Table. Clinical and Demographic Patient Characteristics

Characteristic	Patient Group			P Value
	FTLD Without ALS (n = 11)	FTLD-ALS (n = 9)	ALS-FTLD (n = 23)	
Sex, No. female/male[a]	8/3	3/6	10/13	.16
Age at onset, mean (SD), y[b]	62.4 (9.4)	58.2 (11.3)	61.2 (9.5)	.79
Clinical duration without respirator or tracheotomy, median (range), mo[c]	84.0 (47.0-360.0)	28.0 (7.0-60.0)	22.0 (7.0-71.0)	<.001
Duration between FTLD and ALS, median (range), mo[d]		18.0 (4.0-48.0)	19.0 (0-60.0)	.92
Patients with tracheotomy, No. (%)[a]	0	0	2 (9)	.40
Patients with respirators, No. (%)[a]	0	1 (11)	8 (35)	.047
Duration with respirator or tracheotomy, median (range), mo		30.0	39.0 (1.0-141.0)	...
Causes of death, No. (%)[a]				
Respiratory failure	0	6 (67)	20 (87)	<.001
Pneumonia	3 (27)	3 (33)	3 (13)	.37
Other	8 (73)	0	0	<.001
Subtypes of dementia, No. (%)				
Behavior-variant FTD	7 (64)	7 (78)	19 (83)	.29
Language impairments	4 (36)	2 (22)	4 (17)	.62
Motor symptoms/signs, No. (%)				
Muscle weakness[a]	0	9 (100)	23 (100)	<.001
Muscle atrophy	0	7 (78)	22 (96)	<.001
Fasciculation	0	4 (44)	15 (65)	.002
Hyperreflexia	3 (27)	5 (56)	17 (74)	.009
Babinski sign	1 (9)	4 (44)	3 (13)	.08
Spasticity	1 (9)	0	1 (4)	.63
Electromyography, No. (%)				
Total examined	2 (18)	4 (82)	21 (91)	...
Active denervation[a]	0	3 (75)	12 (57)	.054

Abbreviations: ALS, amyotrophic lateral sclerosis; ALS-FTLD, onset of ALS symptoms/signs preceding those of frontotemporal lobar degeneration (FTLD); ellipses, not significant; FTD, frontotemporal dementia; FTLD-ALS, onset of FTLD symptoms/signs preceding those of ALS.

[a] χ^2 Test.

[b] Kruskal-Wallis test.

[c] Log-rank test.

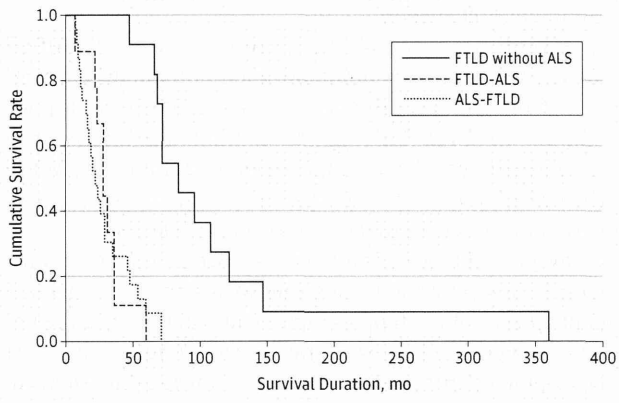
[d] Mann-Whitney test.

ALS-FTLD generally exhibited both upper motor neuron and LMN symptoms/signs except for 3 who exhibited only LMN symptoms/signs. Based on the electromyographic data, active denervation potentials (positive sharp waves and fibrillation potentials[18]) were identified in 3 patients with FTLD-ALS and 12 with ALS-FTLD but not in any of those with FTLD without ALS.

Pathological Evaluations of the LMN System

The results of semiquantitative pathological evaluations of the 3 clinical groups are summarized in **Figure 2**. In the FTLD without ALS group, 8 of 9 patients (89%) showed pTDP-43-positive neuronal inclusions. In addition, neuronal loss and gliosis in the spinal anterior horns were observed in 5 of 11 patients (45%) and Bunina bodies were present in 4 (36%). The pathological changes in LMN systems were most severe in the ALS-FTLD group, followed by the FTLD-ALS group, and were rather mild in the FTLD without ALS group. Among control patients, 1 had a pTDP-43-positive glial inclusion in the lumbar anterior horn, but this patient did not show neuronal loss, gliosis, or Bunina bodies (eFigure 2 in Supplement).

Figure 1. Survival by Clinical Group



Kaplan-Meier plot showing the survival rates of patients with frontotemporal lobar degeneration (FTLD) without amyotrophic lateral sclerosis (ALS) (solid line; n = 11), those in whom the onset of FTLD symptoms/signs preceded those of ALS (FTLD-ALS) (dashed line; n = 9), and those in whom the onset of ALS symptoms/signs preceded those of FTLD (ALS-FTLD) (dotted line; n = 23). Survival times were significantly shorter in patients with FTLD without ALS than in those with FTLD-ALS or ALS-FTLD ($P < .001$).

