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Clinical neurophysiology in ALS

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) belongs to a group of disorders known as motor neuron diseases. Despite being one of the most devastating diseases known, there is little evidence for diagnosing and managing patients with ALS.

Clinical neurophysiologic tests are essential, when no biological marker exists to aid early diagnosis, not only in relation to diagnosis, but also in the development of disease progression, and perhaps, in the future, in measuring patients' response to therapy. The electrophysiological features used in the diagnosis of ALS are based on Awaji-shima consensus recommendations for the application of electrophysiological tests, as applied to the revised El Escorial Criteria. Measurements of axonal excitability through nerve conduction study (ENG) is useful to evaluate axonal degeneration. Electromyography (EMG) recordings with needle examination are essential for confirming lower motor neuron involvement in the initial diagnosis of ALS. EMG abnormalities are frequent and these include fibrillation potentials or positive sharp wave potentials, or both, with fasciculation potentials in resting muscle, and an incomplete interference pattern, with abnormal motor unit potentials. Collateral or terminal nerve sprouting is common in ALS and is frequent large macro-motor unit potentials (MUPs). Motor unit number estimation (MUNE) may be useful in measuring loss of functioning motor units and is an attractive endpoint measure in clinical drug trials in ALS because it directly assesses loss of lower motor neurons and is sensitive to disease progression. Transcortical magnetic stimulation protocols, and cortical excitability may be useful to assess the involvement of upper motor neuron system.

In this chapter the advantages, limitations and promise of these various methods are discussed, in order to indicate the direction for further neurophysiological studies in this disorder.

Key words

ALS • EMG • ENG • Transcranial magnetic stimulation

Introduction

Amyotrophic lateral sclerosis (ALS) belongs to a group of disorders known as motor neuron diseases and consists of progressive although variable degeneration of the corticospinal tract, brainstem, and spinal anterior horn neurons, with a markedly heterogeneous clinical presentation and course. ALS is the most common motor neuron disease, a grouping that includes classic sporadic ALS, progressive bulbar palsy, progressive muscular atrophy and primary lateral sclerosis (PLS; Swash, 2001). In about 8% of the cases ALS has a genetic basis, and 20% of patients carry a mutation in the copper-zinc superoxide dismutase (CuZn-SOD1) gene (Al Chalabi and Leigh, 2000). The mechanisms involved in motor neuron death in ALS became clearer after the development of a transgenic mouse model of the SOD1 form (Gurney, 2000). The role of the causative factors in the common sporadic form of

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ALS remains unknown (Shaw, 1999). Although therapy is more effective when commenced early in the natural history of the disease (Kalra et al., 1999; Swash, 2001) when no biological marker exists to aid early diagnosis, the diagnosis relies on clinical neurophysiological methods to detect clinically non-apparent motor system involvement. Clinical neurophysiological assessment is also a sensitive method in assessing disease progression, and perhaps, in the future, in measuring patients' response to therapy. Neuroimaging using magnetic resonance imaging (MRI), magnetic resonance spectroscopy (1HMRS), positron emission tomography (PET) and functional MRI may provide valuable diagnostic information (Kalra et al., 1999; Pohl et al., 2001), although they are complex and expensive procedures.

ALS can be difficult to diagnose in the early stages when patients still have few signs and symptoms and few other diagnostic possibilities exist without an established biological marker (Li et al., 1991). Equally important, to test a treatment that will cure the disease or slow down its course patients ALS must be diagnosed early and correctly. Achieving these aims requires sensitive and specific diagnostic criteria.

