Presymptomatic Imaging in ALS

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Abstract

The failure of many therapeutic trials in ALS may be the consequence of a diagnostic delay, where the affected neuronal structures can no longer be rescued, and the absence of pre-clinical biomarkes prevents any possibility for primary prevention of this disease. Neuroimaging studies of pre-symptomatic individuals carrying monogenetic abnormalities such as mutations in superoxide dismutase 1, TARDBP, FUS, C9orf72, could provide invaluable information in order to detect early changes in the disease process. Although such studies have ethical challenges and are confounded by issues of incomplete penetrance, this strategy represents a major opportunity to identify biomarkers that can be applied to sporadic disease as recently demonstrated in dominantly inherited Alzheimer's disease.

The failure of many therapeutic trials in ALS may be the consequence of a diagnostic delay, where the affected neuronal structures can no longer be rescued, and the absence of pre-clinical biomarkers prevents any possibility for primary prevention of this disease [1]. Neuroimaging studies of pre-symptomatic individuals carrying monogenetic abnormalities such as mutations in superoxide dismutase 1 (SOD1), TARDBP, FUS, C9orf72, could provide invaluable information in order to detect early changes in the disease process. Although such studies have ethical challenges and are confounded by issues of incomplete penetrance, this strategy represents a major opportunity to identify biomarkers that can be applied to sporadic disease as recently demonstrated in dominantly inherited Alzheimer's disease [2]. This syllabus summarizes the main results obtained from the application of advanced MRI techniques in ALS patients, with a greater focus on studies of patients carrying genetic mutations.

Voxel-based morphometry and cortical thickness measures

In ALS, voxel-based morphometry (VBM) and surface-based morphometry have revealed cortical atrophy/thinning of the precentral gyrus [3-5]. With respect to the regional distribution of brain atrophy beyond the primary motor cortex, the pattern and extent of volume loss in MND patients vary across studies [1]. Differences in image pre-processing and statistical analysis, as well as in the clinical, cognitive and genetic characteristics of the cohorts of patients studied, may all contribute to explain this variability. In ALS patients with no cognitive impairment, several MRI studies found extra-motor GM loss or thinning of the frontotemporal and parietal regions [3-7]. The involvement of extra-motor regions is more severe in ALS patients with cognitive impairment and ALS-frontotemporal dementia (FTD) [8, 9].

A VBM study showed that cortical atrophy in patients homozygous for the D90A (homD90A) SOD1 mutation is more pronounced in the frontal lobes, while sporadic ALS patients had areas of atrophy mainly confined to motor and premotor cortices bilaterally [10]. Patients with ALS and the C9orf72 repeat expansion showed a considerable non-motor cortical atrophy when compared with ALS patients without the repeat expansion [11, 12]. Mutations of the Senataxin gene are associated with autosomal dominant juvenile ALS (ALS4) and autosomal recessive ataxia-ocular apraxia 2 (AOA2). In a two-generation family, whose affected individuals had a clinical phenotype combining typical features of AOA2 and ALS4, MRI revealed severe cerebellar atrophy [13].

Diffusion tensor MRI

DT MRI studies of ALS patients have consistently reported decreased fractional anisotropy (FA) of the CST [1], which was found to correlate with disease severity, rate of disease progression, and clinical or electrophysiological measures of UMN degeneration [14-18]. ALS patients show also FA decrease of the corpus callosum [3, 16, 17, 19], which has been found to correlate with disease severity and central motor conduction time obtained by transcranial magnetic stimulation. The strongest FA decrease was

found in the middle-posterior parts of the corpus callosum, linking to the motor and premotor cortices [17, 20]. DT MRI studies that employed a voxel-wise approach to investigate differences in FA between ALS patients and controls, reported a decreased FA in regions outside the "classic" motor network [3, 16, 19].

Despite a similar degree of clinical UMN dysfunction and disability, less extensive white matter changes in motor and extramotor pathways were found in patients homozygous for the homD90A SOD1 mutation compared to sporadic ALS patients [21, 22]. A study of eight presymptomatic SOD1 mutation carriers reported decreased FA in the posterior limb of the internal capsule compared with healthy controls [23]. These findings might be among the earliest detectable changes in those subjects who are at risk for UMN involvement.

