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Pre-Symptomatic Amyotrophic Lateral Sclerosis: From Characterization to Prevention

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Abstract

Purpose of review: Significant progress in characterizing pre-symptomatic amyotrophic lateral sclerosis (ALS) is ushering in an era of potential disease prevention. While these advances have largely been based on cohorts of deep-phenotyped mutation carriers at elevated risk for ALS, there are increasing opportunities to apply principles and insights gleaned, to the broader population at risk for ALS (and frontotemporal dementia, (FTD)).

Recent findings: The discovery that blood neurofilament light chain (NfL) level increases pre-symptomatically and may serve as a susceptibility biomarker, predicting timing of phenoconversion in some mutation carriers, has empowered the first-ever prevention trial in *SOD1*-ALS. Moreover, there is emerging evidence that pre-symptomatic disease is not uniformly clinically silent, with mild motor impairment (MMI), mild cognitive impairment (MCI), and/or mild behavioral impairment (MBI) representing a prodromal stage of disease. Structural and functional brain abnormalities, as well as systemic markers of metabolic dysfunction, have emerged as potentially even earlier markers of pre-symptomatic disease. Ongoing longitudinal studies will determine the extent to which these reflect an endophenotype of genetic risk.

Summary: The discovery of pre-symptomatic biomarkers and the delineation of prodromal states is yielding unprecedented opportunities for earlier diagnosis, treatment, and perhaps even prevention of genetic and apparently sporadic forms of disease.

Keywords

ALS/FTD gene mutation carriers; biomarkers; pre-symptomatic; prodromal disease; prevention

Introduction

The neurodegenerative disorder amyotrophic lateral sclerosis (ALS) is traditionally regarded as a clinical syndrome characterized by progressive weakness alongside evidence of degeneration of both upper and lower motor neurons. A broader cerebral, extra-motor pathological spectrum with frontotemporal dementia (i.e. ALS-FTD) is also recognized. In addition to phenotypic overlap, ALS and FTD have shared genetic risk and a common

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molecular signature in the form of cytoplasmic inclusions of the 43KDa transactive response DNA binding protein, TDP-43 (1).

Akin to other neurodegenerative disorders, the clinical syndrome of ALS is preceded by a pre-symptomatic phase of disease (2–5). This phase is characterized by biological processes that directly reflect either the pathology responsible for disease, or a reactive or compensatory state. The clinical syndrome emerges only once the threshold of system redundancy is exceeded. The pre-symptomatic phase of disease, combined with the latency from typically insidious onset of symptoms to diagnosis, raises concern that therapeutic interventions are currently initiated too late in the course of disease to permit meaningful functional recovery (6). Given the general principle that earlier treatment is likely to be better treatment, there has been significant interest in understanding pre-symptomatic disease with a view to earlier initiation of treatment, and perhaps even disease prevention (7).

Studying Pre-symptomatic Disease Through Genetic ALS

Most ALS cases (~90%) arise apparently sporadically with no family history of disease. Neuropathology is typically established and severe by the time of diagnosis. The seminal finding in 1993 that variants in the superoxide dismutase-1 (*SOD1*) gene are responsible for a subset of familial ALS (8), empowered the study of the pre-symptomatic phase of disease among carriers of pathogenic variants who have not yet developed clinically manifest ALS (4). Rapid growth in the discovery of a much wider range of genetic risk factors – with an intronic GGGGCC hexanucleotide expansion in *C9ORF72* being the most common cause of familial cases of both ALS (40%) and FTD (50%) (9) -- has dramatically broadened opportunities to study pre-symptomatic disease among those at markedly elevated risk for ALS (and FTD).

Furthermore, studying pre-symptomatic carriers of a range of genetic variants illuminates similarities and differences across a range of biological pathways and clinical phenotypes. Importantly, this is necessary considering the recognition that ALS is biologically and clinically heterogeneous, and that the pre-symptomatic phase of *SOD1* ALS may not be representative of all forms of ALS (10). Indeed, there is evidence that the temporal evolution and nature of biomarkers in the pre-symptomatic stage of FTD also differ across the three major implicated genotypes (11). With the study of pre-symptomatic genetic ALS as the starting point, the long-term goal is to parlay the insights obtained from these studies into the identification of underlying risk factors (environmental and polygenic) and development of therapeutic strategies for the larger group of apparently sporadic cases of ALS (12).

Characterizing Pre-Symptomatic Disease

A distinction should be made between an elevated risk for (or susceptibility to) ALS, and the evidence of pre-symptomatic disease. An individual may be at risk of ALS based on their harboring a pathogenic *SOD1* variant, but this does not imply that the cascade of biological events that ultimately leads to neurodegeneration has begun. Cross-sectional biomarker data

should, therefore, be interpreted with caution as they may simply reflect, for example, an endophenotype of the underlying genetic cause of disease.

