Amyotrophic lateral sclerosis: an update

- The Awaji recommendations for electrophysiological diagnosis will permit earlier clinical trials entry.
- The use of ultrasound to visualize fasciculations, even in deep muscles, will contribute to earlier diagnosis.
- The most exciting advances in ALS arise from protein studies and genetics. Recognition that the ubiquitinated cytosolic inclusions in sporadic ALS, as well as in some patients with frontotemporal dementia (FTD), contain TDP-43, and that some familial cases (and a few sporadic cases) have mutations of the TDP-43 gene has transformed previous concepts on ALS pathogenesis. Other newly recognized mutations linked to ALS, such as fused-in-sarcoma (FUS) and valosin-containing protein (VCP), have not only widened the spectrum of genes involved in ALS but also consolidated the close relation between ALS and FTD.
- The consensus El Escorial criteria for diagnosis of ALS codified the steps required to establish a clinically definite, probable, or possible diagnosis, principally based on the distribution of upper and lower motor neuron clinical signs. These criteria defined four body regions: cranial, cervical, thoracic, and lumbosacral, and agreed diagnostic changes on concentric needle electromyography (EMG) as a combination of positive sharp waves or fibrillation potentials, representing denervation change, and large motor units firing faster than 10Hz, with a reduced interference pattern as characteristic of chronic partial denervation. However, these consensus criteria proved insensitive to a diagnosis of ALS made by conventional clinical assessment.
- The use of electrophysiological data in ALS diagnosis was reviewed at a consensus conference held in Awaji- shima, Japan in 2006. First, it was recommended that electrophysiological findings should be taken as equivalent to clinical assessment in the recognition of lower motor neuron involvement. Second, in the context of a suspected clinical diagnosis of ALS, fasciculation poten- tials should be taken as equivalent to fibrillation potentials and positive sharp waves in recognizing denervation, in particular in strong limb muscles and in cranial-innervated muscles. Third, the importance of searching for instability in fasciculation potentials and in motor unit potentials in ALS was stressed. The topographic criteria set out in the El Escorial criteria were unchanged.
- Krarup noted that the number of regions affected by EMG was predictive of survival.
- Mills helpfully reported that a recording time of 90 seconds was the minimum time required to find fasciculation potentials in a muscle of an ALS patient.
- Frontotemporal lobe degeneration (FTLD) is characterized by progressive frontal lobe dysfunction, especially executive dysfunction, antisocial behavioural/personality abnormalities, disinhibition, and loss of interest in activities and family; temporal lobe signs, especially defective working and semantic memory, and language deficits also

occur. These deficits appear in varying degrees in individual patients. The disorder usually presents before the age of 65 years. A positive familial history is found in 30 – 50% of cases. Executive dysfunction is noted in up to 50% of ALS patients, although overt dementia is much less common (15 – 20%). Cognitive impairment carries a poor prognosis.

- TDP-43 deposits in spinal and cortical motor neurons have been described in chronic posttraumatic encephalopathy, a tauopathy with neurofibrillary tangles in cortical neurons in temporal and frontal lobes, not associated with amyloid deposits. This association raises interesting questions about the relation between trauma, collision sports, and ALS.
- Cerebrospinal fluid (CSF) studies have identified elev- ated levels of tau protein in patients with upper motor neuron-predominant ALS and in classic ALS itself, but not in LMN-predominant disease. CSF S100beta levels were lower in LMN disease and both S100 beta and sCD14 levels correlated with survival. These markers were chosen to represent neuronal degeneration (tau), astroglial activation (S100beta), and neuroinflammation (sCD14). Cystatin C levels have been reported elevated in plasma and decreased in CSF in ALS patients, and to correlate with survival and rate of progression.
- Phrenic nerve motor studies show that motor amplitude decreases overtime and is predictive of hypoventilation.

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