Invited review

Neuromyotonia

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Abstract

Neuromyotonia is a rare condition of spontaneous and continuous muscle fibre activity of peripheral nerve origin. It represents the more severe phenotype of peripheral nerve hyperexcitability, and when acquired is often associated with antibodies to voltage-gated potassium channels. There are no specific published electromyographic or clinical diagnostic criteria for this disorder.

This review highlights the classical clinical, electrophysiological and immunological features of this disorder from what is currently known in the literature to date, and also from the author’s own patients’ studies.

Neuromyotonia is best classified as a moderately severe disorder of peripheral nerve hyperexcitability, with electromyographic features of spontaneous, continuous, irregularly occurring doublet, or multiplet single motor unit (or partial motor unit) discharges, firing at a high intraburst frequency (30–300 Hz). Invariably, patients develop persistent muscle contraction, often worse following exercise. About 40% of patients with acquired neuromyotonia will have detectable voltage-gated potassium-channel antibodies.

Clinical, electrophysiological and immunological measurements are important in defining the phenotype of neuromyotonia, and other, milder forms of peripheral nerve hyperexcitability.

Keywords: Neuromyotonia; Electromyography; Peripheral nerve hyperexcitability; Voltage-gated potassium channels

1. Introduction

Neuromyotonia (NMT) is a disorder of generalised peripheral nerve hyperexcitability (PNH), manifesting as spontaneous, continuous muscle activity of peripheral nerve origin. It is characterised clinically by muscle twitching at rest (visible myokymia), cramps, which can be triggered by voluntary or induced muscle contraction, and impaired muscle relaxation, or pseudomyotonia (Isaacs, 1961; Newsom-Davis and Mills, 1993). Patients may exhibit excessive sweating, paraesthesiae or mild muscle weakness.

Denny-Brown and Foley’s (1948) electrophysiological account of ‘undulating myokymia’, was the first report which characterised the clinical and electrophysiological motor features of generalised PNH. The first full description of the syndrome of ‘continuous muscle-fibre activity’ was made by Isaacs in 1961, who established the peripheral nerve origin of the spontaneously occurring discharges. He showed that: (1) there was persistence of abnormal electromyographic (EMG) activity after proximal nerve brachial block; (2) there was no change in spontaneous muscle activity during general anaesthesia with thiopentone; (3) the depolarising muscle relaxant succinylcholine and neuromuscular blocking agent curare produced electrical silence after a few minutes.

Since these initial reports, a number of different terms have been used to describe the same electrophysiological and motor features of PNH in small numbers of patients, including: quantal squander; Armadillo syndrome; Isaacs’ syndrome; neuromyotonia; Mertens’ syndrome; Mertens–Isaacs’ syndrome; neurotonia; continuous motor nerve discharges; myotonia with impaired muscular relaxation; and

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generalised myokymia (reviewed by Hart et al., 1999). The terms myokymia and neuromyotonia refer to syndromes with similar electrophysiological and clinical features found in patients with PNH (Gutmann et al., 2001). Electrophysiologically, the only difference between myokymic and neuromyotonic discharges is that the latter fire at higher frequencies and the amplitude of the motor unit potentials within neuromyotonic bursts can decrement, or wane (Gutmann et al., 2001; Gutmann, 2002). The term neuromyotonia has been used by some authors to identify patients with PNH who exhibit persistent muscle contraction, with or without post-exercise enhancement: other PNH patients with a generalised or focal myokymia syndrome may have identical symptoms of muscle twitching, without sustained or persistent muscle contractions as seen in neuromyotonia. As both disorders are probably mediated by altered neuronal voltage-gated potassium-channel conductances, and can exhibit the same underlying electromyographic ‘neuromyotonic’ or ‘myokymic’ discharges, they probably fall within the same spectrum of disorders of PNH. This review focuses on the clinical and electrophysiological features of patients with the neuromyotonia phenotype of PNH.

2. Pathophysiology of neuromyotonia

As one of the causes of PNH, neuromyotonia can be seen in isolation, or in association with other disorders (Table 1). In many cases, there seems to be an autoimmune association.

