Neuromyotonia in hereditary motor neuropathy

A F Hahn, A W Parkes, C F Bolton, S A Stewart

Abstract

Two siblings with a distal motor neuropathy experienced cramping and difficulty in relaxing their muscles after voluntary contraction. Electromyographic recordings at rest revealed repetitive high voltage spontaneous electrical discharges that were accentuated after voluntary contraction and during ischaemia. Regional neuromuscular blockage with curare indicated hyperexcitability of peripheral nerve fibres and nerve block suggested that the ectopic activity originated in proximal segments of the nerve. Symptoms were improved with diphenylhydantoin, carbamazepine and tocainide.

The term "neuromyotonia" was coined by Mertens in 1965¹ to define a syndrome of delayed muscle relaxation after voluntary contraction resulting from a disorder of peripheral nerve rather than muscle. Affected patients complain of muscle stiffness and cramping and show fasciculations and myokymia. Regional neuromuscular blockade with curare established the neural origin;^{1,2} in fact, hyperexcitability and ectopic impulse generation may occur along the whole length of the motor axon, including the terminal arborisations.³ Moreover, hyperexcitability of nerve membranes may be present in sensory, as well as motor axons, in spite of few sensory symptoms.²

Neuromyotonia has been observed with or without overt peripheral neuropathy.⁴ There are, however, few descriptions of hereditary neuropathies with associated neuromyotonia,^{2,5-9} and the precise mechanisms of the neuromyotonia are still in some doubt.

We report our observations in two siblings of Chinese origin, born to unrelated, healthy parents. Symptoms of neuromyotonia had been present since early childhood, accompanied by a progressive motor deficit in distal muscles of the upper and lower limbs. Electrophysiological studies provided further clues on the mechanisms of the abnormal spontaneous nerve activity. A favourable therapeutic response was seen with diphenylhydantoin, carbamazepine and tocainide.

Case reports

The family tree is illustrated in fig 1. All family members received a full clinical and electrophysiological examination. Only II₂ and II₅ were affected.

Case II₂

This 15 year old boy had always been clumsy. Since the age of 10, he had noticed generalised muscle stiffness which increased with physical activity such as walking upstairs, running and skating. For some time, he was aware of difficulty in releasing his grip and his fingers tended to cramp on writing. He had noticed involuntary twitching of his fingers, forearm muscles and thighs at rest and it was more pronounced after a forceful voluntary contraction. Muscle cramping and spontaneous muscle activity were particularly unpleasant when he re-entered the house in the winter, for example, after a game of hockey. Since the age of twelve, he had noticed a tendency to trip. Subsequently he developed bilateral foot drop and weakness of his hands. He denied sensory symptoms and perspired only with exertion.

He was muscular with well-developed proximal muscles. This contrasted with moderate wasting and weakness of the wrist and finger extensors, the intrinsic hand muscles and also the peroneal and intrinsic foot muscles. Sensory examination was normal. Deep tendon reflexes were reduced and ankle jerks were absent. The plantar responses were flexor. When he was fully relaxed, brief, repetitive twitching of his fingers and myokymia and fasciculations in the proximal muscles were clearly apparent. After forceful flexion of the fingers, the grip release was slow and delayed, with the appearance of action myotonia, yet percussion of the thenar eminence produced no abnormal muscle contraction. Percussion of the tongue, however, resulted in a focal tonic contraction, lasting several seconds, which subsided into fasciculations. Strong voluntary contraction of his quadriceps was followed for 10 to 30 seconds by a persisting, involuntary contraction of the muscles, which subsided into myokymic activity and fasciculations. The Trousseau sign was positive. Within 10 seconds after inflation of a blood pressure cuff, the fingers began to twitch and by 35 seconds they were drawn into a carpal

Department of
Clinical Neurological
Sciences, University of
Western Ontario,
London and the
Victoria Hospital,
London, Ontario

A F Hahn
A W Parkes
C F Bolton

St Joseph's Hospital,
London, Ontario,
Canada
S A Stewart

Correspondence to:
Dr Hahn, Department of
Clinical Neurological
Sciences, Victoria Hospital,
375 South Street, London,
Ontario N6A 4G5, Canada

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Figure 1 Family tree, only II₂ and II₅ were affected. Detailed electrophysiological testing and biopsies were performed in II₂.

spasm, which resolved quickly when the cuff was deflated.

