Frontotemporal syndromes in amyotrophic lateral sclerosis: consensus criteria for diagnosis.

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Introduction

Although amyotrophic lateral sclerosis (ALS) has been traditionally considered as a progressive neurodegenerative disorder in which the motor system is selectively targeted, the finding of dementia or cognitive impairment in a significant proportion of ALS patients has challenged this concept. This has contributed to the contemporary conceptualization that ALS is in fact a multisystems disorder in which the motor system is selectively involved early in the course of the disease, but in which non-motor manifestations can also be prominent. The presence of frontotemporal impairments in ALS is of particular concern in that its presence is prognostically relevant in that a shorter survival time is observed in ALS patients with a frontotemporal dysfunction syndrome, perhaps due to the lack of compliance or interest in invasive therapies such as enteral nutrition or in the use of non-invasive positive pressure ventilation. Compared to individuals afflicted with Alzheimer disease, overall survival amongst those affected with a frontotemporal lobar degeneration (FTLD; the neuropathological correlate of the majority of FTD patients) is shorter – a phenomenon that is most marked in those patients with FTLD coexistent with motor neuron disease.

The presence of FTLD in ALS is of biological importance. In a proportion of cases, including the western Pacific variant of ALS and a number of sporadic forms of ALS, pathological findings typical of the FTLD can be observed, including the finding of microtubule associated tau protein (tau) immunoreactive neuronal and non-neuronal cells in addition to the more typical feature of ubiquitin-positive, tau and α-synuclein negative neuronal inclusions. This suggests, at some level, an overlap of ALS with other degenerative disease states in which FTLD is the primary neuropathological finding. This postulate is highlighted by the finding of ubiquitin immunoreactive intraneuronal aggregates within both bulbar and spinal motor neurons in a population of FTLD autopsies in which there is no obvious antemortem evidence of a motor neuron disease. The recent observation of abnormal TDP-43 intracellular localization, with or without ubiquitinization, in a number of FTLDs and ALS further highlights this overlap.

The recognition that frontotemporal syndromes may be associated with ALS is relatively recent and thus there remains a considerable lack of knowledge regarding their characterization. This includes aspects of clinical phenomenology, imaging and neuropathology. Clinical phenomenological, imaging and neuropathological characteristics of a FTD or FTLD in ALS...
need to be addressed and a framework for discussion within this field needs to be developed. A workshop on FTD in ALS was convened in June 2007 focused on defining consensus criteria for diagnosis of a frontotemporal syndrome in ALS. The following article summarizes these discussions.

**The core diagnostic criteria for ALS**

The El Escorial criteria (revised) for the diagnosis of ALS have been internationally accepted and should form the core of any diagnosis of ALS in the context of a frontotemporal syndrome. In their revised format, these criteria make use of clinical, electrophysiological, genetic and to some extent neuroimaging modalities to apply a level of certainty to the diagnosis of ALS. Although not studied in a fashion that speaks to the co-existence of ALS and a frontotemporal lobar syndrome, the sensitivity and specificity of the El Escorial criteria as diagnostic criteria for ALS have been validated in neuropathological studies.

Using the El Escorial criteria, ALS can be defined as clinically definite, probable, possible and suspected. In essence, the diagnosis of ALS requires the presence of lower motor neuron (LMN) degeneration (by clinical, electrophysiological or neuropathological criteria), evidence of upper motor neuron degeneration (UMN) (by clinical exam) with evidence of progression of symptoms or signs within a region or to other regions. These features must be present in the absence of neuroimaging, electrophysiological or pathological evidence of alternate disease processes that would explain the signs. Ross et al (1998) have simplified these criteria (Table 1). Laboratory and genetically supported categories can be utilized in those individuals in whom the full clinical and electrophysiological criteria are not met.

- **Clinically definite ALS**: defined on clinical evidence alone by the presence of LMN as well as UMN signs in the bulbar region and at least two spinal regions, or the presence of UMN and LMN signs in at least three spinal regions.
- **Clinically probable ALS**: defined on clinical evidence alone by UMN and LMN signs in at least two regions with some UMN signs necessarily rostral to the LMN signs.
- **Clinically probable ALS – Laboratory supported**: defined when clinical signs of UMN and LMN dysfunction alone are present in one region, and LMN signs defined by EMG criteria are present in at least two regions, with proper application of neuroimaging and clinical laboratory protocols to exclude other causes.
• **Clinically possible ALS:** defined when clinical signs of UMN and LMN dysfunction are found together in only one region, or UMN signs are found alone in two or more regions; or LMN signs are found rostral to UMN signs and the diagnosis of clinically probable ALS – Laboratory supported cannot be proven.

