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# ALS-Plus syndrome: Non-pyramidal features in a large ALS cohort ☆

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ABSTRACT

*Objective:* Autopsy studies show widespread pathology in amyotrophic lateral sclerosis (ALS), but clinical surveys of multisystem disease in ALS are rare. We investigated ALS-Plus syndrome, an understudied group of patients with clinical features extending beyond pyramidal and neuromuscular systems with or without cognitive/behavioral deficits.

*Methods:* In a large, consecutively-ascertained cohort of 550 patients with ALS, we documented atypical clinical manifestations. Genetic screening for *C9orf72* hexanucleotide expansions was performed in 343 patients, and *SOD1*, *TARDBP*, and *VCP* were tested in the subgroup of patients with a family history of ALS. Gray matter and white matter imaging was available in a subgroup of 30 patients.

*Results:* Seventy-five (13.6%) patients were identified with ALS-Plus syndrome. We found disorders of ocular motility, cerebellar, extrapyramidal and autonomic functioning. Relative to those without ALS-Plus, cognitive impairment (8.0% vs 2.9%, $p = 0.029$), bulbar-onset (49.3% vs 23.2%, $p < 0.001$), and pathogenic mutations (20.0% vs 8.4%, $p = 0.015$) were more than twice as common in ALS-Plus. Survival was significantly shorter in ALS-Plus (29.66 months vs 42.50 months, $p = 0.02$), regardless of bulbar-onset or mutation status. Imaging revealed significantly greater cerebellar and cerebral disease in ALS-Plus compared to those without ALS-Plus.

*Conclusions:* ALS-Plus syndrome is not uncommon, and the presence of these atypical features is consistent with neuropathological observations that ALS is a multisystem disorder. ALS-Plus syndrome is associated with increased risk for poor survival and the presence of a pathogenic mutation.



## 1. Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder with survival of 3–5 years [1]. Phenotypic classification has been based on clinical observations such as site of onset and pattern of weakness involving upper and lower motor neurons [2]. However, recent observations have emphasized considerable heterogeneity in clinical presentation. Single cases and small series of patients with atypical features have been reported [3], including ocular motility abnormalities [4–6], cerebellar [7,8] and extrapyramidal signs [9–15], and autonomic dysfunction [16,17]. While this has been long recognized [18], consensus criteria for the diagnosis of ALS more recently encompass these atypical clinical manifestations in a phenotype known as ALS-Plus syndrome [2]. This clinical heterogeneity is consistent with the widespread pathology found in ALS at autopsy, extending beyond the pyramidal and neuromuscular motor systems into other brain areas [19,20], and supports the characterization of ALS as a multisystem disorder [21]. However, the frequency of these findings and their clinical consequences are not well documented.

Here we assess the frequency of ALS-Plus syndrome features in a large, consecutively-ascertained series of 550 ALS patients. We demonstrate that ALS-Plus syndrome may not be as uncommon as previously thought, and appears to be associated with poorer survival and increased risk for an inherited disorder. These observations are consistent with the hypothesis that ALS is a multisystem disorder, and provide clinical validation of pathologic observations suggesting widespread disease in ALS.

## 2. Methods

### 2.1. Participants

We identified a consecutively-ascertained series of 550 patients clinically diagnosed with ALS using a query report from an integrated clinical database at the University of Pennsylvania. All patients were

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assessed by a neurologist with expertise in neuromuscular diseases (LM, LE). Patients were diagnosed according to El Escorial-revised criteria and assigned to a diagnostic category when first seen [2]. Patients with isolated upper or lower motor neuron disease were included in the cohort. All of these patients were followed longitudinally, and all but 16.3% converted to possible, probable or definite ALS, or are deceased. Please see supplemental table for the longitudinal outcomes of patients in this category. Consensus ascertainment for ALS-Plus features between the examiners was accomplished by co-examination of patients with an ALS-Plus feature until 100% agreement was consistently achieved. There was on-going cross-confirmation for any questionable findings. Observations were collected and recorded at intervals of 2–6 months during routine clinic visits between June, 1999 and August, 2013. Age at symptom onset was defined as the age at which the earliest ALS symptom manifested, and we tabulated disease duration at time of death. Survival for living patients was based on clinical data until censored on August 28th, 2013. ALS Functional Rating Scale-Revised (ALSFRS-R) was used to quantify functional impairment at presentation [22], with scores ranging 0–48 (normal). Examiners were blinded to genetic status. Demographic and clinical characteristics of the entire cohort are summarized in Table 1. All patients participated in an informed consent procedure approved by the University of Pennsylvania's Institutional Review Board.

