BAISHIDENG PUBLISHING GROUP INC
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242 Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com http://www.wjgnet.com

Name of Journal: *World Journal of Methodology*

ESPS Manuscript NO: 22847

Manuscript Type: REVIEW

Dear Sir/Madam,

Thank you for your review of our manuscript. We have addressed each of the editor's and the reviewer's points in turn below and have made amendments within the manuscript using tracked changes.

Editor's suggestions:

1. We have included the postcodes for each institution.
2. We enclose signed PDFs detailing no conflicts of interest exist from both authors.
3. We have altered the corresponding author's address as suggested.
4. We have amended the telephone number as suggested.
5. We have included a core tip summary.
6. We have included DOIs for all the references where possible – a minority of the references do not have an accessible DOI.

Reviewer's suggestions:

1. **The wording "Notably, a minority of spinal cord regions are bilaterally innervated from projections running in the anterior corticospinal tracts, which do not cross at the medullary pyramids but remain ipsilateral and cross at the appropriate spinal segment" is not clear regarding the presence of a ipsilateral corticospinal tract.**

We have amended the text for clarity to:

"There are also anterior corticospinal tracts, which do not cross at the medullary pyramids but remain ipsilateral. Notably, a minority of spinal cord regions are

innervated by these anterior corticospinal projections, which branch and innervate on both sides of the spinal cord, crossing at the appropriate spinal segment."

2. **Bulbar presentation is poorly described, in particular dysarthria (the typical presentation of bulbar-onset patients) is never mentioned.**

We have now amended the text to clearly explain the symptoms of bulbar onset disease.

3. **Pseudo-bulbar presentation is not limited to emotional liability**

We have now clarified that pseudo-bulbar presentation includes a number of other clinical features, and detailed these in the text.

4. **Fasciculations are an essential EARLY marker of the disease, this is not properly stressed.**

We have now explained that fasciculations are an early marker of disease, and included a reference for this statement.

5. **The critical role of electromyography to support diagnosis is missing.**

We have now included a detailed paragraph about the revised El Escorial criteria and the Awaji electrodiagnostic criteria and added a new box (Box 3) to specify these criteria for clinical diagnosis. We have explained that the Awaji criteria have a key role in determining lower motor neuron involvement and that they increase the sensitivity of diagnosis.

6. **Revised El Escorial criteria for clinical assessment and Awaji criteria for electrodiagnosis should be reported.**

As stated above, we have now included these criteria in depth and in Box 3.

7. **In addition to combined UMN and LMN signs, progression and electromyography are essential in the diagnostic process.**

As stated above, we have emphasised the importance of progression and electromyography for the diagnosis.

8. **Sialorrhea derives from dysphagia and not from hypersalivation.**

We have now included a statement about the cause of sialorrhoea and cited a reference for this.

9. **The following sentence seems displaced "It is noteworthy that parotid / submandibular botulinum toxin injections can be helpful for hypersalivation".**

We have now moved this sentence to the section about disease management and we have changed the word 'hypersalivation' to 'sialorrhoea'.

10. **The authors should state that frank FTD only affects 10-15% of ALS patients.**

We have now added a statement about the proportion of ALS patients with clinically diagnosed FTD and the proportion of FTD patients with clinically diagnosed ALS and included appropriate references for this.

11. **The European guidelines for ALS should be mentioned as well (Andersen et al., 2012).**

We have now included the European guidelines for ALS.

12. **It has been described cases of FTD negative for TDP-43.**

We have included a statement about the different subtypes of FTD, with disease caused by pathological inclusion of the proteins TDP-43, tau or FUS, to be clear that not all cases of FTD are characterised by cytoplasmic inclusions of TDP-43.

13. **The most important point is that the authors need to approach the link between UMN-LMN degeneration, discussion markers of cortical hyperexcitability and LMN hyperexcitability (fasciculations and fasciculation potential on electromyography).**

We have now included a detailed paragraph about transcranial magnetic stimulation, and evidence of cortical hyperexcitability early in the disease process. We have explained that this gives strength to a 'dying-forward' hypothesis for motor neuron disease, that corticomotoneurons induce lower motor neuron death.

In the new section on the revised El Escorial and Awaji electrodiagnostic criteria we have detailed the use of fasciculation potentials and fibrillation potentials in the diagnosis.

Thank you for reviewing our manuscript and we look forward to hearing from you.

With kind regards,

Rickie

==========

Rickie Patani, BSc MBBS MRCP PhD

Wellcome Trust Clinician Scientist

Anne Rowling Fellow in Regenerative Neurology

Department of Molecular Neuroscience,

UCL Institute of Neurology

Queen Square, London, WC1N 3BG, UK

==========