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The Miami Framework for ALS and related neurodegenerative disorders: an integrated view of phenotype and biology

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Author contributions

M.B. prepared the initial draft of the manuscript. J.W., M.R.T., A.A.-C., E.D.H., C.T.M., R.C.P., and R.P. substantively edited the initial draft. All authors contributed to discussion of the content, and reviewed or edited the manuscript. M.B. and J.W. prepared the figures and finalized the manuscript for submission.

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Abstract

Increasing appreciation of the phenotypic and biological overlap between amyotrophic lateral sclerosis (ALS) and frontotemporal dementia, alongside evolving biomarker evidence for a pre-symptomatic stage of disease and observations that this stage of disease might not always be clinically silent, is challenging traditional views of these disorders. These advances have highlighted the need to adapt ingrained notions of these clinical syndromes to include both the full phenotypic continuum — from clinically silent, to prodromal, to clinically manifest — and the expanded phenotypic spectrum that includes ALS, frontotemporal dementia and some movement disorders. The updated clinical paradigms should also align with our understanding

of the biology of these disorders, reflected in measurable biomarkers. The Miami Framework, emerging from discussions at the Second International Pre-Symptomatic ALS Workshop in Miami (February 2023; a full list of attendees and their affiliations appears in the Supplementary Information) proposes a classification system built on: first, three parallel phenotypic axes — motor neuron, frontotemporal and extrapyramidal — rather than the unitary approach of combining all phenotypic elements into a single clinical entity; and second, biomarkers that reflect different aspects of the underlying pathology and biology of neurodegeneration. This framework decouples clinical syndromes from biomarker evidence of disease and builds on experiences from other neurodegenerative diseases to offer a unified approach to specifying the pleiotropic clinical manifestations of disease and describing the trajectory of emergent biomarkers.

Introduction

Clinical diagnostic criteria for amyotrophic lateral sclerosis (ALS) and behavioural variant frontotemporal dementia (bvFTD) have existed for decades, with periodic updates and revisions¹⁻⁸. Although some classification systems have recognized the spectrum between ALS and frontotemporal dementia (FTD)⁹, most offer limited integration of motor, cognitive, behavioural and neuropsychiatric symptoms across the ALS–FTD spectrum. Moreover, all criteria have focused on clinically manifest disease, insufficiently addressing early disease states analogous to mild cognitive impairment (MCI) and pre-MCI states in Alzheimer disease (we use the term ‘prodromal’ to describe these early clinical stages of disease). The growing understanding of phenotypes associated with particular genes or pathogenic variants in ALS and FTD, and the evolving landscape of biomarkers, are not considered in current criteria. These gaps have practical ramifications; for example, clinical trials in populations at genetic risk for both ALS and FTD but where the measured outcomes focus exclusively on only one of the diseases would miss ~50% of early phenoconversion events that are crucial to determining the success of possible neuroprotective treatments.

ALS is traditionally considered a clinical syndrome characterized by progressive muscle weakness alongside signs of both upper motor neuron (UMN) and lower motor neuron (LMN) pathology. This view is challenged by clinical evidence for a prodromal stage of disease — termed mild motor impairment (MMI)¹⁰ — and biological evidence of neurodegeneration prior to phenoconversion among those at elevated genetic risk for ALS¹¹⁻¹³. An alternative paradigm considers ALS as a biological entity that manifests phenotypically along a continuum, from a clinically silent stage to a prodromal stage and, eventually, to a fully manifest stage. Further complexity arises from the overlap between ALS and FTD. Some people with ALS, with or without an identifiable genetic cause, develop FTD. Others can show mild signs of cognitive impairment (ALSci) or behavioural impairment (ALSbi), supporting the idea that ALSci and ALSbi represent stages of an ALS frontotemporal spectrum disorder⁹. Although less attention has been paid to the possibility that MCI or mild behavioural impairment (MBI) might emerge before motor manifestations of ALS¹⁴, the foregoing considerations have prompted calls to consider incorporating cognitive and behavioural manifestations of disease into staging systems for ALS⁴. Key terminology and associated definitions are summarized in Table 1.

The FTD community similarly recognizes the overlap between FTD and ALS but, in considering the emergence of motor signs that are insufficient to warrant a diagnosis of ALS, many have proposed lumping motor neuron and extrapyramidal motor manifestations under the umbrella term of MMI¹⁵. Alternatively, considering all prodromal aspects of disease under the overarching term of mild cognitive and/or behavioural and/or motor impairment (MCBMI) has been suggested¹⁶. Although the spectral relationship between FTD and extrapyramidal disorders, such as corticobasal degeneration and progressive supranuclear palsy (PSP), is recognized by the umbrella concept of frontotemporal lobar degeneration (FTLD), the relationship between ALS and these extrapyramidal syndromes has garnered much less attention.

The phenotypic, biological and genetic overlap between this group of neurodegenerative diseases as well as considerations around definitions of prodromal clinical syndromes, including MMI, MCI and MBI, and how best to place biomarkers in the context of these varying clinical phenotypes, were topics of discussion at the Second International Pre-Symptomatic ALS Workshop held in Miami on the 27 February 2023. This workshop brought together, from academia, industry and non-profit organizations, an interdisciplinary group of clinicians and researchers with expertise in ALS, FTD, Alzheimer disease, movement disorders, neuroanatomy, genetic counselling, health policy and law, and bioethics as well as representatives of the presymptomatic carrier community and from patient advocacy groups. Recognizing the crucial role that careful phenotyping has in interpreting biomarker data, workshop discussions centred around the best approaches to defining prodromal disease and the diagnosis of clinically manifest disease, with a secondary focus on the sociolegal, psychological and ethical complexity of communicating prodromal diagnoses to pre-symptomatic carriers of pathogenic variants.

In this Perspective, we first summarize the current and emergent issues related to pre-symptomatic disease in ALS, FTD and extrapyramidal disorders, which form the three axes of the phenotypic component of the proposed Miami Framework for ALS and Related Neurodegenerative Disorders (named after the location of the workshop). We then consider the role that biomarkers, which are decoupled from phenotype in the framework, have in informing the underlying biology of disease. We discuss the challenges related to communicating prodromal findings to pathogenic variant carriers and conclude with some thoughts about future research directions. Importantly, though developed based on insights initially gleaned from multiple genetic forms of these diseases, we venture that the Miami Framework is also relevant to non-genetic forms of ALS and FTD.

Amyotrophic lateral sclerosis

The established view of ALS as a clinical syndrome is informed by the perspective of the health-care arena. People with ALS present for a diagnostic evaluation an average of ~12 months¹⁷ after initial symptom onset and the disease is presumed to have been clinically silent prior to the reported symptom onset. However, the prospective and systematic study of pathogenic variant carriers from the pre-symptomatic state through phenoconversion to clinically manifest ALS calls this traditional view into question^{14,18}. Observations from a much earlier stage of disease, at least among carriers of pathogenic variants, have uncovered

signs of UMN and LMN dysfunction, typically without weakness, a hallmark of clinically manifest ALS. These changes in motor function represent a departure from normal but are of insufficient severity or extent to conclude that ALS has clinically manifested. The term ‘MMI’¹⁰ has been used to describe this prodromal stage of ALS¹⁹.

