An Observational Study of Cognitive Impairment in Amyotrophic Lateral Sclerosis

Gregory A. Rippon, MD, MS; Nikolaos Scarmeas, MD; Paul H. Gordon, MD; Peregrine L. Murphy, PhD; Steven M. Albert, PhD; Hiroshi Mitsumoto, MD; Karen Marder, MD, MPH; Lewis P. Rowland, MD; Yaakov Stern, PhD

Background: Cognitive impairment is increasingly recognized in patients with amyotrophic lateral sclerosis (ALS). Clinical and pathologic features overlap in frontotemporal lobar dementia and ALS. Demographics, respiratory status, bulbar site of onset, and disease severity are potential risk factors for cognitive impairment in ALS.

Objectives: To further delineate the frequency, nature, and implications of cognitive impairment in ALS and to assess previously identified risk factors.

Design: Case-control and retrospective cohort study.

Setting: Academic referral center.

Participants: Forty consecutive patients with ALS underwent baseline neurologic and neuropsychologic examinations. Cognitive test performance was compared in patients with ALS and matched controls. An exploratory analysis of the relationship between cognitive performance and ALS survival was performed.

Main Outcome Measures: Neuropsychologic test performance, ALS severity, and survival.

Results: Twelve patients (30%) showed evidence of cognitive impairment, including 9 (23%) who met the neuropsychologic criteria for dementia. No statistically significant differences were found between demented and nondemented ALS groups regarding demographics, family history, site of onset, bulbar dysfunction, or ALS severity. Only 1 patient with dementia had bulbar-onset disease. An association was observed between increasing ALS severity and declining verbal fluency performance. Demented patients with ALS showed predominant impairment in free recall, executive function, and naming, with relative preservation of attention, psychomotor speed, and visuospatial function. No association was observed between cognition and survival, controlling for ALS severity.

Conclusions: Nearly a third of the patients with ALS showed evidence of cognitive impairment in a pattern consistent with frontotemporal lobar dementia. Cognitive performance was not related to site of onset or survival.

Arch Neurol. 2006;63:345-352

Author Affiliations:
Department of Neurology (Drs Rippon, Scarmeas, Gordon, Mitsumoto, Marder, and Rowland), Gertrude H. Sergievsky Center (Drs Rippon, Scarmeas, Murphy, Albert, Marder, and Stern), Taub Institute for Research on Alzheimer's Disease and the Aging Brain (Drs Rippon, Scarmeas, Murphy, Albert, Marder, and Stern), Eleanor and Lou Gehrig MDA/ALS Research Center (Drs Gordon, Albert, Mitsumoto, and Rowland), and Department of Psychiatry (Drs Marder and Stern), Columbia University College of Physicians and Surgeons, New York, NY.

ALTHOUGH AMYOTROPHIC lateral sclerosis (ALS) is a relentlessly progressive disorder of the upper and lower motor neurons,[1] increasing recognition of cognitive impairment suggests that ALS is a multisystem neurodegenerative disorder.[2] Results of neuropsychologic studies[3-9] have suggested that the predominant cognitive deficits in patients with ALS involve executive function and free recall, with relative sparing of recognition memory, suggesting frontal lobe dysfunction. Cognitive impairment in ALS may appear along a clinical continuum, ranging from mild impairment to frontotemporal lobar dementia (FTLD).[10] In ALS patients with cognitive impairment, imaging studies show frontal atrophy and hypometabolism in the frontotemporal regions and the anterior cingulate gyrus.[4,5,8,11,12] The neuropathologic correlate of cognitive impairment in ALS is frontal and temporal lobar atrophy, with neuronal loss, superficial linear spongiosis, and ubiquitinated tau-negative and synuclein-negative intraneuronal inclusions.[2,13-16] Other evidence linking FTLD and ALS includes clinical and pathologic findings of motor neuron disease in some patients with FTLD,[17,18] motor neuron disease–type inclusions at autopsy in demented patients without clinical motor neuron disease,[19] and familial syndromes, including FTLD and amyotrophy.[20-22]

CME course available at www.archneurol.com

For editorial comment see page 319

The prevalence of cognitive impairment in ALS is unknown. Estimates were originally 2% to 5%,[23,24] but they vary up to 35%

to 52%.[9,25] However, small sample size, selection bias, diverse definitions of cognitive impairment, and differing test batteries make estimates unreliable. Although older age, male sex, low education, family history, low forced vital capacity, pseudobulbar palsy, bulbar site of onset, and increasing disease severity may be risk factors for dementia in ALS,[9,25-27] these associations have not been consistently replicated. Some studies suggest that patients with bulbar onset are disproportionately represented in the cognitively impaired group[25,28] and that patients with bulbar onset may experience more profound neuropsychologic deterioration,[28] but the largest study[9] to date did not confirm these associations. The relationship between cognitive impairment and survival in ALS has not been well studied.