2.1. Autoimmune aetiology

The possibility of an autoimmune aetiology in some patients with NMT was suggested by its association with myasthenia gravis (Martinelli et al., 1996), thymoma (García-Merino et al., 1991), Addison’s disease (Vilchez et al., 1980), vitiligo (Vilchez et al., 1980), Hashimoto’s thyroiditis (Sigwald et al., 1966), vitamin B12 deficiency (Vasilescu et al., 1987), coeliac disease (Hadjivassiliou et al., 1997), rheumatoid arthritis (Le-Gars et al., 1997) and penicillamine treatment (Reeback et al., 1979) (Table 1). Spontaneous remission had been observed in patients with NMT (Isaacs and Heffron, 1974), a finding also consistent with autoimmunity. In addition, NMT had also been reported in patients with small-cell lung cancer (Partanen et al., 1980), raising the possibility that tumour antigenic determinants were perhaps capable of triggering an autoimmune response producing antibodies that cross-react with neuronal voltage-gated ion channels (as had already been shown in autoimmune Lambert–Eaton myasthenic syndrome). A number of haematological malignancies have been found in association with neuromyotonia (Zifko et al., 1994; Gutmann et al., 1996; Caress et al., 1997) (Table 1) and these tumours are known to be associated with an increased incidence of autoimmune neurological paraneoplastic disorders.

Table 1
Clinical associations of neuromyotonia

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<tr>
<th>Autoantibody mediated or autoimmune associated</th>
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<td>Plasmacytoma with IgM paraproteinaemia</td>
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<td>Myasthenia gravis without thymoma</td>
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The first direct evidence of an autoimmune aetiology came from the demonstration of a significant reduction in the number of neuromyotonic discharges recorded by needle EMG in a patient with NMT after two courses of plasma exchange (Sinha et al., 1991). Further, when purified IgG from the same NMT patient was injected intraperitoneally into mice, there was a significant enhancement of in vitro resistance to d-tubocurarine at the neuromuscular junction of phrenic nerve-hemidiaphragm preparations. Further studies showed significantly increased quantal content in similarly treated mice (Shillito et al., 1995), mimicking the K⁺ channel blocking effect of 3,4-diaminopyridine. These studies suggested that the increase in nerve terminal excitability could be due to interference with the function of neuronal K⁺ channels that ordinarily stabilise membrane potential. Several other NMT patients were subsequently reported as showing an improvement in symptoms and signs following plasma exchange (Newsom-Davis and Mills, 1993), confirming the presence of a pathogenic circulating factor.

2.2. Anti-voltage-gated potassium-channel antibodies and autoimmune neuromyotonia

Voltage-gated potassium channels (VGKCs) play an important role in signal transduction within the central and peripheral nervous system. The a-subunits of VGKCs...
comprise a family of related proteins (Kv1.1–1.6) coded for by genes that show homology with the VGKC gene in the fruit fly Drosophila melanogaster. The phenotypic and electrophysiological similarities between the Shaker mutant of Drosophila (Butler et al., 1989) and patients with NMT further suggested that VGKCs were functionally blocked by antibodies in NMT. However, it was not until the neurotoxin dendrotoxin was first used in radiolabelled form in an immunoprecipitation assay that the nature of the putative antibody in NMT was identified (Hart et al., 1997).

Dendrotoxin is an eastern green mamba snake (Dendroaspis) venom peptide that is capable of occluding the pore of VGKCs (Harvey and Anderson, 1991). Dendrotoxin homologues have been shown to specifically bind to and block some isoforms of VGKCs. A radioimmunoassay using 125I-α-dendrotoxin labelled extracts of human frontal cortex was developed that was capable of detecting anti-VGKC antibodies in about 50% of patients with acquired autoimmune NMT (Shillito et al., 1995). Subsequent immunohistochemical and immunoblotting studies using serum from a patient with acquired NMT showed evidence of binding to α-dendrotoxin, with additional staining of intramuscular nerve axons (Arimura et al., 1997). However, as dendrotoxin is not capable of blocking all members of the Shaker-related VGKC family, a more sensitive assay was developed. Using a molecular immunohistochemical assay, VGKC antibody binding was detected in every one of 12 NMT patients and not in controls by expressing different human brain VGKCs in Xenopus oocytes (Hart et al., 1997). Thus, anti-VGKC antibodies found in NMT are probably heterogeneous in terms of their target specificities on one or more different types of neuronal VGKCs.

