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Revealing the microstructural brain damage in amyotrophic lateral sclerosis: the relentless pursuit to approach an imaging biomarker

Revelando o dano cerebral microestrutural na esclerose lateral amiotrófica: a busca incansável por um biomarcador em imagem

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Amyotrophic lateral sclerosis (ALS) is the commonest clinical form of the wider neurodegenerative syndrome encompassed by the term motor neuron disease (MND). ALS has a consistent incidence of 1-2/100,000/year, and a lifetime risk estimated at 1 in 400. The disease is characterized by the progressive death of upper motor neurons (UMNs) of the cerebral primary motor cortex and corticospinal tract, in combination with degeneration of lower motor neurons (LMNs) whose origins lie in the brainstem and spinal anterior horns. Loss of motor neurons in general results in weakness, but specifically loss of LMNs results in secondary wasting of the downstream musculature and spasticity arises from loss of UMNs[1].

About 10% of cases are considered as being familial (fALS), whereas the remaining 90% seem to occur sporadically (sALS) with no family history of ALS. Since the first discovery of SOD1 mutations being causative for ALS in 1993[2], researchers all over the world have made great effort to further delineate the genetic basis underlying ALS. Today, more than 30 confirmed major disease genes are listed by the Amyotrophic Lateral Sclerosis Online genetics Database (ALSoD), the most frequently affected being C9orf72 (40% fALS, 5–6% sALS; pathogenic repeat expansion in the non-coding region between exons 1a and 1b, detection by repeat analysis), SOD1 (20% fALS, 3% sALS), FUS (5% fALS, <1% sALS) and TARDBP (3% fALS,2% sALS)[3].

In addition to this clinically heterogeneous syndrome a pathologically overlapping with frontotemporal dementia motor signs have been detected by neuropsychological tests in about 50% of sALS patients. Furthermore typical frontotemporal dementia (FTD) occurs in approximately 10% of the patients[4], and the term frontotemporal dementia-motor neuron disease (FTD-MND) continuum was proposed to describe this association[4], which occurs mostly in C9ORF72-linked fALS[5].

Despite all this clinical and etiopathogenic complexity, some faces of ALS, including FTD-MND continnum, have been elucidated by magnetic resonance imaging (MRI) techniques, which have proved to be useful to reveal microstructural brain abnormalities associated with different rates of symptom progression[6,7]. A plausible biomarker for upper motor neuron degeneration in ALS is becoming tangible after recent advances in high-throughput MRI techniques, through which one can believe that we are going to the forefront of a breakthrough able to translate research findings into reliable clinical tests that will support the practice of personalized medicine[8,9,10].

Advances in neuroimaging have enabled mapping of some endpoints in functional, structural, and molecular aspects of ALS pathology. Menke et al.[8] have recently reported imaging abnormalities even before clinical symptoms, offering the potential for neuroprotective intervention, particularly in familial cases. Current literature points to DTI technique as the most promising candidate for imaging biomarker in ALS, able to elucidate the brain phenotype of ALS and also detect white matter tract changes in extramotor regions[8,10].

The results of Chaves et al.[11] using a 1.5 Tesla MR equipment reinforce the clinical use of fractional anisotropy (FA) to detect extra-motor brain abnormalities in ALS patients. Despite this further multicenter validation with larger cohorts of patients remains mandatory prior to the integration of this technique into the clinical routine as biomarker able to contribute in standard clinical decision-making algorithms.

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