Neurophysiological features of ALS

Clinical neurophysiological examination is especially important in patients with suspected ALS (de Carvalho et al., 2005), because it can extend the clinical findings by disclosing lower motor neuron involvement in muscles in body regions otherwise regarded as unaffected. The electrophysiological features used in the diagnosis of ALS are based on the set of criteria originally proposed by Lambert (Lambert and Mulder, 1957; Lambert, 1969). Although the revised El Escorial criteria for the diagnosis of ALS as Laboratory Supported ALS incorporated an algorithm for using electrophysiological data in diagnosis (Brooks et al., 2000), as currently understood, EMG and clinical abnormalities cannot be combined in a single limb. Rather, the limb must be determined to be abnormal by one technique or the other (Brooks et al., 2000). Another factor that has limited the usefulness of clinical neurophysiology in the diagnosis of ALS is that the current criteria for defining affected muscles require EMG evidence of ongoing denervation, fibrillation or positive sharp waves, and chronic partial reinnervation implying frequently unstable, increased duration motor unit action potentials with a reduced interference pattern (Table I). Whereas an EMG finding of active denervation and chronic denervation/reinnervation in the same muscle could be diagnostically useful, the clinical neurophysiologist is left with insufficient findings to make the diagnosis of ALS (Behnia and Kelly, 1991; de Carvalho et al., 1999). In December 2006 an IFCN-sponsored consensus conference was convened on Awaji Island, Japan, to consider how clinical neurophysiology could be used more effectively to facilitate early diagnosis (Swash, 2000).

Motor nerve conduction studies

Motor nerve conduction studies in ALS usually elicit normal values in recordings from relatively unaffected muscles. Values under 70% of the average age-based normal value in recordings from severely affected muscles reflect axonal degeneration (de Carvalho and Swash, 2000a). Recordings obtained in the early stages of disease often show increased distal motor latencies in mildly affected muscles. Conduction block is not a feature of ALS, but during disease progression compound motor action potential (CMAP) amplitude elicited by distal stimulation may be small and dispersed and proximal stimulation may induce greater physiological phase cancellation, such as pathological conduction block (Kimura, 1997). Motor conduction block is a major characteristic of the motor neuropathies associated with autoimmune disease and is a characteristic feature of multifocal motor neuropathy (MMN), a disorder that may mimic ALS at presentation, though unassociated with clinical signs of upper motor neuron (UMN) involvement.

F-wave studies

An F-wave study has reported increased F-wave latency with normal frequency and increased amplitude, and slowing of F-wave velocity with decreased F-wave frequency in patients with ALS (de Carvalho and Swash, 2000b).

Table I. - Awaji-shima consensus recommendations for the application of electrophysiological tests to the diagnosis of ALS, as applied to the revised El Escorial Criteria (Airlie House 1998).
1. Principles (from the Airlie House criteria)
The diagnosis of amyotrophic lateral sclerosis [ALS] requires
(A) the presence of
(1) evidence of lower motor neuron (LMN) degeneration by clinical, electrophysiological or neuropathological examination
(2) evidence of upper motor neuron (UMN) degeneration by clinical examination; and
(3) progressive spread of symptoms or signs within a region or to other regions, as determined by history, physical examination, or electrophysiological tests
(B) the absence of
(1) electrophysiological or pathological evidence of other disease processes that might explain the signs of LMN and/or UMN degeneration, and
(2) neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs.
2. Diagnostic categories
Clinically definite ALS is defined by clinical or electrophysiological evidence by the presence of LMN as well as UMN signs in the bulbar region and at least two spinal regions or the presence of LMN and UMN signs in three spinal regions. Clinically probable ALS is defined on clinical or electrophysiological evidence by LMN and UMN signs in at least two regions with some UMN signs necessarily rostral to (above) the LMN signs.
Clinically possible ALS is defined when clinical or electrophysiological signs of UMN and LMN dysfunction are found in only one region; or UMN signs are found alone in two or more regions; or LMN signs are found rostral to UMN signs. Neuroimaging and clinical laboratory studies will have been performed and other diagnoses must have been excluded.

Sensory nerve action potentials (SNAPs)

Pathological studies have shown that, although ALS is a degenerative disease involving the upper and lower motor neurons, it may involve multisystems, including the sensory system. Objective sensory loss is not a feature of ALS and sensory symptoms are infrequent. Patients with ALS nevertheless often have sub-clinical, non-progressive, sensory system abnormalities (Theys et al., 1999). A study investigating patients with non-progressive ALS during a 6 month follow-up reported that more than 60% had abnormalities in nerve conduction studies, and somatosensory evoked potentials (SEPs) (Georgesco et al., 1997).