The emergence of MMI as a prodromal stage of ALS, intermediate between clinically silent and clinically manifest disease, raises a host of challenging issues. What are the roles of symptoms versus signs in establishing the presence of MMI? How should MMI be distinguished from clinically manifest disease? How should the discordance between individuals deemed to have phenoconverted to clinically manifest ALS but not yet meeting traditional diagnostic criteria be resolved? These issues are explored in detail below.

Symptoms versus signs

In considering the different roles that symptoms and signs have in the diagnosis of ALS and designation of MMI, it is worth noting that symptoms are subjective and perceived only by the affected person; by contrast, signs are manifestations of disease that can be observed or detected by an evaluator, typically the physician. Weakness or impaired motor function (a term intended to capture symptoms such as dysarthria and gait abnormalities that might reflect UMN dysfunction even in the absence of weakness) are the hallmarks of clinically manifest ALS, especially when accompanied by signs of UMN and/or LMN dysfunction. Electromyographic (EMG) findings of ongoing denervation changes, often combined with evidence of chronic reinnervation, provide evidence of LMN pathology even in the absence of physical examination findings^{20,21}. Importantly, people with ALS typically report weakness as a symptom, which should also be apparent on physical examination. MMI, by contrast, is defined primarily based on signs rather than symptoms. The reason is that physical examination findings — for example, absent or pathologically brisk reflexes, atrophy, spasticity, slowness of movement, and EMG abnormalities such as fibrillations and positive sharp waves — result in trivial (if any) symptoms, and thus the individual typically has no subjective awareness of their presence.

Mild motor impairment

MMI is conceptualized as constituting signs of UMN or LMN dysfunction that represent a departure from normal but are of insufficient severity or extent to conclude that ALS has become clinically manifest¹⁰. Importantly, LMN signs can be clinically apparent or only detectable by EMG, underscoring the need for EMG as part of the evaluation for MMI. Moreover, in the proposed definition of MMI¹⁰, non-specific symptoms, such as cramps and fasciculations, are neither required nor sufficient; for example, fasciculations alone, whether as a symptom or sign, do not constitute MMI. We also recognize that individual neurologists might differentially detect and interpret clinical findings as they pertain to MMI and the same is true for ALS²².

The concept of MMI has been proposed as the ALS equivalent of MCI in Alzheimer disease²³. MMI, like MCI, is regarded as both a transitional state between clinically silent and clinically manifest stages of disease and an indeterminate state insofar as not everyone with MMI will progress to develop ALS. Practical use of MMI as a recognizable clinical

syndrome will require formal development of criteria that might initially be used in the research arena but with eventual application in the clinical realm. Additionally, in time, as biomarkers of underlying biology, such as TDP43, mature, differentiation between MMI with or without evidence of underlying ALS pathology could become possible, thereby better stratifying the risk of progression to clinically manifest ALS. Again, the analogy to Alzheimer disease with or without evidence of amyloid and/or tau pathology is helpful (see ‘Biomarkers’ section below).

ALS phenoconversion

Phenoconversion, the transition from the pre-symptomatic to the symptomatic phases of disease, can emerge from the prodromal stage or, in the absence of an observed prodrome, directly from the clinically silent pre-manifest state. The gradual accumulation of motor deficits in ALS makes the precise definition of when phenoconversion occurs difficult. Although the emergence of ALS is a process that evolves over time, for multiple reasons, it is necessary to distinguish, at roughly the right point in the evolution of disease, the transition between pre-symptomatic disease and clinically manifest ALS. Clear communication that phenoconversion has occurred, and thus that the individual now has ALS, enables the individual to access appropriate clinical care and potentially participate in treatment trials at an earlier, less advanced stage of disease than previously possible¹⁴. In addition, an operational definition of phenoconversion is essential for use as an outcome measure in early therapeutic intervention or disease prevention trials. To this end, phenoconversion to ALS has been defined by the emergence of symptoms and objective motor (clinical or EMG) signs that a trained evaluator would reasonably interpret as unequivocal evidence of clinically manifest ALS^{14,24}. Of note, EMG stands alone as a biomarker integrated into clinical practice and has a long track record of use in the evaluation of suspected ALS. On the other hand, other biomarkers, such as neurofilament light chain (NfL), do not currently contribute to the definition of phenoconversion. In clinical practice, where patients are often seen after substantial delay, their reported onset of muscle weakness is the closest proxy for the timing of phenoconversion.

ALS diagnosis

Fundamentally, the diagnosis of ALS rests on the demonstration of progressive muscle weakness from a history of symptoms or serial evaluations, typically with evidence of UMN and LMN dysfunction on physical examination often supported by EMG, and the exclusion of other disease processes that can produce similar signs^{2,3,8,25}. Various iterations of ALS diagnostic criteria have operationalized the diagnostic process by conceptualizing four body regions — bulbar, cervical, thoracic and lumbosacral — and considering the distribution of UMN and LMN signs within and across these regions. Importantly, these regions are considered topographic rather than neuroanatomic, which is why ‘cervical’ comprises both arms as well as neck weakness despite being dually innervated by bulbar and cervical roots, ‘lumbosacral’ comprises both legs, and respiratory muscle weakness, despite being primarily innervated through cervical roots via the phrenic nerve, is considered ‘thoracic’. Historically, the number of regions affected by both UMN and LMN pathology has determined the ‘degree of confidence’ in the diagnosis between possible, probable and definite, even though all categories represent ALS. The most recently proposed Gold Coast criteria⁸ aimed to

simplify the diagnostic process by collapsing the revised El Escorial criteria for possible, laboratory-supported probable, probable and definite disease² into a single category.

Although the evolution of ALS diagnostic criteria over the years has generally been towards increased sensitivity, one notable exception exists. For example, the revised El Escorial criteria² minimally required either UMN or LMN signs in a single region when combined with the presence of a known pathogenic variant. However, the Gold Coast criteria require both UMN and LMN signs in a single region, even when there is an identifiable pathogenic variant^{2,8}. Although the requirement for both UMN and LMN signs in a single region might be reasonable in the clinical setting where patients often have established disease, this requirement is less suited to declaring the emergence of clinically manifest ALS in genetically at-risk pre-symptomatic individuals who are prospectively followed and in whom clinically manifest disease is detected early when still confined to either the LMN or UMN axis. For example, in a person who carries a pathogenic variant in *SOD1*, initial progressive LMN signs, such as weakness, atrophy and ongoing denervation changes on EMG, are very likely to reflect ALS despite the absence of UMN signs on examination. This problem could be resolved by reverting to the revised El Escorial criterion for familial ALS that requires either UMN or LMN signs (combined with progressive weakness and exclusion of alternate causes) for the diagnosis of ALS in the presence of a pathogenic variant known to cause ALS. Although this proposed change to the Gold Coast criteria would not alter the diagnostic threshold for those with non-genetic forms of ALS, this change would avoid the need to consider different sets of diagnostic criteria for genetic versus non-genetic ALS or the need for different frameworks when seeing patients in a clinical setting rather than in a research context. The question of what constitutes an ALS-causing variant is being addressed systematically by the ALS Spectrum Disorders Gene Curation and Variant Curation Expert Panels, with the expectation that our understanding of the genetic landscape of ALS will continue to evolve. As our understanding evolves, the key consideration will be the extent to which the presence of a particular genetic variant increases the likelihood that progressive weakness with either LMN or UMN dysfunction represents ALS, which will also entail some degree of clinical judgement.