Treatment with carbamazepine, 400 mg/day resulted in a marked improvement of the neuromyotonic symptoms in that he could release his grip promptly, movements were smooth and he could run up two flights of stairs with only mild muscle stiffening. Tongue myotonia was no longer present. Unfortunately, carbamazepine had to be discontinued after two weeks because of thrombocytopenia. Diphenylhydantoin, 300 mg/day was less effective. While there was little spontaneous muscle activity at rest, it was readily recorded with surface and needle electrodes after voluntary contraction and during ischaemia. Tocainide, 1200 mg/day resulted in excellent symptomatic improvement of the delayed muscle relaxation and generalised muscle stiffness. Yet involuntary, brief muscle twitching persisted, provoked by muscle activation and nerve ischaemia. The favourable therapeutic response has been maintained, but muscle cramping recurred promptly when the drug was discontinued.

Case II₅

Symptoms were much milder in his younger sister who was examined at the age of 11. She denied any limitations. Examination showed no spontaneous involuntary muscle activity at rest. Muscle tone was normal. Selective weakness was demonstrable in wrist and finger extensors and peroneal muscles. Definite percussion myotonia was present in the tongue but none in the thenar eminence. Grip release was not delayed. Deep tendon reflexes and the sensory examination were normal. In spite of only mild clinical findings, bursts of high voltage, spontaneous electrical activity were recorded in many proximal and distal limb muscles at rest and accentuated after activity.

Material and methods

Electrophysiology

Standard nerve conduction studies were performed—orthodromic for motor and antidromic for sensory, utilising surface electrodes. Needle electromyography was carried out with a concentric needle electrode. Polygraph recordings were made with a Model 8-16 Grass EEG machine while respiration was recorded with a Phipps and Bird pneumograph.

Table Electrophysiological studies of affected individuals

Nerve studied	Patient	Conduction Velocity (m/s)	Distal latency (m/s)	Action potential amplitude sensory μ V: Motor mV
Median (M)	II ₂	57.1	5.2	7.0
	II ₅	50.8	4.8	14.0
	II ₃	64.1	4.2	8.0
Ulnar (M)	II ₅	—	—	—
	II ₂	unrecordable	—	—
	II ₃	42.8	7.6	1.4
Peroneal (M)	II ₅	40.9	5.2	2.8
	II ₂	—	—	—
	II ₃	—	—	—
Tibial (M)	II ₂	53.1	2.6	38.0
	II ₅	57.5	2.4	40.0
	II ₃	50.0	2.5	30.0
Median (S)	II ₂	—	—	—
	II ₅	39.7	3.6	22.0
	II ₃	45.0	2.4	28.0

Regional neuromuscular blockade: an intravenous regional infusion of delta-tubocurare was given to patient II₂ in the right forearm. This was performed after informed consent with proper precautions according to the methods of Torda and Klonymus.¹⁰ A total of 17 ml of a 0.028% solution of delta-tubocurare was injected over a period of 21 minutes. This resulted in the gradual disappearance of all abnormal spontaneous activity.

Ulnar nerve block: 7 ml of 2% xylocaine were injected near the ulnar nerve at the elbow. Assessment of the block was made by recording the maximum hypothenar muscle compound action potential in response to supramaximal stimulation of the ulnar nerve at the wrist, below the elbow and above the elbow, before, during and after the xylocaine injection. Polygraph recordings of spontaneous activity from both hypothenar muscles were made with surface electrodes before, during and after recovery of the xylocaine block.

Polygraph recordings: simultaneous recordings were made with surface electrodes from all four limbs, while monitoring EKG and respiration. **Muscle Biopsy:** cryostat sections of the anterior tibial muscle were stained or reacted for haematoxylin and eosin, Gomori trichrome, DPNH and ATPase. A piece of muscle was fixed in 2.5% buffered glutaraldehyde and processed for electron microscopy according to standard techniques. One micron toluidine blue-stained sections were examined with the light microscope; ultrathin sections of selected areas were viewed with an electron microscope (Philips 410).

