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Letter to the Editor

The Identification of Diagnostic Biomarkers for Presymptomatic ALS or Early ALS Requires Appropriately Designed Studies

[1] Josef Finsterer, [2] Carla A Scorza, [3] Fulvio A Scorza

[1] Department of Neurology, Neurology & Neurophysiology Center, Vienna, Austria
[2, 3] Federal University of Sao Paulo (UNIFESP/EPM), São Paulo, Brazil

Corresponding Author: **Josef Finsterer**

Letter to the Editor

We read with interest the article by Tzeplaeff *et al*. on the study design of a planned prospective international study to identify clinical-molecular signature features of preclinical and early amyotrophic lateral sclerosis (ALS) [1]. The plan is to examine 220 asymptomatic or early-symptomatic ALS patients for mutations in two ALS genes (C9orf72, PAX), clinical neurological deficits, olfactory dysfunction, cognitive deficits, and biological abnormalities in body fluids and tissues [1]. The protocol for the planned study is promising, but some points should be discussed.

The first point is that familial ALS may not only be due to mutations in C9orf72 or PAX, but also to mutations in several other genes (e.g., FUS, TARDBP, SOD1, TBK1, OPTN, ATXN8OS, POLG, etc.) [2]. What is the reason for testing only two genes for mutations according to Table 1?

The second point is that the diagnosis of patients in the second group with early-onset ALS is made according to the El Escorial criteria [3]. The El Escorial criteria have since been replaced by more recent criteria such as the Awaji-Shima criteria and the revised Gold Coast criteria. Therefore, the revised Gold Coast criteria should be used for the diagnosis of ALS, rather than the El Escorial criteria.

The third point is that the group of ALS mimics is insufficiently defined [1]. All types of motor neuron diseases (including spinal muscular atrophy, hexosaminidase deficiency, adrenoleukodystrophy, GM1 gangliosidosis, poliomyelitis, Kennedy's disease, cervical spinal stenosis), hereditary polyneuropathy, mitochondrial disorders, lysosomal disorders, and beta-oxidation defects) must be considered and excluded.

The fourth point is that no cerebral imaging is planned for patients [1]. In order to assess whether structural brain lesions (e.g., atrophy of the corticospinal tract, atrophy of the frontal lobe, white matter lesions, gray matter lesions) are present that could explain the motor symptoms and ALS mimics, it is essential that all patients undergo an MRI of the brain.

The fifth point is that there are no plans to match ALS patients with control subjects in terms of gender and age. In order to be able to assess more accurately whether the tests used differ between sick and healthy subjects, it is recommended that the two groups be matched not only in terms of environmental influences, but also in terms of age and gender. Differences in age and gender are known to exist among ALS patients [4, 5].

In summary, it is recommended that the study protocol for the planned primodiALS study be improved by performing whole exome sequencing in all patients with asymptomatic ALS, diagnosing ALS according to the Gold Coast criteria, matching ALS patients with control subjects in terms of age and gender, including cerebral imaging in the protocol, and expanding the range of differential diagnoses to be excluded.

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