

Longitudinal Neurophysiologic Assessment of Disease of the Peripheral Nervous System



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Electrophysiologic methods used to assess peripheral nerve, neuromuscular junction and muscle are collectively known as electrodiagnostic studies. As the name implies, they provide valuable tools for diagnosis of neuromuscular disorders; their utility, however, extends beyond initial diagnosis. Longitudinal electrodiagnostic studies can assess the progression of neuromuscular disease and guide therapeutic decisions. This review summarises the role of longitudinal studies in evaluating disorders of peripheral nerves, motor neurons, neuromuscular transmission and muscle.

Peripheral nerve

Electrodiagnostic studies play a pivotal role in the prognosis and management of traumatic nerve injuries. Initial studies, usually performed within the first month, serve to determine the location and degree of injury. Both of these will influence prognosis and management decisions. Nerve conduction studies may identify conduction block, the hallmark of neurapraxia, which typically portends spontaneous recovery within a few months.¹ For cases with more axonal injury, initial needle EMG determines the level of denervation. Particularly important is detection of low-level innervation remaining within clinically paralysed muscles. Since this may eventually provide considerable recovery, it argues for conservative management.

Repeated electrodiagnostic assessment guides management of nerve injuries that have completely denervated muscles. It is important to identify early evidence of successful regeneration as it generally contraindicates surgical intervention. Needle EMG will often demonstrate reinnervation of muscles months before clinical return of motor function.^{2,3} This is of particular importance in assessing muscles at some distance from the site of injury. If surgical intervention is required, it cannot be delayed for too long since axons regenerating through sutured or grafted segments must ultimately reach their target muscles before atrophy and fibrosis supervene.

If standard EMG does not provide evidence of regeneration within a reasonable time window, surgical exploration with intraoperative nerve

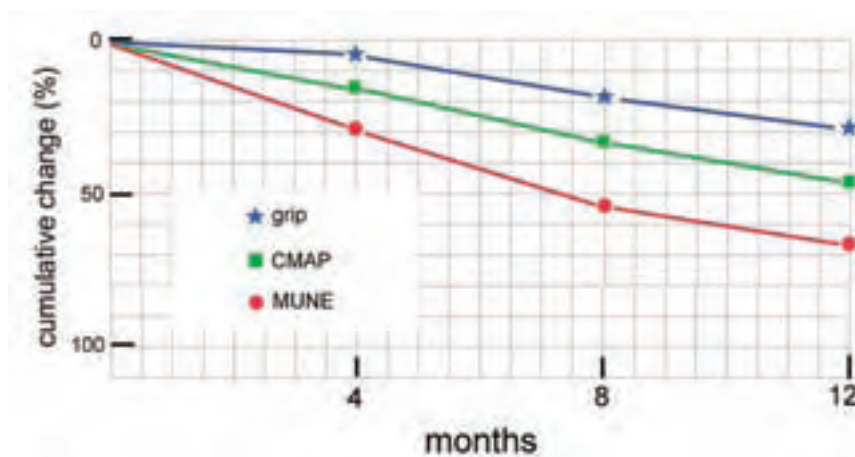
conduction studies becomes the best guide for management. The crucial question is whether there has been significant regeneration of axons through injured segments or neuromas remaining in gross continuity. Following surgical exposure, the injured nerve segment is suspended between paired hook electrodes. A nerve action potential recorded across the segment signifies sufficient regeneration to obviate any nerve resection, suturing or grafting.⁴

The electrodiagnostic evaluation of polyneuropathy serves to identify the relative contributions of demyelination versus axonal loss. Decrease in compound motor action potential (CMAP) and sensory nerve action potential amplitude correlates reasonably well with axonal loss, though a few caveats bear consideration. Occasionally, low CMAP and SNAP amplitudes reflect very distal conduction block rather than denervation.⁵ Furthermore, CMAP amplitude may vary with electrode placement. Summed values of CMAP amplitudes from multiple nerves, therefore, provide a more consistent and reliable assessment of severity. Inflammatory demyelinating neuropathies such as CIDP or MMN will typically evolve with an increasing burden of secondary axonal degeneration. If repeated electrodiagnostic studies document progressive axonopathy, then a prolonged course of immunomodulating therapy may be required before any clinical improvement becomes apparent.

Nerve conduction studies can influence the management of diabetic neuropathy by identifying features of coexistent inflammatory neuropathy or nerve entrapments. Apart from these features, conduction studies add little to the management of neuropathy in individual diabetic patients. Clinical trials investigating treatments for diabetic neuropathy, on the other hand, have made use of serial nerve conduction studies. Composite scores of multiple nerve conduction parameters appear to be a particularly helpful tool for assessing the course of neuropathy in multicenter clinical trials.⁶

Motor neuron

Given the paucity of established treatments for motor neuron disease, serial electrodiagnostic



Serial measurements documenting the progression of ALS over one year. Motor unit number estimates (MUNE) decline earlier and faster than isometric grip strength or thenar compound motor action potential (CMAP) amplitude. Adapted from ref. 7.

studies currently play more of a role in clinical trials than in guiding management of individual patients. Techniques aimed at estimating the number of anterior horn cells innervating a particular muscle (Motor Unit Number Estimation or MUNE) provide a more direct and more sensitive measure of disease progression than standard nerve conduction studies or EMG. A number of MUNE techniques have been employed to follow the course of ALS. They generally show good test-retest reliability and document decline earlier than standard nerve conduction parameters, quantitative strength testing or global functional scales.⁷ (see figure). However, one particular MUNE technique applied in a clinical trial of Celecoxib became less useful once extensive reinnervation led to unstable motor units.⁸ Though this issue poses a major challenge to certain techniques, there is hope that alternative MUNE methods could prove more reliable.

