

SESSION 4B CLINICAL ELECTROPHYSIOLOGY

C32 UNDERSTANDING THE PATHOPHYSIOLOGY OF ALS

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Establishing the presence of a combination of upper and lower motor neurone abnormalities affecting the same region is critical for the diagnosis of ALS. As such, a clear focus of current ALS research relates to the identification of the pathophysiological processes that may induce such an environment.

In terms of the lower motor neurone involvement, recent studies have identified widespread dysfunction of axonal membrane, with increased persistent Na⁺ conductances, and abnormalities of fast paranodal and internodal slow K⁺ channel function. Together, these changes contribute to the peripheral hyperexcitability typical of ALS, leading to the almost inevitable symptoms of cramps and fasciculations.

When considering upper motor neuronal involvement, ALS is characterised by progressive degeneration of the corticospinal tract, running from the brain through the spinal cord, to anterior horn cells that control all voluntary movements. Of relevance, most ALS aetiologies have been linked to an excitotoxicity cascade, with excessive activation of glutamate receptors triggering destruction of motor neurones.

Recent studies that assessed cortical excitability using novel threshold tracking transcranial magnetic stimulation (TMS), demonstrated that cortical hyperexcitability was an early feature in sporadic ALS. Cortical hyperexcitability was also evident in familial patients with mutations in superoxide dismutase (SOD-1), suggesting similar pathophysiological processes operate in both sporadic and familial ALS patients. Some have argued that reduction of short interval intracortical inhibition in ALS, and thereby the development of cortical hyperexcitability, was not a primary event, and merely reflected downregulation of inhibitory control compensating for spinal motor neurone loss. To consider this possibility, threshold tracking TMS studies undertaken in patients with spinobulbar muscular atrophy (SBMA) revealed normal cortical excitability when compared to ALS patients. Further comparison of SBMA to a pure lower motor neurone flail-arm ALS variant, established the presence of cortical hyperexcitability in the latter cohort of patients. Together, these findings indicate that the development of cortical hyperexcitability does not simply represent downregulation of intracortical inhibitory processes in ALS.

Longitudinal studies in asymptomatic SOD-1 mutation carriers recently established that cortical hyperexcitability may develop prior to the clinical onset of ALS. Reduction of short interval intracortical inhibition in ALS appears to be determined by a combination of a loss of inhibitory cortical interneurone and glutamate-mediated downregulation. These findings in SOD-1 mutation carriers were further supported in the G93A SOD-1 mouse model, where degeneration of spinal cord motor neurones occurred secondary to dysfunction within central nervous system motor pathways. Taken in

total, these more recent findings may lend further support for the 'dying forward' hypothesis, with corticomotoneurones inducing anterograde excitotoxic motoneuron degeneration. From a therapeutic perspective, neuroprotective strategies aimed at preserving the integrity of intracortical inhibitory circuits, as well as antagonizing excitatory cortical circuits, may provide novel therapeutic targets in ALS.

C33 THE NEW ELECTRODIAGNOSTIC CRITERIA FOR ALS: A RETROSPECTIVE STUDY

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Keywords: Awaji, diagnostic, criteria

Background: Recently, a modification of the electrodiagnostic criteria for ALS was proposed by the Awaji commission in order to improve the sensitivity without diminishing the specificity. The commission did so, mainly by introducing 2 new concepts: 1) to accept neurophysiological evidence of lower motor neuron involvement as equivalent to clinical evidence; 2) to accept fasciculation potentials as an equivalent to fibrillation potentials or positive sharp waves. As a consequence 'probable-laboratory-supported ALS' was no longer accepted as a separate category.

Objective: To evaluate the effect of the new diagnostic neurophysiological Awaji criteria for the diagnosis of ALS.

Methods: In a retrospective study we reviewed both clinical and neurophysiological data of 213 consecutive patients, that visited our outpatient clinic for motor neuron diseases, from October 2006 until December 2008.