The functional effect of NMT anti-VGKC antibodies has been studied by direct exposure of dorsal root ganglion cells to NMT IgG (Shillito et al., 1995). Spontaneous, repetitive electrical discharges were seen in these neurones after 24 h incubation in NMT IgG, similar to the effect of VGK blocking with 3,4-diaminopyridine. However, the degree to which anti-VGKC antibodies in NMT are capable of breaching the blood–nerve barrier and causing peripheral nerve hyperexcitability in vivo is unknown. Functional studies using patch-clamp techniques in human neuroblastoma cell lines have demonstrated the suppression of voltage-gated K+ currents in cells that had been co-cultured with acquired NMT patients’ immunoglobulin, without affecting Na+ currents (Nagado et al., 1999). More recent human neuroblastoma cell line functional studies have demonstrated that suppression of VGKC currents using anti-VGKC antibodies from patients’ sera is independent of added complement, but probably requires cross-linkage of K+ channels by divalent antibodies (Tomimitsu et al., 2004).

Neurophysiological strength-duration time constant studies on patients with autoimmune acquired NMT have shown that nodal membrane properties are abnormal in motor axons, indicating increased excitability at these sites, perhaps in part due to reduced K+ conductance (Maddison et al., 1999). Further neurophysiological studies of axonal hyperexcitability in patients with NMT revealed normal threshold electrotonus recordings, but significantly greater late subexcitability after an impulse and greater excitability overshoots after depolarisation or hyperpolarisation (Kiernan et al., 2001).

As had first been proposed by Isaacs (1961), these studies of peripheral nerve excitability also suggest that the spontaneous neural activity is often generated focally (or multifocally) at sites distant from the recording electrode over the trunk of the nerve. In most patients, the probable site for the generation of spontaneous discharges is at the motor nerve terminal, or its intramuscular arborisations (Arimura et al., 2005; Deymeer et al., 1998). At these distal sites, the potassium channels producing fast K+ currents are unprotected by the blood–nerve barrier, and thus presumably more susceptible to antibody-mediated immune attack.

2.3. Genetic disorders of potassium channels and peripheral nerve hyperexcitability

Symptoms and electrophysiological features of generalised myokymia are present in patients with episodic ataxia type 1, and mutations in the neuronal VGKC α-subunit gene KCNA1 were found to be causative (Browne et al., 1994). Since then, novel point mutations in the KCNA1 gene have been found in families with myokymia in isolation (Eunson et al., 2000), or with additional muscle contractions and stiffness (Kimali et al., 2004), suggesting that the PNH disorders of NMT or myokymia may be due to either an acquired autoimmune, or genetic effect on neuronal VGKC kinetics.

2.4. Neuromyotonia and associated non-immune-mediated conditions

Several different manifestations of PNH, including neuromyotonia, may be found in patients with pre-existing disorders such as amyotrophic lateral sclerosis, drugs (Petiot et al., 1993; Lehky et al., 2004) and toxin exposure (Wallis et al., 1970; Devathasan et al., 1984; Brick et al., 1987; Voiculescu et al., 1995) (Table 1). In many of these associated conditions, there is an underlying peripheral neuropathy, including genetic forms (Lance et al., 1979), and examples with a possible immune association such as Guillain–Barré syndrome (Vasilescu et al., 1984) or chronic inflammatory demyelinating polyradiculoneuropathy (Odabasi et al., 1996), raising the possibility that nerve damage per se may trigger peripheral nerve hyperexcitability either directly, or through immune effector mechanisms. Indeed, the coexistence of VGKC antibodies in one of the author’s patients who had an idiopathic axonal peripheral neuropathy would lend weight to this suggested pathophysiological mechanism. Conversely, however, there is no evidence that chronic nerve hyperexcitability directly leads to peripheral neuropathy.
Two case reports have described patients developing NMT following staphylococcal infection, the symptoms of which resolved on treatment of the infection (Liu et al., 1998; Maddison et al., 1998). It is possible that surface epitopes on the staphylococcal organism are capable of generating cross-reacting VGKC antibodies.

These data suggest that acquired neuromyotonia is not a single disease process, but may arise as a result of peripheral nerve dysfunction or damage arising from numerous different mechanisms.