• **Clinically suspected ALS:** where the diagnosis could not be regarded as sufficiently certain to include the patient in a research study.

In those families in which a genetic linkage is known, the term “**clinically definite familial ALS – laboratory supported**” may be applied when ALS presents with progressive UMN and/or LMN signs in at least one region (in the absence of another cause for the abnormal neurological signs).

**Frontotemporal lobar syndromes in ALS**

There is considerable evidence supporting the existence of cognitive and behavioral dysfunction in ALS, including a spectrum of frontotemporal syndromes and more classically defined dementias. These include pure ALS in which only motor neuron degeneration occurs, ALS in association with cognitive impairment (ALSci), ALS with behavioral impairment (ALSbi), ALS with a dementia meeting the Neary criteria for FTD (ALS-FTD). In addition, a more florid dementia can precede ALS that has been described amongst the Japanese population can be included in this categorization. A frontally predominant variant of Alzheimer’s disease can also occur in ALS, although it is not clear whether this is a chance association. Estimates of the prevalence of cognitive impairment in ALS range from 10% to 75%, with the prevalence of dementia ranging from 15 to 41%.

Frontotemporal lobar degeneration consists of 3 clinically recognized subtypes. The most common (FTD) is a behavioural syndrome marked by altered social conduct, impaired regulation of interpersonal conduct, emotional blunting and loss of insight. In addition, both a progressive nonfluent aphasia (characterized by progressive nonfluent agrammaticism, paraphasia or anomia) and semantic dementia (characterized by fluent speech with loss of word meaning) are considered to be within the FTLD spectrum.

Whereas the classification of patients with frontotemporal syndromes into FTD, progressive nonfluent aphasia and semantic dementia has in general proven very useful, this approach may not serve to adequately describe the spectrum of cognitive and behavioural...
syndromes associated with ALS. For example, a frontal dysexecutive syndrome may occur in ALS in the absence of the typical behavioural features associated with FTD based on the Neary criteria. None of the standard criteria for FTD speak directly to the issue of executive dysfunction in ALS, deficits of which may impact directly on the ability to organize information mentally, to shift attention, or inhibit behavior. Additionally, the most common frontal lobe impairment in ALS reflects a combination of both cognitive and behavioral dysfunction. Detailed neuropsychological testing, using paradigms sensitive to frontotemporal lobar dysfunction, suggests that the prevalence of cognitive impairment in the ALS population may approach 50%.

Defining a minimum set of criteria that will be both sensitive and specific to these various syndromes is important. In part, this is a reflection of the fact that the neuropsychological impairments in ALS are often subtle, with the commonly observed deficits in the areas of problem solving, attention/mental control, continuous visual recognition memory, word generation, and verbal free recall. The interpretation of deficits can potentially be confounded by numerous extraneous variables can confound the interpretation of neuropsychological studies. These variables need to be controlled for (Table 2). While sampling the major cognitive domains, neuropsychological assessments should include tests weighted towards executive functioning, including a verbal fluency measure, as well as a caregiver interview measuring emotional and behavioral functioning. The latter is critical for assessing the full spectrum of frontotemporal impairments in that many reported series have not addressed the behavioral aspects, but rather have focused on alterations in cognition when assessing frontotemporal dysfunction in ALS. Tests which minimize the impact of speech and motor dysfunction are also critical to utilize, particularly in the setting of longitudinal analysis. Finally, all patients should be evaluated with regards to whether they meet the Neary criteria for FTD. Applying such an evaluative approach will allow for a crisper categorization of the frontotemporal lobar syndromes in ALS (Table 3). While the development of a brief screening tool for a frontotemporal lobar syndrome in ALS would be a highly valued clinical tool for those clinics and researchers for whom a full neuropsychological assessment is not available, such a tool has not yet been validated in this population.

