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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 the motor system is selectively involved early in the course of the disease, but in which non-motor manifestations can also be prominent<sup>1</sup>. 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<sup>2</sup>. 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<sup>3;4</sup>.

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 a 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  $\alpha$ -synuclein negative neuronal inclusions<sup>5-7</sup>. 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<sup>8;9</sup>. The recent observation of abnormal TDP-43 intracellular localization, with or without ubiquitination, in a number of FTLDs and ALS further highlights this overlap<sup>10-13</sup>.

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<sup>14</sup>. 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<sup>15; 16</sup>. 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<sup>17</sup>.

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)<sup>18</sup>. Laboratory and genetically supported categories can be utilized in those individuals in whom the full clinical and electrophysiological criteria are not met<sup>16</sup>.

- **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<sup>19</sup>. Estimates of the prevalence of cognitive impairment in ALS range from 10% to 75%<sup>20; 21</sup>, with the prevalence of dementia ranging from 15 to 41%<sup>22; 23</sup>

Frontotemporal lobar degeneration consists of 3 clinically recognized subtypes<sup>24</sup>. 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 agramaticism, 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<sup>25</sup>. Detailed neuropsychological testing, using paradigms sensitive to frontotemporal lobar dysfunction, suggests that the prevalence of cognitive impairment in the ALS population may approach 50%<sup>22</sup>.

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<sup>24</sup>. 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 ALS<sup>25;26</sup>, 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<sup>27;28</sup>, 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<sup>29;30</sup>.

The co-occurrence of ALS and FTLN have also been described in families outside Guam as the disinhibition-dementia-parkinsonism-amyotrophy complex<sup>31;32</sup>. In the most extensively studied family (Mo family), personality and behavioral changes were the first symptoms in 12 of 13 affected patients<sup>32</sup>. 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 FTLN and linkage to chromosome 17 has been described<sup>33;34</sup>. 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 FTLN-ALS cases are caused by known tau mutations<sup>35-38</sup>. The relationship between chromosome 17 linkage and FTLN is complex, and while over 25 different mutations have been identified in the tau gene (localized to chromosome 17) that are presumed to cause FTLN symptoms, non tau linked chromosome 17 linked FTLN with ALS is evident<sup>39</sup>. In addition, another FTLN-ALS family has been localized to chromosome 9q21-q22<sup>40</sup>.

### **Neuropathological correlates**

There have been considerable advances in the neuropathological characterizations of the FTLNs, including the development of a classification based on the presence or absence of a tauopathy<sup>41</sup>. The recognition that a subgroup of FTLN 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 FTLNs associated with ALS remain to be fully clarified. The core component of the neuropathological diagnosis of a ALS-FTLN 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 FTLN 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 FTLN with ubiquitin inclusions<sup>10; 11</sup>.

As with the clinical criteria for the diagnosis of ALS, there are minimum criteria for the neuropathological diagnosis of ALS<sup>15</sup>. 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<sup>42-47</sup>. 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 ALS<sub>ci</sub>, the neuropathological features are typical of FTL<sub>D</sub><sup>5;7</sup>, including spongiform degeneration in frontal and precentral gyrus cortical layers II and III with diffuse subcortical gliosis<sup>7;24;48-59</sup>. There is neuronal loss in the anterior cingulate gyrus, substantia nigra and amygdala<sup>60</sup>. 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 FTL<sub>D</sub> 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<sup>59;61-63</sup>. It is the fact that these ubiquitin immunoreactive inclusions lack immunoreactivity to either microtubule associated protein tau or  $\alpha$ -synuclein that has led to their being considered unique to ALS<sup>54;59;61;62;64;65</sup>. However, there is evidence to suggest that alterations in tau metabolism may also be associated with ALS<sub>ci</sub>, including aberrant tau phosphorylation at the threonine 175 site<sup>6;66</sup>. 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.

### **FTL<sub>D</sub> with ALS-like pathology**

There remains a group of FTL<sub>D</sub>s in which motor neuron degeneration is only observed at neuropathological examination. The FTL<sub>D</sub>s, 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 FTL<sub>D</sub>s is a work in evolution, modified by newer neurochemical studies, and by newer immunohistochemical markers<sup>41</sup>. 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 (FTL<sub>D</sub>) with ubiquitin-only immunoreactive neuronal changes<sup>67</sup>. Other diagnoses included Pick's disease, FTD with parkinsonism linked to chromosome 17 (FTDP-17), FTL<sub>D</sub> (also known as dementia lacking

distinctive histopathology – DLDH), FTLN with motor neuron disease (FTLN-MND), and neurofilament inclusion body disease (NIBD).