Notwithstanding the foregoing, drawing a conceptual distinction between phenoconversion and diagnosis is important²⁴. Diagnosis requires the documentation of clinical evidence of disease through physical examination and EMG as needed, which are both typically conducted in person. By contrast, phenoconversion can retrospectively be attributed, after subsequent diagnosis, to the time that clear symptoms of disease, for example, focal weakness, were initially reported. However, when symptoms and signs emerge insidiously with clinical or EMG findings accruing during prospective follow-up, the determination of phenoconversion can be made based on the totality of evidence accumulated to date. Under such circumstances, phenoconversion and diagnosis will in practice occur simultaneously.

When clinical manifestations of disease evolve gradually, recognition that progressive weakness is the core clinical feature of ALS is helpful, with the presence of both UMN and LMN signs helping to differentiate ALS from other disease processes. As such, progressive weakness determined by history or serial examination is the most robust yardstick for differentiating MMI from clinically manifest disease. When based on history, progressive

weakness entails a subjective report of weakness that has worsened over time and is demonstrable on examination. By contrast, based on serial examinations, the threshold of progressive weakness can be met if new weakness, not previously apparent, has emerged.

Frontotemporal dementia

FTD as a clinical entity describes a group of related disorders characterized by changes in behaviour, executive dysfunction and impaired language function as well as neuropsychiatric symptoms. Many distinct clinical syndromes are recognized under the FTD umbrella, including bvFTD⁷, semantic variant primary progressive aphasia (PPA) and non-fluent variant PPA²⁶. FTLT encompasses the spectrum of proteinopathies and neuropathology that cause FTD, including TDP43 or tau-positive inclusions²⁶.

Akin to ALS, the traditional view of FTD as a clinical syndrome is shaped by clinical experience with a ~33-month delay between symptom onset and diagnosis²⁷. The presumption is that the disease is clinically silent prior to the reported or observed onset of symptoms. Natural history studies of pathogenic variant carriers at genetic risk for FTD have led to similar conclusions drawn by the ALS community, with increasing recognition that the clinical continuum of FTD also extends from the clinically silent phase, through a prodrome of mild cognitive, behavioural or psychiatric impairment, and with eventual phenoconversion to clinically manifest FTD^{28,29,30}. Defining the emergence of mild cognitive or behavioural impairment is perhaps even more challenging than defining MMI in ALS, in part because recognition of aberrant behaviours requires input from a reliable informant as well as partly owing to the challenges inherent to demonstrating that current cognitive or behavioural function represents a change from a premorbid state. Moreover, proposed research criteria published in 2022 for mild behavioural and/or cognitive impairment in bvFTD (MBCI-FTD) have also blurred the distinction between prodromal disease and possible bvFTD partly because the established diagnostic criteria are not explicit about the need for functional impairment to warrant a diagnosis of dementia^{7,30}. Details of diagnostic criteria for FTD and prodromal states are considered in greater detail below.

FTD-related diagnostic criteria

The 2011 revised criteria for bvFTD⁷ (henceforth ‘Rascovsky criteria’) recognize varying degrees of diagnostic confidence, somewhat akin to the El Escorial (original and revised^{2,31}) criteria for ALS. ‘Possible bvFTD’ is based on the presence of at least three out of six clinical features, including disinhibition, apathy or inertia, loss of sympathy or empathy, perseverative or compulsive behaviours, hyperorality, and dysexecutive neuropsychological profile. ‘Probable bvFTD’ requires the additional evidence of functional decline from caregiver report or tools that measure basic and instrumental activities of daily living, as well as frontal and/or temporal atrophy (on MRI or CT) or hypoperfusion or hypometabolism (on PET or SPECT). ‘bvFTD with definite FTLT pathology’ requires that criteria for possible or probable bvFTD be met, alongside the presence of a known pathogenic variant or histopathological evidence on biopsy or post-mortem study.

Building upon these criteria for bvFTD, the 2017 revised consensus criteria for the diagnosis of frontotemporal dysfunction in ALS (henceforth ‘revised Strong criteria’) recognized the clinical heterogeneity of associated cognitive and behavioural impairment and embraced the concept of a frontotemporal spectrum disorder in ALS⁹. These criteria differentiate between the motor neuron disease variant (axis I) and the accompanying neuropsychological deficits (axis II). The diagnosis of ALSbi can be made based on apathy alone or the presence of at least two other behavioural features recognized by the Rascovsky criteria. ALSci might be diagnosed based on either executive dysfunction or language impairment. Executive dysfunction is defined by impaired verbal fluency or impairment on two other non-overlapping measures of executive function, including social cognition; language dysfunction entails impairment on two non-overlapping tests in which language impairment is not solely explained by verbal fluency deficits. ALS-FTD was broadly defined based on evidence of progressive deterioration of behaviour and/or cognition along with either at least three behavioural or cognitive symptoms as defined in the Rascovsky criteria; at least two behavioural or cognitive symptoms together with loss of insight or psychotic symptoms; or language impairment meeting criteria for semantic variant PPA or non-fluent variant PPA. The frequent occurrence of both executive dysfunction and language impairment among individuals with ALS^{32,33,34} is sometimes under-recognized given the preponderance of bvFTD as the clinical syndrome most commonly associated with motor neuron disease⁹.

MCI and MBI as prodromal states of ALS and FTD

In the revised Strong criteria, the notion that people with ALS might exhibit signs of MCI or MBI that do not (yet) meet criteria for established FTD is addressed by the concepts of ALSci and ALSbi⁹. However, these criteria were developed for people who already have clinically manifest ALS; are heavily focused on cross-sectional rather than longitudinal evaluations; and are silent on the question of MCI and MBI as prodromal states that might precede clinically manifest ALS. Nonetheless, the dual-axis approach (see section ‘FTD-related diagnostic criteria’) used by the revised Strong criteria could well accommodate a construct in which the motor neuron syndrome in Axis I is expanded to include pre-symptomatic ALS (either clinically silent or prodromal MMI), and similarly for Axis II and frontotemporal syndromes, as discussed below.