We attempted to elucidate the frequency, nature, and implications of cognitive impairment in 40 patients with ALS seen in a neuromuscular clinic. We addressed 3 main questions: (1) Do patients with ALS perform differently on neuropsychologic tests than controls of similar age, sex, and education? (2) Do patients with ALS exhibit evidence of cognitive impairment when given a neuropsychologic test battery? (3) Is there an association between cognitive impairment and previously identified cognitive risk factors in ALS? We also performed an exploratory survival analysis to investigate the potential effect of cognitive impairment on ALS survival.

METHODS

SETTING AND PARTICIPANTS

Between August 1, 1991, and August 31, 1992, 40 patients with classic ALS were consecutively recruited from neurologists' private offices and the Eleanor and Lou Gehrig MDA/ALS Research Center at the Neurological Institute, Columbia University. Inclusion criteria were a history and neurologic examination findings consistent with motor neuron disease in a patient older than 18 years, supplemented by confirmatory electromyographic findings. We excluded individuals with sensory abnormalities, results of nerve conduction studies suggestive of neuropathy, and serious concomitant conditions, including stroke, depression, and other psychiatric disease. Patients with a family history of neurodegenerative disease were eligible for inclusion.

All the participants were English speaking. Informed consent was obtained from all the patients, and institutional review board approval was obtained for the protocol. Controls were from a continuous series of English-speaking patients referred to the Memory Disorders Center at the New York State Psychiatric Institute New York, between January 1, 1992, and June 30, 2003, and underwent standardized evaluations leading to a consensus diagnosis per Columbia University's Alzheimer Disease Research Center protocol. Controls were matched 2:1 to patients with ALS for age, sex, and education via stratified random sampling. Controls with concomitant conditions that may affect test performance (eg, stroke, depression, and other psychiatric disease) or who were reclassified as impaired on follow-up testing were excluded before sampling.

DATA COLLECTION

Participants underwent a baseline semistructured clinical interview, a formal neurologic examination, neuropsychologic testing, and a functional rating scale evaluation. All the information was collected in a standardized manner and entered into a database at the time of clinical evaluation. For purposes of survival analysis, vital status information was obtained in January 2004 from public records (Social Security Death Index) and medical records.

DIAGNOSTIC EVALUATIONS

Clinical interview included inquiry into the approximate date and location of symptom onset, the nature of the first symptom, clinical features, and medical and family history. Clinical and laboratory evaluations were performed by neuromuscular disease specialists. Each patient underwent an ALS functional assessment as outlined by Appel et al[29] using a scale shown to reliably measure deterioration of motor systems as ALS progresses and to predict survival time.[30] The subscale scores (bulbar, respiratory, muscle strength, upper extremity function, and lower extremity function) generate a total score ranging from 30 to 164. Patients with scores of 52 or lower have minimal or mild disability, whereas those with scores of 135 or greater are typically quadriplegic and bedridden, requiring respiratory support and gastrostomy. Data were obtained before validation of the ALS Functional Rating Scale,[31] now widely in use.

Neuropsychologic testing was performed within 2 months of the clinical interview and neurologic examination in all cases. All the patients were given the Columbia University–modified version of the Mini-Mental State Examination (mMMSE)[32] and formal neuropsychologic testing. The test battery consisted of measures selected to assess cognitive functions that are typically affected in dementia, and it effectively distinguishes between normal aging and dementia.[33,34] The evaluation included measures of learning and memory,[35,36] executive function,[37-40] attention and psychomotor speed,[41] language,[40,42] and visuospatial ability.[36,43] Criterion scores were determined based on a review of the performance of 172 patients from the Memory Disorders Center and controls as previously described[33] and validated.[34] Briefly, criterion scores were established by inspection of mean scores and variability between demented and nondemented groups, and the score that best separated the 2 groups was chosen as the criterion score. Impaired performance on each test was defined as performing below the criterion score as determined by this method.