Results

Laboratory examinations were normal, including serum sodium, potassium, chloride, calcium, magnesium, bicarbonate, inorganic phosphate, creatinine and thyroid indices. Creatinine phosphokinase was elevated in II₂ to 1248 U/L (36–188). It was normal in all other family members.

Electrophysiology: nerve conduction studies in II₂ and II₅ revealed entirely normal motor and sensory conduction velocities, however, compound muscle action potentials were reduced in amplitude and distal latencies were considerably prolonged (table). F-wave latencies could not be measured, due to the persistent neuromyotonia. Needle electromyography of distal muscles revealed reduced motor unit

Figure 2 Illustrations of the types of abnormal electrical activity recorded in Case II₂: A) Two typical neuromyotonic discharges, the first ending, and the second beginning, quite suddenly. Recorded with a concentric needle electrode in the tongue. B) A typical myokymic discharge recorded with a concentric needle electrode in the deltoid muscle. The grouped discharges recurred at the rate of 10/s. C) A single neuromyotonic discharge in the hypothenar muscle of high enough amplitude to be recorded with skin surface electrodes. D) Abundant abnormal spontaneous activity recorded with a concentric needle electrode in the hypothenar muscle. The discharges were neuromyotonic. The muscle was at a normal temperature 37.5°C. E) The same hypothenar muscle as in D, but cooled to 22°C, at which time much of the abnormal activity had disappeared.

recruitment patterns, but considerably increased amplitudes of single motor unit action potentials. Firing rates were also increased. The motor unit action potentials were often polyphasic and mildly increased in duration. These electrophysiological findings indicated a motor neuropathy, with chronic partial denervation of muscle and collateral reinnervation.

The unusual feature of these cases was the presence in resting muscles, of frequent, very high voltage, spontaneous discharges which appeared in a variety of forms, the most constant being typical neuromyotonic discharges, but also occasional myokymic and random discharges. These were recorded from the tongue and from proximal and distal limb muscles (fig 2). In the relaxed patient, frequent, repetitive bursts of high voltage electrical activity were easily recorded with surface electrodes from the hypothenar eminence. The abnormal electrical activity in resting muscle was increased by voluntary activation of the muscle, but not by mechanical or electrical stimulation of the nerve supplying the muscle. The spontaneous activity was also greatly enhanced by nerve ischaemia after tourniquet application. Cooling of the limb to 22°C almost eliminated all abnormal spontaneous activity yet it was prominent during rewarming (fig 2).

A regional curare test was given to assist in determining the origin of the abnormal discharges. During the test, frequent recordings were made from the hypothenar muscle with a concentric needle electrode. Inflation of the tourniquet resulted in a marked increase in the amount of abnormal electromyographic (EMG) activity. Five millilitres of delta-tubocurare were injected at one and three minutes after tourniquet application. This promptly reduced the EMG activity and the carpal spasm. EMG activity provoked by

voluntary muscle activation also gradually disappeared. A further 3 ml were injected at 12 minutes and 2 ml at 20 and 21 minutes. At this point, after a total of 17 ml had been injected, there was EMG silence. Further insertion of the needle electrode into the muscle failed to evoke any abnormal discharges. The first abnormal EMG activity began within five minutes after the cuff was deflated. Initially, the discharges looked like discrete normal motor unit action potentials, then neuromyotonic discharges began to reappear and after 20 minutes all forms of abnormal activity could be recorded. These test results indicate that the abnormal discharges were arising from the nerve and not from the muscle membrane.

To further study the ectopic impulse generation along the length of the nerve, a right ulnar nerve block was induced at the elbow. The local injection of 7 ml 2% xylocaine resulted in an almost complete ulnar nerve block and in virtual disappearance of the neuromyotonic discharges recorded from the right hypothenar muscles (fig 3). With the gradual recovery from the nerve block neuromyotonic discharges returned after 60 minutes.

Polygraph recordings disclosed that neuromyotonic discharges occurred randomly and in a multifocal fashion in all four limbs and had no relationship to either respiration or EKG.