In addition to the revised Strong criteria, at least two approaches to defining MCI and MBI have been described, each with a different intended use. The first of these considered MCI and MBI separately¹⁴; as proposed, MCI would require evidence that the current level of cognitive function represents a decline from a previous level, which can be determined by a longitudinal decline on serial neuropsychological assessments, ‘presumed’ decline from estimated premorbid IQ, or a reported change by the individual or an informant. Within this framework, which emanated from discussions at the First International Pre-Symptomatic ALS Workshop in January 2020 (ref. 14), MCI is defined based on evidence of impairment with meaningful decline on at least two tests that assess different cognitive processes or, as proposed by the revised Strong criteria⁹, a single measure of letter fluency. Individuals with high premorbid functioning might be classified as having MCI even in the absence of impairment as determined by comparison with normative data.

MBI is defined according to changes in one or more behaviour domains associated with bvFTD and is ascertained using a standardized interview or validated self-completed questionnaire completed by a reliable caregiver or the participants themselves. Importantly, these criteria for MBI, which were built upon the foundation of the Rascovsky criteria, were proposed based on expert opinion and rely on neuropsychological testing with standardized measures and a structured interview with an informant but without clinical assessment by a cognitive or behavioural neurologist. However, the criteria are not yet supported by data. Moreover, basing new criteria for MCI and MBI on the Rascovsky criteria maximizes compatibility but runs the risk of failing to include cognitive, behavioural and neuropsychiatric symptoms that are not included in the Rascovsky criteria, especially since prodromal symptoms might differ from clinically manifest symptoms of an illness³⁵. These criteria from the first Workshop were developed with the goal of identifying, with high sensitivity, early cognitive and behavioural changes in people at risk for ALS and FTD, for example, carriers of pathogenic variants that can cause ALS and FTD.

A parallel endeavour by the ALLFTD (ARTFL LEFFTDS Longitudinal Frontotemporal Lobar Degeneration) investigators aimed to identify the cognitive and behavioural features that best differentiate pathogenic variant carriers with prodromal bvFTD from family-based controls and people with prodromal Alzheimer disease³⁰. This approach, which combines behaviour and cognition into an entity referred to as MBCI-FTD, is agnostic to the Rascovsky criteria and was empirically developed according to the profile of people with prodromal disease (defined as a global Clinical Dementia Rating plus National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration score of 0.5) who subsequently developed bvFTD. These criteria recognize seven core features, many of which align with the Rascovsky criteria, such as apathy (without moderate–severe dysphoria), behavioural disinhibition, reduced empathy or sympathy, repetitive behaviours, and appetite changes or hyperorality, but additionally extend to include irritability or agitation and joviality or gregariousness. The criteria also identify several supportive features, including a neuropsychological profile of impaired executive function or naming, reduced insight, and poor social cognition³⁰. The diagnosis of MBCI-FTD requires three of the core features or two core features plus one supportive feature. However, these criteria do not address prodromal disease in individuals who progress to develop PPA; moreover, an independent concept of mild language impairment is currently lacking, although this feature is generally encompassed by impairment on neuropsychological testing that is sufficient to constitute MCI.

The three proposed approaches to defining prodromal cognitive and behavioural impairment share many similarities but also differ in important ways. Notably, they were each developed to serve a different purpose. The revised Strong criteria⁹ largely use cross-sectional data to detect cognitive and behavioural impairment among people with ALS but these could also be applied to identify prodromal cognitive and/or behavioural impairment. By contrast, discussions at the First International Pre-Symptomatic ALS Workshop¹⁴ were focused on developing an approach to identify early cognitive and behavioural dysfunction in pre-symptomatic individuals who carry pathogenic variants in ALS-associated genes. On the other hand, the MBCI-FTD criteria³⁰ aimed to differentiate prodromal bvFTD from family

members without pathogenic variants and individuals with other forms of MCI. Given their differing intended purposes, the differences among these criteria are perhaps not surprising.

Irrespective of which criteria are eventually adopted for prodromal disease, a strong rationale exists for defining the presence of cognitive and/or behavioural impairment independently of the motor neuron syndrome. Moreover, the criteria for defining cognitive and behavioural impairment should ideally be consistent irrespective of whether someone has MMI or ALS. This aim will require some reconciliation between the previously proposed approaches across the ALS–FTD spectrum^{7,9,14,30}.

Extrapyramidal disorders

Parkinsonism, corticobasal syndrome (CBS) and PSP are the dominant extrapyramidal syndromes associated with underlying FTLN. Parkinsonism is encountered in *MAPT*, *PGRN* and *C9orf72* repeat expansion carriers and across the spectrum of tau and TDP43 pathology³⁶. The phenomenology of parkinsonism includes axial and limb rigidity that is often symmetric, bradykinesia (typically without decrement, unlike in Parkinson disease) and postural instability. Tremor of varying types has been reported but rest tremor is unusual³⁷. Levodopa responsiveness is poor compared with Parkinson disease but ~30% of individuals report some benefit³⁸. Typical PSP is characterized by supranuclear gaze palsy, axial rigidity, postural instability and early falls^{39,40,41,42}. PSP is most often sporadic but *MAPT* pathogenic variants are the most frequently identified genetic cause⁴³. CBS — characterized by asymmetric rigidity, apraxia, cortical sensory loss, alien limb syndrome, focal dystonia and myoclonus — is similarly most often sporadic but *PGRN* pathogenic variants are the most frequently identified genetic cause. Movement disorders are more typically linked to FTLN-tau pathology⁴⁴ but can also occur in individuals with FTLN-TDP43 (ref. 45).

Prominent extrapyramidal movement disorders are infrequent among people with ALS, and phenotypic overlap between CBS or PSP and ALS is uncommon^{36,46}. A rare Guam ALS–parkinsonism–dementia complex, where motor neuron disease and parkinsonism frequently co-occur, has a distinct pathogenesis from the ALS–FTD spectrum and is beyond the scope of this discussion⁴⁷. Among people with pathogenic *C9orf72* repeat expansions, parkinsonism and tremor, most often with posture and action, are the most common movement disorder features¹⁹. However, the phenotypic spectrum is broad and can include, albeit rarely, myoclonus (most often distal stimulus-sensitive jerks of the arms), dystonia, chorea and ataxia¹⁹. Indeed, the *C9orf72* repeat expansion might be the most common genetic cause of Huntington disease phenocopies⁴⁸. Importantly, the movement disorder phenotype could be the initial clinical manifestation of disease and might occur concurrently with either ALS or FTD.

Within the spectrum of movement disorders encountered, we consider definable syndromes, such as parkinsonism, CBS and PSP, as clinically manifest disease, which require the presence of several defined features but regard individual clinical phenomena, such as tremor, dystonia, myoclonus or combinations, that are insufficient to meet diagnostic criteria^{49,50} as constituting a prodromal state.