Figure 2. Semiquantitative Evaluations of Pathological Changes by Clinical Group

	FTLD Without ALS									FTLD-ALS								ALS-FTLD											P Values	r Values
Patients	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29		
Clinical duration, mo	47	66	84	108	147	360	68	96	122	22	23	28	28	31	36	36	60	7	8	9	10	16	20	22	24	26	54	60	71		
Neuronal loss																															
Facial nuclei	+	-	-	-	+	-	-	-	-	++	NA	+	+	+	+	++	+	+	++	+	+	++	++	NA	++	+	+++	+++	+	<.01	0.730
Hypoglossal nuclei	-	-	-	-	-	-	-	-	-	+++	NA	++	+++	++	+	+++	++	+++	+	+	+++	+++	+++	+++	++	+++	+++	+++	+++	<.01	0.823
Anterior horn of Cx	+	++	-	-	+	-	-	-	+	++	++	+	++	++	+	++	+	+++	++	++	++	++	++	NA	+++	+++	++	+++	++	<.01	0.804
Anterior horn of Tx	+	+	NA	+	+	-	NA	-	+	+	++	++	++	++	++	+	++	++	+	+++	++	++	+++	++	++	+++	+++	+++	++	<.01	0.768
Anterior horn of Lx	-	-	NA	+	+	-	NA	-	-	+	+	+	+	+	+	++	+	++	++	+++	+	++	++	NA	++	+++	++	++	++	<.01	0.856
Anterior horn of Sx	-	-	NA	+	-	-	NA	-	-	+	NA	+	+	+	+	++	+	++	++	NA	NA	++	++	NA	++	++	+++	NA	+	<.01	0.880
Gliosis																															
Facial nuclei	++	-	-	-	+	-	-	-	-	++	NA	+	+	+	+	++	+	++	++	+	++	++	++	NA	+	++	+++	+++	++	<.01	0.768
Hypoglossal nuclei	-	-	-	-	-	-	-	-	-	+++	NA	++	++	++	+	+++	++	+++	+	+	+++	+++	+++	+++	++	+++	+++	+++	++	<.01	0.828
Anterior horn of Cx	+	++	-	-	+	-	-	-	+	++	++	+	+++	++	+	++	+	+++	+	++	++	++	++	NA	++	+++	++	+++	+++	<.01	0.730
Anterior horn of Tx	+	+	NA	-	+	-	NA	-	+	+	++	+	++	++	++	+	++	++	+	+++	++	++	+++	++	+	+++	+++	+++	++	<.01	0.740
Anterior horn of Lx	-	-	NA	+	+	-	NA	-	-	+	+	+	++	+	+	++	+	++	++	+++	++	++	++	NA	+++	+++	++	++	++	<.01	0.878
Anterior horn of Sx	-	-	NA	+	-	-	NA	-	-	+	NA	+	++	+	+	++	+	++	++	NA	NA	++	++	NA	+++	+++	+++	NA	++	<.01	0.904
pTDP-43-positive neuronal inclusions																															
Facial nuclei	+	-	-	-	+	-	-	-	-	++	NA	+	+	+	+	+	+	+	++	+	++	+++	+	NA	+	++	+	+	++	<.01	0.729
Hypoglossal nuclei	-	+	+	-	-	-	+	-	-	+	NA	+	+	+	+	++	+	+	+	-	+	+++	+	-	+	+	-	+	+	.08	0.348
Anterior horn of Cx	+	+	+	+	+	-	+	+	-	++	++	+	+	+	+	+	++	++	+++	+	+++	++	++	NA	+	+	+	+	+	<.01	0.511
Anterior horn of Tx	+	+	NA	-	+	-	NA	+	+	+	+	++	+	+	+	+	+	+	+	+	++	+	++	+	+	+	+	+	+	<.05	0.403
Anterior horn of Lx	+	+	NA	+	-	-	NA	+	+	+	+++	++	++	+	+	++	++	+	++	++	++	+	+++	NA	+	+	+	++	+	<.05	0.412
Anterior horn of Sx	+	-	NA	-	-	-	NA	+	-	++	NA	++	+	+	+	+	+	+	+	NA	NA	+	+++	NA	-	+	+	NA	+	<.05	0.458
Aggregation of macrophages																															
Facial nuclei	++	-	+	-	+	-	-	-	-	++	NA	+	-	++	+	++	+	++	+	+	+	+	++	NA	+	++	++	+	+	<.01	0.518
Hypoglossal nuclei	+	-	-	-	-	-	-	-	-	+	NA	-	+	++	+	+	-	+++	+	++	+	+	+++	-	++	+++	+	++	-	<.01	0.634
Anterior horn of Cx	+	+	-	+	+	-	-	+	+	++	+	+	+	++	+	++	++	+	+	+	+	-	++	NA	+	+	+	-	-	0.78	0.073
Anterior horn of Tx	+	+	NA	-	-	-	NA	+	+	++	+	++	+	++	+	+	+	+	+	++	++	+	++	+	+	+	+	+	+	<.05	0.435
Anterior horn of Lx	-	++	NA	+	-	-	NA	-	-	+	-	-	+	+	+	++	+	+++	++	+++	++	+	+++	NA	+	+++	++	++	++	<.01	0.721
Anterior horn of Sx	-	+	NA	+	-	-	NA	-	-	+	NA	-	+	+	+	+	+	+++	++	NA	NA	+	++	NA	+	+++	++	NA	+	<.01	0.751
Bunina bodies	+	+	-	+	+	-	-	-	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+		
Brain TDP-43 disease type	A	A	A	A	A	A	C	C	C	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B		

Findings shown include the severity of neuronal loss, gliosis, phosphorylated TAR DNA-binding protein of 43 kDa (pTDP-43) pathological changes, and aggregations of macrophages and the presence of Bunina bodies in the lower motor neuron systems. The severity of each pathological change was graded as 0 (none [–, not colored]), 1 (mild [+, green]), 2 (moderate [++, yellow]), or 3 (severe [+++, red]). Neuropathological changes became increasingly severe in those in whom amyotrophic lateral sclerosis (ALS) symptoms/signs preceded those of frontotemporal lobar degeneration (FTLD; ALS-FTLD), as well as the FTLD-ALS (FTLD symptoms/signs preceding those of ALS) and FTLD without ALS groups (Spearman rank order). Cx indicates cervical cord; Lx, lumbar cord; NA, not assessed; Sx, sacral cord; TDP-43, TAR DNA-binding protein of 43 kDa; and Tx, thoracic cord.