The finding of motor neuron ubiquitin-immunoreactive aggregates in the presence of the pathological features of a FTLN but in the absence of overt clinical features of motor neuron disease, has led to the concept of an unique FTLN termed “motor neuron disease inclusion dementia” (MNDID)<sup>8</sup>. 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<sup>9</sup>. 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 FTLN MND-like cases<sup>68</sup>. It is likely however that these inclusions can be seen in both ALS-D and FTLNs with motor neuron degeneration not typical of ALS (referred to as FTLN-MND-like)<sup>69</sup>. A FTLN with neurofilament inclusion bodies (NIBD) has also been described in which tau-negative, neurofilament immunoreactive inclusions have been observed<sup>70</sup>.

## 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 FTLN 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<sup>71</sup>. 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) <sup>18</sup>

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Exclude disorders known to mimic ALS

Diagnosis of ALS is tenured if:

- Lower motor neuron signs in at least two regions
- Upper motor neuron signs in at least one region
- Progression

Absence of:

- Sensory signs
  - Neurogenic sphincter abnormalities
  - Clinically-evident peripheral nervous system disease with natural history of progression, distinct from ALS
  - Clinically-evident peripheral nervous system disease with a natural history of progression
  - ALS-like syndromes
-

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. psychotropic and analgesic meds)
- Level of motor impairment

Table 3. Diagnostic classification for ALS cognitive and behavioural dysfunction.

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

## Reference List

- (1) Strong MJ. The evidence for ALS as a multisystems disorder of limited phenotypic expression. *Can J Neurol Sci* 2001;28:283-298.
- (2) Lomen-Hoerth C, Strong MJ. Cognition in amyotrophic lateral sclerosis. In: Mitsumoto H, Przedborski S, Gordon P, De Bene M, eds. Amyotrophic lateral sclerosis. London: Marcel Dekker, 2006:115-138.
- (3) Roberson ED, Hesse JH, Rose KD, et al. Frontotemporal dementia progresses to death faster than Alzheimer disease. *Neurology* 2005;65:719-725.
- (4) Rascovsky K, Salmon DP, Lipton AM, et al. Rate of progression differs in frontotemporal dementia and Alzheimer disease. *Neurology* 2005;65:397-403.
- (5) Wilson CM, Grace GM, Munoz DG, He BP, Strong MJ. Cognitive impairment in sporadic ALS. A pathological continuum underlying a multisystem disorder. *Neurology* 2001;57:651-657.
- (6) Yang W, Sopper MM, Leystra-Lantz C, Strong MJ. Microtubule-associated tau protein positive neuronal and glial inclusions in amyotrophic lateral sclerosis. *Neurology* 2003;61:1766-1773.
- (7) Yoshida M. Amyotrophic lateral sclerosis with dementia: The clinicopathological spectrum. *Neuropathology* 2004;24:87-102.
- (8) Jackson M, Lennox G, Lowe J. Motor neuron disease-inclusion dementia. *Neurodegeneration* 1996;5:339-350.
- (9) Woulfe J, Kertesz A, Munoz DG. Frontotemporal dementia with ubiquitinated cytoplasmic and intranuclear inclusions. *Acta Neuropathol* 2001;102:94-100.
- (10) Neumann M, Sampathu DM, Kwong LK, et al. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Science* 2006;314:130-133.
- (11) Arai T, Hasegawa M, Akiyama H, et al. TDP-43 is a component of ubiquitin-positive tau-negative inclusions in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. *Biochem Biophys Res Comm* 2006;351:602-611.
- (12) Kwong LK, Neumann M, Sampathu DM, Lee VMY, Trojanowski JQ. TDP-43 proteinopathy: the neuropathology underlying major forms of sporadic and familial frontotemporal lobar degeneration and motor neuron disease. *Acta Neuropathol* 2007;DOI: 10.1007/s00401-007-0226-5.

