Summary

This lecture focuses on the impact of classic and modern electrophysiological techniques on the diagnostic approach to patients with neuromuscular disorders, placing emphasis on the limitations of currently used techniques and on the future prospects of clinical neurophysiology.

The refinement of old techniques together with the development of new ones will hopefully improve the diagnostic capability of neurophysiology, improve understanding of the complex pathogenic mechanisms underlying neuromuscular disorders and help further the research of new therapeutic strategies.

KEY WORDS: electromyography, evoked potentials, myopathy, neuropathy.

Introduction

The diagnostic contribution of clinical neurophysiology in the field of neuromuscular disorders was clearly defined in the course of the 1950s and 1960s. The laboratory of clinical neurophysiology of the Institute of Neurology at the University of Pavia, where I worked from the early 1960s, participated intensively in the development of electrophysiological techniques useful for the diagnosis of neuromuscular disorders. It was during those years that the main electrophysiological criteria (based on myopathic and neurogenic changes demonstrated by electromyographic recordings) were established; this was also the period in which the concepts of axonal and demyelinating neuropathy were developed, the former characterised by a reduction in the amplitude of sensory and motor responses, the latter by reduced nerve conduction velocity (NCV). I had the opportunity to participate actively in studies that made a significant contribution to the electrophysiological definition of the motor conduction block, located proximally or distally along peripheral nerves, and in studies that shed light on the pathophysiological mechanisms involved in peripheral nerve lesions with diffuse or focal slowing of NCV (1-5).

These neurophysiological concepts have not been substantially modified by more recent studies and thus remain valid, and the techniques we used are still widely used today, since the fundamental criteria for exploring and analysing the function of the different parts of the motor unit have neither changed substantially, nor been substituted by alternative non-invasive methods of investigation.

On the other hand, the striking progress made in the field of molecular genetics in the past decade has had a remarkable impact on our understanding of inherited neuromuscular disorders: phenotypically different diseases have turned out to be allelic, while mutations in many different genes have been shown to cause apparently similar disorders; the range of the phenotypic manifestations of different diseases has grown and an increasing number of disorders that were considered acquired have been shown to be mild variants of genetic diseases; finally, non-penetrant gene carriers can now be unequivocally detected and prenatal diagnosis of many diseases is available.

In addition to molecular genetics, muscle imaging techniques and immunological tools are also becoming increasingly important in the field of neuromuscular disorders and are progressively restricting the role of neurophysiology – an approach claimed to provide unspecific data – in the diagnostic process.

In this new scenario, we need to answer two main questions: to what extent is clinical neurophysiology still useful for the diagnosis of neuromuscular disorders? and, since it is likely that new biological methods will be applied to diagnosis, what role might neurophysiology have in the future?

The value of neurophysiological studies in the diagnosis of neuromuscular disorders

To answer the first question, we need to consider the large number of studies performed daily in all neurophysiology laboratories on subjects possibly affected by a neuromuscular disease. In clinical practice, neurophysiological examination, an important step in the di-
agnostic assessment of most conditions in which impairment of one or more parts of the peripheral nervous system (PNS) or muscle is suspected, is clearly far from obsolete. In fact, highly specific molecular genetic studies are carried out only in a relatively small number of cases and the decision to perform them (or not to perform them) is determined by a diagnostic screening process that in many cases includes a neurophysiological study. Although neurophysiological techniques are unspecific, providing only limited information on the aetiology of a given disease, they constitute a very sensitive tool in the hands of clinical neurophysiologists, who use them in order: to establish whether there is PNS involvement and to locate the lesion (in the lower motor neuron, the root, the peripheral nerve, the muscle or the neuromuscular junction); to determine its severity and spatial extent; to shed light on the pathogenetic mechanisms; to help monitor the rate of progression; to help select a muscle for biopsy; and to obtain information from non-collaborative patients.