ALS patients identified in this query were further characterized based on clinical phenotype as ALS-Plus syndrome or without ALS-Plus features. The criteria for ALS-Plus syndrome included a clinical diagnosis of ALS in combination with features extending beyond motor and neuromuscular systems during neurological examination. ALS-Plus features were clustered into deficits of one of four systems: ocular motility abnormalities (gaze abnormalities, horizontal, up-gaze, down-gaze, impersistence, and/or head movements), cerebellar features (ataxia and/or limb dysmetria), extrapyramidal features (resting tremor, masked face, startled appearance, bradykinesia, rigidity, dystonia, retropulsion, apraxia of eye closure and/or gait apraxia), and autonomic dysfunction (excessive sweating, special sensory, and/or loss of taste and smell). We noted the first visit at which a non-pyramidal feature was present [three ALS-Plus patients had only one clinical appointment]. Since we sought to identify features ascertainable by clinical neurological exam, we did not consider cardiovascular and bladder/bowel control abnormalities. Although we recognize cognitive impairment as an ALS-Plus feature, we analyzed cognitive impairment separately here because we sought to determine whether cognitive impairment was found more often in patients with other ALS-Plus features or those without ALS-Plus features. A nonspecific measure of cognitive impairment was assessed as part of routine clinical care using the Mini Mental State Examination (MMSE) [23]. The diagnosis of frontotemporal degeneration (FTD) co-occurring with ALS was determined on the basis of published criteria for behavioral variant FTD [24]. Diagnostic criteria for pseudobulbar affect (PBA) were based on a CNS-LS score $\geq 13$. Twelve patients (2.5%) without ALS-Plus features presented with respiratory-onset and were excluded to minimize survival bias associated with a very rare clinical presentation [25], and respiratory-onset was not observed among ALS-Plus patients. Patients missing four or more clinical data points (e.g. age, complete neurologic exam at presentation) were excluded.

### 2.2. Genetic analysis

DNA was available from 343 (62.4%) patients, extracted from blood, saliva, or brain tissue using commercial reagents; of these, 298 (86.9%) were in the ALS group and 45 (13.1%) were categorized as ALS-Plus. The proportions of cases with DNA thus were not significantly different in ALS-Plus compared to those without ALS-Plus in the source cohorts ($p = 0.8$). All 343 were tested for a hexanucleotide expansion in *C9orf72* (defined as greater than 30 repeats), as described [26]. In addition, we ascertained family risk using a screening instrument [27] validated in frontotemporal degeneration (FTD) with or without ALS that has been demonstrated in unpublished data to be equally effective for those with ALS alone. Subsets from both ALS-Plus and non-ALS-Plus groups with a high- or medium-risk family history of ALS and/or FTD were tested for mutations in other ALS genes, including *SOD1*, *TARDBP*, and *VCP*, as previously described [28–30].

### 2.3. Statistical analysis

Data analysis was performed using SPSS v22 (IBM, NY). Clinical and demographic variables were assessed using descriptive statistics, including mean, standard deviation and percentages. T-tests were used to assess interval variables, and categorical variables were analyzed using a chi-square test.

**Table 1**
Mean ± standard deviation, range of demographic and clinical characteristics of ALS-Plus syndrome and ALS patients without ALS-Plus features.[a]

