normal	Generalised ataxia	CK 1629·7 iu/litre	ND	ND
4	Normal	Ataxia of all four limbs	CK 362·5 iu/litre	Normal	ND
5	Facial rubbing, rhythmic, undulating muscle contractions, collapse with extensor rigidity hyperthermia, muscle hypertrophy	Generalised ataxia	AST 97·0 iu/litre ALT 118 iu/litre CK 1577 iu/litre	Normal	Abnormal
6	Facial rubbing, rhythmic, undulating muscle contractions, collapse with extensor rigidity, hyperthermia	Normal	Normal	ND	Abnormal

EMG Electromyogram, AST Aspartate aminotransferase, ALT Alanine aminotransferase, CK Creatine kinase, AP Alkaline phosphatase, ND Not done

recumbency. A blood sample taken three months after its first examination revealed slightly high activities of AST (43·0 iu/litre), ALT (57·0 iu/litre) and CK (255·0 iu/litre). The dog died during a collapse four-and-a-half months after it was first examined.

A mild dilation of the oesophagus was the only abnormality observed during a postmortem examination. A histological examination of skeletal, temporal, oesophageal and cardiac muscles stained with haematoxylin and eosin revealed no abnormalities.

Case 2: Yorkshire terrier

In 1992, a three-year-old male Yorkshire terrier was examined after it had had daily episodes of rhythmic, involuntary, generalised muscle contractions for two-and-a-half years; the episodes lasted for several hours and the contractions were most severe over the dog's body, but were also present on the limbs. They were generally precipitated by stressful situations and on most occasions the dog collapsed into lateral recumbency but the dog did not lose consciousness. It was said to be clinically normal between episodes.

The results of the examinations are summarised in Table 1. The owner refused to allow muscle biopsies to be taken. The dog was given no treatment because it had been living with the condition without difficulties; 11 years after the diagnosis the dog is still alive but still has occasional episodes of rhythmic, undulating muscle contractions.

Case 3: Jack Russell terrier 1

In 1994, an 11-month-old male Jack Russell terrier was examined because it had suffered ataxia of its head, body and limbs from the age of three months which had become progressively worse. The results of the examinations are summarised in Table 1.

A presumptive diagnosis of hereditary ataxia in Jack Russell terriers was made. However, 10 days after it was first examined the dog developed rhythmic, undulating contractions of the muscles of the limbs and, to a smaller extent, of the muscles of the body, which induced vermicular movements of the overlying skin. The dog finally collapsed into lateral recumbency, with moderate forelimb and severe hindlimb extensor rigidity; it panted rapidly and became hyperthermic (43°C), but did not lose consciousness. The referring veterinarian had treated the dog intravenously with 1 mg/kg diazepam, which had no effect. It was anaesthetised with 15 mg/kg pentobarbital (Nembutal; Ceva) administered intravenously, and put into a cold water bath. The dog's extensor rigidity resolved slowly over approximately 15 minutes, but its recovery from anaesthesia was prolonged. The next day the ataxia was much worse and the dog was euthanased at the owner's request.

Case 4: Jack Russell terrier 2

In 1994, an eight-month-old male Jack Russell terrier with a history of ataxia of all four limbs was examined. The owners had bought the dog when it was four months old, when the ataxia in its hindlimbs was already evident; the ataxia developed slowly until it also involved the forelimbs. The results of the examinations are summarised in Table 1.

A presumptive diagnosis of hereditary ataxia in Jack Russell terriers was made. However, over the following two weeks the dog had several episodes of rhythmic, undulating muscle contractions that induced vermicular movements of the overlying skin; the contractions were most clearly visible in the muscles of the limbs. At the end of the second week, after one of the episodes of muscle contractions, the dog collapsed into lateral recumbency, with moderate forelimb and severe hindlimb extensor rigidity; it panted rapidly and became hyperthermic, but did not lose consciousness. At the owner's request, the dog was euthanased during the collapse.

Case 5: Jack Russell terrier 3

In 1996, a five-month-old female Jack Russell terrier with a history of ataxia of all four limbs was examined. The owners had bought the dog when it was two months old and thought that it was already showing signs of ataxia. The owners also reported that, on four occasions, the dog had collapsed into lateral recumbency but without losing consciousness. During these episodes the dog was unable to rise, developed stiffness in its fore and hindlimbs, and panted. The episodes were triggered by excitement, for example, at puppy school or a family party. The dog was said to be clinically normal between the episodes.