**Neuroimaging studies**
Although both right hemispheric atrophy and a loss of neurons in the anterior cingulate gyrus have been associated with ALSci \(^{25,26}\), it is less clear that these tools are yet robust enough to be utilized as diagnostic tools in the evaluation paradigm for cognitive dysfunction in ALS. The presence of frontotemporal atrophy, whether defined by CT scan or MR imaging, may be a sensitive early indicator of a frontotemporal lobar degeneration in ALS. More dynamic tests of metabolic function, cerebral perfusion, astrocytic proliferation, or microglial activation remain investigative tools at this time but do show significant promise.

**Molecular and genetic diagnosis**

The western pacific variant of ALS may well be the prototypic example of the co-existence of ALS with significant nonmotor manifestations. First reported after World War II in Guam among native Chamorros and termed the amyotrophic lateral sclerosis-parkinsonism dementia complex of Guam \(^{27,28}\), approximately 50% of the siblings of these patients develop Parkinsonism and dementia, 25% develop ALS, and 5% of the siblings develop Parkinsonism, dementia, and ALS \(^{29,30}\).

The co-occurrence of ALS and FTLD have also been described in families outside Guam as the disinhibition-dementia-parkinsonism-amyotrophy complex \(^{31,32}\). In the most extensively studied family (Mo family), personality and behavioral changes were the first symptoms in 12 of 13 affected patients \(^{32}\). Symptom onset was around age 45 on average and the mean duration to death was 13 years. There was early memory loss, anomia, and poor construction with later involvement of orientation, speech, and calculations. All affected members had rigidity, bradykinesia, and postural instability. On neuropathology, there was atrophy and spongiform change in the frontotemporal cortex, and neuronal loss and gliosis in the substantia nigra and amygdala. Two individuals had anterior horn cell loss and one subject had fasciculations and muscle wasting. There were no Lewy bodies, neurofibrillary tangles, or amyloid plaques. The genetic locus was linked to chromosome 17q21-22 and a mutation found in the intron adjacent to exon 10 in the tau gene.

An extensive number of kindreds with FTLD and linkage to chromosome 17 has been described \(^{33,34}\). In a small proportion of these patients, corticospinal disturbances, muscle wasting, and fasciculations are observed. Mutations in the tau gene, located on chromosome 17, are found in many of these families, particularly those with extrapyramidal disturbances;
however few FTLD-ALS cases are caused by known tau mutations\textsuperscript{35-38}. The relationship between chromosome 17 linkage and FTLD is complex, and while over 25 different mutations have been identified in the tau gene (localized to chromosome 17) that are presumed to cause FTLD symptoms, non tau linked chromosome 17 linked FTLD with ALS is evident\textsuperscript{39}. In addition, another FTLD-ALS family has been localized to chromosome 9q21-q22\textsuperscript{40}.

**Neuropathological correlates**

There have been considerable advances in the neuropathological characterizations of the FTLDs, including the development of a classification based on the presence or absence of a tauopathy\textsuperscript{41}. The recognition that a subgroup of FTLD patients will have evidence of a motor neuron degeneration at the time of autopsy, based on a variety of immunohistochemical markers, has led to overlapping the development of neuropathological terminologies that are often taken to imply the presence of a clinical syndrome. However, the neuropathological characterization of the FTLDs associated with ALS remain to be fully clarified. The core component of the neuropathological diagnosis of a ALS-FTLD syndrome should remain the presence or absence of the neuropathological features of ALS (reviewed below). The problem then becomes the classification of those patients in whom there is neither antemortem evidence of ALS, but in whom the features of FTLD are found concurrently with one or more aspects of the neuropathology of ALS. This dilemma has been highlighted by the recent discovery that abnormal intraneuronal accumulations of TDP-43 are found within both ALS and FTLD with ubiquitin inclusions\textsuperscript{10; 11}.