The overlap between ALS and FTD, including recognition that cognitive and behavioral features are an important manifestation of at least some forms of disease (e.g. *C9ORF72*, *TBK1*, *VCP*, *TARDBP*), underscores the importance of both motor and cognitive/behavioral phenotyping as components of characterizing pre-symptomatic ALS. Moreover, detection of subtle clinical signs requires a meticulous approach and the use of sensitive tools (e.g. EMG for detecting sub-clinical LMN signs; detailed neuropsychological testing and informant interviews for detecting subtle cognitive and behavioral manifestations of disease) (7). In addition, the success of multi-center efforts to characterize pre-symptomatic disease relies on shared definitions of phenotransition and phenoconversion (7); standardization of assessments – with examiners demonstrating high inter-rater reliability; and standardized operating procedures for biospecimen collection, processing, and storage. Given the unknown sensitivity of different biomarkers to detecting the earliest manifestations of disease and that the site of initial onset in ALS is unpredictable, the use of both a multi-modal and a multi-regional approach to characterizing disease is essential.

Prodromal Clinical States

The traditional view of ALS as a clinical syndrome is from the vantage point of the neurologist seeing a patient for a diagnostic evaluation, on average 11–12 months after symptom onset (6). In this context, patient-reported initial symptoms are presumed to be the earliest clinical manifestation of disease – with disease prior to that point assumed to have been clinically silent. The prospective study of pre-symptomatic gene carriers, however, has revealed more subtle clinical and electromyographic signs of disease that may not have been overtly symptomatic to the individual. These signs of upper and lower motor neuron dysfunction, collectively termed *mild motor impairment*, represent a prodromal clinical stage of disease (13). Moreover, similar prodromal syndromes characterized by mild cognitive impairment (MCI) and mild behavioral impairment (MBI), may emerge in some of those at genetic risk for ALS-FTD (e.g. *C9ORF72* expansion carriers) (7). If these prodromal syndromes are also a feature of apparently sporadic forms of ALS, the recognition of MMI in the general population provides an opportunity to study pre-symptomatic ALS at a much larger scale and, in combination with emerging biomarkers, to effect earlier diagnosis and treatment. To appreciate the potential importance of these prodromal states to understanding pre-symptomatic ALS, it is helpful to consider the role of MCI in Alzheimer's disease and the role of prodromal clinical markers such as REM sleep behavior disorder in Parkinson's disease (14).

Biomarkers

The application of advanced MRI, notably quantitative grey matter volumetry and white matter tractography, but also functional network-based sequences, has revealed significant differences in pre-symptomatic genetically at-risk populations for ALS (or FTD), compared to age-matched non-carriers. The exemplar is the *C9ORF72* repeat expansion-associated ALS-FTD syndrome, in which very widespread changes have been observed in individuals

likely to be many years (even decades) from the emergence of clinical symptoms. To date, however, longitudinal follow-up in these studies has been relatively short (1.5–2 years), and cross-sectional regional involvement has varied across studies apart from a consistent observation of thalamic involvement (reviewed in (15)). A recent cohort study, including *post-mortem* gene expression profiling, has provided intriguing evidence for a potential influence of the *C9ORF72* repeat expansion on very early neurodevelopment (16).

The discovery that blood levels of neurofilament light chain (NfL) rise in advance of the emergence of clinically manifest disease was a key milestone in the understanding, as well as the detection, of pre-symptomatic ALS (17). These data provided strong evidence for a pre-symptomatic stage characterized by accelerating axonal degeneration (10). A subsequent study has suggested that NfL levels may be elevated up to 5 years prior to diagnosis among sporadic ALS patients compared to controls (18), though this conclusion rests on cross-sectional statistical comparisons between groups rather than longitudinal NfL trajectories showing an elevation above a normative threshold. Similar modeling-based approaches have suggested that NfL may also increase pre-symptomatically among those at genetic risk for FTD (11, 19, 20).

Other potential biomarkers of pre-symptomatic ALS have begun to emerge in novel areas. Among these, alterations in various markers of metabolic function have been most frequently described. One of the most consistent observations is the association between lower premorbid body mass index (BMI) and a higher risk of ALS, an effect particularly pronounced among *C9ORF72* expansion carriers (21). In another more nuanced view, lower lean body mass and a higher ratio of metabolically active/inactive cells was reported among pre-symptomatic carriers, with all tissue types affected among *C9ORF72* expansion carriers, but only metabolically active tissue in the *SOD1* population (22). It has been suggested that these changes precede rises in NfL, but the data were cross-sectional; it is therefore impossible to disentangle what might represent an endophenotype from an early pre-symptomatic stage of disease. Plasma microRNA signatures associated with the *C9ORF72* repeat expansion have also been identified, with cross-sectional, differential expression between healthy controls, pre-symptomatic and symptomatic individuals (23).

Several studies have identified premorbid lipid profiles that are associated with an increased risk of developing ALS. For example, higher levels of low density lipoprotein cholesterol (LDL), Apolipoprotein B (ApoB), and ApoB/ApoA1 ratio have been associated with an increased risk (24); and higher levels of high density lipoprotein cholesterol (HDL) and ApoA1 with a lower risk of ALS (25). Population-based models of the longitudinal trajectories of these lipid biomarkers are conflicting, however, with one suggesting increasing levels of LDL and ApoB before diagnosis (24) and one suggesting the opposite (25). Moreover, these population-based observations belie a greater complexity with large overlap between concentrations of these lipid biomarkers among individuals who do versus do not subsequently develop ALS.