- (13) Neumann M, Mackenzie IR, Cairns NJ, et al. TDP-43 in the ubiquitin pathology of frontotemporal dementia with VCP gene mutations. *J Neuropathol Exp Neurol* 2007;66:152-157.
- (14) Strong MJ, Grace GM, Orange JB, Leeper HA. Cognition, language and speech in amyotrophic lateral sclerosis: A review. *J Clin Exp Neuropsych* 1996;18:291-303.
- (15) World Federation of Neurology Research Group on Neuromuscular Disease. El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. *J Neurol Sci* 1994;124 (suppl.):96-107.
- (16) Brooks BR, Miller RG, Swash M, Munsat TL, for the World Federation of Neurology Research Group on Motor Neuron Diseases. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. *ALS and other motor neuron disorders* 2000;1:293-299.
- (17) Chaudhari KR, Crump S, Al-Sarraj S, Anderson V, Cavanagh J, Leigh PN. The validation of El Escorial criteria for the diagnosis of amyotrophic lateral sclerosis: a clinicopathological study. *J Neurol Sci* 1995;129:11-12.
- (18) Ross MA, Miller RG, Berchert L, et al. Toward earlier diagnosis of amyotrophic lateral sclerosis. *Neurology* 1998;50:768-772.
- (19) Hamilton RL, Bowser R. Alzheimer disease pathology in amyotrophic lateral sclerosis. *Acta Neuropathol* 2004;107:515-522.
- (20) Poloni M, Capitani E, Mazzini L, Ceroni M. Neuropsychological measures in amyotrophic lateral sclerosis and their relationship with CT scan-assessed cerebral atrophy. *Acta Neurol Scand* 1986;74:257-260.
- (21) Frank B, Haas J, Heinze HJ, Stark E, Munte TF. Relation of neuropsychological and magnetic resonance findings in amyotrophic lateral sclerosis: evidence for subgroups. *Clin Neurol Neurosurg* 1997;99:79-86.
- (22) Ringholz GM, Appel SH, Bradshaw M, Cooke NA, Mosnik DM, Schulz PE. Prevalence and patterns of cognitive impairment in sporadic ALS. *Neurology* 2005;65:586-590.
- (23) Lomen-Hoerth C, Murphy J, Langmore S, Kramer JH, Olney RK, Miller B. Are amyotrophic lateral sclerosis patients cognitively normal? *Neurology* 2003;60:1094-1097.
- (24) Neary D, Snowden JS, Gustafson L, et al. Frontotemporal lobar degeneration. A consensus on clinical diagnostic criteria. *Neurology* 1998;51:1546-1554.
- (25) Murphy JM, Henry RG, Langmore S, Kramer JH, Miller BL, Lomen-Hoerth C. Continuum of frontal lobe impairment in amyotrophic lateral sclerosis. *Arch Neurol* 2007;64:530-534.

- (26) Strong MJ, Grace GM, Orange JB, Leeper HA, Menon R, Aere C. A prospective study of cognitive impairment in ALS. *Neurology* 1999;53:1665-1670.
- (27) Hirano A, Kurland LT, Krooth RS, Lessell S. Parkinsonism-dementia complex, an endemic disease on the island of Guam. I. Clinical features. *Brain* 1961;84:642-661.
- (28) Hirano A, Malamud N, Kurland LT. Parkinsonism-dementia complex, an endemic disease on the island of Guam. II. Pathological features. *Brain* 1961;84:662-679.
- (29) Plato CC, Reed DM, Elizan TS, Kurland LT. Amyotrophic lateral sclerosis/Parkinsonism-dementia complex of Guam. IV. Familial and genetic studies. *Am J Hum Genet* 1967;19:617-632.
- (30) McGeer PL, Schwab C, McGeer EG, Haddock RL, Steele JC. Familial nature and continuing morbidity of the amyotrophic lateral sclerosis-parkinsonism dementia complex of Guam. *Neurology* 1997;47:400-409.
- (31) Gilbert JJ, Kish SJ, Chang L-J, Morito C, Shannak K, Hornykiewicz O. Dementia, parkinsonism and motor neuron disease: neurochemical and neuropathological correlates. *Ann Neurol* 1988;24:688-691.
- (32) Lynch T, Sano M, Marder KS, et al. Clinical characteristics of a family with chromosome 17-linked disinhibition-dementia-parkinsonism-amyotrophy complex. *Neurology* 1994;44:1878-1884.
- (33) Lee VMY, Goedert M, Trojanowski JQ. Neurodegenerative tauopathies. *Ann Rev Neurosci* 2001;24:1121-1159.
- (34) Foster NL, Wilhelmsen K, Sima AAF, et al. Frontotemporal dementia and parkinsonism linked to chromosome 17: A consensus conference. *Ann Neurol* 1997;41:706-715.
- (35) Clark LN, Poorkaj P, Wszolek Z, et al. Pathogenic implications of mutations in the tau gene in pallido-ponto-nigral degeneration and related neurodegenerative disorders linked to chromosome 17. *Proc Natl Acad Sci USA* 1998;95:13103-13107.
- (36) Hutton M, Lendon CL, Rizzu P, et al. Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. *Nature* 1998;393:702-705.
- (37) Spillantini MG, Goedert M. Tau protein pathology in neurodegenerative diseases. *TINS* 1998;21:428-433.
- (38) Poorkaj P, Bird TD, Wijsman E, et al. Tau is a candidate gene for chromosome 17 frontotemporal dementia. *Ann Neurol* 1998;43:815-825.
- (39) Wilhelmsen KC, Forman MS, Rosen HJ, et al. 17q-Linked frontotemporal dementia-amyotrophic lateral sclerosis without *tau* mutations with tau and  $\alpha$ -synuclein inclusions. *Arch Neurol* 2004;61:398-406.