As with the clinical criteria for the diagnosis of ALS, there are minimum criteria for the neuropathological diagnosis of ALS\textsuperscript{15}. There must be evidence of motor system degeneration that includes the loss of anterior horn cells (AHC), brainstem motor nuclei, and the descending supraspinal pathways involved in motor function. This degenerative process is accompanied by a wide array of neuropathological features in which both cortical (upper motor neurons, UMN) and either brainstem motor neurons or AHC (lower motor neurons, LMN) are involved. Amongst the neuropathological hallmarks of ALS are a variety of intracellular inclusions, including Bunina bodies, ubiquitinated inclusions or skein-like structures, and hyaline conglomerates\textsuperscript{42-47}. Although none of these findings are pathognomic, many are sufficiently unique to ALS to render the diagnosis of ALS highly likely.
The full extent of the neuropathological basis of the frontotemporal dysfunction syndromes of ALS remains to be defined. For those individuals with ALSci, the neuropathological features are typical of FTLD, including spongiform degeneration in frontal and precentral gyrus cortical layers II and III with diffuse subcortical gliosis. There is neuronal loss in the anterior cingulate gyrus, substantia nigra and amygdala. The finding of microglial activation and proliferation throughout the affected neocortex is reminiscent of the PET imaging studies using markers of microglial activation.

The neuropathological hallmark of FTLD in ALS is the presence of ubiquitin immunoreactive intraneuronal inclusions within the dentate granule cells, the superficial frontal and temporal cortical layers, and the entorhinal cortex. It is critical to note however that these are not specific to cognitively-impaired ALS cases and can be observed in other forms of neurodegeneration. It is the fact that these ubiquitin immunoreactive inclusions lack immunoreactivity to either microtubule associated protein tau or α-synuclein that has led to their being considered unique to ALS. However, there is evidence to suggest that alterations in tau metabolism may also be associated with ALSci, including aberrant tau phosphorylation at the threonine 175 site. In addition to these findings, ubiquitin immunoreactive dystrophic neurites in the extramotor cortices with a predominance of involvement in the frontal, temporal and hippocampal cortex are also observed.

**FTLD with ALS-like pathology**

There remains a group of FTLDs in which motor neuron degeneration is only observed at neuropathological examination. The FTLDs, are a heterogeneous group of diseases, sharing in common features of frontotemporal lobar degeneration but in which there is also considerable overlap in neuropathological features. In addition to this, the classification of the FTLDs is a work in evolution, modified by newer neurochemical studies, and by newer immunohistochemical markers. To highlight this, in a recent analysis of 29 cases derived from a brain bank which had been previously classified neuropathologically as FTD, the majority of cases were non-tauopathies, with the most common diagnosis that of frontotemporal lobar degeneration (FTLD) with ubiquitin-only immunoreactive neuronal changes. Other diagnoses included Pick’s disease, FTD with parkinsonism linked to chromosome 17 (FTDP-17), FTLD (also known as dementia lacking
distinctive histopathology – DLDH), FTLD with motor neuron disease (FTLD-MND), and neurofilament inclusion body disease (NIBD).

The finding of motor neuron ubiquitin-immunoreactive aggregates in the presence of the pathological features of a FTLD but in the absence of overt clinical features of motor neuron disease, has led to the concept of an unique FTD termed “motor neuron disease inclusion dementia” (MNDID)\(^8\). Of interest has been the observation of ubiquitinated intranuclear inclusions (Ub-INI) in the striatum of patients with familial MNDID only. Ub-INI had previously been described in 9 cases of MNDID, none of which had ALS\(^9\). Of these, one has subsequently developed ALS. It is not clear whether this is the same entity as described by MacKenzie and Feldman (2004) in which intranuclear ubiquitin immunoreactive inclusions were observed in the majority of familial FTLD MND-like cases\(^68\). It is likely however that these inclusions can be seen in both ALS-D and FTLDs with motor neuron degeneration not typical of ALS (referred to as FTD-MND-like)\(^69\). A FTLD with neurofilament inclusion bodies (NIBD) has also been described in which tau-negative, neurofilament immunoreactive inclusions have been observed\(^70\).