Results: Using the original criteria 93 patients were diagnosed with ALS: 13 definite, 38 probable, 14 probable-laboratory-supported, 28 possible. An alternative diagnosis was present in 120 patients. Using the new criteria 93 patients were diagnosed with ALS: 13 definite, 53 probable, 27 possible. Seven patients changed from possible to probable. Of the patients diagnosed as probable-lab-supported, 8 changed to probable, and 6 changed to possible. No patients with an ALS-mimic changed to the diagnosis ALS.

Discussion: The new criteria for ALS do not result in a loss of specificity and can potentially improve the sensitivity by 16% percent (15 patients). However, the fact that not all patients with 'probable-lab-supported ALS' (requiring UMN signs in one region) fulfilled the new criteria for probable ALS (requiring two regions), nearly eliminated the diagnostic yield. For this, we propose an adaptation to the new criteria in the sense that patients fulfilling the presence of LMN in two regions and UMN in one region are also categorized as probable ALS.

Conclusions: The Awaji modifications of the El Escorial Criteria do not result in a loss of specificity and might substantially improve the sensitivity.

C34 MODIFIED INCREMENTAL MOTOR UNIT ESTIMATION IN A LONGITUDINAL NATURAL HISTORY STUDY OF SUBJECTS WITH ALS

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Keywords: motor unit number estimation, physiology, biomarker

Background: Motor unit number estimation (MUNE) has been used in previous ALS trials to assess the progress of motor axon loss and consequent re-ennervation of denervated muscle fibers by surviving neurons. A number of different MUNE methods have been described, but each method has limitations that have limited utility. Recently, we developed a method of MUNE that incorporates elements of both the incremental and multiple point stimulation technique, is rapidly performed, and has excellent test-retest variability. This method (called modified incremental MUNE) has been employed in a multicenter natural history study of electrical impedance myography and MUNE in ALS subjects at 8 participating sites.

Objectives: To determine test retest variability in normal subjects across multiple data collection sites, and assess the changes in MUNE and associated measures in subjects with ALS.

Methods: After informed consent was obtained, subjects underwent MUNE evaluation of a distal hand muscle that was felt to be moderately affected by axon loss. Either the ulnar or median nerve was stimulated at three sites that were rigidly defined, and three incremental responses were obtained at each site. The response of the third increment was added together for all three sites and divided by nine to obtain an estimate of single motor unit potential (SMUP) amplitude. This value was divided into the maximum compound motor unit action potential to yield the MUNE value. Subjects were studied approximately every 2–3 months for up to one year.

Results: Thirty-three normal subjects were tested twice at 8 centers, after rigorous training of the evaluators. Average MUNE for normal subjects was 229 (SD: 93) for 33 median nerves, and 211 (SD: 68) for 14 ulnar nerves. Average test retest variability was 13% for median nerve studies, and 17% for ulnar nerve. Fifty one subjects with ALS have been studied longitudinally at the 8 participating sites. At onset average MUNE was 50 (range 3–192), and declined consistently over the course of the study. Average SMUP amplitude was 210 uV at study onset, and increased as disease progressed.

Discussion and Conclusions: Modified incremental MUNE can be reliably performed in a multicenter trial and yields results that show a consistent decline of MUNE over time, with corresponding increase in SMUP amplitude. This technique can be easily performed on any EMG machine, and requires no specialized software. These attributes make this method attractive for use in multicenter therapeutic trials.

C35 A PROSPECTIVE AND BLIND STUDY OF THE TRIPLE STIMULATION TECHNIQUE IN THE DIAGNOSIS OF ALS

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Keywords: magnetic stimulation, upper motor neuron, prospective diagnostic study

Background: Demonstration of upper motor neuron (UMN) signs in several regions of the body increases the accuracy of the diagnosis of ALS, but validated tests are lacking. The importance of demonstrating subclinical UMN involvement in another region may even increase with the Awaji criteria. The triple stimulation technique (TST) combines transcranial magnetic stimulation of the motor cortex with nerve stimulation at intervals appropriate for collision. In open studies TST has a high sensitivity.