Treatment effect: no electrophysiological recordings were performed while the patient was on carbamazepine. The complicating thrombocytopenia precluded needle electromyography. During treatment with diphenylhydantoin abnormal spontaneous discharges were almost totally abolished at rest. Yet high voltage, spontaneous activity was quite marked during nerve ischaemia. While medicated with tocainide—which successfully reduced the symptoms of generalised muscle stiffness and cramping—

Figure 3 Effect of a xylocaine block on the neuromyotonia. Tracing on the left shows polygraph recordings from hypothenar muscles of the right and left hand. The figures on the right show hypothenar compound muscle action potentials from stimulation of the right ulnar nerve at the wrist, below the elbow and above the elbow, before, during and after the xylocaine block. The block of the right ulnar nerve at the elbow resulted in an almost complete disappearance of the hypothenar compound muscle action potential when the ulnar nerve was maximally stimulated above the elbow. The neuromyotonic discharges also disappeared almost completely (B). The upper (A) and lower (C) figures depict results immediately before and after the xylocaine block. Note also that discharges were of such high amplitude that they could be recorded with surface electrodes, and at this time they were occurring asynchronously between the two hands, but semi-rhythmically on the left at approximately 2–3/s.

abnormal spontaneous activity could still be recorded in resting muscle and after voluntary activity and ischaemia. A variety of forms was observed from single to repetitive discharges of myokymic or neuromyotonic pattern, yet there were no prolonged trains of high frequency discharges.

Muscle biopsy findings: The muscle biopsy of II₂ showed typical findings of chronic partial denervation and reinnervation. Groups of small angular fibres of either fibre type were seen next to large groups of hypertrophic muscle fibres (fig 4). Examination with the electron microscope revealed changes of denervation. Endplate regions and intramuscular nerve twigs were not observed. An attempted biopsy of the sural nerve was technically unsatisfactory.

Discussion

It is likely that the two children in this report have an inherited motor neuropathy with accompanying neuromyotonia.

The first description of such a familial occurrence of distal muscle atrophy, delayed grip release, muscle cramping and fasciculations in two brothers is by Grund.⁷⁸ Grund accurately recognised the myokymic features as being possibly neuronal in origin, but con-

sidered an abnormality of the autonomic nervous system as their cause. Gamstorp and Wohlfahrt⁵ described two patients (Cases 2 and 3 of their report) with classic clinical and electrophysiological signs of neuromyotonia in association with a profound, slowly progressive distal motor neuropathy. Case 2 appears to have been sporadic, while case 3 was inherited, with onset of symptoms in early childhood.

Figure 4 Biopsy anterior tibial muscle; haematoxylin and eosin; bar = 500 μ m small and large grouped atrophy of muscle fibres indicating chronic denervation.

When examined in his early twenties, the patient showed advanced atrophy of all muscles below the knee and moderate wasting of the small hand muscles. The patient's father had had signs of a neuropathy since early life, yet apparently had no neuromyotonic symptoms. There is, however, no record of an electromyographic examination. As illustrated by our case II, abnormal spontaneous nerve activity may not be detected on clinical examination, even when it is abundant on electromyography.

The most detailed documentation of a familial axonal form of this condition is that of Lance *et al.*² The two siblings both had chronic weakness and atrophy in distal muscles and associated symptoms of neuromyotonia and myokymia, dating back to early childhood. In elegant electrophysiological studies, the authors documented an abnormal hyperexcitability of motor and sensory nerve fibres. Although there were no clinical sensory abnormalities, examination of a sural nerve biopsy illustrated mild, longstanding degeneration of sensory axons. Thus their findings indicated a hereditary motor and sensory neuropathy. Similar observations were made in two unrelated families by Vasilescu *et al.*⁶

In a subsequent second report, Lance and colleagues⁹ pointed out, that neuromyotonia may also be associated with what they consider to be a pure motor and spinal form of Charcot-Marie-Tooth disease. They describe a family in which eight affected members in three generations showed moderately severe, distal atrophy, absent deep tendon reflexes but no sensory abnormalities, neither on clinical, electrophysiological or pathological examination. The clinical findings in these cases bear close resemblance to our patients.

Hereditary forms of neuromyotonia without muscle weakness or atrophy^{4,11-13} may constitute separate entities.