The results of a clinical examination were normal, except for very strong muscle development on the proximal limbs (Table 1). A neurological examination revealed severe generalised ataxia, with the hindlimbs being affected more than the forelimbs. During the examination the dog became more and more excited; it started to rub its nose intensely with its forelimbs, and shortly thereafter developed rhythmic, undulating muscle movements that induced vermicular movements of the overlying skin all over the body, but particularly on the proximal limbs and the abdomen; the contractions worsened progressively and finally the dog collapsed into lateral recumbency, with severe forelimb and hindlimb extensor rigidity.

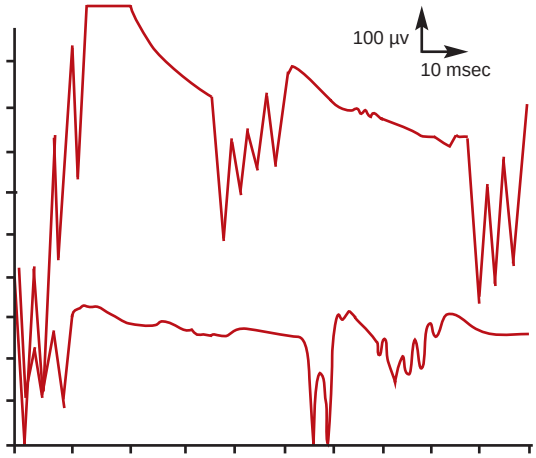

FIG 1: Spontaneous electromyographic activity in case 5, consisting of regular, high-frequency bursts of two, three, four or five motor unit action potentials, occurring rhythmically at frequencies of approximately 20 Hz. The firing rates within each burst were 300 to 400 Hz. Over the loudspeaker, the bursts sounded like soldiers marching

The dog seemed to be in pain and tried to bite when approached; it also panted rapidly and developed mild cyanosis and severe hyperthermia (41°C), but did not lose consciousness. The dog was sedated with 1 mg/kg diazepam, which had no effect on the muscle contractions. It was put into a cold water bath, which decreased its temperature, and the extensor rigidity slowly disappeared after approximately 30 minutes. However, rhythmic, undulating muscle contractions were still visible when the dog was taken home by the owner, approximately one hour later.

The dog was examined again the next day; the rhythmic, undulating muscle contractions were no longer visible in the forelimbs, but still clearly visible in the hindlimbs and on the abdomen. A blood sample was taken, the dog was sedated with diazepam and a light plane of anaesthesia was induced and maintained with propofol (Rapinovet; Schering-Plough). The anaesthesia had little effect on the rhythmic, undulating muscle contractions. A sample of CSF was taken from the cisterna magna and an electromyographic examination was performed. A complete blood count was normal, but biochemical tests showed high activities of AST (97·0 iu/litre), ALT (118·0 iu/litre) and CK (1577 iu/litre). The CSF was normal, with no cells (reference value <8 µl) and 0·12 g/litre protein (reference value <0·275 g/litre). The results of the electromyography were abnormal in the muscles that showed rhythmic, undulating contractions but normal in the other muscles. There was spontaneous activity consisting of regular, high-frequency bursts of two, three, four or five motor unit action potentials (Fig 1), which occurred rhythmically at frequencies of approximately 20 Hz. The firing rates during each burst were 300 to 400 Hz; over the loudspeaker, the bursts sounded like soldiers marching. A presumptive diagnosis of CMFA was made.

The dog was discharged on a course of procainamide hydrochloride (Pronestyl; Bristol-Myers Squibb), at 6 mg/kg orally three times a day. This treatment had no effect on the dog's ataxia but decreased the intensity of the rhythmic, undulating muscle contractions, and the dog no longer collapsed into lateral recumbency. However, in the second month after it was first examined, the dog collapsed again twice and died during the second collapse, probably as a result of hyperthermia.

