Degenerative and regenerative processes in amyotrophic lateral sclerosis: motor reserve adaptation and putative compensatory changes

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Advances in amyotrophic lateral sclerosis (ALS) research: Research in ALS has gained unprecedented momentum in recent years, fueled by important conceptual developments, establishment of international consortia, breakthrough genetic discoveries and relentless technological advances. The first genotype-specific pharmaceutical trials signal the paradigm shift from the notion of ‘one-drug-for-all’ to precision, individualized therapies. The arcane presymptomatic phase of the disease is gradually unravelled by seminal studies of asymptomatic mutation carriers (Geevesinga et al., 2015; Querin et al., 2019). The meticulous analysis of data from large population-based registries has contributed to the identification of etiological factors, genetic modifiers, therapeutical targets and environmental modifiers. Progression patterns have been characterized in vivo by robust clinical, neurophysiology and neuroimaging studies and led to the development of clinical staging systems and biomarkers with practical utility in clinical trials (Chipika et al., 2019). While ALS was once considered a ‘pure’ motor system disorder, it is now widely regarded as multisystem condition with frontotemporal, cerebellar, and subcortical grey matter involvement and a range of extrapyramidal, cognitive, and behavioral manifestations (Elamin et al., 2017). Disease-specific functional rating scales are now routinely used and screening instruments have been developed to assess the most commonly affected cognitive and behavioral domains in ALS. Advances in genetics paved the way for the first large presymptomatic studies which confirmed considerable cerebral and spinal cord alterations decades before symptom manifestation (Vucic et al., 2008; Querin et al., 2019). The characterization of genotype-associated molecular cascades, pathological signatures and clinical features were important milestones for the development of novel therapies, and the first antisense oligonucleotide trials are now underway. It is also apparent that considerable phenotypic heterogeneity exists in observation that rates and disability profiles. It is therefore likely that patients may benefit from individualized pharmacological interventions tailored to their genotype, phenotype and disease-stage as opposed to the notion of ‘one-drug-for-all’. Despite the enthusiasm generated by the first antisense oligonucleotide studies, it is noteworthy that the vast majority of patients with ALS are seemingly sporadic and test negative for large panels of mutations linked to ALS such as SOD1, ALS2, SETX, SPSG11, FUS, VAPB, ANG, TARDBP, FIG4, OPTN, ATXN2, VCP, C9orf72, UBQLN2, SQSTM1, NEK1, FUS, TBK2 etc. Accordingly, the majority of patients with ALS are not candidates for genotype-specific interventions, cannot be included in presymptomatic studies and the risk of their relatives developing neurodegenerative change is uncertain. On the other hand, a successful clinical trial is the relatively late inclusion of patients into clinical trials due to stringent inclusion criteria. Large epidemiology studies in ALS have repeatedly demonstrated that the interval between symptom onset and diagnosis is in the range of 12–14 months which is a considerable delay with a multitude of adverse ramifications. Quantitative radiology studies have shown that by the time a patient fulfills diagnostic criteria would potentially capture ALS patients at an earlier stage, with limited disease burden, increasing the benefits of any future intervention. Another shortcoming of current clinical trial designs is the exclusive reliance on respiratory measures, functional rating scales and survival as primary end-points at a time when a multitude of quantitative in vivo neurophysiological and imaging biomarkers show promise in tracking pathological changes in vivo. Neuroradiological end-points are firmly integrated in the clinical research of ALS, such as multiple sclerosis, are non-invasive and can be quantitatively interpreted in an observer-independent fashion. From a practical biomarker perspective, neurophysiology techniques have the added advantage of appraising both upper and lower motor neuron function, being relatively cost effective, and applicable to patients with considerable disability. The addition of quantitative biomarker panels to clinical outcome measures may allow a more nuanced appraisal of response to therapy.