| | ALS (entire cohort) | ALS-Plus | Without ALS-Plus |
|---|---|---|---|
| Cohort size (%) | 550 (100%) | 75 (13.6%) | 475 (86.4%) |
| Gender, F/M | 256/302 | 41/34 | 209/266 |
| Education, y | 13.87 ± 3.0, 0–22 (n = 478) | 13.57 ± 3.5, 0–22 (n = 64) | 13.92 ± 2.9, 4–22 (n = 414) |
| Age at ALS symptom onset, y | 61.14 ± 12.5, 20–94 (n = 547) | 62.85 ± 12.5, 26–83 (n = 74) | 60.87 ± 12.4, 20–94 (n = 473) |
| Disease duration at plus symptom onset, m | na | 32.34 ± 31.7, 1–175 (n = 74) | na |
| Disease duration at death, m[b] | 40.77 ± 36.8, 3–280 (n = 348) | 29.66 ± 20.5, 3–109 (n = 47) | 42.50 ± 38.4, 5–280 (n = 301) |
| Age at death, y | 66.18 ± 11.6, 26–96 (n = 350) | 68.79 ± 11.1, 45–86 (n = 47) | 65.78 ± 11.6, 26–96 (n = 303) |
| Clinical presentation | N = 538 | n = 70 | n = 460 |
| El Escorial-revised possible | 150 (27.9%) | 21 (30.0%) | 129 (28.0%) |
| El Escorial-revised probable | 146 (27.1%) | 20 (28.6%) | 126 (27.4%) |
| El Escorial-revised definite | 94 (17.5%) | 19 (27.1%) | 75 (16.3%) |
| Isolated upper or lower motor neuron disease[c] | 140 (26.0%) | 10 (14.3%) | 130 (28.3%) |
| Bulbar onset[b] | 147 (30.9%) | 37 (49.3%) | 110 (23.2%) |
| Limb onset | 393 (71.5%) | 36 (48.0%) | 357 (75.2%) |
| Cognitive onset | 6 (1.1%) | 2 (2.6%) | 4 (0.8%) |
| Cognitive diagnosis[b] | 20 (3.6%) | 6 (8.0%) | 14 (2.9%) |
| Pseudobulbar affect[b] | 155 (28.2%) | 37 (49.3%) | 118 (24.8%) |
| ALSFR-R score (range 0–48)[b] | 33.46 ± 8.8,4–48 (n = 521) | 25.45 ± 9.4,4–45 (n = 71) | 34.72 ± 8.0,6–48 (n = 450) |

[a] When data were not available in all patients, the n of the available cohort is provided.
[b] Differs significantly between ALS-Plus and those without ALS-Plus.
[c] These patients are not included in the Revised El Escorial Criteria, although all but 16.3% met El Escorial-revised criteria at follow-up or were deceased (see Supplement 1).

### 2.4. Imaging acquisition and analysis

Thirty patients had high resolution, 3 Tesla T1-weighted MRI assessing gray matter (GM) atrophy and 30-direction diffusion-weighted imaging assessing fractional anisotropy (FA) in white matter (WM), as described [31], including patients with ALS-Plus syndrome (n = 7) and without ALS-Plus syndrome (n = 23). Patients were not imaged because of difficulty breathing in the supine position, transportation difficulties, intercurrent medical complications that interfered with scheduling, and a decision to decline participation in the imaging component of the study. The two imaged patient groups were comparable for age, disease duration, gender, and education (all p-values >0.10). We also found no statistical differences in age, disease duration, gender, and education between the subset of patients with MRI imaging and the larger study cohort (all p-values >0.10). Imaging was also collected in a control group of 27 healthy seniors, comparable to the patient groups for age, gender, and education (all p-values >0.10). Imaging contrasts of each group relative to controls are provided in Appendix e-1.

GM atrophy in ALS-Plus directly contrasted to those without ALS-Plus was determined in SPM8 using a whole-brain voxel-wise analysis with height threshold $p < 0.01$ (uncorrected), minimum cluster size of 40 adjacent voxels, and peak voxel threshold $p < 0.001$. We compared FA between the two patient groups using an extent threshold of 200 voxels, height threshold $p < 0.001$ (uncorrected), and peak voxel threshold $p < 0.001$.