The three Jack Russell terriers (cases 3, 4 and 5) were examined postmortem. There were no gross changes in the central nervous system, the characteristic lesions being only microscopic. Throughout the neuraxis the white matter was mildly spongy in appearance owing to the presence of scattered swollen myelin sheaths, which occasionally included macrophages, and swollen or fragmented axons. Axonal swelling also occurred rarely in the nuclei of the brainstem. The astrocytes in the cerebral white matter had a conspicuous, eosinophilic cell body with fine processes, but the nuclei were normal. There was neuronal degeneration with chromatolysis and eccentric nuclei in the vestibular nuclei and reticular formation. In the spinal cord, the white matter of all the funiculi was involved; there was a bilaterally symmetrical, mild but generalised myelopathy with swollen myelin sheaths and occasional macrophages or swollen axons. The main pathological changes were located in the myelin tracts between the superior olivary and cochlear nuclei (olivocerebellar fibres and spinothalamic tracts) and consisted of large swollen axons. Some of these axons contained inner structures, but most were homogenous or finely granular. There were prominent changes with peripheral nerves and they were more severe in the nerves of the hindlimbs. The changes were dominated by axonal degeneration, but some demyelination was visible. Axonal degenerative changes were also observed in the roots of the cauda equina. There was no apparent selective loss of small or large calibre fibres on semi-thin sections, but there may have been some loss of myelinated fibres. The muscle changes were mild, with occasional angular fibres but no obvious neurogenic atrophy, fibre type grouping or muscle inflammation.

Case 6: Border collie

In 1999, a three-and-a-half-year-old male border collie with an 18-month history of episodes of collapse into lateral recumbency without loss of consciousness was examined. These episodes were triggered by exercise or excitement and were always preceded by redness of the eyes and intense rubbing of the face with the forepaws. During the episodes, the dog was unable to rise and became stiff in both its fore- and hindlimbs; the episodes were always accompanied by muscle tremors and lasted from 10 minutes to several hours. A blood sample taken by the referring veterinarian was normal. The dog had been treated with barbiturates without effect, and it was said to be clinically normal between episodes.

The results of clinical and neurological examinations were normal. However, since the owner reported that clinical signs could be produced by exercising or exciting the dog, it was taken out to play; after about 10 minutes of playing with a ball, the dog developed clinical signs (Table 1).

The dog was sedated with 1 mg/kg diazepam administered intravenously, which had no effect, and anaesthetised with 4 mg/kg propofol administered intravenously, which made the stiffness disappear, though very slowly. A blood sample was taken and an electromyographic examination was performed (Table 1). In the tarsal flexors and in the extensors of the toes of the hindlimbs the electromyographic activity consisted of regularly occurring high-frequency bursts of four motor unit action potentials; the firing rates within each burst were 400 Hz, and over the loudspeaker the bursts sounded like soldiers marching.

The dog was discharged on a course of mexiletine hydrochloride (Mexitil; Boehringer Ingelheim) at 4 mg/kg orally, twice a day. Initially, the dog was able to work in agility exercises normally with this treatment. However, after a few months the clinical signs gradually returned and the dog was taken out of work. At present, four years after its diagnosis, the dog is still alive.

DISCUSSION

The most characteristic clinical signs shown by all six dogs were the episodes of rhythmic, undulating muscle contractions that induced vermicular movements of the overlying skin and generally led to their collapse into lateral recumbency, with rigid limbs and delayed muscle relaxation. These episodes were triggered by excitement or exercise. To the authors' knowledge, only one case with comparable findings