- (40) Hosler BA, Siddique T, Sapp PC, et al. Linkage of familial amyotrophic lateral sclerosis with frontotemporal dementia to chromosome 9q21-q22. *JAMA* 2000;284:1664-1669.
- (41) Mott RT, Dickson DW, Trojanowski JQ, et al. Neuropathological, biochemical, and molecular characterization of the frontotemporal dementias. *J Neuropathol Exp Neurol* 2005;64:420-428.
- (42) Migheli A, Pezzulo T, Attanasio A, Schiffer D. Peripherin immunoreactive structures in amyotrophic lateral sclerosis. *Lab Invest* 1993;68:185-191.
- (43) Wong N, He BP, Strong MJ. Characterization of neuronal intermediate filament protein expression in cervical spinal motor neurons in sporadic amyotrophic lateral sclerosis (ALS). *J Neuropathol Exp Neurol* 2000;59:972-982.
- (44) Strong MJ. Neurofilament metabolism in sporadic amyotrophic lateral sclerosis. *J Neurol Sci* 1999;169:170-177.
- (45) Leigh PN, Dodson A, Swash M, Brion J-P, Anderton BH. Cytoskeletal abnormalities in motor neuron disease. An immunohistochemical study. *Brain* 1989;112:521-535.
- (46) van Welsem ME, Hogenhuis JA, Meininger V, Metsaars WP, Hauw JJ, Seilhean D. The relationship between Bunina bodies, skein-like inclusions and neuronal loss in amyotrophic lateral sclerosis. *Acta Neuropathol* 2002;103:583-589.
- (47) Wharton S, Ince PG. Pathology of motor neuron disorders. In: Shaw PJ, Strong MJ, eds. *Motor Neuron Disorders*, 1 ed. Philadelphia: Butterworth Heinemann, 2003:17-50.
- (48) Noda K, Katayama S, Watanabe C, Yamamura Y, Nakamura S. Gallyas- and tau-positive glial structures in motor neuron disease with dementia. *Clin Neuropath* 1999;18:218-225.
- (49) Morris HR, Khan MN, Janssen JC, et al. The genetic and pathological classification of familial frontotemporal dementia. *Arch Neurol* 2001;58:1813-1816.
- (50) Caselli RJ, Windebank AJ, Petersen RC, et al. Rapidly progressing aphasic dementia and motor neuron disease. *Ann Neurol* 1993;33:200-207.
- (51) Ferrer I, Roig C, Espino A, Peiro G, Matias Guiu X. Dementia of frontal lobe type and motor neuron disease. A Golgi study of the frontal cortex. *J Neurol Neurosurg Psychiat* 1991;54:932-934.
- (52) Kato S, Oda M, Hayashi H, Kawata A, Shimizu T. Participation of the limbic system and its associated areas in the dementia of amyotrophic lateral sclerosis. *J Neurol Sci* 1994;126:62-69.
- (53) Kawashima T, Kikuchi H, Takita M, et al. Skein-like inclusions in the neostriatum from a case of amyotrophic lateral sclerosis with dementia. *Acta Neuropathol* 1998;96:541-545.