DIAGNOSTIC PROCEDURE

The diagnosis of ALS was made at the time of clinical evaluation by experienced neuromuscular specialists conforming to El Escorial criteria.[44] Cognitive diagnosis was made retrospectively in January 2004 on the basis of neuropsychologic test performance by a consensus panel of neurologists (G.A.R., N.S., and K.M.) and a neuropsychologist (Y.S.). Because no measure of functional limitation due to cognitive impairment was available (thus precluding a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,*[45] diagnosis of dementia, which requires impairment in social or occupational functioning), we operationally defined dementia on the basis of neuropsychologic testing, as has been described previously.[33] This approach has previously been shown to reliably correlate with a physician diagnosis of dementia, especially in a well-educated sample such as the study group.[33,34] The neuropsychologic paradigm considers memory impairment to be the key defining feature of dementia and defines memory impairment as impairment in 2 of 3 memory domains (short- and long-term verbal memory and short-term nonverbal memory). A diagnosis of dementia was given to individuals who exhibited memory dysfunction and impaired performance in at least 2 additional domains (executive functioning, attention, language, or visuospatial ability). Individuals categorized as mildly

impaired exhibited impaired neuropsychologic test performance insufficient for a diagnosis of dementia, defined as scoring below criterion levels on 2 or more individual tests. All primary analyses were performed using these definitions of cognitive status. Herein, use of the term *cognitive impairment* refers to cognitive function meeting the previously mentioned criteria for either mild impairment or dementia.

Given concerns regarding the potential effect of bulbar or respiratory impairment on neuropsychologic test performance in the ALS population,[6,25] we performed additional exploratory univariate analyses in which patients were subclassified as having probable or possible dementia. Particular attention was given to Appel scale measures of bulbar, respiratory, and motor dysfunction when performing this subclassification. Patients subclassified as having probable dementia conformed to the previously mentioned criteria and exhibited neuropsychologic test performance deficits out of proportion to their apparent ALS severity. Patients subclassified as having possible dementia met the previously mentioned criteria and either (1) showed less substantial, but still impaired, performance in memory or other domains or (2) exhibited sufficient severity of bulbar or respiratory dysfunction (as measured using the Appel swallowing, speech, and respiratory subscales) to possibly contribute to impaired test performance. This approach has not been validated and is purely exploratory.

DATA ANALYSIS

All analyses were performed using statistical software (SPSS version 11.0; SPSS Inc, Chicago, Ill). Univariate analyses were performed using Pearson χ^2, Fisher exact, and 2-tailed *t* tests as appropriate. Bonferroni correction for multiple comparisons was applied to all univariate analyses. All univariate analyses involving dementia status were repeated using the conservative case definition of probable dementia only.

Demographic and Clinical Data

Demographic, natural history, and clinical data were compared between ALS groups defined by cognitive status. Neuropsychologic testing performance was compared between groups of patients with ALS defined by the presence or absence of subjective memory difficulties and emotional lability (dichotomous variables extracted from clinical interview).

Neuropsychologic Test Performance in Patients With ALS vs Controls

Mean neuropsychologic test performance was compared in the ALS and control groups. Similar analyses were performed comparing the performance of the ALS demented (probable + possible), probable dementia, and cognitively intact groups with that of controls. To verify the adequacy of the control group, performance of the matched controls was compared with our institutional control data[41] (derived from the same Alzheimer Disease Research Center population described previously herein [mean age, 67.9 years; mean education, 15.1 years]).

ALS Severity and Cognitive Status

Neurologic examination findings (treated as dichotomous variables) and functional rating scale scores were compared between ALS groups defined by cognitive status. Neuropsychologic test performance was also compared between groups of patients with ALS defined by the presence or absence of bulbar (dysarthria and dysphagia) and respiratory dysfunction. Simple linear regression models were used to determine the relationship between Appel scale scores and cognitive test performance. Multivariate linear regression analysis was used to further evaluate the association between Appel scale total score and letter fluency performance, with age, education, and years symptomatic at testing as covariates. The observed association was further investigated by adding Appel speech scores to the multivariate model with attention to collinearity diagnostics.

