Clinical Neurophysiology 127 (2016) 2643–2660

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Review

Assessment of the upper motor neuron in amyotrophic lateral sclerosis

William Huynh [a,b,*], Neil G. Simon [c], Julian Grosskreutz [d], Martin R. Turner [e], Steve Vucic [f], Matthew C. Kiernan [a]

[a] Brain and Mind Centre, University of Sydney, NSW, Australia
[b] Prince of Wales Clinical School, University of New South Wales, NSW, Australia
[c] Department of Neurology, St Vincent's Hospital, Darlinghurst, Australia
[d] Hans-Berger Department of Neurology, University Hospital Jena, Jena, Germany
[e] Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK
[f] Western Clinical School, University of Sydney, Sydney, Australia

ARTICLE INFO

Article history:
Accepted 27 April 2016
Available online 5 May 2016

Keywords:
Amyotrophic lateral sclerosis
Motor neuron disease
Upper motor neuron
Imaging
Transcranial magnetic stimulation

HIGHLIGHTS

- Clinical signs of UMN involvement are an important component in diagnosis of ALS.
- Novel neuroimaging and electrophysiology may facilitate demonstration of UMN degeneration in ALS.
- Improving early ALS diagnosis can facilitate the development of effective therapies.

ABSTRACT

Clinical signs of upper motor neuron (UMN) involvement are an important component in supporting the diagnosis of amyotrophic lateral sclerosis (ALS), but are often not easily appreciated in a limb that is concurrently affected by muscle wasting and lower motor neuron degeneration, particularly in the early symptomatic stages of ALS. Whilst recent criteria have been proposed to facilitate improved detection of lower motor neuron impairment through electrophysiological features that have improved diagnostic sensitivity, assessment of upper motor neuron involvement remains essentially clinical. As a result, there is often a significant diagnostic delay that in turn may impact institution of disease-modifying therapy and access to other optimal patient management. Biomarkers of pathological UMN involvement are also required to ensure patients with suspected ALS have timely access to appropriate therapeutic trials. The present review provides an analysis of current and recently developed assessment techniques, including novel imaging and electrophysiological approaches used to study corticomotoneuronal pathology in ALS.

Contents

* Corresponding author at: Brain and Mind Centre, University of Sydney, and Institute of Neurological Sciences, Prince of Wales Hospital, NSW, Australia
E-mail address: w.huynh@neura.edu.au (W. Huynh).

http://dx.doi.org/10.1016/j.clinph.2016.04.025
1388-2457/

1. Introduction

The term amyotrophic lateral sclerosis was first coined by Charcot, who postulated the primacy of the upper motor neuron in ALS pathogenesis (Charcot and Joffroy, 1869) with loss of Betz cells in the motor cortex being a well-recognised pathological feature (Kaufmann et al., 2004). The clinical diagnosis of classical amyotrophic lateral sclerosis (ALS) is determined by identification of progressive dysfunction of both cortical ('upper') and spinal ('lower') motor neurons across multiple body regions (chiefly limb and bulbar), much of which was encapsulated by the El Escorial criteria (Brooks, 1994; Brooks et al., 2000b). The variable mix of upper motor neuron (UMN) and lower motor neuron (LMN) signs contribute to the clinical heterogeneity of ALS (Sabatelli et al., 2011).

The initial clinical presentations constituting 90% of all ALS, may be classified according to region: (1) limb-onset ALS; (2) bulbar-onset ALS; or sub-divided into much rarer extremes of LMN or UMN involvement: (1) progressive muscular atrophy, with pure LMN involvement, and typically limb-onset; or (2) primary lateral sclerosis, characterised by predominant UMN involvement, typically lower limb or bulbar in site of onset, both of which are rare (Kiernan et al., 2011). While ALS or Lou Gehrig's disease is the term used to describe all forms of the disease in the USA, motor neuron disease (MND) is the preferred term in Australia and the UK, with ALS reserved for the classical phenotype that presents with a combination of upper and lower motor neuron involvement. In this review, the term MND/ALS will be used to encompass all clinical phenotypes that include the classic ALS, progressive bulbar palsy, progressive muscular atrophy (PMA), and primary lateral sclerosis (PLS).