**Summary**

Increasingly, the nonmotor cognitive manifestations of ALS can be considered reflective of a heterogeneous group of “frontotemporal dysfunction syndromes” that include cognitive dysfunction (including a dysexecutive syndrome), behavioral impairment, and in a proportion, a florid FTD consistent with the Neary criteria. However, the impairments in the vast majority of these syndromes are relatively subtle and are not characteristic of a fulminant dementia. Consequently, cognitive and behavioural features are often overlooked in a neurological exam of an ALS patient, even amongst those attuned to their potential existence. Day to day variability in decision making, impulsivity and emotional lability are less critically inventoried in an individual in whom the devastating nature of the illness mandates a broadly based multisystems and multidisciplinary approach to management. The administration of a detailed neuropsychological examination to detect the nuances of a dysexecutive syndrome exceeds the resources of the majority of clinics. However, in careful studies of cognitive function in ALS, such phenomenon are frequent, suggesting that the conceptualization of ALS as a pure motor system disorder needs a radical overhaul.
There is some urgency to resolving these issues. If the frontotemporal lobar syndromes of ALS are simply intersecting diseases, independent in their biology from “pure” ALS, then defining what is “pure” ALS becomes critical to future therapeutic trials in ALS. If however a frontotemporal lobar syndrome, and its attendant biological processes, is an integral component of ALS and related motor neuron disorders, then our research focus needs to dramatically shift from understanding a motor system specific disorder, to one in which motor neurons are but the “singing canaries” of the demise of the nervous system. Either way, the recognition and acceptance of the presence of a frontotemporal degenerative state in the context of ALS heralds a new direction in our understanding of this disorder.
Table 1: a diagnostic algorithm (modified from Ross et al., 1998)\textsuperscript{18}

<table>
<thead>
<tr>
<th>Exclude disorders known to mimic ALS</th>
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<tbody>
<tr>
<td>Diagnosis of ALS is tenured if:</td>
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<tr>
<td>- Lower motor neuron signs in at least two regions</td>
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<tr>
<td>- Upper motor neuron signs in at least one region</td>
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<tr>
<td>- Progression</td>
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<tr>
<td>Absence of:</td>
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<tr>
<td>- Sensory signs</td>
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<tr>
<td>- Neurogenic sphincter abnormalities</td>
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<tr>
<td>- Clinically-evident peripheral nervous system disease with natural history of progression, distinct from ALS</td>
</tr>
<tr>
<td>- Clinically-evident peripheral nervous system disease with a natural history of progression</td>
</tr>
<tr>
<td>- ALS-like syndromes</td>
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</tbody>
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Table 2: Extraneous variables to consider in the neuropsychological evaluation of ALS

- Depression
- Pseudobulbar affect
- Educational level/baseline intellectual functioning
- Presence of bulbar dysfunction (e.g., dysarthria)
- Level of disease progression
- Pulmonary status
- Pain
- Fatigue
- Medications (esp. psychotrophic and analgesic meds)
- Level of motor impairment
Table 3. Diagnostic classification for ALS cognitive and behavioural dysfunction.

<table>
<thead>
<tr>
<th>Heading</th>
<th>Subheadings</th>
<th>Existing, synonymous terms within the literature</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS</td>
<td>ALS</td>
<td></td>
<td>A pure motor system disorder as defined by the El Escorial criteria; no clinical evidence of frontotemporal dysfunction</td>
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<td></td>
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<tr>
<td>Frontotemporal lobar degeneration with ALS</td>
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<tr>
<td>ALSci</td>
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<td></td>
<td>Deficits in frontal cognitive function but insufficient to meet the Neary criteria for FTD.</td>
</tr>
<tr>
<td>ALSbi</td>
<td></td>
<td></td>
<td>Behavioral dysfunction but insufficient to meet the Neary criteria</td>
</tr>
<tr>
<td>ALS-FTD</td>
<td>ALS-D, FTDMND</td>
<td></td>
<td>ALS patient meeting Neary criteria for FTD</td>
</tr>
<tr>
<td>ALS-PA</td>
<td></td>
<td></td>
<td>ALS patient meeting Neary criteria for PA</td>
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<tr>
<td>ALS-SD</td>
<td></td>
<td></td>
<td>ALS patient meeting Neary criteria for SD</td>
</tr>
<tr>
<td>FTD-MND-like</td>
<td></td>
<td></td>
<td>Cases of FTLD in which there is neuropathological evidence of motor neuron degeneration, but insufficient to be classified as ALS</td>
</tr>
<tr>
<td>ALS-dementia</td>
<td></td>
<td></td>
<td>ALS with dementia, not typical of FTLD</td>
</tr>
<tr>
<td>ALS-parkinsonism-dementia complex</td>
<td>Western Pacific variant of ALS; lytico bodig.</td>
<td>ALS concurrent with dementia and/or parkinsonism occurring in hyperendemic foci of the western pacific</td>
<td></td>
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Reference List