3. Clinical description

The original descriptions of NMT describe several features that are characteristic of this condition.

3.1. Muscle twitching

This is usually the commonest symptom associated with NMT, seen in over 90% of patients. Muscle twitching or ‘visible myokymia’ is observed as a continuous, undulating, wave-like rippling of muscles, likened to a bag of worms under the skin (Irani et al., 1977; Hosokawa et al., 1987). Twitching generally occurs in the limbs but can also be seen in the trunk muscles (Greenhouse et al., 1967; Ono et al., 1989) and the face (Irani et al., 1977; McGuire et al., 1984; Teive et al., 1988; Newsom-Davis and Mills, 1993), including the tongue (Black et al., 1972). Facial muscle twitching is seen in about 25% of cases (personal data from 48 patients), not associated with cranial or neck irradiation. Rarely, the laryngeal muscles can be involved causing hoarseness and exertional dyspnoea (Jackson et al., 1979). Occasionally, there may be an absence of visible muscle twitching but needle electromyography reveals continuous motor unit activity (Magnuson et al., 1972; Newsom-Davis and Mills, 1993; Le-Gars et al., 1997). However, muscle rippling can sometimes be felt on palpation even when it is invisible to the naked eye.

3.2. Cramps

Muscle cramps that can be painful at times are a prominent feature of NMT (in over 70% of cases) and are sometimes the first symptom that is noticed by the patient (Halbach et al., 1987; Odabasi et al., 1996; Torbergsen et al., 1996). They may be associated with spasms (Hughes and Matthews, 1969; Lance et al., 1979) and are sometimes worsened by attempted voluntary muscle contraction (Isaacs, 1961; Lütschg et al., 1978; Zisfein et al., 1983; Carress et al., 1997) or electrical nerve stimulation (Isaacs, 1961). Cold weather can also precipitate muscle cramps (Magnuson et al., 1972).

3.3. Muscle stiffness

This can occur in association with cramps and can be severe enough so as to hinder walking and manual dexterity (Isaacs, 1961; Wallis et al., 1970; Lütschg et al., 1978; Kukowski and Feldmann, 1992; Deymeer et al., 1998). As a result, patients may adopt an abnormal posture. Muscle stiffness can present with remarkably focal abnormalities, especially in the hands, with continuous painless finger flexion (Modarres et al., 2000; Jamora et al., 2006). Stiffness can also occur in the muscles of respiration (Isaacs, 1961; Sigwald et al., 1966) resulting in breathlessness, and sometimes patients are unable to stand on their heels due to stiffness in the lower limbs (Wallis et al., 1970; Torbergsen et al., 1996). Occasionally, stiffness can improve with repeated exercise (Hughes and Matthews, 1969; Wallis et al., 1970). It is sometimes impossible to elicit the tendon reflexes in patients with NMT due to impaired muscle relaxation (Isaacs, 1967).

3.4. Increased sweating

Hyperhidrosis is a systemic feature of NMT that is thought to arise as a result of an increase in the basal metabolic rate, perhaps due to continuous muscle activity (Isaacs and Frere, 1974). There has been no evidence as yet of continuous neural activity in the sudomotor nerves which would offer an alternative explanation for the increased sweating seen in almost half the cases of NMT.

3.5. Muscle hypertrophy

Like hyperhidrosis, muscle hypertrophy is thought to arise as a result of continuous muscle activity. Most often, the calves are hypertrophied (Vasilescu et al., 1984; Griffiths et al., 1995) but muscle hypertrophy can also be seen in the forearm (Deymeer et al., 1998) and hand muscles (Askanas et al., 1981; Brown, 1984). The degree of hypertrophy seems to correlate with the severity of overactivity in individual muscle groups (Newsom-Davis and Mills, 1993) and is usually bilateral. Successful treatment with phenytoin or prednisolone can result in a reduction in muscle hypertrophy (Zisfein et al., 1983; Vasilescu et al., 1984).