In the presence of progressive LMN weakness, features of UMN involvement are an important component supporting the diagnosis of MND/ALS (de Carvalho, 2012), but often clinical signs of UMN dysfunction may not be easily appreciated in a limb that is concurrently affected by LMN degeneration particularly in the early stages of MND/ALS (Swash, 2012; Geevasinga et al., 2014). Clinical UMN signs are found to be initially absent in 7–10% of MND patients (Rocha and Maia Júnior, 2012). UMN dysfunction may be identified by the presence of some or all of hyperreflexia with pathological reflex spread, spasticity, and clonus, preserved reflexes in weak wasted limbs and Babinski sign (Brooks et al., 2000b); as well as in some cases, the paucity or impairment in motor control and clumsiness may often be early features of UMN deficit. However, the various components of the UMN syndrome reflect different physiological abnormalities in the descending motor system that is expressed by the intact LMN system, the latter being invariably affected in MND/ALS (Pierrot-Deseilligny and Burke, 2005; Swash, 2012). Furthermore, simultaneous alpha and gamma spinal motor neuron loss in conjunction with spinal interneuron degeneration has an effect on the expression of UMN signs (de Carvalho, 2012; Swash, 2012).

Objective UMN markers are critical to the diagnosis, as purely LMN syndromes may be caused not only by MND/ALS (Turner et al., 2013; Simon et al., 2014), but mimics including progressive muscular atrophy, various motor neuropathies, Kennedy's disease and adult-onset spinal muscular atrophy (SMA). Importantly, autopsy reports have identified UMN degeneration in 50–75% patients without apparent clinical signs affecting the corticospinal tract (Lawyer and Netsky, 1953; Ince et al., 2003; Kaufmann et al., 2004). Failure to recognise UMN features in patients presenting with suspected MND/ALS consequently results in diagnostic uncertainty and thereby delay which according to population studies is more than a year from symptom onset to diagnosis. This will inevitably delay the commencement of potentially disease modifying or neuroprotective therapy, most effective when started early in the disease course, in addition to adversely affecting enrolment into therapeutic trials (Turner et al., 2009; Hardiman et al., 2011; Vucic et al., 2013a).

The more recent Awaji criteria, developed to increase diagnostic sensitivity for MND/ALS, incorporated objective neurophysiological biomarkers of LMN dysfunction which included chronic neurogenic changes and features of active denervation that also incorporated the presence of MND fasciculations (de Carvalho et al., 2008; Costa et al., 2012). Assessment of UMN involvement however, has remained clinically-based despite the improved diagnostic sensitivity using the Awaji criteria. For this reason, there remains a critical need to develop better in vivo UMN markers to improve diagnostic certainty that would in turn facilitate enrolment of patients with suspected MND/ALS into appropriate treatment and clinical trials. As such, the current review will provide an overview of recently developed techniques, including functional and structural imaging as well as novel electrophysiological approaches to study the integrity of the corticomotoneuronal (that part of the corticospinal tract with monosynaptic connections to spinal cord motor neurons) system in MND/ALS. There is no formal definition for the "early stages" of MND with some investigators suggesting that this may encompass those with minimal disability as defined by the ALS-FRS score, within a year of symptom onset, or based on the revised El-Escorial subgroups. In this current review, "early stages" of MND will be referred to those patients in either the clinically "suspected" or "possible" El-Escorial groups and especially those without clinically evident UMN signs. A detailed description of the actual methodology of the techniques discussed are beyond the scope of this review and readers are encouraged to refer to referenced papers for such discussion.

2. Literature search strategy

A systematic literature review was performed using PubMed (National Library of Medicine) during the period between 1970 and 2016. The search strategy used the following key words or