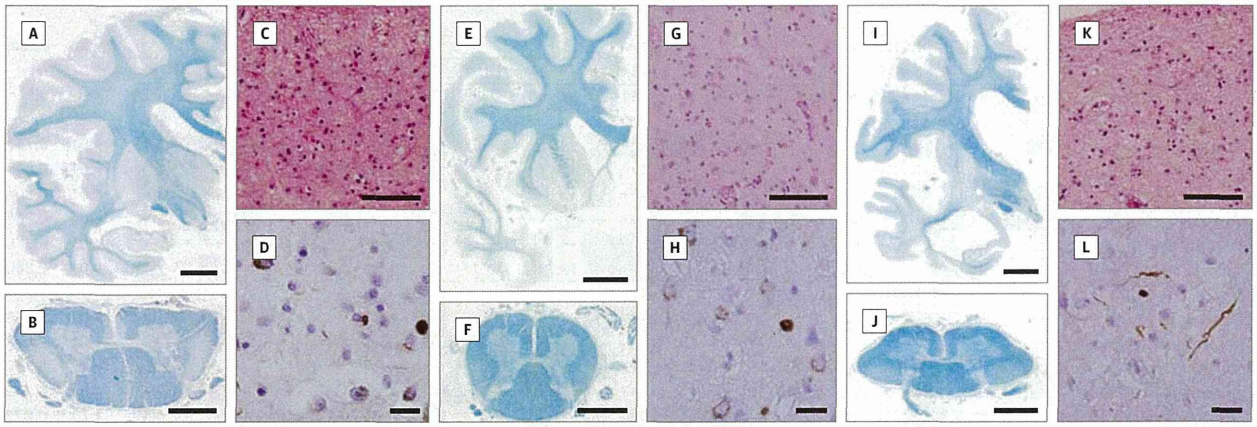
According to cortical TDP-43 pathological findings,[5] 29 patients were classified into 3 subtypes: A (n = 6), B (n = 20), or C (n = 3). Patients with FTLD without ALS showed type A or C disease, whereas those with FTLD-ALS or ALS-FTLD all showed type B disease (Figure 2 and **Figure 3**). For all the subtypes, the LMN system showed neuropathological changes that were indicative of ALS, including pTDP-43-positive neuronal and glial inclusions, neuronal loss, and gliosis. In patients with type A disease (**Figure 4**A-H), the severity of neuronal loss and gliosis in LMN systems ranged from none to moderate. Five patients (83%) in this group had pTDP-43-positive, skeinlike cytoplasmic and/or nuclear inclusions (Figure 4B and C), and 4 (67%) had Bunina bodies (Figure 4E and F) in the LMNs.

All 20 patients in the type B group (Figure 4I-L) showed neuronal loss, gliosis, and pTDP-43-positive skeinlike cytoplasmic inclusions in the LMN systems, and 18 (90%) had Bunina bodies. Among the 3 patients with type C disease (Figure 4M-P), 1 (33%) had mild loss of the LMNs (Figure 4M), and all 3 (100%) had pTDP-43-positive skeinlike cytoplasmic inclusions in the LMNs (Figure 4N). Unlike patients with the other subtypes, those with type C disease lacked Bunina bodies. Moreover, thick dystrophic neurites were prominent in the spinal anterior horn in patients with type A or C disease but rarely present in those with type B disease (Figure 4G and O). These dystrophic neurites were larger in diameter (8-12 µm) than those found in the cortices. In a double immunohistochemical analysis, pTDP-43-positive inclusions were found within the cytoplasm of ChAT-positive neurons in patients with type A, B, and C disease (Figure 4H, L, and P).

Pathological Evaluations of the Upper Motor Neuron System

In the primary motor cortex, neuronal loss and gliosis were evident in 5 patients with FTLD without ALS (56%), 2 with FTLD-ALS (25%), and 3 with ALS-FTLD (25%). Myelin pallor in the CST was evident in 6 patients with FTLD without ALS (67%), 1 with FTLD-ALS (12%), and 2 with ALS-FTLD (17%). Aggregations of macrophages in the CST were evident in 4 patients with FTLD without ALS (44%), 5 with FTLD-ALS (62%), and 6 with ALS-FTLD (50%).

Figure 3. Semimacroscopic Appearances and Brain Pathological Findings in Patients With Type A, B, and C Pathological Changes



Findings in patients with type A (A-D) , B (E-H), and C (I-L) pathological changes. In a patient with type A pathological change, cerebral coronal sections showed cortical atrophy of the parasylvian region (A). Transverse section of the cervical cord showed marked myelin pallor in the corticospinal tract (B). Microscopically, the frontal cortices showed marked neuronal loss (C) and phosphorylated TAR DNA-binding protein of 43 kDa (pTDP-43)–positive neuronal inclusions and short dystrophic neurites (D). In a patient with type B pathological change, the cerebral cortex showed severe temporal atrophy (E), neuronal loss (G), and pTDP-43–positive neuronal inclusions (H). The corticospinal tract showed mild myelin pallor (F). In a patient with type C patholgoical change, the frontal and temporal cortices showed severe atrophy (I), marked neuronal loss (K), and pTDP-43–positive long dystrophic neurites (L). The corticospinal tract showed marked myelin pallor (J). Klüver-Barrera staining (A, B, E, F, I, and J), hematoxylin-eosin staining (C, G, and K), and pTDP-43 immunohistochemistry (D, H, and L) were performed. Scale bars represent 1 cm (A, E, and I), 3 mm (B, F, and J), 100 µm (C, G, and K), and 20 µm (D, H, and L). Original magnifications are ×1 (A, B, E, F, I, and J), ×200 (C, G, and K), and ×400 (D, H, and L).