has been reported in the veterinary literature (Reading and McKerrell 1993); those authors compared the clinical signs in the dog, a Yorkshire terrier, to the human syndrome of myokymia. However, strictly, myokymia refers to a contraction of independent small bands or strips of muscle fibres which induce an undulating movement of the overlying skin (Walton 1988). Myokymia is one of the clinical signs of neuromyotonia (Mertens and Zschocke 1965), also called Isaac's syndrome for the author who gave the first modern description of patients with this syndrome (Isaacs 1961). Neuromyotonia is characterised by hyperexcitability of motor nerves leading to muscle twitching (myokymia), persistent muscle contraction and impaired muscle relaxation (Kimura 1983, Newsom-Davis and Mills 1993, Layzer 1995, Shillito and others 1995). Generalised myokymia developing into muscle stiffness and delayed muscle relaxation was present in all six dogs in the present study, and their disorder therefore resembled the human syndrome of neuromyotonia. However, the characteristic stiffness in neuromyotonia is initially brought on by exercise, but later may occur at rest or even during sleep (Kleopa and Barchi 2002), and this was not observed in the six dogs. Myokymia and neuromyotonia may be aspects of the same underlying abnormality (Gutmann and others 2001). In addition to myokymia and neuromyotonia, the terms CMFA, continuous motor unit activity, neurotonia, pseudomyotonia and others have been used to describe related syndromes in the human literature; these syndromes may be the same disorder (Jamieson and Katirji 1994) or they may constitute different diseases that vary in their clinical presentation, associated electrophysiological abnormalities and morphological findings, but share the feature of involuntary sustained muscle contraction (Auger and others 1984, Auger 1991, 1994). Until such disorders in both human beings and dogs have been more clearly defined, the more descriptive term 'CMFA' has been used here.

The clinical signs of CMFA included hyperthermia in five of the dogs, facial rubbing in three, and ataxia in all three Jack Russell terriers. The hyperthermia may be comparable to the excessive sweating that is sometimes observed in human patients (Auger 1991, 1994, Jamieson and Katirji 1994), and is probably due to the heat generated by the sustained muscle contractions. However, the hyperthermia in these six dogs was potentially life-threatening. Such extreme hyperthermia has also been described in a woman with neuromyotonia (Griffiths and others 1995). The facial rubbing that was observed in the crossbred dog, the border collie and in one Jack Russell terrier was probably caused by an unusual sensation at the muzzle. Similarly violent pawing at or rubbing of the muzzle, eyes and ears, and rubbing of the muzzle on the ground has been recorded in dogs with hypocalcaemia (Feldman and Nelson 1987), but none of the six dogs was hypocalcaemic. An itchy sensation sometimes affects people with myokymia (Kaji and Shoji 1993). Generalised ataxia, with the hindlimbs affected more than the forelimbs, was observed in the Jack Russell terriers. Because of the ages of these dogs, these clinical signs suggested hereditary ataxia (Hartley and Palmer 1973). The histopathological findings also correlated grossly with the first descriptions of hereditary ataxia. However, in previous reports of hereditary ataxia in Jack Russell terriers the clinical signs of generalised myokymia, muscle stiffness and delayed muscle relaxation were not described. Furthermore, hereditary ataxia is generally not considered a lethal disease, whereas all three Jack Russell terriers died during an episode of collapse into lateral recumbency. It therefore seems probable that these are two different clinical syndromes.

In human beings, hyperactivity of abnormal peripheral nerve motor axons is the cause of CMFA; the precise level of origin appears to vary from case to case (Odabasi and others 1996). Multiple trigger zones may be present anywhere in the axon from the ventral horn cell down to the nerve terminal (Newsom-Davis and Mills 1993, Jamieson and Katirji 1994, Odabasi and others 1996, Torbergsen and others 1996, Vincent 2000). In human beings, CMFA may have a known precipitating cause, for example, hereditary neuropathy, or it may be an acquired disorder with or without evidence of an associated neuropathy (Newsom-Davis and Mills 1993, Auger 1994, Shillito and others 1995, Odabasi and others 1996). However, most human cases are considered to be idiopathic (Auger 1991, 1994, Jamieson and Katirji 1994, Layzer 1995), and it is likely that many of them are due to an autoimmune disease (Sinha and others 1991, Newsom-Davis and Mills 1993, Auger 1994, Layzer 1995, Odabasi and others 1996). Many human patients have antibodies to voltage-gated potassium channels of peripheral nerve axons which are likely to be implicated in the disease process (Newsom-Davis and Mills 1993, Layzer 1995, Shillito and others 1995, Hart 2000, Gutmann and others 2001). Abnormalities of peripheral nerve sodium and potassium channels result in clinical manifestations which are unrelated to axonal degeneration or demyelination (Gutmann and Gutmann 1996). Potassium channels normally stabilise the membrane potential and regulate repetitive firing (Auger 1994). Potassium channel abnormalities result in high-frequency repetitive action potentials (Newsom-Davis and Mills 1993, Gutmann and Gutmann 1996), often firing in a burst-like fashion associated with clinical myokymia (Gutmann and Gutmann 1996). In these cases, nerve conduction studies and needle electromyography often fail to demonstrate electrophysiological features that might implicate a polyneuropathy by the generally accepted criteria. Ion channelopathies are an important pathophysiological mechanism, in addition to axonal degeneration and demyelination, which affect the normal function of nerve axons (Gutmann and Gutmann 1996). It is possible that similar mechanisms may have played a role in the pathogenesis of the disease in these six dogs. No clinical evidence of peripheral nerve disease was found in any of them, but there were histological abnormalities in the peripheral nerves of the Jack Russell terriers.