Neurophysiological studies frequently disclose marked alterations in SEP cortical components elicited by lower limb nerve stimulation in ALS. In clinical practice, a significantly reduced sensory nerve action potential (SNAP) amplitude in a patient with clinical features consistent with ALS therefore requires an explanation, and indicates investigations to seek a cause other than ALS. Small, or absent SNAPs are nonetheless also a feature of other motor neuron disorders.

Needle EMG abnormalities in ALS

EMG recordings are essential for confirming lower motor neuron involvement in the initial diagnosis of motor neuron disease. Needle EMG is a sensitive indicator of axon loss. EMG abnormalities are frequent in clinically strong muscles in ALS (McComas, 1987; Daube, 2000). These include fibrillation potentials or positive sharp wave potentials, or both, with fasciculation potentials in resting muscle, and an incomplete interference pattern, with abnormal motor unit potentials (MUPs).

Collateral or terminal nerve sprouting is common in ALS but may not always be functionally useful (Schmied et al., 1999). In their study measuring single MUP twitch tensions in patients with ALS, Schmied et al. (1999) noted that about half of the patients studied had large macro-MUPs.

Neurogenic fasciculations

Although fasciculation potentials (FPs) have long been recognised as a characteristic *electrodiagnostic* feature of ALS, they can be seen also in normal muscles (benign fasciculations) and may be absent

in some muscles in patients with ALS. Certain FP features in ALS confirm their importance, however, and allow them to be distinguished from benign FPs. FPs associated with neurogenic disease, especially ALS, show a complex morphology and when studied with a high band pass filter and a trigger delay line reveals increased jitter and blocks, they also often exhibit instability indicating their origin from reinnervated motor units (de Carvalho and Swash, 1998). FPs therefore have a useful place in the diagnosis of ALS, a feature long recognised in clinical neurology. Although ALS cannot be diagnosed on the basis of FPs alone, FPs provide useful information in patients with a clinically suspected diagnosis of ALS. The occurrence of FPs in other neurogenic disorders, for example peripheral neuropathies, exemplifies the importance of clinical context in diagnosis. They are a typical *electrophysiological* abnormality in any disease characterized by denervation or muscle damage. Conversely, when FPs coexist with chronic neurogenic abnormalities, in patients with clinical findings suggesting a diffuse or root-related disorder with superimposed upper motor neuron signs, they strongly suggest a diagnosis of ALS.

Finally, because clinical neurophysiologists still have no specific diagnostic test for ALS (Pradat et al., 2007), they need to reassess a diagnosis of ALS during the disease course, especially if patients manifest atypical ALS features, or lack of progression. Fasciculations in ALS, are probably generated at several sites including the anterior horn cell, axon and distal axon terminal (Roth, 1982; 1984; de Carvalho and Swash, 1998), but also supraspinally, possibly at a site in the motor cortex (Kohara, 1999; Hirota et al., 2000). In an earlier study, de Carvalho and Swash (1998) found that, late in the course of ALS, FPs arose distally, and that their morphology was complex and often unstable. These observations suggest that FPs originate in damaged axons with dysfunction in the terminal arborisation. Threshold tracking studies also suggest that FPs in ALS have a distal origin: in fact in ALS, sodium conductance is increased and potassium conductance is decreased (Kanai et al., 2006), and these changes result in axonal hyperexcitability, thereby helping to generate FPs.

Motor unit number estimation

Motor unit number estimation (MUNE) is an attractive endpoint measure in clinical drug trials in ALS because it directly assesses loss of lower motor neurons and is sensitive to disease progression (Felice, 1997), whereas virtually all other force and electrophysiological measures decline with time after diagnosis. MUNE studies would be important if they added information to the clinical examination. First, any measure that could document early abnormalities in minimally affected or asymptomatic patients would be useful, especially as more treatment options emerge. Second, if MUNE proved a more sensitive measure of disease progression than other commonly used measures, this could have implications in the design of clinical trials. Evidence that MUNE is in fact more sensitive than other measure in detecting patient progression comes from a study in which MUNE generated using multiple points of stimulation, compound motor action potential amplitude, hand grip, strength testing, and vital capacity were all measured at regular intervals over time during a clinical trial in ALS (Felice, 1997) and could also be used to stratify patients according to rate of progression. This application would be critical both for the design of clinical trials, and to provide prognostic information to patients in a clinical setting. In a recent study, the rate of change in statistical MUNE was a strong predictor of survival in patients with ALS (Olney et al., 2000). Using a single MUNE evaluation and extrapolation to normal values assumed to be present just before disease onset, incremental MUNE predicted patient survival, and provided a means of stratifying patients into slowly progressing and rapidly progressing groups (Armon and Brandstater, 1999). Notwithstanding these advantages, the Food and Drug Administration (FDA) feels that MUNE is not suitable as a primary endpoint measure because its clinical meaning remains insufficiently established, nor does it have the ability to predict clinical outcome (Bryan, 2003).