Molecular biomarkers based on the biology of TDP-43 dysfunction have begun to emerge, including elevated levels of cryptic HDGFL2 expression in the CSF of *C9ORF72* expansion carriers (26), though data to date have been cross-sectional. How levels of neo-peptides,

resulting from TDP-43-related loss or gain of function in cryptic exon splicing, change over time and their relationship to the timing of phenoconversion to clinically manifest ALS, are yet to be determined.

Contemplating Prevention

Preventing ALS will require an understanding of causes and risk factors beyond monogenic variants. Viable strategies to intervene, mitigating risk factors or treating the underlying biology of disease before symptoms emerge, are required in addition to methods for predicting the timing of clinical manifestations so that the initiation of treatment is tuned to the intervention's risk-benefit ratio. NfL has emerged as a leading susceptibility biomarker for the imminent emergence of clinically manifest ALS in carriers of highly penetrant *SOD1* variants associated with rapidly progressive disease (17). An intrathecally-administered antisense oligonucleotide targeting SOD1 mRNA, tofersen, has been shown to lower SOD1 protein levels in CSF – alongside what the FDA has acknowledged to be a "reasonably likely" surrogate marker of clinical benefit, namely significant lowering of blood NfL levels (27), (28). As a result of these combined developments, it has been possible to design and initiate the first-ever preventative trial in ALS (ATLAS) in which tofersen is initiated during the pre-symptomatic phase of disease in *SOD1* carriers once blood NfL increases above a pre-defined threshold. The trial goals are to delay or prevent the emergence of clinically manifest ALS, and to slow the rate of functional decline should clinically manifest disease emerge (29). Expanding such preventative approaches to encompass other genetic (and even non-genetic) forms of ALS, however, will require the discovery of new biomarkers (i.e. in addition to NfL).

Immediate Priorities

Major efforts have been underway to develop and refine the concepts, as well as an accompanying lexicon, to describe the pre-symptomatic phase of the natural history of ALS that had, heretofore, not been systematically studied and described (7),(30). Cohering around a set of agreed upon concepts, operational definitions, and terms to ensure consistent data collection and reporting of the pre-symptomatic phase (including the prodromal stage) of disease will be essential to future research efforts (7). The study of pre-symptomatic ALS has also necessitated a complex ethical framework to protect the confidentiality and support the psychosocial wellbeing of genetically at-risk individuals who wish to take part in research with or without disclosure of genetic results (4). Similar considerations apply to the disclosure of non-genetic biomarker results, for which even fewer legal protections exist (7),(29).

In contemplating the future of disease prevention trials in other genetic and non-genetic forms of ALS and related disorders (most notably FTD), it is informative to reflect on the milestones that enabled the first prevention trial in *SOD1* ALS. Eligibility criteria and trial outcome measures should be carefully considered. Therapeutic trials in pre-symptomatic or prodromal populations are most likely to use phenoconversion to clinically manifest disease as the primary outcome measure for how "patients feel or function" (31). Biomarkers, or combinations of prodromal clinical markers and biomarkers, will likely be essential for

identifying the population at greatest short-term risk for phenoconversion – an "enrichment" strategy essential for efficient trial design. The development of surrogate markers, either those that have been validated or those that are "reasonably likely to predict a clinically meaningful outcome" (32), will also catalyze the development of preventive therapies.

Conclusion

The era of disease prevention in ALS has begun, with emerging opportunities to apply insights and principles in furtherance of the broader goal of ALS (and FTD) prevention in the non-genetic population. These developments begin to affirm the stated hope of the originator of the ALS clinical syndrome, Jean-Martin Charcot (1825–1893), namely that, through continued searching, "*the verdict we will give such a patient tomorrow will not be the same we must give this patient today.*"

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Conflicts of Interest

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Key Points

- The study of unaffected carriers of pathogenic variants conferring markedly elevated risk for ALS has enabled development of a conceptual framework and lexicon for understanding, describing, and further studying the pre-symptomatic phase of ALS.
- Identification of neurofilament light chain (NfL) as a biomarker of impending phenoconversion to clinically manifest ALS has empowered design and initiation of the ATLAS study, the first-ever ALS prevention trial among carriers of highly penetrant *SOD1* variants associated with rapidly progressive disease.
- The extent to which the difference between asymptomatic pathogenic variant carriers and age-matched controls – in structural and functional neuroimaging and in systemic markers of metabolic function – reflect endophenotypes versus early manifestations of disease is currently unclear.
- The pre-symptomatic stage of disease is not uniformly clinically silent, with mild motor impairment (MMI), mild cognitive impairment (MCI), and/or mild behavioral impairment (MBI) representing prodromal states that precede phenoconversion to clinically manifest disease.
- The discovery of pre-symptomatic biomarkers and the delineation of prodromal states in genetic forms of ALS yields new opportunities for earlier diagnosis, therapeutic intervention, and even prevention, with applicability to apparently sporadic forms of ALS.