Conceptual barriers: Academic efforts to characterize progressive changes are limited by a multitude of methodological and conceptual constraints. Clinical studies typically rely on batteries of clinical and neuropsychological instruments, the scores of which have to carefully adjusted for fatigue, motor disability, motivation, mood, and medications. Neuroradiological studies suffer from selection bias to patients who can tolerate MR scanning, able to lie flat, comply with instructions, and therefore tend to represent patients with limited motor disability, limited bulbar involvement, no orthopnoea, no behavioral deficits and no sialorrhoea. Post mortem studies only capture the terminal phase of the disease and brain banking is only available in certain centers due to a number of financial and cultural factors which limit the widespread availability of brain and spinal cord donation. Conceptual constraints also limit the interpretation of large clinical, neurophysiology, radiology and histology studies. Cross-sectional and longitudinal studies overwhelmingly focus on disease burden and evaluate the most affected anatomical regions. These studies typically also seek correlations with clinical metrics and propose phenotype or genotype-associated anatomical patterns. This conservative approach overlooks compensatory changes which are ill-characterized contributors to the clinical picture. Direct correlations between focal imaging metrics and clinical scores are often requested during peer-review, even though the majority of motor and cognitive functions are mediated by multi-synaptic networks, making the allocation of a specific function to a single structural contentious. In addition, hippocampal volumes have been linked to memory scores, motor cortex metrics to ALSFRS-r, accumbens nucleus volume to apathy etc. over-looking the contribution of other areas and the selection of a specific function. One of the biggest shortcomings of existing studies however is the exclusive focus on degenerative changes and the lack of attention to functional compensation, which may also occur. Analogous to the concept of ‘cognitive reserve’ in Alzheimer’s disease, the notion of ‘motor reserve’ merits consideration in ALS. Corticospinal tract alterations and spinal cord atrophy have been described in relation to ALS patients without overt clinical signs or symptoms (Querin et al., 2019). The striking discrepancy between the severity of radiological changes and limb function impairment is significant and suggests a degree of network redundancy, functional resilience or ‘motor reserve’.
Evidence for compensatory and adaptive changes: Imaging studies have consistently suggested a degree of cerebral reorganization and proposed that key functions may be taken over by structurally less affected brain regions. These processes however are poorly characterized despite their proposed role in delaying symptom manifestation and compensating for the effects of relentless neurodegeneration (Abidi et al., 2020). Adaptive processes underpin multidisciplinary rehabilitation efforts and anecdotal observations from physical therapists, occupational therapists, and speech and language therapists suggest that functional gains can be made with individualized exercise regimes. Neural plasticity and rehabilitation has a robust literature in other neurological conditions such as stroke, multiple sclerosis, traumatic brain and spinal cord injury, yet adaptive mechanisms in ALS are woefully understudied. Functional MRI studies using motor paradigms have consistently demonstrated an activation shift from the primary motor cortex to premotor, supplementary motor, ipsilateral motor, basal ganglia, and cerebellar regions (Figure 1). Resting state functional studies often identify increased connectivity (Nasseroleslami et al., 2019), typically in the default mode and cortico-cerebellar networks. While these alterations are typically interpreted as ‘compensatory’, the confounding effects of medications (Riluzole, Baclofen) and hypoxia on fMRI signal are seldom acknowledged. Abrant network activity and increased connectivity could equally be considered pathological and the binary categorization of functional observations into ‘adaptive’ and ‘pathological’ is likely to be simplistic. Structural imaging studies in ALS provide limited evidence of compensatory processes (Bede et al., 2018), but increased cortical volumes in supplementary motor regions have been reported (Christidi et al., 2018). PET studies primarily report patterns of hypometabolism in brain regions susceptible to ALS pathology, and clusters of hypermetabolism are likely to represent microglial activation rather than compensatory changes. Post mortem studies in ALS have also primarily concentrated on the characterization of affected brain regions and the molecular analysis of intraneuronal inclusions. Pathological staging systems have been developed and robust post mortem imaging studies have been undertaken, but only a few post mortem studies specifically investigated stem cell mobilization, adaptive or regenerative processes.

Demographic and clinical variables are likely to influence the efficacy of adaptive processes in ALS. Plasticity is thought to be more significant in younger patients and ALS patients with slower progression rates are likely to permit more from efficient compensatory mechanisms. There is considerable variation in progression rates in ALS; patients with restrictive phenotypes, such as monomeric forms of the disease, or upper motor neuron predominant phenotypes typically have longer survival. Bulbar onset, respiratory compromise, older age at onset, and comorbid dementia, are established negative prognostic indicators. Pharmacological targets in ALS typically focus on ‘neuroprotection’, glutamate inhibition, anti-inflammatory effects, oxidative stress mitigation, iron chelation and antisense therapy, but recent studies have also shown promise in mobilizing stem cells through granulocyte colony stimulation (Peters et al., 2018).

Conclusions: Due to the striking biological heterogeneity of ALS, the concept of ‘one-drug-for-all’ should be superseded by precision, phenotype-, genotype-, and stage-specific therapeutic strategies. Regenerative and adaptive processes are poorly characterized in ALS despite offering a potential target for intervention. Robust, dedicated studies are urgently required to study compensatory mechanisms in ALS and explore therapies that facilitate stem cell mobilization and network reorganization.

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