Anti-UBQLN-2 and Anti-p62N Immunohistochemistry

No patients showed any cerebellar UBQLN-2–positive or p62N-positive structures. In the temporal lobes, UBQLN-2–positive structures were occasionally observed in 8 patients, but abundant, thick, and aggregatelike structures, which are found in patients with C9ORF72 expansions, were not observed (eFigure 3 in Supplement). We presumed that our patients did not have C9ORF72 expansions.

Discussion

Our study demonstrated that pTDP-43–associated pathological changes were common in the spinal anterior horns of the FTLD without ALS, FTLD-ALS, and ALS-FTLD groups. Neuronal loss and gliosis were most severe among the ALS-FTLD group, followed by the FTLD-ALS and then the FTLD without ALS groups. Our results clearly demonstrated the pathological continuum among TDP-43–associated FTLD and ALS, even at the LMN level.

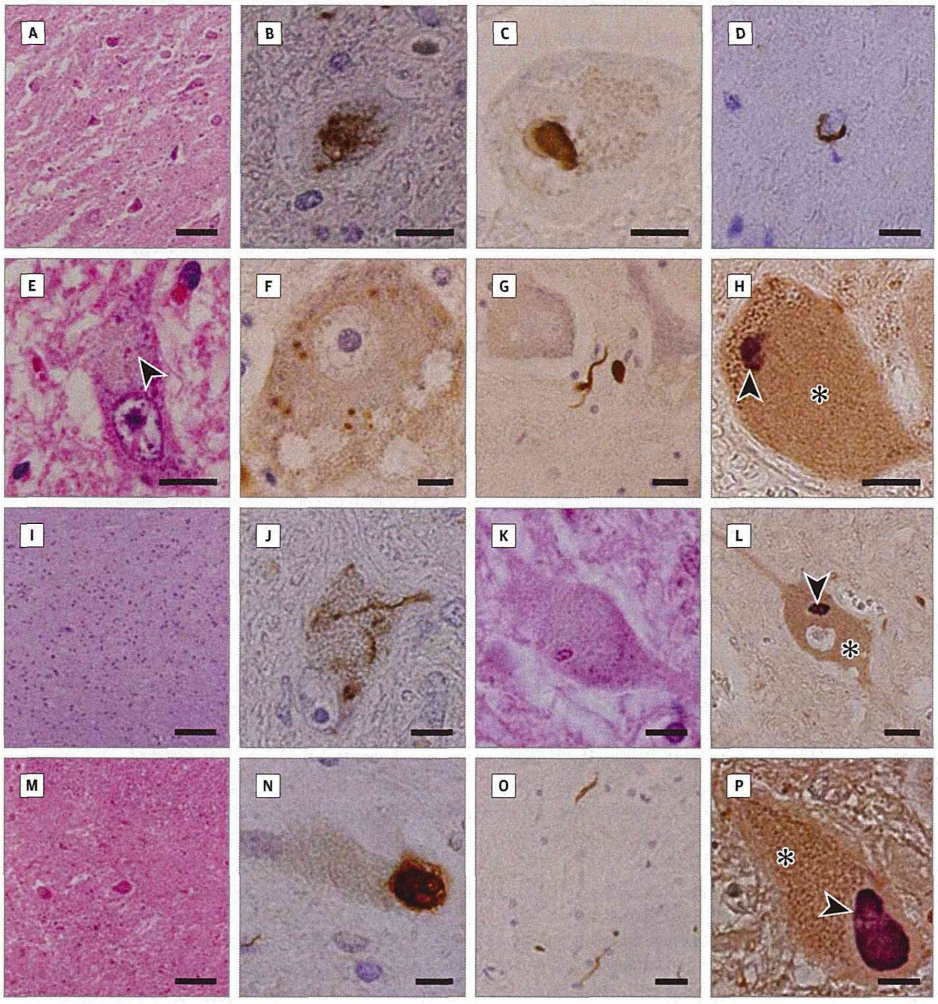
Although the FTLD without ALS group that lacked LMN symptoms showed a loss of LMNs, the degree of neuronal loss and TDP-43 disease were generally mild in this group. Experiment data using ALS mouse models revealed that symptoms developed when approximately 29% of spinal motor neurons were lost.[25] Further investigation will be needed to clarify whether LMN involvement occurs in a later stage of illness or progresses very slowly compared with cerebral involvement in FTLD without ALS.

Our results revealed that the FTLD-TDP types A, B, and C were associated with neuropathological changes corresponding to ALS in the spinal motor neurons. The severity of neuronal loss and pTDP-43 disease in the spinal motor neurons may differ quantitatively among these neuropathological subtypes. Based on cortical TDP-43 pathological findings, patients in the type B group had severe neuronal loss and diffuse pTDP-43–positive neuronal inclusions, which were entirely identical to ALS, whereas these changes were mild in the type C group. In type A, LMN pathological findings were diverse regardless of clinical duration; their severity and extension may be heterogeneous among patients with type A disease, unlike those with type B or C disease. Indeed, type A disease has also been identified in the FTLD with ALS phenotype in sporadic or familial (C9ORF72 expansion or progranulin gene mutations) form.[2,5,21,26] Dystrophic neurites were prominent in the spinal anterior horn of patients with type A or C disease. In our patient series, Bunina bodies were observed in most patients with type A or B disease but were absent in those with type C disease, findings consistent with those of previous studies.[3,17]

Several studies have demonstrated that some patients with FTLD-TDP, particularly type C, showed marked CST degeneration.[3,11,17,27] We also observed a marked myelin pallor in the CST in 67% of patients with FTLD without ALS, 12% with FTLD-ALS, and 16% with ALS-FTLD (50% for type A, 15% for type B, and 100% for type C). Some patients showed neuronal loss or gliosis in the primary motor cortex to varying extents. Furthermore, patients with FTLD without ALS often exhibited severe degenerative changes in broad areas of the frontal cortices. The broad involvement of the frontal lobes might also contribute to the CST degeneration because CST fibers arise not only from the primary motor cortex but also from the premotor cortex and supplementary motor areas.[28]