Three of the dogs had moderately high activities of AST and ALT and five had similarly high activities of CK. A high CK activity sometimes also occurs in people with neuromyotonia (Kimura 1983, Odabasi and others 1996). The increases were probably the result of the increased muscle activity. Two of the dogs also had muscle hypertrophy, particularly affecting the proximal limbs. Muscle hypertrophy can occur in people with myokymia or neuromyotonia, and usually affects the calves (Gutmann 1996), but may also affect other muscles, particularly in the proximal arm and thigh (Kleopa and Barchi 2002).

Electromyographic measurements were made in four of the dogs. In cases 1 and 2 no abnormalities were found, but the measurements were made when the dogs were clinically normal. In cases 5 and 6 electromyographic abnormalities were observed; they consisted of regular bursts of two (doublets), three (triplets) or more (multiplets) motor unit action potentials occurring rhythmically at frequencies of up to 20 or 30 Hz. The firing rate within each burst was about 300 to 400 Hz, and over the loudspeaker the bursts sounded like soldiers marching. These electromyographic abnormalities resemble myokymic discharges in human beings, which are spontaneously generated bursts of individual motor unit potentials firing at rates of 5 to 150 Hz. The bursts may appear as doublets, triplets or multiplets, and they fire at regular or irregular intervals (Auger and others 1984, Gutmann 1991, Layzer 1995, Gutmann and others 2001). Myokymic discharges can arise spontaneously in the motor axon where there is hyperexcitability of the axon membrane (Gutmann 1991, Gutmann and others 2001). In CMFA in people, needle

electrode examinations reveal an abnormal pattern of motor unit firing, consisting of myokymic discharges, neuromyotonic discharges, doublets, triplets and multiplets, fasciculations, fibrillation potentials and cramp discharges (Newsom-Davis and Mills 1993, Auger 1994, Jamieson and Katirji 1994). These abnormalities may occur either alone or in combination (Auger 1994). Some CMFA disorders are associated with electrophysiological evidence of peripheral neuropathy and some are not.

In most affected people, phenytoin or carbamazepine is effective for the treatment of CMFA (Auger and others 1984, Auger 1994, Jamieson and Katirji 1994, Layzer 1995, Odabasi and others 1996). Phenytoin has a stabilising effect on all cell membranes, including those of the peripheral nerves, and this effect probably results either directly or indirectly from the decreased flux of sodium ions during action potentials (Auger and others 1984, Auger 1991, Layzer 1995, Odabasi and others 1996). Carbamazepine probably acts by decreasing sodium conductance in nerve membranes (Auger and others 1984, Auger 1991). Sodium valproate may be used in patients who do not respond to phenytoin or carbamazepine or who cannot tolerate either drug (Auger and others 1984, Valilescu and others 1987). In dogs, however, phenytoin, carbamazepine and sodium valproate are metabolised so rapidly that even with extremely high doses it is impossible to attain therapeutic serum concentrations (Frey 1989). Procainamide and mexiletine hydrochloride are both membrane-stabilising drugs that have been used successfully in the treatment of CMFA in a dog (Reading and McKerrell 1993) and in people (Wasserstein and others 1992). Dog 5 was treated with procainamide but dog 6 was treated with mexiletine, because procainamide was no longer commercially available in 1999. Both gave a temporary improvement. The treatment, during a collapse, of four dogs with diazepam intravenously and one orally had no effect.

Research should be aimed at determining the peripheral nerve origin of CMFA, by assessing the affected animals' responses to neuromuscular and proximal nerve blocks and by taking peripheral nerve biopsies. The aetiology and pathogenesis of the syndrome should also be clarified, and strategies for its treatment should be improved.

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