In some cases the information provided by the neurophysiological study alone is sufficient to reach a definite diagnosis, while in many other cases the study provides clues for further diagnostic assessment that may involve techniques of molecular genetics, biochemistry, immunology, or histopathology: each of these is able to provide specific information, but none offers the promptness and breadth of screening allowed by the neurophysiological approach. When a diagnostic conclusion can be reached on the basis of a careful history and rigorous clinical examination there is obviously no need to duplicate information through a neurophysiological study. Consider, for instance, the case of a patient displaying unequivocal features of Duchenne or limb girdle muscular dystrophy and with very high levels of serum CK. In such a patient, electrophysiological studies cannot provide any additional information. Furthermore, the abnormalities demonstrated by an electromyographic study would not indicate a specific muscle disease. A muscle biopsy and molecular studies would be more appropriate in order to arrive at a diagnosis. However, there are many conditions in which diagnosis must be based on both clinical and electrophysiological findings, as, for example, in cases of inclusion body myopathy or acute quadruplegic myopathy, whether or not the latter is related to steroids. In the same way, the differentiation, through a neurophysiological approach, between a myopathic and a neurogenic lesion in patients presenting a unilateral shoulder girdle motor deficit, a scapuloperoneal syndrome or a distal muscle atrophy, determines what further diagnostic studies are appropriate. In some cases muscle and peripheral nerve involvement may coexist, as in some patients with congenital muscular dystrophy due to merosin deficiency (6) or in patients with histological evidence of desmin accumulation: in these patients electrophysiological findings demonstrate a nerve involvement that is almost impossible to identify clinically, since it is masked by the severity of the muscular features.

During the years I was working in Pavia, I had the chance to study a patient affected by Morvan’s syndrome (7), and many other patients with nerve and muscle hyperexcitability, conditions that are now known to be caused by either antibody-mediated or inherited alterations of the ion channels. In these rare diseases the electrophysiological features are part of the phenotypic assessment and need to be correlated either with the specific gene lesion or, in the case of peripheral nerve hyperexcitability that is mediated by autoantibodies against the potassium channels (8), with more diffuse immune dysfunction (9).

On the subject of autoantibody-mediated diseases we cannot disregard the role played by electrophysiologists in the detection of neuromuscular transmission disorders such as myasthenia gravis (MG). Although the diagnosis of MG is now established in most cases by the detection of circulating antibodies to specific end-plate receptor proteins, it should be remarked that autoantibodies are still undetectable in at least 10% of generalised MG and in about 50% of ocular MG cases (10). Therefore, a negative antibody test cannot exclude a diagnosis of MG. Besides the “classic” technique of repetitive stimulation, the more recently developed single-fibre electromyography (SFEMG) measurements of neuromuscular jitter and blocking have a high sensitivity in the detection of end-plate dysfunction. Although it is true that “not all increased jitter is due to myasthenia” (11), a negative test will rule out this disease (12).

Electrodiagnostic testing can be extremely useful in identifying and characterising motor neuron diseases (MNDs) and particularly amyotrophic lateral sclerosis (ALS). In the assessment of patients with suspected MND the neurophysiologist can provide useful information to confirm a suspected diagnosis, to identify subclinical lower motor neuron loss, to define the extent and distribution of the disease, to exclude other peripheral neuromuscular diseases, to provide quantitative monitoring of the rate of functional change, and to monitor responses to clinical or experimental therapies. In addition to traditional tools, the recently developed somatosensory (SEPs) and motor evoked potentials (MEPs) can provide additional useful information in the diagnosis of these diseases.

Historically, one of the main contributions made by neu-rophysiology has been in the field of inherited and acquired neuropathies. Evidence of diffuse or focal nerve conduction slowing or the presence of the so-called conduction block are classic features of demyelinating neuropathies, while the presence of denervation and of reduced response amplitude are characteristic of axonal neuropathies. In the latter case, the persistence of normal sensory nerve potentials and conduction velocities may suggest a diagnosis of motor neuron rather than peripheral nerve disease. Both the classification of the inherited neuropathies and the distinction between familial and acquired disorders have historically been based on these electrophysiological parameters. These concepts still have practical value, but they now need to be critically revised.

On the basis of NCV, inherited neuropathies have been classified as CMT-1 (or demyelinating form of Charcot-Marie-Tooth) when the motor NCV is lower than 38 m/sec, and as CMT-2 (or axonal form) when the NCV is normal or only slightly reduced. Intermediate NCV values, ranging between 30 and 45 m/sec, are found in X-linked-CMT (CMT-X), while severe, homogeneous reduction to less than 12 m/sec may be compatible with a
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diagnosis of Dejerine-Sottas neuropathy. Finally, an unhomogeneous reduction of NCV, more evident at the nerve entrapment points, is characteristic of hereditary neuropathy with liability to pressure palsy (HNPP). In 1991, a duplication on chromosome 17p11.2 was identified as the genetic defect in most cases of CMT-1 (called CMT-1A); since then, causative mutations have been identified in 18 different genes in patients affected by inherited neuropathy. Although the pathophysiological processes are largely unknown, it is clear that there are multiple factors that determine the clinical and electrophysiological phenotype of the different genetic defects. These include the specific protein involved, and the type and location of the mutation.