Relationship Among Cognition, ALS Severity, and Survival

We defined disease onset as the date of the first ALS symptom as determined by clinical interview. For univariate analyses, comparisons were made between groups defined by dementia status. Kaplan-Meier survival curves were constructed to compare total survival time (defined as time from symptom onset to death) among the nondemented, mildly impaired, and demented groups. Multivariate survival analyses using Cox proportional hazards models used duration of illness from neuropsychologic evaluation to death (for those 37 patients who died) or to last follow-up (for 1 survivor) as the time-dependent variable. All Cox models included age, sex, education, and duration of illness at testing as covariates. To investigate the relationship of cognition and survival, a cognitive indicator variable was included in the Cox models. In 1 of these analyses, a summary variable consisting of the sum of *z* scores for representative test performance for each cognitive domain was used. *z*-Transformations were performed using Columbia University's normative data for this test battery.[41] To investigate the relationship between ALS severity and survival, Appel scale scores were included as the predictor variable in separate Cox models. Finally, to investigate the relationship between cognition and survival controlling for ALS severity, a cognitive variable was included in a Cox model with an Appel scale score and age, sex, education, and duration of illness at testing as covariates. Because the natural history of cognitive decline in ALS is not fully established, all survival analyses were repeated treating total disease duration as the time-dependent variable, with and without treating the cognitive or motor predictor variables as time-dependent covariates. These analyses did not include disease duration from symptom onset to testing as a covariate. One patient diagnosed as having ALS (cognitively normal at baseline) was last known to be alive 1 month before analyses and was considered to be alive in the Cox models. All the survival analyses were repeated without this patient to account for the possibility of clinical misdiagnosis.

RESULTS

DEMOGRAPHIC AND CLINICAL DATA

The ALS and control groups were similar in age (58.8 vs 63.0 years; $P=.08$), education (14.4 vs 14.4 years; $P=.99$), and sex (65% vs 65% male; $P>.99$). Twelve patients (30%) in the ALS sample showed evidence of cognitive impairment on neuropsychologic testing, of whom 9 (23%) met the criteria for dementia (**Table 1**). Of the 9 demented patients, 5 were subclassified as probable and 4 as possible. Of the 4 possible cases, 3 were so classified owing to evidence of bulbar or respiratory impairment. No significant differences were found between the demented (probable + possible) and nondemented (cognitively intact + mildly impaired) groups regarding age, sex, education, site of onset (limb vs bulbar), emotional lability,

Table 1. Characteristics of 40 Patients With ALS Who Underwent Cognitive Evaluation

	No Dementia (Cognitively Intact + Mildly Impaired) (n = 31)	Dementia (Possible + Probable) (n = 9)	*P* Value*
Age, mean, y	57.7	62.4	.33
Sex, M/F, No.	20/11	6/3	.62
Education, mean, y	14.7	13.4	.32
mMMSE score, mean (range)	49.8 (39-57)†	41.3 (19-49)‡	.001§
Site of onset	5 Bulbar, 26 limb	1 Bulbar, 8 limb	.59
Emotional lability, No. (%)	13 (42)	5 (56)	.36
Subjective memory loss, No. (%)	3 (10)	3 (33)	.12
FHx of dementia, No. (%)	1 (3)	0	.78
FHx of PD, No. (%)	1 (3)	0	.78
FHx of ALS, No. (%)	0	0	NA

Abbreviations: ALS, amyotrophic lateral sclerosis; FHx, family history; mMMSE, modified Mini-Mental State Examination; NA, not applicable; PD, Parkinson disease.

*Corrected for multiple comparisons using the Bonferroni method (for $\alpha = .05$, the corrected significance level is .05/10 = .005).

†Corresponds to a Folstein MMSE mean score of 26.1 (range, 21-30).

‡Corresponds to a Folstein MMSE mean score of 21.9 (range, 11-26).

§Statistically significant difference at $P<.005$.

subjective memory loss, or family history. Baseline mMMSE scores were significantly lower in the demented group ($P=.001$). Only 1 of the 9 demented patients had bulbar-onset ALS. Of the 5 other bulbar-onset cases, 4 were cognitively normal and 1 was mildly impaired. Repeated analyses using the more conservative case definition (probable dementia only) revealed similar results. Patients with ALS and subjective memory difficulties performed worse on the mMMSE ($P=.001$), Selective Reminding Test recognition ($P<.001$), Benton Visual Retention Test recognition ($P=.001$), and naming ($P<.001$). Differences on the Identities and Oddities test ($P=.02$) did not survive correction for multiple comparisons. Emotional lability was not associated with overall performance on the mMMSE or other neuropsychologic tests.