The Miami Framework

The proposed Miami Framework for ALS and Related Neurodegenerative Disorders recognizes in parallel the clinical syndromes and the underlying biology of disease (Fig. 1). The clinical syndromes comprise three axes: Axis I for motor neuron disease, Axis II for frontotemporal disorders and Axis III for extrapyramidal movement disorders (Table 2). Within each axis, disease can be clinically silent, prodromal or clinically manifest. Furthermore, each axis can exist on an independent timeline, for example, being prodromal in one axis does not mean being prodromal in the other axes. The key clinical features to consider for each axis are summarized in Table 3.

MMI is the prodromal state for ALS. MCI and MBI, or some combination of cognition, behaviour and neuropsychiatric symptoms, are the prodromal states for FTD. Phenomenologically described movement disorder phenotypes, such as tremor or dystonia, occurring in isolation or in combinations, are the prodromal states for clinically manifest movement disorders such as parkinsonism, CBS or PSP; these prodromal syndromes might be termed mild extrapyramidal impairment (MEPI). Although some have suggested grouping mild motor and mild extrapyramidal features under the umbrella of MMI¹⁵, we see these as manifestations of involvement of distinct neuroanatomical axes. For example, notwithstanding the foregoing, MMI might precede FTD whereas MCI and MBI might precede ALS, underscoring the need to characterize disease presentation across the three phenotypic axes. Moreover, disease presentation can appear to ‘switch’ axes when prodromal disease develops in one axis but phenoconversion occurs in another where the prodrome was not apparent. For example, someone with a tremor might develop bvFTD without prior report or documentation of MBI. Based on the Miami Framework, this person would still be prodromal in Axis III but clinically manifest in Axis II. The ‘missed’ MBI is presumed to have been present but not detected or recognized.

The term phenotransition should be used to mark the appearance of a prodromal syndrome and the term phenoconversion should be reserved for the emergence of clinically manifest disease such as ALS, FTD or an extrapyramidal syndrome^{14,51}. For the diagnosis of ALS, we recommend the use of either the revised El Escorial criteria (especially if categorization based on the number of body regions with both UMN and LMN signs, such as in definite ALS, is of interest) or the Gold Coast criteria but with the caveat that people with a known pathogenic variant, as described in the revised El Escorial criteria, require progressive weakness in only LMN or UMN for the diagnosis of ALS. This special consideration for pathogenic variant carriers is necessary for the consistency in how ALS is diagnosed among prospectively followed pre-symptomatic individuals who phenoconvert and those first seen in the clinic with already clinically manifest disease. On the other hand, for diagnosis of bvFTD as well as of PPA and its variants we recommend use of published criteria by Rascovsky et al. and Gorno-Tempini et al., respectively^{7,52}.

Operational criteria for the diagnosis of prodromal syndromes are areas of active work. A conceptual definition of MMI — specifically, the emergence of clinical and EMG findings that represent a departure from normal but are not accompanied by clear weakness and do not meet minimum criteria for the diagnosis of ALS — has previously been proposed^{10,14}.

Development of formal research criteria for MMI, based on extensive clinical experience and longitudinal data from the Pre-fALS study¹⁸, is currently under way. Moreover, pending broadly agreed-upon definitions of MCI and MBI within the FTD community and across the ALS and FTD communities as well as the availability of more robust evidence, we urge investigators to always specify the criteria used and to be mindful of the intended context-of-use.

Irrespective of the diagnostic criteria used, under the Miami Framework, full specification of the clinical phenotype encompasses the motor neuron disease, the frontotemporal spectrum disorder and the extrapyramidal movement disorder axes (Fig. 1). For example, an individual with ALS might also have MCI and/or MBI, in which case the revised Strong criteria nomenclature of ALS_{ci}, ALS_{bi} or ALS_{cbi} is preferred⁹. Likewise, an individual with bvFTD might also have MMI, in which case they would be designated as bvFTD_{mi}. Importantly, this framework recognizes the clinical and biological heterogeneity of ALS, FTD and related disorders. As illustrated in Fig. 2, patient A might represent someone with a pathogenic A4V variant in the *SOD1* gene, for whom the phenotype is dominated by motor neuron disease but with mild cognitive or behavioural features emerging. By contrast, patient B might represent someone with a *C9orf72* repeat expansion, in whom early disease is characterized by MCI and/or MBI prior to emergence of MMI and phenoconversion to bvFTD. MMI then evolves into clinically manifest ALS but not before the emergence of MEPI characterized by tremor or mild parkinsonian features.

Unlike the clinical syndromes, which progress from being clinically silent, through the prodromal stage and into the clinically manifest stage, biomarker trajectories might vary. The temporal course of different biomarkers depends on whether they reflect underlying neurodegeneration, for example, increased neurofilament light chain (NfL) levels; the consequences of specific cellular pathway perturbations or molecular events, such as cytoplasmic aggregation of TDP43; or a compensatory response, for example, functional brain network changes. As such, biomarkers are not considered a fourth axis but are instead considered separately and in a way that is agnostic to the clinical syndrome, akin to similar approaches in some other neurodegenerative diseases^{53,54,55}.

Biomarkers

Although blood NfL has emerged as an ALS risk biomarker — for example, predicting imminent phenoconversion to clinically manifest ALS among carriers of highly penetrant *SOD1* pathogenic variants associated with rapidly progressive disease^{11,56} — a rise in NfL does not always precede phenoconversion, and MMI and other prodromal states might sometimes precede the rise in NfL¹⁰. The evidence for NfL having a similar context-of-use in FTD is less clear, as the existing literature relies heavily on NfL data from pre-symptomatic individuals who have not yet phenoconverted as well as on an estimated age of onset based on symptomatic family members, which has poor predictive value except perhaps among *MAPT* carriers^{57,58,59,60,61,62,63}. Nevertheless, from the evidence available to date, NfL is an ‘aggressivity’ marker, reflecting the prevailing rate rather than the absolute extent of axonal degeneration⁶⁴. As such, a pre-symptomatic increase in NfL might be expected to be more readily apparent among individuals with the more aggressive and

rapidly progressive forms of ALS and FTD but less so among those with more insidious and gradually progressive disease. In the context of FTD, NfL will probably need to be combined with other markers, such as imaging-based markers, to more reliably predict the timing of phenoconversion.