Neuromuscular Transmission

Neuromuscular transmission is amenable to physiologic assessment over time because electrodiagnostic tools accurately quantify the underlying physiologic deficit. Disease at the neuromuscular junction results in reduction of the safety factor of neuromuscular transmission, which when insufficient, causes failure of neuromuscular transmission and muscle weakness. Single fibre EMG (SFEMG) measures jitter, a manifestation of the variation in time it takes the endplate potential to reach threshold for action potential activation, this variation indicating the robustness of the safety factor.^{9,10,11} Repetitive nerve stimulation is limited to measuring only those instances in which neuromuscular transmission fails, and does not appreciate endplates in which safety factor is impaired but not deficient. Repetitive nerve stimulation showed no change in decrement despite significant improvement in quantitative myasthenia gravis score in a treatment trial of myasthenia gravis.¹² Serial studies of myasthenia gravis indicate individual fibre pair jitter, mean jitter, and percentage of block-

ing fibres all reflect disease change, for better or for worse.¹³ In two thirds of patients with clinical worsening between SFEMG studies, there was at least a 10% rise in mean jitter. A decline in jitter of 10% or more had a strong correlation with clinical improvement.¹³ Serial SFEMG jitter measurement is also valid in individuals,^{14,15} as jitter and blocking closely mirror any changing clinical picture, including improvement after treatment, and postpartum exacerbation. SFEMG also mirrors treatment response as studies of myasthenic patients before and after treatment with cholinesterase inhibitors or immunomodulation found improvement in jitter corresponded to clinical improvement after immunomodulatory therapy.^{14,16} No changes were seen in jitter in patients treated with only cholinesterase inhibitors.

The situation is somewhat different in pre-synaptic disorders. Repetitive nerve stimulation remains a poor physiologic measure of clinical course, as shown by treatment trials of Lambert-Eaton myasthenic syndrome which found little or no change in decrement despite improvement of clinical and other electrodiagnostic measures.¹¹ Serial SFEMG has been shown to be an accurate measure of clinical improvement.¹⁷ But CMAP amplitude at rest is the most useful parameter to follow in pre-synaptic disorders. Virtually every serial study of LEMS has measured resting CMAP amplitude, whether or not the patient was treated.¹¹ With one exception,¹⁸ resting CMAP amplitude

always increased as the patient improved, and declined as the patient worsened. It has correlated with changes in treatment, strength, endurance, and clinical status.¹¹ Pre-synaptic disorders may be thought of as rapidly reversible distal motor axonopathies. CMAP amplitude accurately reflects the number of functioning distal motor axonal termini, i.e., pre-synaptic membranes, with precision.

Muscle

In general, needle electromyography parallels the course of myopathy, particularly those characterised by muscle fibre necrosis. Simulation studies indicate that conditions increasingly likely to occur over time, such as reduced number of muscle fibres, increasing variability of mean fibre diameter, and regenerating muscle fibres, will result in complex MUPs, with longer durations and higher amplitudes than normal.^{19,20} In contrast, early in the course of myopathy, loss of muscle fibres occurs alone, creating simple MUPs of normal amplitude but short duration.¹⁹ Correlation of EMG with muscle pathology in polymyositis confirms these conclusions, with worse EMG findings indicative of more severe pathology.¹⁹ Short-duration MUPs become longer-duration polyphasic MUPs as disease progresses from acute to chronic,^{21,22} corresponding to the presence of regenerating muscle fibres on muscle biopsy. Abnormal spontaneous activity, common in the acute phases of polymyositis/dermatomyositis, becomes less prevalent with duration of symptoms and with response to treatment.^{21,22,23}

The longitudinal pattern is somewhat different in muscular dystrophy. In pre-symptomatic muscular dystrophy, muscles are unlikely to show abnormalities using conventional EMG.²⁴ However, QEMG has shown increased MUP amplitudes in apparently normal muscles of patients with muscular dystrophy. This may arise from either hypertrophy from overuse to compensate for other weak muscles or from fibre splitting.²⁴ As disease progresses and muscles weaken, polyphasic MUPs appear,²⁵ most likely due to fibre-diameter variation and fibre necrosis causing desynchronisation of muscle fibre electrical potentials within the MUP.²⁴ The interference pattern is full and recruitment of MUPs is early.²⁵ Fibrillation potentials and positive waves indicate ongoing muscle fibre necrosis.²⁶ As the dystrophy

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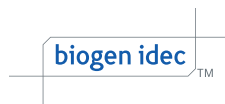
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progresses, MUP amplitude declines, MUP duration shortens and fibrillations become scarcer, from further fibre loss and fibrosis, and the small diameter of surviving muscle fibres.²⁵ Satellite potentials are also seen, secondary to dramatic slowing in propagation velocity in regenerating or small muscle fibres.²⁷ In endstage muscle, electrical silence ensues, with no voluntary MUPs and decreased insertional activity. Fibrillation potentials are no longer seen. CMAP amplitudes decline over time but at a less useful pace for following the disease and usually do not become obviously abnormal until the muscle is overtly atrophic. ♦

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