NEUROPSYCHOLOGIC TEST PERFORMANCE IN PATIENTS WITH ALS VS CONTROLS

Comparison of mean test performance of all patients with ALS (unimpaired and cognitively impaired) with that of controls revealed similar performance in most domains (**Table 2**). As a group, patients with ALS performed better than controls on the repetition task ($P<.001$) and made fewer omissions than controls on 1 of the 2 cancellation tasks ($P=.002$). Despite similar age, sex, and educational attainment, the nondemented patients with ALS performed better than controls on several measures of memory, executive function, attention, and language. Adequacy of the control group was verified by comparison with Columbia University's normative data, with the only deviation from the normative data being borderline better performance among the (younger) matched control group on the Selective Reminding Test ($P=.003$). Comparison of the performance of ALS patients without dementia with this normative data revealed similar results as in the case-control analysis.

As expected (given that memory impairment was specified as a requirement for a dementia diagnosis), both groups of ALS patients with dementia (probable + possible and probable only) performed worse than matched controls on the Selective Reminding Test ($P<.001$ and $P=.001$, respectively). The pattern of memory impairment was that of poorer free recall than recognition memory. Outside of the memory domain, the performance of ALS patients with dementia was most impaired in executive function (letter fluency, category fluency, and Identities and Oddities task) and naming, although differences did not survive correction for multiple comparisons. Language comprehension was preserved, and the demented group performed better than controls on the repetition task ($P<.001$). This latter difference was not seen after possible cases were excluded. Attention, processing speed, and visuospatial function were relatively preserved in patients with ALS.

ALS SEVERITY AND COGNITIVE STATUS

The ALS patients with and without dementia did not differ significantly in the presence or degree of bulbar, respiratory, or other motor dysfunction (**Table 3**). Analysis considering only participants with probable dementia compared with nondemented patients also did not show differences on these measures.

Bulbar and respiratory dysfunction did not seem to affect test performance. In simple linear regression analyses, no association between performance on the Appel swallowing, speech, or respiratory subscale and neuropsychologic test performance was observed. Appel scale total score was not associated with mMMSE, category fluency, verbal memory, or nonverbal memory. However, controlling for age, education, and duration of illness, increasing Appel scale total scores showed borderline association with declining letter fluency performance ($b=-0.06355$; $t=-2.037$; $P=.05$). This indicates a 1.5-point decline in mean letter fluency performance for each 25-point increase in Appel scale total score. This association remained when additionally controlling for Appel speech scale score (for Appel scale total score: $b=-0.06980$; $t=-2.048$; $P=.049$).

COGNITIVE STATUS, ALS SEVERITY, AND SURVIVAL

Survival data were available for 38 (95%) of 40 patients with ALS, including all the patients with cognitive impairment. Two patients were lost to follow-up after the baseline assessment and were excluded from survival analyses. Median survival for the cohort was 3.8 years (mean, 5.0 years; range, 1.5-14.1 years). Median survival time from neuropsychologic evaluation was 2.3 years (mean, 3.4 years; range, 0.3-12.4 years). Demented patients did not differ from nondemented patients in overall survival, disease duration at testing, or survival from the date of testing (**Figure** and **Table 4** and **Table 5**). Cognition showed no asso-