## 3. Results

### 3.1. Clinical characteristics of ALS-Plus

Seventy-five patients were identified with ALS-Plus syndrome, representing 13.6% of 550 cases (Table 1). The most common ALS-Plus feature was an ocular motility abnormality, found in 63 (84%) of ALS-Plus patients. This was present more commonly than an extrapyramidal abnormality (n = 17, 22.7%), autonomic dysfunction (n = 4, 5.3%) and cerebellar disorder (n = 1, 1.3%) [$p < 0.01$ for each contrast]. The median number of plus features per patient was four (range 1–11). PBA [$\chi^2 = 19.20$; $p < 0.001$] and cognitive impairment associated with ALS-FTD [$\chi^2 = 4.72$; $p = 0.029$] occurred more than twice as frequently in ALS-Plus compared to those without ALS-Plus. ALS-Plus patients had worse ALSFRS-R scores at presentation than those without ALS-Plus [$t(519) = 6.82$; $p < 0.001$].

Table 1 shows shorter disease duration in ALS-Plus compared to those without ALS-Plus. The mean time between disease onset and appearance of the first ALS-Plus feature in the entire cohort was 32.3 months. The appearance of the first ALS-Plus feature in the subgroup of ALS-Plus patients for whom disease-duration-to-death was available (n = 47, 62.7% of the cohort) averaged 21.57 (±16.40, range 1–93) months. Mean disease-duration-to-death was significantly shorter in these 47 ALS-Plus patients compared to patients without ALS-Plus (n = 301, 63.4%) for whom disease-duration-to-death was available [$t(346) = 2.24$; $p = 0.02$].

**Table 2**
Mean ± standard deviation, range of survival in ALS-Plus and patients without ALS-Plus.

| | ALS-Plus | Without ALS-Plus |
|---|---|---|
| Bulbar onset, m | 29.00 ± 16.0, 9–84 (n = 27) | 28.38 ± 13.6, 10–95 (n = 74) |
| Non-bulbar onset, m[a] | 30.55 ± 25.8, 3–109 (n = 20) | 47.11 ± 42.6, 5–280 (n = 227) |
| Mutation positive, m | 22.10 ± 9.2, 3–34 (n = 10) | 35.11 ± 25.9, 11–135 (n = 27) |
| No mutation detected, m | 31.70 ± 22.3, 6–109 (n = 37) | 43.23 ± 39.4, 5–280 (n = 274) |

[a] Differs significantly between ALS-Plus and those without ALS-Plus (see text).

Table 1 shows that bulbar-onset presentation was evident in almost half of ALS-Plus patients, more than twice as common as those without ALS-Plus [$\chi^2 = 22.19$; $p < 0.001$]. Among those without ALS-Plus, survival was poorer in patients with bulbar-onset compared to those with non-bulbar onset [Table 2: $t(299) = 3.72$; $p < 0.001$], resembling other cohorts of typical ALS patients. However, survival was equally poor in ALS-Plus patients regardless of bulbar-onset status [$t(45) = 0.80$; ns].

### 3.2. Genetic characteristics of ALS-Plus

Of 343 ALS patients tested for a *C9orf72* expansion, 30 (8.7%) had a significant expansion (Table 3). Seven (15.6%) expansion-positive cases were present in 45 tested ALS-Plus patients compared to 23 (7.7%) of 298 without ALS-Plus. In addition, detailed family history was available in 246 of these cases. High- or medium-risk family history of ALS and/or FTD was present in 27 (11.0%) of these 246 cases, including 4 (12.1%) of 33 ALS-Plus patients and 23 (10.8%) of 213 without ALS-Plus. All but one of the 27 with family history were screened for mutations in *SOD1*, *TARDBP*, and *VCP* (Table 3). Among those with ALS-Plus, pathogenic mutations were identified in *SOD1* (n = 1) and *TARDBP* (n = 1); among those without ALS-Plus, a mutation was identified in *VCP* (n = 1) and *TARDBP* (n = 1). Mutation rate thus was more than twice as common in ALS-Plus (n = 9, 20.0%) compared to those without ALS-Plus (n = 25, 8.4%; $\chi^2 = 5.95$, $p = 0.015$).

The presence of a mutation shortened survival in both ALS-Plus (mutation: 22.10 months; no-mutation: 31.70 months) and those without ALS-Plus (mutation: 35.11 months; no-mutation: 43.23 months) (Table 2), but there was no survival disadvantage within or between ALS subgroups as a function only of genetic status [all p-values >0.10]. We also considered an additive model combining genetic status with bulbar-onset disease, but survival did not differ among ALS-Plus patients with mutations depending on the presence of bulbar-onset disease [$t(45) = 0.80$; ns].