Two limitations of our study is that the evaluation of slight or very mild muscle weakness was not completed and that there were few patients with electromyographic data in

Figure 4. Pathological Findings of Spinal Motor Neuron in Subtypes of TAR DNA-Binding Protein of 43 kDa (TDP-43) Pathological Changes



Patients with type A (A-H), type B (I-L), and type C (M-P) pathological changes. A patient with type A pathological change showed mild neuronal loss (A), phosphorylated TDP-43 (pTDP-43)–positive skeinlike cytoplasmic inclusions (B), nuclear inclusions (C), and glial inclusions (D), Bunina bodies (E [arrow] and F) in the spinal anterior horn, and dystrophic neurites (G). In a patient with type B pathological change, neuronal loss (I), pTDP-43–positive skeinlike cytoplasmic inclusions (J), and Bunina bodies (K) were markedly observed. In a patient with type C pathological change, the spinal anterior horn showed mild neuronal loss (M), pTDP-43–positive skeinlike cytoplasmic inclusions (N), and dystrophic neurites (O). Double immunohistochemistry for choline acetyltransferase (ChAT) and pTDP-43 revealed cytoplasmic inclusions (violet [arrows]) present within the cytoplasm of a ChAT-positive spinal motor neuron (brown [asterisks]) of patients with type A (H), B (L), or C (P) pathological change. Hematoxylin-eosin staining (A, E, I, K, and M), pTDP-43 immunohistochemistry (B, C, D, G, J, N, and O), cystatin-C (F), and double immunohistochemical analysis for pTDP-43 and ChAT (H, L, and P) were performed. Scale bars represent 100 (A, I, and M), 20 (G, L, and O), and 10 (B-F, H, J, K, N, and P) μm. Original magnifications are ×100 (A, I, and M), ×400 (G, L, and O), and ×1000 (B-F, H, J, K, N, and P).

the FTLD without ALS group. However, our clinical data demonstrated that patients with FTLD without ALS had significantly longer survival times than those with FTLD-ALS or ALS-FTLD. These prognostic data correspond well to previous results.[29,30] In addition, the causes of death differed considerably between the FTLD without ALS group and the FTLD-ALS and ALS-FTLD groups. Respiratory failure was observed in patients with FTLD-ALS or ALS-FTLD but not in those with FTLD without ALS, and respiratory failure was strongly associated with severity of LMN loss. These results support the view that classification of FTLD based on the presence of LMN involvement was applicable in this study.

In conclusion, the LMN systems of FTLD-TDP generally show neuropathological changes that are indicative of ALS, although the severity of pathological changes differs among clinical phenotypes or subtypes of cortical TDP-43 disease. A pathological continuity between FTLD-TDP and ALS is supported by evidence of LMN involvement.

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ORIGINAL ARTICLE

Factors affecting longitudinal functional decline and survival in amyotrophic lateral sclerosis patients

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Abstract

Our objective was to elucidate the clinical factors affecting functional decline and survival in Japanese amyotrophic lateral sclerosis (ALS) patients. We constructed a multicenter prospective ALS cohort that included 451 sporadic ALS patients in the analysis. We longitudinally utilized the revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) as the functional scale, and determined the timing of introduction of a tracheostomy for positive-pressure ventilation and death. A joint modelling approach was employed to identify prognostic factors for functional decline and survival. Age at onset was a common prognostic factor for both functional decline and survival ($p < 0.001$, $p < 0.001$, respectively). Female gender ($p = 0.019$) and initial symptoms, including upper limb weakness ($p = 0.010$), lower limb weakness ($p = 0.008$) or bulbar symptoms ($p = 0.005$), were related to early functional decline, whereas neck weakness as an initial symptom ($p = 0.018$), non-use of riluzole ($p = 0.030$) and proximal dominant muscle weakness in the upper extremities ($p = 0.01$) were related to a shorter survival time. A decline in the ALSFRS-R score was correlated with a shortened survival time ($p < 0.001$). In conclusion, the factors affecting functional decline and survival in ALS were common in part but different to some extent. This difference has not been previously well recognized but is informative in clinical practice and for conducting trials.

Key words: *ALS, ALSFRS-R, functional decline, survival*

Introduction

The clinical course and rate of disease progression in amyotrophic lateral sclerosis (ALS) patients vary widely. Therefore, in clinical practice, patient care and design of clinical trials, it is important to understand the factors affecting the clinical course of these patients.

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Progressive functional decline, which influences the activities of daily living (ADLs) and quality of life (QoL), is a key feature of neurodegenerative diseases. Accordingly, in considering the clinical course of ALS, functional status and survival are equally important. Hence, the revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) (1), which is the most widely used scale for the functional evaluation of ALS patients, has been used in many clinical trials for ALS as the primary or secondary outcome measure along with survival (2–5).

A number of cohort studies have elucidated the factors affecting survival in ALS patients using survival analyses, such as the Kaplan-Meier method, which have also been utilized in clinical trials for ALS (3,6). However, the factors affecting functional decline in ALS patients have not been well demonstrated. Therefore, it is uncertain whether the factors affecting functional decline in ALS are similar to those that affect survival. Because the collection of longitudinal functional rating scale data, such as that from the ALSFRS-R, would be discontinued by death or drop-out due to a loss during follow-up, a discontinuity in the sequential data might contain ambiguous findings that are related either to death or drop-out caused by various factors. Evaluations that do not adjust for these informative discontinuations would lead to beta errors in the clinical trials, which could mask the effectiveness of the tested drugs (7). Recently, the importance of handling informative discontinuations of sequential data in clinical trials has been noted (7).