Whatever the mechanisms underlying the disease in each individual, an accurate electrophysiological study serves to establish the molecular diagnosis, since a duplication on chromosome 17p11.2, which includes the gene for the myelin protein PMP22, is found in about 70% of patients with an NCV lower than 30 m/s, while a mutation in the gene encoding Connexin32 (Cx32), localised to Xq13.1 should be suspected (and is actually found in many cases) in the presence of NCV of between 30 and 40 m/s. However, as an example of the increasing complexity of this field, mutations of Cx32 are emerging as the second most common cause of CMT and may also account for some families classified as having CMT-2 (i.e., displaying normal NCV); in fact, although Cx32 is expressed by myelinating Schwann cells, it still remains to be determined whether CMT-X is primarily an axonal or a demyelinating disease. It is conceivable that some mutations affect the channel properties of Cx32 and may not affect conduction velocity as much as they influence Schwann cell-axonal interactions. Other mutations may affect conduction to a greater extent. Further genotype, phenotype, electrophysiological and pathological correlations will clarify the true nature of the pathophysiology of Cx32 disorders.

HNPP is genetically highly homogeneous, since approximately 85% of cases are caused by a deletion encompassing the PMP22 gene on chromosome 17p11.2, the same gene which is tandemly duplicated in CMT-1A. Some cases of HNPP are also caused by point mutations of the PMP22 gene often leading to the insertion of a stop codon or a frame-shift. It is well known that CMT-1, the most common form of inherited demyelinating neuropathy, has uniform conduction slowing; while different inherited disorders (such as HNPP or, to a lesser extent, Cx32 disorders) may present multifocal conduction slowing. These latter conditions may be confused with acquired autoimmune PNS disorders such as chronic inflammatory demyelinating polyneuropathy and its variants, which are potentially treatable diseases. A thorough family history, an examination of family members, and appropriate use of genetic testing may be required before a definitive diagnosis can be made.

At present, one of the main contributions of nerve conduction studies is in the diagnosis of acquired PNS disorders, particularly of those forms that are of autoimmune origin. Diagnosis of these forms is particularly important, as most peripheral nerve disorders can be treated. Acquired autoimmune neuropathies are often characterised by motor conduction blocks, therefore it is of the utmost clinical importance to increase the sensitivity of nerve conduction studies in order to demonstrate the presence of these blocks.

Conventional techniques for investigating conduction blocks are usually based on the comparison of surface motor responses obtained through the stimulation of the nerve in different sites. The American Association of Electrodagnostic Medicine has recently published very useful consensus criteria for the diagnosis of partial conduction blocks (13).

In spite of the generally good sensitivity of conventional nerve conduction evaluations, normal findings still emerge in a number of patients whose clinical data suggest the presence of conduction blocks. In fact, if the conduction block involves only a very small part of the nerve, comprehensive evaluation of the muscle using surface electrodes might give normal findings.

In the laboratory of clinical neurophysiology at the Catholic University of Rome, a simple new technique has recently been developed to increase the sensitivity of nerve conduction studies in demonstrating conduction blocks. The technique is based on the assumption that, stimulating proximally and distally to a partial conduction block, the registration from a few muscle fibres could show some “blocked” fibres (innervated by “blocked” axons). The test is based on SFEMG recording after peripheral nerve stimulation and has the advantage of focusing attention on a small portion of the muscle, thus allowing evaluation of the conduction of a portion of the nerve (which innervates that portion of the muscle) across the suspected conduction block. In a preliminary clinical study, the sensitivity of this new test was greater than that of conventional tests, and it was found to have a specificity of 100% (no abnormal findings in healthy subjects or patients with diseases other than neuropathy) (14).

Recently developed neurophysiological tests

The above example demonstrates how, through technical refinement, the sensitivity, and thus the diagnostic capability, of old electrophysiological tests may still be increased.

Added to this, it should be remembered that the diminishing role of some diagnostic electrophysiological tests has been counterbalanced by the development of expensive new diagnostic tests like somatosensory evoked potentials and the technique of transcranial magnetic stimulation.