Considering the variability in the timing of NfL elevation and that other pre-symptomatic biomarkers of neurodegeneration, of molecular, cellular or network dysfunction, or of functional compensation will emerge, an approach similar to the ATN (amyloid–tau–neurodegeneration) framework in Alzheimer disease^{53,54} and the SynNeurGe (α -synuclein–neurodegeneration–genetic) model in Parkinson disease⁵⁵ might be applied to ALS and FTD. In the Miami Framework, the designation ‘N’, meaning evidence of neurodegeneration, currently best determined by an elevation in NfL, might be appended to a clinical state, including clinically silent, prodromal or clinically manifest, as appropriate. On the other hand, the designation ‘T’ refers to tau neuropathology, which can be captured by cerebrospinal fluid phosphorylated tau (p-tau)⁶⁵. Plasma p-tau, however, is less specific, as evidenced by its elevation in ALS that can simply reflect LMN dysfunction⁶⁶. Ultimately, more specific tau biomarkers, such as the ultrasensitive tau seed amplification (4R RT-QuIC) cerebrospinal fluid assay⁶⁷, will be needed to better capture underlying tau pathology. Moreover, biomarkers of TDP43 pathology (designated ‘TDP’) have begun to emerge^{68,69}. Thus, in the future, for example, someone with evidence of TDP43 pathology but no increase in NfL could be identified as TDP⁺N⁻ and someone with evidence of tau pathology and an increase in NfL would be identified as T⁺N⁺.

Although the presence of a pathogenic variant associated with disease, when identifiable, is a biomarker relevant to disease biology, we have not recommended incorporation of genetic status into the Miami Framework. The reasons are twofold. First, germline genetic status is static and does not inform the evolution or stage of disease. Second, the Miami Framework, as described, is relevant to all genetic forms of disease and probably also relevant to non-monogenic forms of disease.

Communicating the emergence of prodromal disease

Published guidelines for the management of patients with ALS and FTD have highlighted the need for timely and effective communication of the diagnosis. For example, the European Federation of Neurological Societies guidelines⁷⁰ recommend that the diagnosis of ALS be communicated in person by a physician with good knowledge of the patient, that the physician should start by asking what the patient already knows or suspects, that printed materials and referrals to relevant support groups should be provided, and that the patient be reassured of access to appropriate health-care services. For FTD, this list should include education and services specific to this group of disorders, including behavioural interventions and speech therapy⁷¹. On the other hand, and unsurprisingly, existing guidelines have not addressed the need for, or the complexity of, communicating the presence of a prodromal syndrome owing to the prior lack of awareness that such a state in the ALS–FTD spectrum even exists.

A major challenge in communicating the presence of prodromal MMI, MCI, MBI or MEPI is the current lack of consensus on their definition. Moreover, as noted in the section ‘Mild motor impairment’, these prodromal states are non-specific and do not always represent an early stage of a neurodegenerative disease; the potential for an alternate aetiology is especially relevant in the context of individuals who do not carry a known pathogenic variant. Therefore, given the current knowledge, communication that a prodromal syndrome has emerged would require addressing the considerable uncertainty around the definition of the syndrome and, indeed, whether or not the individual meets prevailing views on operational criteria. As such, if the prodromal ‘diagnosis’ is to be communicated, this should be done with caution and care.

In contemplating how best to approach communication of a prodromal syndrome, differentiating between doing so clinically versus in a research study is helpful. Protections, such as a Certificate of Confidentiality in the USA, exist in the research arena and could be used to prevent the use of legal measures to compel the disclosure of sensitive information. However, in jurisdictions outside of the USA, available protections vary. In the clinical arena, by contrast, the ‘diagnosis’ of a prodromal state could be discoverable and potentially impact eligibility for disability and long-term care insurance⁷²; although statutes such as the Genetic Information Non-Discrimination Act in the USA protect against discrimination based on the genetic risk for disease⁷³, similar protections do not extend to non-genetic risk, for example, the presence of a prodromal syndrome⁷⁴. In the European Union, general disability and anti-discrimination laws can afford some protection, with some European Union member countries ratifying specific genetic anti-discrimination laws (summarized in ref. 75).

In the same way that insights and experiences from genetic counselling have informed best practices for disclosure of non-genetic biomarker results⁷⁶, they could also inform how best to approach counselling and communication of the presence of a prodromal syndrome. Unlike genetic test results, which are static — an individual either carries or does not carry a pathogenic variant — both non-genetic biomarker results and clinical status can change over time, requiring a paradigm for repeated counselling as needed and ongoing support. Akin to best practices for genetic counselling, consent for receiving communication of a prodromal state should be fully informed and free of coercion. In longitudinal research studies or clinical follow-up, in addition to initial counselling about the potential to develop a prodromal state, counselling might need to be repeated at the time of each evaluation and before disclosure of a prodromal state. The advantages, disadvantages and implications of learning about a prodromal state should be fully explained and reinforced in writing, either through printed materials or summarized in a letter following counselling.

The psychosocial readiness of an individual to receive information about a potential prodromal state must be adequately assessed — an especially complex undertaking given the potential for impaired insight or anosognosia to impact understanding. Moreover, an infrastructure is needed to support and manage the potential psychosocial impact of receiving a prodromal diagnosis. These issues might more readily be addressed within the context of a research protocol, where the informed consent prospectively describes how information about a (potential) prodromal state would be communicated. However, in both

the research and clinical contexts, appraisal and understanding of the perspective, such as the desires and needs, of the individual who will receive the result is essential. For many, we suspect that a decision of whether or not to receive a prodromal diagnosis will be driven by the extent to which the ‘diagnosis’ is actionable, for example, if the individual is able to access available treatments or clinical trials, while recognizing that ‘actionable’ means different things to different people.

Conclusion and future directions

The Miami Framework offers a unified approach to: first, specifying the pleiotropic manifestations of ALS and FTD; second, recognizing a broader natural history of disease, including clinically silent, prodromal and clinically manifest stages; and last, decoupling descriptions of the clinical syndromes from the underlying pathophysiology that is revealed by the pattern and trajectory of emergent biomarkers. Further work is clearly needed to fully define the prodromal clinical syndromes of MMI, MCI, MBI and MEPI. Moreover, the emergence of new biomarkers that reflect the underlying biology of disease will be essential to refining our understanding of which individuals with each of these syndromes are truly prodromal and most likely to progress to clinically manifest ALS, FTD or an extrapyramidal disorder, and who are not. Although the proposed framework is largely based on observations from the population at markedly elevated genetic risk for ALS and FTD, strong *prima facie* reasons exist for its potential relevance to all forms of disease¹⁰. Ongoing research that will shed light on the generalizability of the framework to non-genetic ALS and FTD includes efforts to identify people with MMI, MCI or MBI based on clinical phenotype rather than on genetic risk and to quantify their risk of phenoconversion to clinically manifest disease.

An open question is the extent to which MMI, MCI, MBI and MEPI might serve as risk or susceptibility markers that predict the timing of phenoconversion. Although the available evidence suggests that these prodromal states do have some predictive value, they are probably insufficient on their own. Instead, they would need to be combined with an array of biomarkers, such as NfL and imaging measures of brain atrophy, for use as eligibility criteria in future ALS or FTD prevention trials⁶³.