3.6. Pseudomyotonia

This term is used in patients with NMT to describe a myotonic-like slow relaxation of muscles after voluntary contraction, for example abnormally slow release of hand grip. Unlike myotonic dystrophy, there is no evidence of percussion myotonia in NMT (Mertens and Zschocke, 1965; Kukowski and Feldmann, 1992; Deymeer et al., 1998). Pseudomyotonia may be the first symptom of NMT and can occur on eye (Oda et al., 1989) and jaw closure (Martinelli et al., 1996) as well as on hand grip. Only about one-third of patients exhibit this phenomenon.

3.7. Muscle weakness

Reduced muscle power is unusual in NMT but has been reported in several cases with no additional cause for
weakness (Barron and Heffner, 1979; Valli et al., 1983), even when the weak muscles were hypertrophied. It has been suggested that one cause for the muscular weakness is due to fatigue in the presence of continuous muscle fibre activity.

3.8. Central nervous system symptoms

Mental disturbance is occasionally seen in NMT patients, with reports of hallucinations, delusional episodes and insomnia, sometimes referred to as Morvan’s fibrillary chorea (Liguori et al., 2001). Although oligoclonal bands have been found in the cerebrospinal fluid (CSF) of patients with autoimmune NMT (Newsom-Davis and Mills, 1993), there is no correlation with disease severity or CNS symptoms. To date, detectable levels of anti-voltage-gated potassium-channel antibodies in the CSF have only been found in one patient with NMT and associated limbic encephalitis (Vincent et al., 2004). Recently, a number of patients have been described with potassium-channel antibody-associated limbic encephalitis, presenting with symptoms of memory loss, confusion and seizures (Vincent et al., 2004). These patients, however, rarely demonstrate NMT either clinically or neurophysiologically.

Neuromyotonia appears sporadically and can occur at any age. It has even been reported in newborn babies of mothers without the condition; these babies all died of respiratory complications in infancy (Black et al., 1972; Thomas et al., 1994).

4. Diagnosis

4.1. Electromyographic features

Although at present, there are no defined electrodiagnostic criteria for disorders of peripheral nerve hyperexcitability, the American Association of Neuromuscular and Electrodiagnostic Medicine have published a glossary of terms in electrodiagnostic medicine (AAEM, 2001). The following descriptions of the electromyographic features of peripheral nerve hyperexcitability encompass their definitions for the terms ‘neuromyotonic’ and ‘myokymic’ discharge.

Electromyographic recordings reveal spontaneous, continuous, irregularly occurring doublet, triplet or multiplet single motor unit (or partial motor unit) discharges, firing at a high intraburst frequency (30–300 Hz) (Fig. 1). Spontaneous discharges at the highest frequencies (150–300 Hz) that fire in prolonged bursts that begin and end abruptly, and often wane in amplitude have been called neuromyotonic discharges (Gutmann et al., 2001). Each burst of electrical activity usually occurs irregularly, with variable interburst frequencies (100 ms to greater than 10 s). Myokymic discharges tend to fire at lower frequencies (often less than 60 Hz), often as doublets, triplets, or multiplets, in short semi-rhythmic bursts, followed by a few seconds of silence. In clinical practice, this distinction is arbitrary and some patients with symptoms of PNH exhibit both ‘neuromyotonic’ and ‘myokymic’ discharges during the same electrophysiological recordings.

In addition, fibrillation potentials and fasciculations are also often present, the former (mostly discharging regularly) indicating the discharge of single muscle fibres. The generation of these fibrillation potentials may arise either primarily from a generator site within the motor nerve terminal arborisations, or secondary to local damage to the motor nerve terminal. The shape or size of the motor unit during a train of discharges can vary, due to the depolarisation of different muscle fibres supplied by the same motor nerve (Fig. 2). Several different motor units may be seen to be discharging in the same EMG recording. Detailed surface EMG recordings in six patients demonstrated that most spontaneous discharges occur in distal muscles and usually no more than 10 different motor unit (or partial motor unit) discharges are seen (Hart et al., 2002).

Characteristicly, electrical stimulation of the nerve may result in increased spontaneous activity seen as after-discharges (Fig. 3) (Isaacs, 1961; Newsom-Davis and Mills,
and voluntary muscle contraction can provoke spontaneous motor unit activity lasting several minutes (Ishii et al., 1994). In addition to voluntary muscle contraction, local nerve ischemia (achieved by application of a tourniquet) can also accentuate the electromyographic features of NMT (Hahn et al., 1991). Neuromyotonic discharges are characteristically present during sleep (Grisold and Mamoli, 1984; Brown, 1984; Ono et al., 1989). Polysomnographic recordings have shown that NMT spontaneous discharges are present during rapid eye movement (REM) and non-REM sleep (Torbergsen et al., 1996).

