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Editorial

Is it time to depart from dichotomization in ALS diagnosis?

See Article, pages 307–314

Diagnosis of amyotrophic lateral sclerosis (ALS) is easy! Yes, provided that the patient has typical clinical and electrophysiological features, such as evidence of progressive upper and lower motor neuron (UMN and LMN) dysfunctions as manifested by clinical signs alone, or in conjunction with electrodiagnostic studies (widespread evidence of ongoing denervation and reinnervation and lack of excluding features). Unfortunately, patients exist who do not demonstrate such straightforward phenomena. In facing with such diagnostic challenges, a number of diagnostic criteria have been proposed. The most widely used criteria are the revised El Escorial criteria (REEC) that have been utilized in many clinical trials (Brooks et al., 2000). However, REEC have been criticized by low diagnostic sensitivity, especially in the early disease course (Zoccolella et al., 2006). In order to improve that weakness, the Awaji electrophysiological criteria (AC) amended the electrophysiological section of REEC by incorporating the following: (1) clinical and electrophysiological findings of LMN involvement should have equal significance to determine involvement of a specific region; (2) the category "Probable Laboratory-supported" was rendered redundant; and (3) the presence of fasciculation potentials (FPs) in muscles with evidence of reinnervation should serve as evidence of ongoing denervation (de Carvalho et al., 2008). Although the incorporation of FPs as evidence of ongoing denervation and other changes by AC appear to be well accepted, AC was criticized by rather poorer sensitivity than REEC, especially because the detection of UMN dysfunction was limited by eliminating the Probable Laboratory-supported subcategory (Higashihara et al., 2012). To overcome this limitation, the "updated AC" was proposed to revive the Probable Laboratory-supported subcategory (Geevasinga et al., 2016). Anyhow, these "refinements" were largely expert-opinion-based and have not been thoroughly assessed with respect to reproducibility or inter-rater reliability, which are the key features for routine clinical practice. Therefore, Johnsen and colleagues conducted a multicenter study to assess inter-rater variation and sensitivity in patients with suspected ALS (Johnsen et al., 2019).

They recruited 399 patients from 11 different centers in Europe and Israel. Eight experts then classified these patients according to REEC and AC. Their inter-rater variation was rather large for both criteria. In terms of diagnostic sensitivity, REEC and AC were comparable (64% and 63%, respectively). Of note, 20 patients were downgraded from "Probable laboratory-supported" to "Possible" category by AC, as previously pointed out (Higashihara et al., 2012). However, AC was significantly more effective in classifying ALS vs. Non-ALS patients than REEC.

Their carefully conducted study poses a very important question. Why do we need diagnostic criteria of ALS at all? Do we really need subcategories such as "Probable Laboratory-supported", despite knowing that the subcategories have considerable inter-rater variability? Diagnostic criteria are probably needed for multiple purposes, such as selection of candidates for a research project, to conduct an epidemiologic study, to provide social support, and so forth. It would be unethical to refuse to provide social support for otherwise significantly disabled patients, on the ground that they do not satisfy overly strict diagnostic criteria. Or it would be equally unethical if patients with ALS-mimics are inadequately enrolled into a clinical trial to receive an unproven therapy due to overly loose diagnostic criteria. As the authors correctly pointed out, dichotomized approach of "Definite/Probable" vs. "Possible/Not-ALS" would oversimplify the heterogenic presentation of ALS and lose flexibility. For instance, once diagnosed as "Not-ALS", the patient might not be provided with any potential opportunity for benefit, even if this patient's data were very near the diagnostic cutoff. In the era of ultra-high definition television, low-resolution images, as seen in a cathode ray tube television, are outdated! What about currently present diagnostic criteria of ALS that have 5 or less subcategories?

A hint could be found in the recently published diagnostic criteria of adult and juvenile idiopathic inflammatory myopathies (IIM) and their major subgroups, developed by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) (Lundberg et al., 2017). This was a multi-center prospective study enrolling 976 patients with IIM and 624 patients with other conditions. They determined "score points" on each variable, such as age of onset, muscle weakness, skin manifestations, laboratory abnormalities, and muscle-biopsy features. Interestingly, given the low frequency of receiving muscle biopsy in patients in pediatric and dermatology departments, two scoring schemes were proposed in patients with and without muscle biopsy findings. Based on the scores, the probability of IIM and its subtypes can be calculated. For simple scoring and classification, a web-calculator is provided (www.imm.ki.se/biostatistics/calculators/iim). The advantage of the EULAR/ACR classification criteria is the continuity of scores, that are not dichotomized any longer. For instance, the cutoff needed for classifying a patient as IIM is a score $\geq$55%, and "definite IIM" corre-

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sponds to a probability of ≥90%, recommended as the expert opinion. But these cutoffs should never be rigid, such that they can be subsequently adjusted if new supporting evidence is available. Their scoring scheme divided into situations "with-biopsy" and "without-biopsy" could be useful in ALS, when electrodiagnostic studies or other tests cannot be conducted for some reasons, but still the clinical diagnostic criteria can be applied.

The impact of this collaborated work is magnificent. An equally important step would be how we can proceed to design better diagnostic criteria for ALS based on the present database. That would hopefully contribute to achieve our big dream: finding an effective therapy for ALS.

Conflict of interest statement

None of the authors has conflict of interest to disclose.

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