To manage the informative discontinuations of sequential data and to evaluate both a longitudinal functional parameter and survival data in combination, a joint modelling analysis was developed in clinical trials for cancer and human immunodeficiency virus (HIV) infection (8,9), and this joint analysis has been extended to ALS clinical trials (6,10,11). In this study, to elucidate the factors affecting functional decline and survival with adjustments for informative discontinuations, we conducted a prospective multicenter cohort study and joint modelling analysis of Japanese ALS patients.

Methods

We developed a multicenter registration and follow-up system entitled the 'Japanese Consortium for Amyotrophic Lateral Sclerosis research (JaCALS)', which consisted of 30 neurology facilities in Japan. ALS patients diagnosed in these facilities were consecutively registered after written informed consent was obtained. The ethics committees of all participating institutions approved the study.

At registration, full clinical examinations were conducted by neurologists in the respective facilities. Muscle strength was manually tested and scored according to the scoring system of the Medical Research Council (MRC score, 6 points; range 0–5) (12) in eight muscle groups as follows: bilateral abductors of the shoulders, as representative of the proximal upper extremity muscles; wrist extensor muscles, as representative of the distal upper extremity muscles; bilateral flexors of the hips, as representative of the proximal lower extremity muscles; and ankle dorsiflexion muscles, as representative of the distal lower extremity muscles. All manual muscle testing was performed by certified neurologists using standard positioning and procedures (13). To standardize the procedures and the examinations, the three organizing doctors (HaW, NA, RN) visited each participating facility and ascertained the evaluation methods for this study.

Disease onset was defined as the time when patients initially became aware of muscle weakness or impairment in swallowing, speech, or respiration. We enrolled patients who fulfilled the revised El Escorial criteria (14). The included patients were prospectively followed up with telephone surveys conducted by clinical research coordinators (CRCs) or examinations by neurologists every three months, and the degree of deterioration in functionality was determined at each time-point. We employed the Japanese version of the ALSFRS-R, which was validated by Ohashi et al. (15), as a scale of functionality. We developed a telephone survey system in which the CRCs conducted a telephone survey every three months that referred to the flow charts of the ALSFRS-R (Japanese version). We previously confirmed the reliability of the system (16), similar to the method used to confirm the English version of the telephone survey in several studies (17,18). Prior to the study, we informed the CRCs of the study plan, procedures for the telephone survey, ethics issues relevant to the study, and requisite considerations for ALS patients and caregivers, and we provided them with general knowledge of ALS.

The introduction of tracheostomy positive-pressure ventilation (TPPV) or the death of a patient was defined as the endpoint, and TPPV-free survival was defined as survival. We also performed an analysis in which actual death, including death after TPPV introduction, was solely defined as the endpoint, and the results are shown in Supplementary Table I – which is only available in the online version of the journal. Please find this material with the following direct link to the article: http://informahealthcare.com/doi/abs/10.3109/21678421.2014.990036.

Patients

A total of 549 sporadic ALS patients with definite, probable, probable laboratory-supported or possible ALS, according to the revised El Escorial criteria, were registered from January 2006 to December 2012. After we screened known gene mutations, nine patients were excluded due to the presence of the following gene mutations: superoxide dismutase-1 (SOD1) mutation ($n = 7$); transactive response

DNA-binding protein 43 kDa (TDP-43) mutation ($n = 1$); and TRK-fused gene (TFG) mutation ($n = 1$). Subsequently we excluded 34 patients in whom the disease duration had been over five years at registration and 55 patients whose clinical data required for analyses were invalid. Finally, we included 451 sporadic ALS patients for this study. Loss during follow-up was addressed if the case was not followed up after January 2012 without attainment of an endpoint.

Clinical data of the registered patients were anonymized in each participating facility within the JaCALS and assigned unique patient numbers. The data were sent to the clinical data centre located at Nagoya University Graduate School of Medicine and entered into the JaCALS database.

Statistical analysis

We used the joint model of the linear mixed-effect model for longitudinal ALSFRS-R data and the relative risk model with a piecewise-constant baseline risk function for TPPV-free survival time (19,20). For the linear mixed-effect model, we calculated the estimated values and the 95% confidence intervals (CIs) regarding the effect of each variable to lower the ALSFRS-R score with adjustments for survival data. In the relative risk model, we calculated the hazard ratio (HR) and 95% CI with an adjustment for decreases in the ALSFRS-R score. We entered candidate factors that had been reported to be related to survival in ALS patients into these models, and we included distributions of muscle weakness in the extremities, which were characteristics that each patient tended to maintain over time.

The following 10 variables were included as candidate prognostic factors: age at onset (≥ 65 vs. < 65 years); gender (male vs. female); upper-limb weakness (yes vs. no), lower-limb weakness (yes vs. no), bulbar symptoms (yes vs. no), and neck weakness (yes vs. no) as initial symptoms; laterality (a 1-point difference in the MRC score in the left side relative to the right side); dominance of a proximal or distal muscle weakness in the upper extremities (a 1-point difference in the MRC score in the proximal muscles relative to the distal muscles) and lower extremities (a 1-point difference in the MRC score in the proximal muscles relative to the distal muscles) as the distribution of muscle weakness of the extremities at registration; and use of riluzole (yes vs. no). We evaluated the presence/absence of each initial symptom; therefore, overlap of the locations of initial symptoms existed. Because we evaluated the impact of these variables on changes in the ALSFRS-R scores and TPPV-free survival times during the five years after onset, the patients who survived more than five years without TPPV were censored five years from onset.

TPPV-free survival time was also graphically displayed using the Kaplan-Meier method. A two-sided $p < 0.05$ was considered statistically significant. The analyses were performed using the R package '**JM**' and SAS software (version 9.3; SAS Institute Inc., Cary, NC, USA).

Table I. Clinical characteristics of the included patients ($n = 451$).