As we advance our understanding of prodromal disease, several considerations should be borne in mind. The definition of motor phenoconversion should seamlessly merge with diagnostic criteria for clinically manifest ALS; the same is true for prodromal cognitive and behavioural syndromes and clinically manifest FTD. Considerable work is needed to identify and refine biomarkers that reflect the underlying pathology of ALS, FTD and related neurodegenerative disorders in order to better characterize the biological underpinnings of the phenotypic manifestations. In addition, little is currently known about the frequency and evolution of prodromal motor, cognitive and behavioural (including neuropsychiatric) manifestations of disease among pre-symptomatic *C9orf72* expansion mutation carriers who ultimately progress to ALS or FTD. Understanding such nuances will be key to ongoing efforts by the ALS and FTD communities to align definitions of these prodromal states. Furthermore, the movement disorder manifestations of a *C9orf72* repeat expansion need further study for us to better understand their frequency and the extent to

which they might reflect prodromal features of ALS or FTD as opposed to an independent phenotype^{19,48,77}.

In the future, the Miami Framework might be expanded to include additional clinical axes, such as neuropsychiatric, neuro-developmental and musculoskeletal, once these aspects of the expanded clinical phenotype become better understood. We propose that the Miami Framework is also relevant to non-genetic forms of ALS and FTD. The applicability of the phenotypic spectrum across axes to non-genetic disease is already apparent and manifestation of these diseases probably evolves along the continuum described here. Finally, these are a set of complex disorders, with experts across an array of disciplines each bringing a different perspective. The ALS, FTD and movement disorder communities stand to benefit enormously from working together to understand similarities and differences between these related disorders and to advance our collective goal of preventing these otherwise fatal neurodegenerative disorders.

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[Consortium authorship] Attendees of the Second International Pre-Symptomatic ALS Workshop

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Related links:

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Key Points

- Amyotrophic lateral sclerosis, frontotemporal dementia and a group of extrapyramidal movement disorders are related across a phenotypic spectrum and have shared biological substrates such as TDP43 or tau pathology.
- Disease evolves along a phenotypic continuum from clinically silent, to prodromal, to clinically manifest disease. Existing diagnostic criteria might require updates given new knowledge of prodromal and early manifest disease.
- Biomarkers reflecting the underlying biology of these diseases and the resulting neurodegenerative changes have begun to emerge, but the temporal relationship of the biomarkers to clinical phenotypes is unclear.
- The Miami Framework offers a unified approach to specifying both the pleiotropic clinical manifestations of these diseases and, in parallel, the temporal course of emergent biomarkers.
- Informed by data and experience from multiple genetic forms of amyotrophic lateral sclerosis and frontotemporal dementia, the Miami Framework probably has relevance to all forms of these diseases.
- Communicating the emergence of prodromal disease to the affected individual is complex and requires great caution but can be informed by experience and insights from genetic and biomarker counselling.

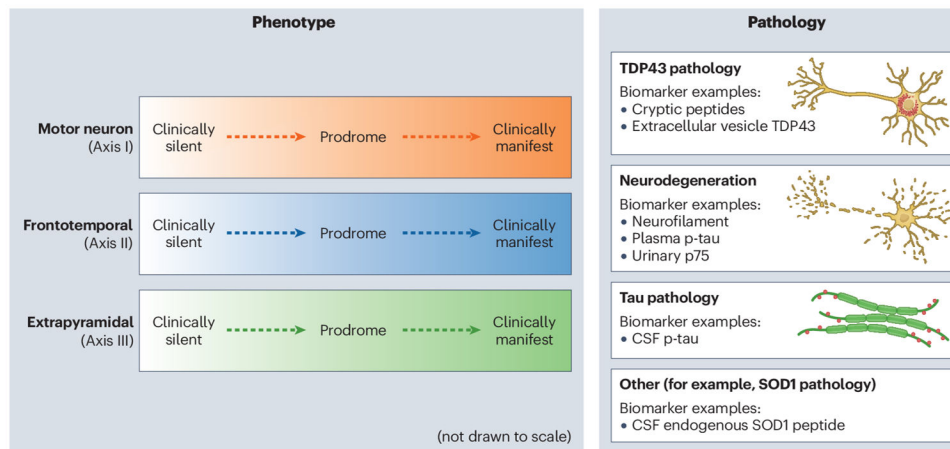


Figure 1. The Miami Framework for amyotrophic lateral sclerosis and related neurodegenerative disorders

The Miami Framework recognizes the clinical syndromes and the underlying biology of disease in parallel. The three phenotypic axes include motor neuron (Axis I, orange), frontotemporal (Axis II, blue) and extrapyramidal (Axis III, green). Within each axis, disease can progress from clinically silent, to prodromal, to clinically manifest, with independent timelines for each axis; for example, being prodromal in one axis does not mean being prodromal in the other axes. Moreover, people might have disease in any (or all) of the three axes. Distinct from the clinical phenotypes are the underlying biology of these disorders, including TDP43, tau, neurodegeneration and others such as SOD1 pathology. Insights into this pathobiology might be gleaned from biomarkers, for example, cryptic peptides for functional loss of TDP43 (ref. ⁶⁹) or extracellular vesicle TDP43 (ref. ⁶⁸); cerebrospinal fluid (CSF) phosphorylated (p)-tau for tau neuropathology⁶⁵; CSF endogenous SOD1 peptide for SOD1 pathology⁸⁵; and neurofilament, plasma p-tau⁶⁶ or urinary p75 (ref. ⁸⁴) for neurodegeneration. As the temporal patterns of the biomarkers are different and still incompletely understood, these are not depicted in the figure.

Clinical vignettes			
Patient A			
Motor neuron (Axis I)	None*	Prodrome (MMI)	Clinically manifest ALS
Frontotemporal (Axis II)	None*	Prodrome (MCI)	
Extrapyramidal (Axis III)	None*		
Patient B			
Motor neuron (Axis I)	None*	Prodrome (MMI)	Clinically manifest ALS
Frontotemporal (Axis II)	None*	Prodrome (MBI)	Clinically manifest bvFTD
Extrapyramidal (Axis III)	None*	Prodrome (MEPI)	

* None = no disease or clinically silent disease

Figure 2. Illustrative examples of the Miami Framework

Two hypothetical patients are presented. Patient A, representing a patient with a *SOD1 A4V* mutation, had mild motor impairment (MMI) followed by clinically manifest amyotrophic lateral sclerosis (ALS); a frontotemporal prodrome then developed and no extrapyramidal phenotype, such as tremor, was present. An increase in serum neurofilament light chain (NfL) would be expected prior to the emergence of MMI. Patient B, representing a patient with a *C9orf72* repeat expansion, first developed mild behavioural impairment (MBI), followed by MMI, and then clinically manifest behavioural variant frontotemporal dementia (bvFTD); after the subsequent emergence of a tremor indicative of mild extrapyramidal impairment (MEPI), clinically manifest ALS also became apparent, yielding a phenotype of bvFTD–ALS with MEPI. Serum NfL might increase during the prodromal period but might also only increase following phenoconversion to bvFTD. MCI, mild cognitive impairment.

Table 1.