Although the principal pathological processes may vary in these different forms of hereditary degenerative conditions, they share the pathophysiological phenomenon of hyperexcitability of peripheral nerve axons. The exact mechanisms and the site of the abnormal impulse generation remain unknown, and in fact, they may differ in the various conditions. In cases of neuromyotonia without overt peripheral neuropathy, morphological changes have been described in the terminal arborisations of motor axons and electrophysiological studies suggested a very distal trigger zone for the abnormal electrical discharges.^{14,14,15} The myokymic activity recorded by needle electromyography consisted of normal motor unit potentials. It was thus postulated that impulses, originating in the terminal branches of motor nerves, are propagated antidromically and activate the entire motor unit by an axon reflex. This concept is based on the observation that the abnormal discharges are not abolished by a peripheral nerve block, but disappear after administration of curare.

Ectopic impulses appear to be generated at multiple trigger sites or along the entire length of the axon in cases with overt peripheral

neuropathy^{2,3,16,17} (and personal observation). Wallis *et al.*³ in an unusual case of 2-4D insecticide poisoning, observed a 53% reduction of spontaneous electrical activity recorded from the hypothenar muscle, with an ulnar nerve block at the elbow. A subsequent ulnar block at the wrist, further reduced the abnormal potentials, thus indicating hyperexcitability of the axonal membrane throughout its length. In our patient the majority of spontaneous ectopic impulses appeared to be generated at a proximal site, since the nerve block at the elbow resulted in such a marked reduction of the neuromyotonic discharges. Our observations also differ from previous reports^{2,4,17} in that the abnormal spontaneous activity was enhanced by voluntary muscle activation, but could not be elicited by either electrical or mechanical stimulation of the nerve supplying the muscle. Localised forearm ischaemia, however, induced a marked enhancement of distal spontaneous activity. These observations suggest that the nerve hyperexcitability is a generalised phenomenon, possibly related to a functional or structural abnormality of the axonal membrane.

Given the beneficial effects of diphenylhydantoin and carbamazepine one may speculate on possible pathomechanisms. Both medications were shown to improve the neuromyotonia in a dose dependent fashion and to significantly reduce abnormal spontaneous discharges recorded from resting muscle^{2,3,8,16,18} (personal observation). However, repetitive brief bursts of spontaneous activity continued to be provoked by nerve ischaemia. Voltage clamp examinations of peripheral nerves have shown that both diphenylhydantoin and carbamazepine reduce sodium conductance by specifically blocking sodium channels in a manner similar to tetrodotoxin.¹⁹⁻²² Diphenylhydantoin thus increases the threshold of rabbit nerve to electrical excitation and abolishes repetitive nerve discharges in response to supramaximal or long duration currents.²³

Local anaesthetics such as lidocaine and its derivative tocainide also block sodium channels and modify their gating properties.²⁴ This constitutes the principal mechanism of action of tocainide in its antiarrhythmic properties^{25,27} and of its beneficial effect on myotonia²⁶ and paramyotonia.²⁷⁻²⁹ Tocainide is also as effective as carbamazepine in the modification of pain in trigeminal neuralgia.³⁰ This likely relates to the property of both drugs to block sodium channels and stabilise hyperexcitable nerve membranes. A beneficial effect of tocainide on neuromyotonia has, to our knowledge, not been described before. We found tocainide to be equal to carbamazepine in the control of muscle stiffness and cramping. Electrically, both drugs abolished the long trains of neuromyotonic discharges at rest, yet they did not eliminate the repetitive, brief bursts of high voltage discharges that were particularly prominent after muscle activation and during nerve ischaemia.

Motor axons are well known to accommodate rapidly to a sustained depolarisation. This,

according to a recent report by Baker *et al.*³¹ is mediated primarily by a slow, rectifying potassium outward current that can be specifically blocked by tetraethylammonium (TEA). These TEA-sensitive potassium channels are localised at the nodes of Ranvier. Their role seems to be to provide accommodation and spike frequency adaptation during prolonged depolarisation. Such depolarisation is, for instance, generated by prolonged voluntary muscle contraction or during nerve ischaemia.³² The hyperexcitability of nerve membranes in these patients with neuromyotonia may be caused by an abnormal behaviour of membrane ion channels and a failure of accommodative mechanism.

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