Somatosensory evoked potentials may be extremely useful in the differential diagnosis of motor neuron versus spinal cord disorders, providing that specific segmental spinal response recording techniques are used (15-19). SEPs may often be more effective than the clinical examination in revealing cord involvement and the actual extent of the damage. This is particularly important in patients presenting with cervical spondylotic myelopathy and no sensory deficits, because these cases can be confused with other degenerative diseases such as amyotrophic lateral sclerosis. SEPs may also be useful in the diagnosis of Hirayama’s disease, a condition whose pathogenesis could be related to microvascular changes caused by neck flexion. Indeed, in five patients with Hirayama’s disease we observed a
significant amplitude decrease of the N13 cervical response during neck flexion (20). Since its introduction in 1985 (21), transcranial magnetic stimulation has been performed in almost all neurological diseases, demonstrating a high sensitivity in revealing corticospinal tract involvement. However, as discussed in reference to electrophysiological tests evaluating peripheral nerve and muscle function, high sensitivity does not imply per se clinical usefulness if the test is used to confirm an abnormality which is already clinically evident. Only when a test is able to detect subclinical involvement of a specific system does it assume real diagnostic value. In our laboratory of clinical neurophysiology we have evaluated, in a large population of patients, the sensitivity of transcranial magnetic stimulation and its ability to demonstrate subclinical involvement of central motor pathways. Over one thousand consecutive patients were included in the study (22). The overall incidence of abnormal central motor conduction was 44%, while the overall incidence of clinical signs of corticospinal tract involvement was 36%. These findings demonstrate that the non-invasive and safe technique of transcranial magnetic stimulation may reveal subclinical lesions of the central motor pathways in several neurological disorders, proving itself to be superior to clinical examination of the motor system.

The most important diagnostic contribution of transcranial magnetic stimulation has been seen in motor neuron diseases in which the highest percentage of subclinical abnormalities (26%) was found. All the patients presenting a pure lower motor neuron syndrome and abnormal findings on transcranial magnetic stimulation had a disease progression that confirmed the diagnosis of ALS. In a remarkable percentage of patients we found an isolated abnormality of the central motor conduction in the biceps muscle with normal central motor conduction in more distal muscles like the abductor digiti minimi and the lower limb muscles. Isolated abnormalities of this kind have never been found in other disorders and, therefore, may be considered specific to ALS. A possible explanation for this rather selective abnormality of central motor conduction in proximal upper limb muscles in the early stages of ALS could lie in the different percentages of fast-conducting corticospinal fibres in proximal and distal muscles (a lower percentage of these fibres being present in proximal muscles). It should be considered that transcranial magnetic stimulation explores almost exclusively the large, fast-conducting corticospinal fibres. The loss of a limited number of fast-conducting fibres in the early stages of ALS will not result in any abnormality of central conduction in distal muscles because the loss of a few fibres does not prevent normal conduction through the remaining intact fast-conducting corticospinal fibres. In proximal muscles, on the other hand, the loss of even a small number of these already more scarce fast-conducting fibres may cause an abnormality of central conduction that can be picked up by transcranial magnetic stimulation.

Future prospects and concluding remarks

Finally, it should be borne in mind that there are exciting new prospects on the horizon for clinical neurophysiology, which is set to evolve, for some neurological disorders, from a simple diagnostic tool to a means of therapeutic intervention. In recent years, direct recording of corticospinal activity during and after repetitive transcranial magnetic stimulation (rTMS) over the motor cortex in conscious subjects has demonstrated that suprathreshold rTMS leads to a rapid rise in the excitability of pyramidal neurons (23), while rTMS at around threshold intensity reduces the excitability of intracortical inhibition for several minutes after the end of stimulation (24). The implication of these studies is that it may be possible to target the lasting effects of rTMS to specific excitory and inhibitory circuits of the human cerebral cortex and the hope is that rTMS could prove useful in the treatment of various neurodegenerative disorders involving both the peripheral nervous system and the central nervous system.

The examples above show just what a dynamic field clinical neurophysiology is. The striking progress made in the area of bioinformatics is increasing the capacity of old techniques and allowing the development of more sophisticated neurophysiological methods of examination intended to offer more specific answers to the questions arising from the new biological discoveries. The future of neurophysiology is already here, in the quantitative tests of central sensory and motor pathways and in the more sensitive tests for motor conduction blocks. It will further the development of new techniques that will help in the quantitative measurement of the outcome or effect of therapies, as well as increase our understanding of the complex pathogenic mechanisms that underlie the diseases of the nervous system.

References

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