Characteristic	
Age at onset (years) (mean ± SD)	61.2 ± 11.5
Males/females (n)	1.87
Initial symptoms (n (%))	
Upper limb weakness	207 (45.9)
Lower limb weakness	136 (30.2)
Bulbar symptoms	114 (25.3)
Neck weakness	12 (2.7)
Use of riluzole (n(%))	265 (58.8)

Results

Characteristics of the included patients

The demographic and clinical characteristics of the included patients are presented in Table I. Supplementary Figure 1 (which is only available in the online version of the journal. Please find this material with the following direct link to the article: http://informahealthcare.com/doi/abs/10.3109/21678421.2014.990036) illustrates the distribution of muscle weakness in the upper and lower extremities at registration, concerning laterality and proximal or distal dominance. The laterality of muscle weakness in the patients was balanced, whereas the distribution of weakness was somewhat proximal-dominant in the upper limbs and balanced in the lower limbs (Supplementary Figure 1 which is only available in the online version of the journal. Please find this material with the following direct link to the article: http://informahealthcare.com/doi/abs/10.3109/21678421.2014.990036). Disease duration at registration ranged from 1.1 to 60.0 months. Average duration of follow-up was 1.7 years (SD, 1.7), and 37 patients

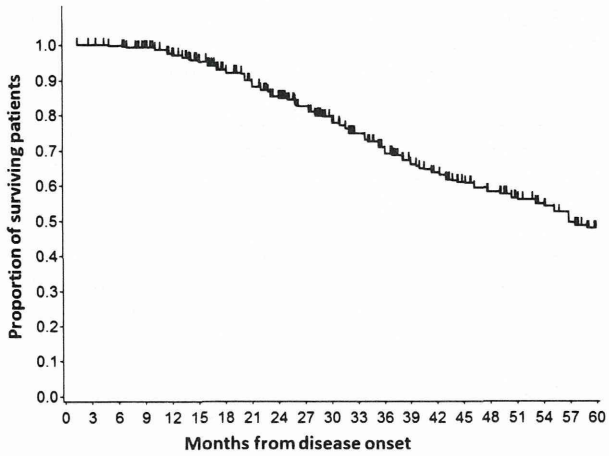

Figure 1. The Kaplan-Meier curve for survival times of the included ALS patients from symptom onset to death or TPPV introduction.

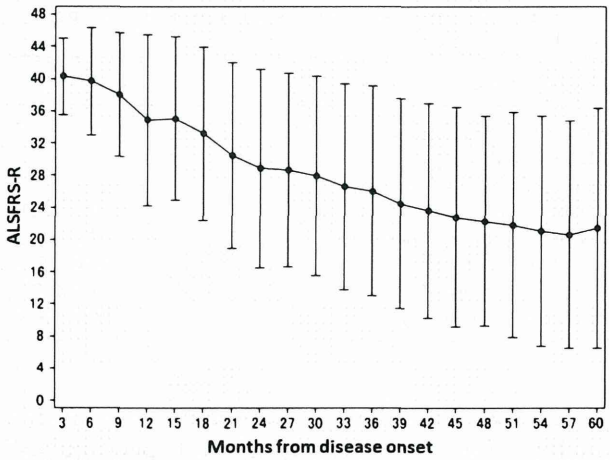

Figure 2. The mean values of the longitudinal ALSFRS-R scores from three to 60 months from disease onset in the included patients with ALS. Error bars indicate standard deviations.

(8.2%) were lost to follow-up. Figure 1 shows the Kaplan-Meier curve for survival time from the onset of symptoms to death or TPPV introduction. The median TPPV-free survival time was 48.0 months (range 3.1–60 months). Figure 2 displays the mean values and standard deviations of the ALSFRS-R scores from three to 60 months after disease onset, which were extremely diverse in the included patients with ALS.

Clinical factors affecting functional decline and survival time

Using the joint model, which evaluated the longitudinal changes in ALSFRS-R scores and survival times in combination, we examined the clinical factors that led to a decline in ALSFRS-R functional scores and survival times (Table II). The negative estimated value in the linear mixed model indicates the effect of each variable to produce a lower ALSFRS-R score or the amount of decrease in the ALSFRS-R score for a one-unit increase in each variable at each time-point. As shown in Table II, older age at onset, female gender and initial symptoms

Table II. Estimated impact on decline of the ALSFRS-R score and TPPV-free survival based on joint modelling.

A. Estimated impact on decline of the ALSFRS-R score with time.

Variable	Estimate	95% CI		*p*-value
Age at onset (≧65.0years vs. <65.0)	−2.95	−4.60	−1.30	<0.0001
Gender (male vs. female)	1.83	0.31	3.36	0.019
Initial symptoms				
Upper limb weakness (presence vs. absence)	−4.04	−7.11	−0.97	0.010
Lower limb weakness (presence vs. absence)	−4.00	−6.97	−1.03	0.008
Bulbar symptoms (presence vs. absence)	−4.43	−7.53	−1.33	0.005
Neck weakness (presence vs. absence)	−1.99	−7.82	3.85	0.504
Distribution of muscle weakness of extremities at registration				
Laterality (1-point difference in the MRC score in the left relative to right side)	0.20	−0.13	0.52	0.236
Dominance of proximal muscle weakness in the upper extremities (MRC score 1 point less in proximal versus distal muscles)	−0.11	−0.56	0.34	0.635
Dominance of proximal muscle weakness in the lower extremities (MRC score 1 point less in proximal versus distal muscles)	0.37	−0.12	0.85	0.139
Riluzole (non-use vs. use)	−1.05	−2.58	0.49	0.181