### 3.3. Imaging characteristics of ALS-Plus syndrome

Fig. 1 panels A and B illustrate areas of significant GM atrophy in ALS-Plus compared directly to patients without ALS-Plus. As summarized in Table 4, areas of GM atrophy in ALS-Plus included regions associated with the atypical clinical features observed in these patients, including cerebellum, frontal cortex, and occipital cortex. Fig. 1 panels C and D illustrate areas of significantly reduced FA in ALS-Plus relative to patients without ALS-Plus. As summarized in Table 4, this included WM in cerebellum and bilateral centrum semiovale including frontal and parietal regions.

## 4. Discussion

In a large cohort of ALS patients, we found a substantial number of individuals who have ALS-Plus syndrome. This is consistent with pathologic observations suggesting that ALS is a multisystem disorder. The presence of non-pyramidal features appears to be a marker of several important clinical characteristics, including poorer prognosis and increased probability of a pathogenic mutation.

Informal estimates suggest that ALS-Plus syndrome is rare [2], but ascertainment in this large cohort revealed that 13.6% of ALS patients have one or more clinical neurological features consistent with ALS-Plus syndrome. While there may be a referral bias for unusual clinical features since this survey was conducted at an academic medical center, the atypical features usually emerged later in the course of disease and after initial presentation to the clinic. Regardless of the time course that clinical features emerged, our observations emphasize the diverse clinical presentations associated with ALS. This underlines the perspective that ALS is a multisystem disorder, consistent with pathological findings [19,20], and emphasizes the importance of ascertaining aspects of

**Table 3**
Genetic characteristics of ALS-Plus syndrome and patients without ALS-Plus.

| | ALS (entire cohort) | ALS-Plus | Without ALS-Plus |
|---|---|---|---|
| Positive family history of ALS or FTD/total with family history information | 27/246 (11.0%) | 4/33 (12.1%) | 23/213 (10.8%) |
| Mutation-positive cases/total screened[a] | 34/343 (9.9%) | 9/45 (20.0%) | 25/298 (8.4%) |
| Mutation-positive cases/cases with family history | 9/27 (33.3%) | 2/4 (50.0%) | 6/23 (30.4%) |
| Mutations by gene/number tested: | | | |
| *C9orf72* | 30/343 (8.7%) | 7/45 (15.6%) | 23/298 (7.7%) |
| C9orf72 in FHx ALS/FTD | 8/27 (29.6%) | 2/4 (50.0%) | 6/23 (26.1%) |
| C9orf72 in apparent sporadic | 5/127 (3.9%) | 1/16 (6.3%) | 4/111 (3.6%) |
| *SOD1* | 1/37 (2.7%) | 1/4 (25%) | 0/33 (0%) |
| *TARDBP* | 2/161 (1.2%) | 1/21 (4.8%) | 1/140 (0.7%) |
| *VCP* | 1/20 (5%) | 0/1 (0%) | 1/19 (5.3%) |

[a] Differs significantly between ALS-Plus and those without ALS-Plus (see text).

neurological functioning in ALS beyond the pyramidal and neuromuscular motor systems [32].

We found that prognosis is significantly poorer in ALS-Plus patients. We also observed that bulbar-onset disease occurs twice as commonly in ALS-Plus compared to patients without ALS-Plus. Bulbar-onset disease is associated with poorer prognosis [33]. We were able to ascertain survival in equal proportions of patients from source cohorts of ALS-Plus and non-ALS-Plus, minimizing the risk of biased sampling across these cohorts. While we confirmed the frequent finding of poorer survival among bulbar-onset patients compared to those without bulbar-onset in the subgroup of patients without ALS-Plus features, a comparison of those with and without bulbar-onset disease in the ALS-Plus cohort revealed equally poor survival. This is consistent with the observation that ALS-Plus itself may contribute to poorer prognosis regardless of bulbar-onset. For most of the patients about whose deaths we know the cause, this was due to an ALS-related disorder, but we cannot rule out that some patients with ALS-Plus died from unrelated conditions such as cardiac disease or stroke.