Objective: To study the utility of TST in the diagnosis of ALS in a prospective study.

Methods: Fifty-nine patients were recruited to undergo TST in addition to the standard work-up for suspected motor neuron disease. The neurologist making the diagnosis was blinded to the TST results. Primary outcome was the number of abnormal TST results in patients with possible ALS. The positivity rate was also converted to the number needed to test with TST (NN-TST) for one extra diagnosis of ALS.

Results: Fifty patients underwent TST. In 19 of these patients, the amplitude ratio was abnormal. In the total patient group (n = 59), 18 patients had a motor neuron disorder but did not fulfill criteria for ‘probable’ or ‘definite’ ALS, and in 4 of these patients the TST was abnormal (NN-TST: 4.5). Most TST abnormalities were found in patients with clinically evident central motor disorders, resulting in an overall NN-TST of 15. In one patient the TST was erroneously interpreted as abnormal. TST findings were normal in all patients with inclusion body myositis and peripheral nerve disorders.

Conclusion: This prospective and blind study confirms open studies of TST in the evaluation of ALS. We suggest that abnormal TST can be used to arrive at a diagnosis of ‘probable’ or ‘definite’ ALS in patients lacking UMN signs in the upper extremities. We suggest that the equivalence of neurological signs and neurophysiological abnormalities, one of the major principles of the Awaji consensus, is valid for the upper and lower motor neuron.

C36 THE UTILITY OF SINGLE FIBER ELECTROMYOGRAPHY IN THE DIFFERENTIAL DIAGNOSIS OF AMYOTROPHIC LATERAL SCLEROSIS AND CERVICAL SPONDYLOSIS

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Keywords: single fiber electromyography, cervical spondylosis, diagnosis

Background: In the El Escorial revised criteria for diagnosis of amyotrophic lateral sclerosis (ALS), single fiber electromyo-

graphy (SFEMG) is regarded as a technique which can demonstrate the chronic partial denervation.

Objective: To assess the utility of single fiber electromyography (SFEMG) in the differential diagnosis of amyotrophic lateral sclerosis (ALS) and cervical spondylotic radiculopathy and myelopathy.

Methods: SFEMG was performed in extensor digitorum communis muscles (EDC) of three groups of patients, including 61 ALS patients with findings of cervical spondylosis on MRI, 59 ALS patients with normal MRI of cervical spine, and 55 patients with cervical spondylotic radiculopathy and myelopathy. The parameters of SFEMG between different groups were compared.

Results: The mean jitter were $(81.2 \pm 25.9)\mu\text{s}$, $(91.6 \pm 32.4)\mu\text{s}$, $(40.9 \pm 11.8)\mu\text{s}$ in ALS patients with findings of cervical spondylosis on MRI, ALS patients with normal MRI of cervical spine, and patients with cervical spondylosis respectively. P_{50} of the percentage of jitter $>55\mu\text{s}$ were 73%, 80% and 5% in the

three groups respectively; P_{50} of the percentage of block were 10%, 20% and 0% in the three groups respectively. Fiber densities were 2.9 ± 0.5 , 2.9 ± 0.6 and 2.4 ± 0.6 in the three groups respectively. There was no significant difference in those parameters of SFEMG between the ALS with findings of cervical spondylosis and those with normal MRI. There was significant difference in those parameters of SFEMG between the patients with ALS and those with cervical spondylosis ($P < 0.01$). In 18 patients with ALS, conventional EMG studies showed active and chronic denervation in only one region at the first visit, including 10 in lower limbs, 5 in one upper limb, 3 in bulbar region. SFEMG was performed in EDC which had normal MRC and EMG. SFEMG showed increased FD in 16 patients, increased jitter in 13 patients and impulse block in 6 patients.

Discussion and Conclusions: SFEMG showed significantly increased jitter and block in ALS whether there are MRI findings of cervical spondylosis or not, which can help to differentiate ALS from cervical spondylosis radiculopathy and myelopathy.