Terminology

Term	Definition
Clinically manifest	Full-fledged clinical syndrome, for example, amyotrophic lateral sclerosis or behavioural variant frontotemporal dementia
Pre-symptomatic	The period between cellular or molecular disease onset, which is currently impossible to detect, and phenoconversion to clinically manifest disease; the pre-symptomatic phase of disease might be clinically silent or prodromal
Clinically silent	The stage of pre-symptomatic disease without any clinical manifestations
Prodromal	The stage of pre-symptomatic disease when symptoms or signs of disease are present but are non-specific and insufficient in severity or extent to declare the emergence of clinically manifest disease
Phenotransition	The transition between clinically silent and prodromal stages of disease
Phenoconversion	The transition from pre-symptomatic — either clinically silent or prodromal — to clinically manifest disease
Diagnosis	Full-fledged clinical syndrome that also meets published diagnostic criteria

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Table 2.

The Miami Framework: phenotypic axes and biomarkers

		Clinically silent disease	Prodromal disease	Clinically manifest disease ^{a,b}
Phenotype	Motor neuron (Axis I)	No motor neuron syndrome	MMI	ALS ^c
	Frontotemporal (Axis II)	No frontotemporal syndrome	MCI, MBI or MCBI	FTD ^d
	Extrapyramidal (Axis III)	No movement disorder	MEPI ^e	Parkinsonism CBS PSP
Biomarkers of underlying biology	TDP-43 ('TDP') pathology	For example, cryptic peptides ⁶⁹ , extracellular vesicle TDP-43 (ref.68)		
	Tau ('T') pathology	For example, CSF p-tau ⁶⁵ , CSF 4R RT-QuIC ⁶⁷		
	Neurodegeneration ('N') pathology	For example, neurofilament ^{58-58,61,64,78-83} , p-tau181 (ref.66), urinary p75 NTR ^{ECD} (ref. 84)		
	Other (for example, SOD1 pathology)	For example, CSF endogenous SOD1 peptide ⁸⁵		

ALS, amyotrophic lateral sclerosis; CBS, corticobasal syndrome; CSF, cerebrospinal fluid; FTD, frontotemporal dementia; MBI, mild behavioural impairment; MCBI, mild cognitive behavioural impairment; MCI, mild cognitive impairment; MEPI, mild extrapyramidal impairment; MMI, mild motor impairment; PSP, progressive supranuclear palsy. ^aPhenoconversion to clinically manifest disease can precede or coincide with diagnosis.

^bCurrent diagnostic criteria, developed primarily for patients with established disease, require modification to ensure that patients with earlier diagnosis, for example, those who have newly phenoconverted to clinically manifest disease, also meet diagnostic criteria. ^c Or alternate motor neuron syndrome such as primary lateral sclerosis or progressive muscular atrophy. Currently, formal diagnostic criteria exist for ALS^{2,8} and primary lateral sclerosis⁸⁶ but not for progressive muscular atrophy. ^d Specify subtype, such as behavioural variant FTD, semantic variant primary progressive aphasia (PPA) or non-fluent variant PPA, if possible. Formal diagnostic criteria are currently available for behavioural variant FTD⁷ and PPA⁵². ^e For example, tremor, rigidity, bradykinesia, myoclonus, dystonia, chorea or ataxia.

Table 3.

The Miami Framework: key phenotypic manifestations

Motor neuron, frontotemporal and extrapyramidal phenomenology		
Axis I: motor regions and associated signs		
Motor regions	LMN signs	UMN signs
Bulbar	Fasciculations (face or tongue) Atrophy (tongue) Weakness (face or tongue) Fibs/PSWs (face, tongue) ^a	Slow movements (tongue) Pathologically brisk reflexes (facial, jaw jerk)
Cervical	Fasciculations (arms) Atrophy (arms) Weakness (arms, neck) ^b Absent reflexes (arms) Fibs/PSWs (arms, neck) ^a	Slow movements (for example, in finger tapping) ^c Pathologically brisk reflexes (biceps, brachioradialis, triceps) ^d or a present Hoffmann response Spasticity
Respiratory	Impaired respiratory function Thoracic paraspinal atrophy or fasciculations Fibs/PSWs (thoracic paraspinal)	None
Lumbosacral	Fasciculations (legs) Atrophy (legs) Weakness (legs) Absent reflexes (legs) Fibs/PSWs (legs) ^a	Slow movements (for example, in foot tapping) ^c Pathologically brisk reflexes (patellar, ankle, crossed adductor) ^d or an extensor plantar response Spasticity
Axis II: frontotemporal dysfunction		
Functional realm	Domain-specific signs	
Cognition	Executive dysfunction ^e Language dysfunction ^f	
Behaviour	Loss of insight ^{f, g} Disinhibition ^{e, f, g} Apathy/inertia ^{e, f, g} Loss of sympathy/empathy ^{e, f, g} Perseverative/compulsive behaviors ^{e, f, g} Hyperorality ^{e, f, g} Irritability/agitation ^g Joviality/gregariousness ^g Psychosis ^f	
Axis III: key extrapyramidal phenotypes		
Movement Disorder	Reported Characteristics	
Tremor	Usually, a low-amplitude, high-frequency postural and intention tremor affecting the upper limbs. Other, and sometimes overlapping, phenotypes include: “jerky” arm tremor, rest tremor (uncommon), tongue tremor, and isolated head tremor ¹⁹ .	
Myoclonus	Distal stimulus-sensitive jerks affecting both upper limbs; isolated cheek myoclonus.	
Parkinsonism	Often asymmetric onset of an akinetic-rigid syndrome with prominent bradykinesia and little or no tremor.	
Ataxia	Appendicular ataxia	
Dystonia	Cervical, hemidystonia (CBS) or bilateral limb	
Chorea	Perioral, hemi-body, generalized	
Apraxia	Ideomotor, ideational	

CBS, corticobasal syndrome; Fibs, fibrillation potentials on electromyography; LMN, lower motor neuron; PSWs, positive sharp waves on electromyography; UMN, upper motor neuron. ^aChronic reinnervation changes might also be present but are not required when denervation is

encountered early (before severity and duration of axonal loss are sufficient for motor unit remodelling changes to become apparent). ^bAlthough neck flexors receive innervation from both cranial and cervical musculature, as the categorization is topographic (rather than neuroanatomic), weakness of neck flexors and extensors are considered part of the cervical region. ^cSlowed, poorly coordinated voluntary movement, not attributable to weakness of LMN origin or parkinsonian features. ^dIncludes preserved reflex in a clinically weak and wasted muscle, or spread to adjacent muscles. ^eCore criteria included in the Rascovsky revised criteria for behavioural variant frontotemporal dementia⁷. ^fIncluded in the revised Strong criteria for amyotrophic lateral sclerosis-associated frontotemporal spectrum disorder⁹. ^gIncluded in the proposed research criteria for prodromal behavioural variant frontotemporal dementia by Barker et al.³⁰.

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