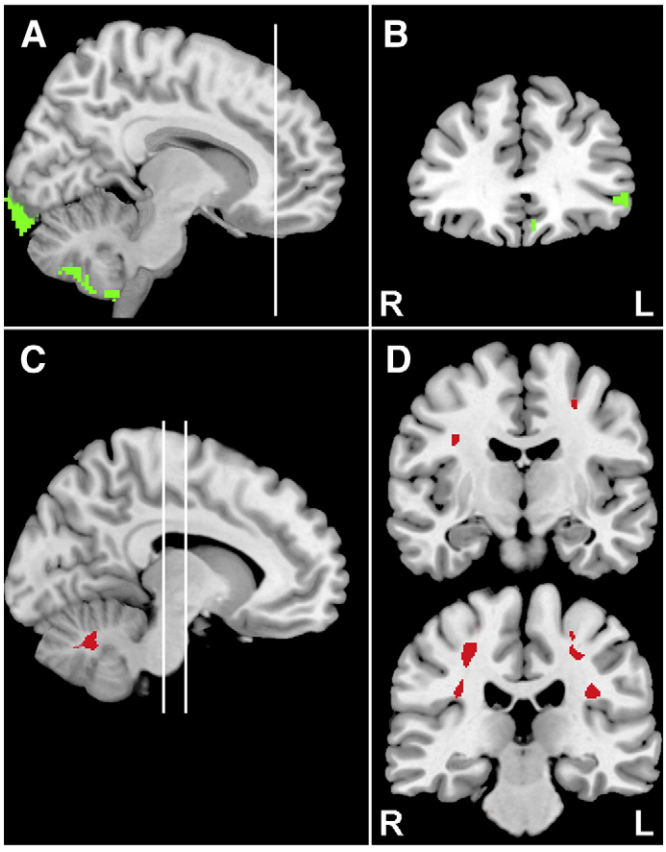


**Fig. 1.** Gray matter atrophy and reduced white matter fractional anisotropy in ALS-Plus compared to those without ALS-Plus. Note 1. Panel A: Gray matter atrophy (green) at x = 1; panel B: Gray matter atrophy y = 34; panel C: Reduced fractional anisotropy (red) at x = −10; panel D: Reduced fractional anisotropy at y = −10 (top), y = −24 (bottom). Vertical white lines indicate location of coronal slices.

Another factor potentially contributing to poor survival in ALS-Plus is the increased frequency of pathogenic mutations found in this cohort. Patients with genetic ALS such as those with a *C9orf72* expansion appear to have shorter disease duration than patients without a *C9orf72* expansion [34–36]. However, we did not find that the presence of a mutation can alone explain poor survival in the ALS-Plus cohort, since a similar disadvantage was associated with mutations in those without ALS-Plus. We also considered an additive model that attributes poor survival to both genetic ALS and bulbar-onset in ALS-Plus. However, we did not find that the combination of genetic ALS and bulbar-onset fully explains poorer survival among ALS-Plus patients. Some have reported increased frequency of bulbar-onset disease in ALS patients with a *C9orf72* expansion [37,38], although others do not confirm this [35,36,39]. This discrepancy may be related in part to differences in the frequency of ALS-Plus in these series, and additional work is needed to resolve this discrepancy. Regardless of the basis for poorer survival in ALS-Plus, ALSFRS-R scores demonstrated more severe disease in the ALS-Plus cohort at initial presentation. The presence of ALS-Plus thus appears to be associated with more severe disease as well. Relative to TDP-43, the most common histopathologic abnormality found in ALS [40], ubiquilin burden appears to be more severe, to correlate with cognitive decline, and to correlate with neuronal dropout in cases with *C9orf72* [26,34], and additional work is needed to determine whether increased ubiquilin burden or some other factors contribute to disease severity in ALS-Plus.

While a pathogenic mutation did not lead to poorer survival selectively in ALS-Plus, the observation of significantly elevated mutation frequency among ALS-Plus patients has important clinical implications. Sporadic ALS and familial ALS have been considered clinically indistinguishable. Our observations suggest that the presence of ALS-Plus should heighten suspicion that a patient may have an identifiable pathogenic mutation. This is particularly important given the observation of *C90rf72* expansion in apparently sporadic cases, and since the frequency of a positive family history is not significantly increased in ALS-Plus, the increased frequency of a pathogenic mutation in ALS-Plus may be due in part to *C9orf72* carriers without a significant family history.