Using electrophysiological techniques, it has been possible to determine the site of origin of the spontaneous electrical activity. Although several accounts have shown a reduction in the number of discharges following local anaesthetic proximal nerve block at the elbow or knee, indicating that the ectopic foci lie in the proximal segments of the nerve and its root (Vasilescu et al., 1984; García-Merino et al., 1991), many reports show no diminution of spontaneous electrical activity after proximal nerve block, even when blocked at the wrist, suggesting a more distal discharge generation site (Askanas et al., 1981; Oda et al., 1989; Newsom-Davis and Mills, 1993; Deymeer et al., 1998). It is most probable that in patients with PNH, the generator sites may lie anywhere along the whole length of the motor nerve, perhaps with a predilection for the terminal arborisations.

A study of other patients with milder symptoms of muscle cramps, twitching, and stiffness, who share similar autoimmune associations as autoimmune NMT, has shown that these patients have electromyographic features similar to the cramp-fasciculation syndrome, but without the doublet, triplet, or multiplet motor unit discharges usually seen in NMT. These electromyographic features reflect quantitative rather than qualitative differences between the diverse clinical syndromes of cramp-fasciculation syndrome at one end, and acquired NMT at the other, more severe end of a spectrum of autoimmune peripheral nerve hyperexcitability (Hart et al., 2002).

Single-fibre EMG studies of the components of NMT discharge bursts have shown sufficient jitter to suggest that the generator site for the spontaneous activity is proximal to the neuromuscular junction (Stålberg and Trontelj, 1994). The constant high rates of motor unit firing (up to 300 Hz) in NMT could be expected to drive the neuromuscular junction close to its safety factor, perhaps resulting in increased jitter in some patients (Singh et al., 1998), but from personal experience, single-fibre EMG recordings are normal in patients with NMT who do not have coexistent myasthenia gravis, even in patients who have detectable spontaneous NMT discharges in the muscle being tested.

Coexistent findings of peripheral neuropathy may be detectable in nerve conduction studies in a minority of patients with NMT, and a number of disorders of peripheral nerve (e.g. Guillain–Barre syndrome, hereditary motor and sensory neuropathy, chronic inflammatory demyelinating polyneuropathy) have been associated with NMT (Vasilescu et al., 1984; Odabasi et al., 1996; De Carvalho and Albuquerque, 1996).

Estimation of motor unit size in NMT using macro-EMG techniques is technically difficult as florid, spontaneous motor unit activity affects the triggering of the EMG display on a single motor unit. Using a macro-EMG needle, Torbergsen et al. (1996) found that spontaneous motor units were slightly larger than the voluntary units in a patient with NMT. Additional studies in two further patients with autoimmune NMT showed opposite findings of smaller spontaneous motor unit potentials than...
voluntarily activated units (Arimura et al., 2005). This was thought to suggest a distal generator site within the terminal axon branches in these two patients.

4.2. Other clinical neurophysiological features

Even in NMT patients with symptoms of possible CNS involvement (e.g. insomnia, hallucinations), electroencephalographic (EEG) recordings and estimates of central motor conduction times using transcranial magnetic stimulation are invariably normal (Maddison et al., 2006). Abnormal focal or generalised slow wave discharges are usually seen in EEG recordings from patients with potassium-channel associated limbic encephalitis (Vincent et al., 2004), although most patients develop seizures (without neuromyotonia).

4.3. Immunological findings

Immunoprecipitation assays can detect anti-VGKC antibodies in the serum of about 40% of patients with acquired NMT (Hart et al., 2002). This figure rises to about 80% if there is an associated thymoma (Fig. 4). Associated autoimmune disorders and other autoantibodies can be detected in approximately 50% of NMT patients, most notably anti-acetylcholine receptor antibodies, indicating coexistent myasthenia gravis in about 20%.