Proton magnetic resonance spectroscopic imaging

Nearly all ^{1}H-MRSI studies in ALS have demonstrated that either N-acetylaspartate (NAA) concentrations or NAA/creatine (Cr), NAA/choline (Cho) and NAA/Cr+Cho ratios are reduced in the motor cortex of these patients [1]. ^{1}H-MRSI studies reported significant correlations between motor cortex NAA concentrations (or ratios) and disease severity (revised ALSFRS), the Norris limb scale, UMN signs, maximum finger tapping rate, and disease progression [1], suggesting that ^{1}H-MRSI might contribute to the understanding of phenotype heterogeneity. A pivotal ^{1}H-MRS study of pre-symptomatic carriers of pathogenic SOD1 mutations identified reduced metabolite ratios in the cervical cord similar to affected ALS patients [24], suggesting that these measures have the potential to serve as very early biomarkers.

Functional imaging

a) Positron emission tomography

Patients with ALS have decreased glucose uptake in the frontal lobe as assessed using PET with [18F]2-fluoro-2-deoxy-D-glucose (FDG), and some have additional abnormalities in the temporal, parietal, and right thalamic regions [1]. Using ligand-based PET, a reduction of cortical ^{11}C-flumazenil binding has been detected in the motor/premotor and extramotor cortical regions of patients with ALS [25]. A less extensive, and more frontal pattern of reduced ^{11}C-flumazenil binding was observed in patients with homD90A SOD1 compared with similarly-disabled patients with sporadic ALS [26]. One PET study with ^{11}C-WAY100635, which binds selectively to the 5-hydroxytryptamine (5-HT) 1A receptor on cortical pyramidal neurons, revealed marked binding reductions in the precentral and cingulate gyri, and frontotemporal regions of ALS patients [27]. Such reduced 5-HT1A receptor binding was also seen in similar areas in frontotemporal patients [28]. The reduction in the cortical binding of ^{11}C-WAY100635 was less severe in homD90A SOD1 patients than in those with sporadic ALS [29].

b) Resting state functional MRI

Initial resting state fMRI studies of ALS reported significantly decreased functional connectivity within the sensorimotor network [30-33], in keeping with the altered structural damage. However, subsequent studies have identified regions of increased functional connectivity, including somatosensory and extra-motor areas [34-37]. The pattern of increased functional connectivity to the left primary motor cortex was found to be more widespread when considering only patients with undetectable CST DT MRI abnormalities than the whole group of patients [35], suggesting that these changes might have a role in compensate for (limited) structural damage and might exhaust with increasing burden of pathology. In ALS, resting state fMRI demonstrated not only sensorimotor network alterations, but also an abnormal connectivity of brain networks related to cognition and behaviour [30, 31, 38]. ALS patients compared with controls showed divergent connectivity patterns, with a decreased connectivity of the frontal cortex and an increased connectivity of the parietal regions in the default mode and frontoparietal networks [38]. The enhanced parietal connectivity was associated with the clinical and cognitive deficits of ALS patients [38], suggesting that it may have a role in maintaining cognitive efficiency in the presence of structural frontotemporal injury.

Other studies lend support to the hypothesis that the high level of functional connectivity in ALS patients is related to a pathogenic loss of local inhibitory circuitry, rather than compensatory recruitment [34, 36, 37]. In a study using a pre-defined ‘ALS-specific’ cortical network, increased functional connectivity was found over a large area spanning sensorimotor, premotor, prefrontal and thalamic regions, which largely overlapped the areas of structural abnormalities identified using DT MRI [36]. Increased functional connectivity within the sensorimotor, frontal, and left frontoparietal networks spanning the pre- and postcentral, medial and dorsal frontal, insular, and superior temporal regions was observed in PLS patients [37]. PLS subjects with the highest functional connectivity showed the greatest clinical disability, executive functional impairment and WM tract microstructural damage [37].

To date, no studies have investigated the pattern of functional connectivity in pre-symptomatic individuals carrying genetic mutations related to ALS and other motor neuron diseases.

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