- (54) Mitsuyama Y. Presenile dementia with motor neuron disease in Japan: clinico-pathological review of 26 cases. *J Neurol Neurosurg Psychiatr* 1984;47:953-959.
- (55) Munoz DG. The pathology of Pick complex. In: Kertesz A, Munoz DG, eds. Pick's disease and Pick complex. New York: John Wiley and Sons, 1998:211-239.
- (56) Horoupian DS, Katzman R, Terry RD, et al. Dementia and motor neuron disease: morphometric, biochemical and golgi studies. *Ann Neurol* 1984;16:305-313.
- (57) Brun A, Passant U. Frontal lobe degeneration of non-Alzheimer type. *Acta Neurol Scand* 1996;168:28-30.
- (58) Giannakopoulos P, Hof PR, Bouras C. Dementia lacking distinctive histopathology: clinicopathological evaluation of 32 cases. *Acta Neuropathol (Berl)* 1995;89:346-355.
- (59) Jackson M, Lowe J. The new neuropathology of degenerative frontotemporal dementias. *Acta Neuropathol* 1996;91:127-134.
- (60) Soni W, Luthert PJ, Leigh PN, Mann DMA. A morphometric study of the neuropathological substrate of dementia in patients with motor neuron disease. *Neuropathol Appl Neurobiol* 1993;19:203.Abstract
- (61) Okamoto K, Hirai S, Yamazaki T, Sun X, Nakazato Y. New ubiquitin-positive intraneuronal inclusions in the extra-motor cortices in patients with amyotrophic lateral sclerosis. *Neurosci Lett* 1991;129:233-236.
- (62) Wightman G, Anderson VER, Martin J, et al. Hippocampal and neocortical ubiquitin-immunoreactive inclusions in amyotrophic lateral sclerosis with dementia. *Neurosci Lett* 1992;139:269-274.
- (63) Lowe J, Blanchard A, Morrell K, et al. Ubiquitin is a common factor in intermediate filament inclusion bodies of diverse type in man, including those of Parkinson's disease, Pick's disease, and Alzheimer's disease, as well as Rosenthal fibres in cerebellar astrocytomas, cytoplasmic bodies in muscle, and mallory bodies in alcoholic liver disease. *J Pathol* 1988;155:9-15.
- (64) Ikemoto A, Hirano A, Akiguchi I, Kimura J. Comparative study of ubiquitin immunoreactivity of hippocampal granular cells in amyotrophic lateral sclerosis with dementia, Guamanian amyotrophic lateral sclerosis and Guamanian parkinsonism-dementia complex. *Acta Neuropathol* 1997;93:265-270.
- (65) Lowe J. New pathological findings in amyotrophic lateral sclerosis. *J Neurol Sci* 1994;124:38-51.
- (66) Strong MJ, Yang W, Strong WL, Leystra-Lantz C, Jaffe H, Pant HC. Tau protein hyperphosphorylation in sporadic ALS with cognitive impairment. *Neurology* 2006;66:1770-1771.

- (67) Josephs KA, Holton JL, Rossor MN, et al. Frontotemporal lobar degeneration and ubiquitin immunohistochemistry. *Neuropathol Appl Neurobiol* 2004;30:369-373.
- (68) Mackenzie IRA, Feldman H. Neuronal intranuclear inclusions distinguish familial FTD-MND type from sporadic cases. *Dement Geriatr Cogn Disord* 2004;17:333-336.
- (69) Bigio EH, Johnson NA, Rademaker AW, et al. Neuronal ubiquitinated intranuclear inclusions in familial and non-familial frontotemporal dementia of the motor neuron disease type associated with amyotrophic lateral sclerosis. *J Neuropathol Exp Neurol* 2004;63:801-811.
- (70) Bigio EH, Lipton AM, White CL, III, Dickson DW, Hirano A. Frontotemporal and motor neurone degeneration with neurofilament inclusion bodies: additional evidence for overlap between FTD and ALS. *Neuropathol Appl Neurobiol* 2003;29:239-253.
- (71) Strong MJ, Gordon PH. Primary lateral sclerosis, hereditary spastic paraplegia and amyotrophic lateral sclerosis – discrete entities or spectrum? *ALS and other motor neuron disorders* 2005;6:8-16.