B. Estimated impact on survival.

Variable	Hazard ratio	95% CI		*p*-value
Age at onset (≧65.0years vs. <65.0)	2.04	1.50	2.76	<0.0001
Gender (male vs. female)	0.92	0.68	1.24	0.574
Initial symptoms				
Upper limb weakness (presence vs. absence)	1.22	0.71	2.08	0.471
Lower limb weakness (presence vs. absence)	0.94	0.56	1.6	0.829
Bulbar symptoms (presence vs. absence)	1.13	0.64	1.98	0.683
Neck weakness (presence vs. absence)	2.35	1.16	4.78	0.018
Distribution of muscle weakness of extremities at registration				
Laterality (1-point difference in the MRC score in the left relative to right side)	1.01	0.95	1.08	0.771
Dominance of proximal muscle weakness in the upper extremities (MRC score 1 point less in proximal versus distal muscles)	1.12	1.03	1.21	0.010
Dominance of proximal muscle weakness in the lower extremities (MRC score 1 point less in proximal versus distal muscles)	1.06	0.96	1.17	0.244
Riluzole (non-use vs. use)	1.41	1.03	1.92	0.030
ALSFRS-R (1 point less)	1.12	1.11	1.14	<0.0001

ALSFRS-R: revised Amyotrophic Lateral Sclerosis Functional Rating Scale.

TPPV: tracheostomy positive-pressure ventilation.
MRC: Medical Research Council.
CI: confidence interval.

of upper limb weakness, lower limb weakness or bulbar symptoms significantly enhanced the decline of the ALSFRS-R score in the linear mixed model ($p < 0.0001$–0.010 with an estimate of –4.43 to –2.95). By contrast, an older age at onset, neck weakness as an initial symptom, proximal dominant muscle weakness in the upper extremities, and non-use of riluzole significantly decreased survival time according to the relative risk model ($p < 0.0001$–0.030 and an HR of 1.41–2.35). Only older age at onset significantly affected both decline in the ALSFRS-R score and survival time. Regarding the initial symptoms, upper limb weakness, lower limb weakness and bulbar symptoms had almost similar impacts on the decline of the ALSFRS-R score with time and had no significant impact on survival. Neck weakness had a significant impact on survival. A 1-point decline in the ALSFRS-R score shortened the TPPV-free survival time significantly ($p < 0.001$ and an HR of 1.12).

Discussion

This is the first report to elucidate the clinical factors affecting the decline in a longitudinal functional parameter and survival in ALS patients using a joint modelling approach. Our results revealed that, except for age at onset, the factors affecting functional decline and survival differed. An older age at onset affected both functional decline and survival.

The symptoms of ALS patients are continuously progressive; however, the rate of progression and the course of the disease among different patients are diverse, as illustrated in Figure 2. Therefore, understanding the factors that relate to the disease course of ALS patients is highly important for clinical practice, nursing care and planning clinical trials. Methods for survival analysis have been established, and a number of cohort studies have elucidated the clinical factors related to survival in ALS patients, such as age at onset and site of onset (21–23). By contrast, few reports have described the factors affecting functional decline of ALS patients. For clinical trials of ALS, stratification factors that allocate the included patients into drug or placebo groups have been selected mainly based on factors found in the survival analyses, such as age, site of onset and respiratory function (3,6). However, a decline in a functional scale, such as the ALSFRS-R, has been employed as the primary or secondary outcome measure in most clinical trials for ALS.

In recent years, statistical methods that can evaluate sequential measurement data and time-to-event data in combination have been developed (8,24). For example, in the recently reported dexpramipexole study, the Combined Assessment of Function and Survival (CAFS) was used as a combined endpoint that ranks patients' clinical outcomes based on survival times and changes in the ALSFRS-R score (10,25). Healey et al. demonstrated that the rank based approach could offer an improvement in power compared with traditional analytical approaches in clinical trials for ALS (26). The joint modelling of longitudinal parameters and survival data was developed in clinical trials for cancer and HIV infection, and this approach has been applied to clinical trials for Parkinson's disease and ALS (6,27). Accordingly, cohort studies that can analyse longitudinal functional measurements and survival data in combination are required. We employed the joint modelling approach for the combined assessment of functional decline and survival.

According to our joint modelling analysis, factors affecting functional decline and survival differed, except for age at onset, suggesting that the previously reported prognostic factors for survival cannot simply be applied for predicting changes in the ALSFRS-R score. Why do the factors that affect functional decline as assessed by the ALSFRS-R score and those that affect survival assessed by death or the introduction of TPPV differ? The ALSFRS-R consists of 12 items, each of which represents bulbar, upper limb, lower limb, body trunk or respiratory functions. A progressive decline in the ALSFRS-R score represents both local progression in a bodily region and the spread of ALS symptoms to other regions of the body in ALS patients. The progression of limb muscle weakness, for example, may produce a decline in the ALSFRS-R score. However, the most common cause of death in ALS patients is respiratory insufficiency resulting from the wasting of respiratory muscles (5,28), and a number of previous studies have shown that respiratory function, measured by the percent-predicted forced vital capacity (%FVC), is a potent prognostic factor that affects survival time in ALS (21,22). Louwerse et al. showed that patients with an initial weakness of respiratory muscles without limb or bulbar symptoms had the worst prognosis, with a median survival of only a few months (29). In our present results, neck weakness as an initial symptom and a proximal dominance of muscle weakness in the upper extremities were associated with a shorter survival time, but these symptoms were not associated with a decline in the ALSFRS-R score. The motor neurons controlling the diaphragm are located between the third and fifth cervical segments (C3–C5). The neck flexor muscles are innervated mainly by C2–C4, the deltoid muscles are innervated by C5–C6, and the muscles in the forearms are innervated by C6–C8. Neck muscle weakness or the proximal dominance of muscle weakness in the upper extremities indicates the involvement of lesions that are close to or overlap the cervical segments that innervate the respiratory muscles. Our results suggest that the distance between the segments innervating the severest lesions and the cervical segments innervating the respiratory muscles could be an influencing factor for survival. These observations suggest that survival times in ALS patients are strongly affected by the