Transcranial magnetic stimulation

Upper motor neuron function can be physiologically assessed using transcranial magnetic stimulation (TMS). TMS uses a brief, powerful magnetic pulse to induce an electric current within the cortex and when delivered to appropriate brain areas, elicits recordable responses in upper extremity and lower extremity muscles. Motor evoked potentials (MEPs) usually

have far smaller amplitudes than motor responses evoked by conventional supramaximal electrical stimulation of a peripheral nerve. Even in normal subjects MEP amplitudes vary with sequential cortical stimuli. This variability in MEP amplitude depends on varying desynchronization of the descending volleys causing variable degrees of phase cancellation. This variability greatly limits the diagnostic sensitivity of MEP amplitude measurements in detecting central motor conduction failure. Subtracting peripheral conduction time from the total response latency after cortical stimulation, yields central motor conduction time (CMCT). Neurophysiological testing discloses prolonged CMCT in 51% to 93% of patients with ALS (Berardelli et al. 1987; Daube, 1999; Pouget et al., 2000). This prolongation may reflect the loss of large myelinated motor axons in the corticospinal tracts subsequent to cortical motor neuronal degeneration but CMCT prolongation is not a sensitive measure of upper motor neuron disease. A magnetic stimulus applied to the motor cortex during a voluntary contraction of a target muscle induces a pause in the EMG activity. This electrical silence is termed the cortical silent period (CSP) (Inghilleri et al., 1993). The CSP recorded from a hand muscle normally lasts about 120 ms and depends on the stimulus intensity. The applied stimulus should be 120-150% of motor threshold (Inghilleri et al., 1993; Mills, 1999a; 1999b). The mechanisms underlying the CSP are complex, multifactorial and incompletely understood (Mills, 1999a; 1999b). Its duration depends mainly on cortical inhibitory mechanisms mediated through local circuit intracortical interneurons (Chen et al., 1999; Wu et al., 2000). A CSP longer should alarm the clinician for the presence of a disorder other than ALS (Schelhaas, 2007). Attarian et al. (2005) found that SP duration decreased with time in the ALS group and a shortening of the TMS-induced CSP has previously been reported to occur in ALS patients in non longitudinal studies (Attarian et al., 2005; Triggs et al., 1992; 1999).

Conclusion

Clinical neurophysiology, in particular needle EMG, until a specific biological marker for clinical diagnosis of ALS becomes available, continues to be the major supportive diagnostic aid when the diagnosis of ALS is suspected. On clinical ground it is seldom possible to establish an early diagnosis of ALS that needs then supported mainly by neurophysiological testing.

Summary

Clinical neurophysiology, in particular needle EMG, until a specific biological marker for clinical diagnosis of ALS becomes available, continues to be the major supportive diagnostic aid when the diagnosis of ALS is suspected. The main role of nerve conduction studies is to rule out other diseases that may mimic early ALS. There is growing understanding of electrophysiological techniques that give insight into the dysfunctional anterior horn cells in ALS, and their central connections. Methods to estimate motor unit numbers is the most promising methods for lower motor neuron studies. Quantitative needle EMG methods can quantified the reinnervation density. Some of these methods may evolve into markers of disease progression, which may enable clinical trials in ALS to become shorter and less cumbersome. Over the last decade significant advances have also occurred in the clinical neurophysiology of the upper motor neuron in ALS and a valid tool for testing cortical excitability in ALS is transcranial magnetic stimulation. Finally innovative neurophysiological studies can be developed to complement the exciting advance occurring in the molecular biology and genetics of ALS.

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