Detailed pathological assessments have demonstrated TDP-43 pathology in brain regions associated with the clinical features of ALS-Plus [20]. Recent work examining staging of ALS pathology suggests that many of the brain regions implicated in ALS-Plus tend to exhibit TDP-43 pathology later in the course of disease [19]. We observed an average onset of ALS-Plus features about two years after onset and only about 6 months prior to death. Our clinical observations thus are consistent with pathology-based observations of disease staging, and may implicate trans-neuronal propagation of abnormal proteins during disease progression [41].

**Table 4**
Gray matter atrophy and reduced white matter fractional anisotropy in ALS-Plus compared to those without ALS-Plus.

| Anatomic locus (Brodmann area) | MNI coordinates | | | Z-score of peak voxel | Cluster size (voxels) |
|---|---|---|---|---|---|
| | X | Y | Z | | |
| *Plus < ALS (GM)* | | | | | |
| L fusiform gyrus [18] | −24 | −94 | −22 | 3.96 | 179 |
| R lingual gyrus [18] | 2 | −88 | −12 | 3.74 | 589 |
| L inferior frontal gyrus [47] | −52 | 36 | −2 | 3.70 | 48 |
| L medial frontal gyrus [10] | −6 | 28 | −12 | 3.08 | 49 |
| L cerebellum | −12 | −60 | −54 | 4.02 | 619 |
| R cerebellum | 26 | −84 | −48 | 3.70 | 425 |
| L cerebellum | −60 | −50 | −32 | 3.62 | 86 |
| *Plus < ALS (FA)* | | | | | |
| R precentral gyrus white matter | 29 | −25 | 49 | 3.93 | 459 |
| R precuneus white matter | 11 | −52 | 61 | 4.17 | 366 |
| L supramarginal gyrus white matter | −36 | −24 | 25 | 3.50 | 430 |
| L superior longitudinal fasciculus | −28 | −12 | 48 | 3.34 | 429 |
| R superior longitudinal fasciculus | 31 | −17 | 33 | 3.21 | 582 |
| R postcentral gyrus white matter | 14 | −36 | 61 | 3.27 | 364 |
| L postcentral gyrus white matter | −26 | −27 | 48 | 3.27 | 275 |
| R middle cerebellar peduncle | 15 | −31 | −35 | 3.32 | 334 |
| L cerebellar white matter | −6 | −61 | −27 | 3.57 | 288 |

Specific brain regions may exhibit pathological changes in mutation-positive ALS, although the majority of ALS-Plus patients did not have a genetic mutation. Nevertheless, the elevated frequency of genetic ALS may contribute to the more frequent observation of atypical features in ALS-Plus. Cerebellar features have been reported in ALS, although not commonly [7,8]. The observation of dysmetria or ataxia in ALS may be uncommon because the pyramidal motor disorder limits the possibility of observing poor motor control mediated by the cerebellum. While cerebellar pathology is not commonly observed in sporadic ALS, imaging and autopsy studies of ALS with a *C9orf72* repeat expansion have reported more prominent cerebellar disease [34,42].

Significant occipital disease may result in gaze impairments, particularly the supranuclear deficits we observed in ALS-Plus [4–6]. Ocular motor neurons are generally said to be unaffected in ALS, and disorders of ocular motility usually present in patients with prolonged survival [4], consistent with our observations of pathological staging [43]. The increased frequency of bulbar disease in ALS-Plus, combined with more severe disease at onset and more rapid disease progression, may increase the risk of an ocular motility disorder related to brain stem pathology. A disorder of ocular motility in the context of ALS also has been observed in association with a *TARDBP* mutation [44].