4.4. Pathological features

There have been over 50 documented muscle biopsies on patients with NMT and the findings have been very variable, ranging from normal muscle (Greenhouse et al., 1967; Gardner-Medwin and Walton, 1969; Walsh, 1976; Reeback et al., 1979; Coërs et al., 1981) to type 2 fibre atrophy (Lütschg et al., 1978; Vasiliscu et al., 1984), fibre type grouping (Isaacs and Frere, 1974) and excessive motor nerve terminal branching (Isaacs and Frere, 1974), suggestive of neurogenic atrophy and reinnervation. Isaacs and Heffron (1974) showed that serial muscle biopsies taken from the same patient had less pronounced fibre type grouping and variation in fibre size over time, which mirrored the recovery from NMT. Widened and hypertrophied synaptic clefts, with absence of synaptic vesicles have been seen on electron microscopy (Sroka et al., 1975; Lütschg et al., 1978), which may be secondary to persistent motor endplate depolarisation.

Pathological peripheral nerve changes in NMT have included large fibre demyelination (Black et al., 1972; Ono et al., 1989), segmental demyelination (Lance et al., 1979; García-Merino et al., 1991), axonal degeneration (Wallis et al., 1970; Arimura et al., 1997) and abnormalities in terminal motor fibre morphology (Isaacs and Frere, 1974), as well as normal nerve histology (Thomas et al., 1994; Zifko et al., 1994). These findings only reflect pathology in sensory nerves and in NMT, abnormal sensation is an unusual finding (Wallis et al., 1970; Riche et al., 1995). However, microneurographic recordings made from cutaneous afferents of the median nerve have demonstrated spontaneous neural activity, indicative of sensory axon hyperexcitability (Lance et al., 1979). The diverse pathological changes seen in sural nerve biopsies may well be non-specific findings relating to age and trauma (Jacobs and Love, 1985) and the variability of these abnormalities suggests that NMT is not always causally linked.

5. Differential diagnosis

The stiff-man syndrome, as described by Moersch and Woltman (1956), is a similar condition of continuous motor unit activity, where abnormal excitability of spinal interneuronal networks and descending control over the anterior horn cell is thought to be the underlying pathophysiology (Meinck et al., 1984). Unlike NMT, axial rigidity is a prominent feature and patients have a characteristic gait, with marked hyperlordosis (Thompson, 1993). Autoantibodies to glutamic acid decarboxylase are present in about 40% of these patients (Vincent et al., 1997). The central rather than peripheral origin of the excess motor unit activity in stiff-man syndrome, in contrast to NMT, is confirmed by the disappearance of discharges during sleep, general anaesthesia and peripheral nerve block (Auger, 1994). Drugs that enhance γ-aminobutyric acid [GABA]-mediated central inhibition, such as diazepam are beneficial in stiff-man syndrome and not NMT.

The early clinical and electromyographic features of motor neuron disease may mimic that of acquired NMT, especially in the absence of marked symptoms or signs of pseudomyotonia and persistent muscle contraction.
Neuromyotonic discharges (doublet, multiplet motor unit discharges) can be seen on EMG recordings at an early stage in patients who subsequently develop motor neuron disease (unpublished observations).

6. Treatment

The symptoms of peripheral nerve hyperexcitability often respond well to anticonvulsants such as phenytoin, carbamazepine, sodium valproate, lamotrigine and acetazolamide (Mertens and Zschocke, 1965; Vasilescu et al., 1981; Co˘er¸s et al., 1998), many of which primarily reduce neuronal repetitive firing through interaction with voltage-gated sodium channels. Often, patients with acquired NMT require additional immunosuppression in the form of prednisolone and azathioprine, although not all will respond fully. Severe symptoms may be ameliorated for up to 4 weeks following plasma exchange (Newsom-Davis and Mills, 1993). In the author’s experience, quantitative clinical and electrophysiological responses to intravenous immunoglobulin therapy are disappointing, although there have been no randomised controlled trials of this, or any other treatments in autoimmune NMT (Maddison et al., 2000). The association of NMT with thymoma, small-cell lung cancer and lymphoma (Caress et al., 1997; Hart et al., 2002) necessitates the search for, and subsequent treatment of these malignancies: the treatment of the tumour often has little effect on the clinical severity of the peripheral nerve hyperexcitability.

References