Extrapyramidal features have been reported in ALS [9–15], although not frequently. Clinical manifestations of extrapyramidal pathology may be reported infrequently because these are overshadowed by the pyramidal disorder that limits abnormal movements. Previous studies have reported imaging [45] and pathological [20,43] evidence of degeneration in extrapyramidal sites such as substantia nigra, caudate and striatum in ALS. Some parkinsonian manifestations in ALS-Plus may be related to *C9orf72* [46] or a *TARDBP* mutation [47]. Perhaps the best recognized ALS patients with parkinsonism have a regional geographic distribution. These include the ALS–Parkinson's-Dementia syndrome reported in Guam [48,49] and the Kii peninsula in Japan [50–52]. There is also adult polyglucosan body disease with extrapyramidal disease [53,54]. We may not have observed GM changes in the striatum because of the small group of ALS-Plus patients for whom imaging was available, and striatal atrophy was present at a less conservative statistical threshold. Additional work is needed to image a larger cohort of ALS-Plus patients.

Autonomic dysfunction has been described occasionally in ALS [16,17]. While one report described autonomic dysfunction early in the clinical course of ALS [16], the mean duration from symptom onset to autonomic dysfunction in ALS-plus in our series was 31 months, that is, late in the disease course. Since our observations of ALS-Plus were based on a clinical neurologic exam, there may be an increased frequency of autonomic dysfunction when also considering EKG and bowel/bladder abnormalities [17]. Additional observations are needed to capture the full extent of autonomic dysfunction in ALS.

ALS-FTD was more common in patients with ALS-Plus syndrome. If a cognitive deficit is considered part of the spectrum of ALS-Plus syndrome, as suggested by El Escorial-revised criteria, then the frequency of ALS-Plus would increase by 14 cases (significant cognitive deficits among those without ALS-Plus), resulting in a frequency of 89 (16.2%) ALS-Plus cases in our total cohort of 550. Cognitive difficulty in ALS has been increasingly recognized [55,56] and may be present in up to 50% of ALS patients [57]. Cognitive difficulty may be underrepresented in the present study because we focused on the clinical diagnosis of ALS-FTD, and we did not obtain neuropsychological measures that would have allowed us to evaluate the presence of more subtle deficits associated with variants of Mild Cognitive Impairment in ALS [58]. Cognitive deficits found in ALS-FTD may be related to more widespread histopathologic disease in frontal regions in ALS-Plus compared to those without ALS-Plus, as suggested by our imaging studies. Likewise, we observed significantly increased frequency of PBA in ALS-Plus. While the exact mechanism is unknown, PBA is hypothesized to result from degeneration of frontal cortex and associated white matter projections that are involved in inhibitory control of motor components of emotional expression [59].

Imaging studies appear to provide converging evidence consistent with the atypical clinical features observed in ALS-Plus syndrome. In a direct contrast of patients with ALS-Plus compared to those without ALS-Plus, we found significantly greater GM atrophy in cerebellum, frontal cortex, and occipital cortex. This corresponds to anatomic areas implicated in the coordination, oculomotor, pseudobulbar and cognitive deficits seen in ALS-Plus. We also found WM changes in the cerebellum and cerebrum related to the clinical deficits in ALS-Plus patients. While our cohort of imaged patients was small, these sensitive and specific observations directly comparing ALS-Plus patients and those without ALS-Plus warrant additional investigation in a larger cohort.

Several caveats should be kept in mind when considering our findings. Although we described a large, consecutively-ascertained series, referral bias associated with an academic medical center is unlikely to have contributed to our findings since atypical clinical features occurred well after initial referral and were present in only three individuals who had a single clinic visit, and a population-based survey is necessary to confirm our observations. Quantitative clinical assessment and autonomic measures would be useful to verify our clinical observations. Although imaging findings in ALS-Plus were consistent with our clinical observations despite the small group of imaged patients, additional

work is needed to confirm these anatomic findings in a larger cohort. Autopsy confirmation is also needed to confirm greater histopathologic burden in brain regions implicated by clinical and imaging observations, and although we observe a secondary pathologic diagnosis only rarely [60], autopsy evaluation would verify that patients do not have co-occurring pathology associated with a second neurodegenerative condition.

With these caveats in mind, we conclude that clinical features associated with ALS-Plus syndrome appear to be more common than previously thought. The detection of ALS-Plus syndrome has important clinical consequences. Among these are poorer survival and increased risk of a pathogenic mutation. Regardless of the basis for this disorder, atypical manifestations found in ALS-Plus are consistent with the hypothesis that ALS is a multisystem neurodegenerative condition.

## Conflict of interest

The authors declare no conflicts of interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jns.2014.07.022.

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