Table 2. Scores on a Core Battery of Neuropsychologic Tests by Clinical Group*

	ALS Group						*P* Value‡		
			Dementia						
	No Dementia (n = 28)	Mildly Impaired (n = 3)	Possible (n = 4)	Probable (n = 5)	All (N = 40)	Control Group (n = 80)†	No Dementia vs Controls	Dementia vs Controls	Probable Dementia vs Controls
Memory									
SRT total	54.2 (40-67)	38.7 (31-45)	36.0 (32-43)	29.5 (24-35)	49.0 (24-67)	46.2 (13-65)	<.001	<.001	.001
SRT recall	8.7 (6-12)	4.3 (0-8)	4.0 (1-6)	4.3 (3-6)	7.5 (0-12)	7.0 (0-12)	<.001	.01	.06
SRT recognition	12.0 (11-12)	10.3 (8-12)	11.7 (11-12)	10.5 (7-12)	11.7 (7-12)	11.6 (8-12)	<.001	.448	.44
BVRT recognition	9.3 (7-10)	7.0 (5-8)	8.3 (6-10)	7.4 (4-10)	8.8 (4-10)	8.5 (4-10)	.003	.16	.10
Executive function									
Letter fluency	14.2 (6-22)	8.0 (6-10)	9.6 (3-15)	8.6 (4-12)	12.8 (3-22)	13.6 (1-23)	.56	.03	.07
Category fluency	22.0 (14-30)	12.5 (11-14)	14.9 (12-20)	12.1 (7-15)	19.60 (7-30)	17.8 (6-35)	.001	.046	.054
Identities/Oddities	15.2 (12-16)	14.0 (13-16)	14.5 (12-16)	13.8 (11-16)	14.9 (11-16)	15.1 (11-16)	.62	.03	.03
Similarities	19.9 (8-25)	13.0 (12-14)	15.7 (12-22)	15.3 (12-17)	18.6 (8-25)	17.1 (2-25)	.02	.47	.54
Attention and psychomotor speed									
CT shape time	51.6 (33-107)	71.3 (53-101)	55.5 (40-79)	66.5 (46-101)	55.2 (33-107)	59.2 (28-226)	.11	.88	.65
CT shape omit	3.2 (0-9)	3.7 (2-6)	4.3 (3-6)	4.8 (2-10)	3.5 (0-10)	4.7 (0-17)	.08	.87	>.99
CT TMX time	62.1 (38-103)	94.3 (71-139)	69.0 (37-95)	82.5 (58-109)	67.7 (37-139)	68.7 (26-225)	.29	.53	.37
CT TMX omit	0.2 (0-2)	0	1.5 (0-4)	0.5 (0-1)	0.4 (0-4)§	1.2 (0-9)	<.001	.80	.46
Language									
Naming	14.8 (12-15)	15.0 ‖	14.8 (14-15)	11.2 (9-13)	14.4 (9-15)	14.3 (10-15)	.009	.09	.03
Repetition	8.0 ¶	8.0 ¶	8.0 ¶	8.0 ¶	8.0 ¶	7.6 (3-8)	<.001	<.001	.38
Comprehension	5.7 (4-6)	5.3 (5-6)	5.8 (5-6)	5.5 (5-6)	5.7 (4-6)	5.5 (0-6)	.33	.75	.98
Visuospatial									
BVRT matching	9.6 (8-10)	9.3 (8-10)	9.8 (9-10)	8.6 (5-10)	9.5 (5-10)	9.4 (5-10)	.33	.50	.15
Rosen	3.7 (2-5)	3.7 (3-4)	3.0 (2-5)	3.0 (2-4)	3.5 (2-5)	3.5 (0-5)	.28	.21	.34

Abbreviations: ALS, amyotrophic lateral sclerosis; BVRT, Benton Visual Retention Test; CT, Cancellation Test; SRT, Selective Reminding Test; TMX, forms of CT.
*Data are given as group mean (range).
†Randomly selected controls matched for age, education, and sex.
‡Corrected for multiple comparisons using the Bonferroni method (for $\alpha = .05$, the corrected significance level is .05/17 = .003).
§*P* = .002 vs controls.
‖All subjects achieved the same test score.
¶*P*<.001 vs controls.

ciation with survival in multivariate analyses, with and without controlling for motor dysfunction. The Appel scale speech, respiratory, and total scores were not associated with survival. Poorer performance on the swallowing subscale was marginally associated with decreased survival (hazard ratio, 1.1; 95% confidence interval, 1.0-1.3; *P* = .02). Analyses using total disease duration as the time-dependent variable, with and without treating the cognitive and motor predictor variables as time-dependent covariates, revealed similar results, as did those excluding the living patient (data not shown).

COMMENT

According to these data, many patients with ALS exhibit cognitive impairment (with or without dementia) as defined by neuropsychologic criteria. We did not observe significant differences in several possible ALS cognitive risk factors[9,25-27] between demented and nondemented groups. Although the present study is one of the largest to date, our failure to demonstrate previously observed associations should be interpreted with caution, especially for comparisons between the demented and nondemented ALS groups. We estimate that our study had 80% power to detect a 25-point difference in Appel scale total score and 80% power to detect a 3-year difference in mean survival between the demented and nondemented ALS groups. Sample size is less of a concern regarding comparisons between patients with ALS and controls. Our study had 99% power to detect a 5-point difference in mean letter fluency test performance between the ALS and control groups and 80% power to detect a 2.7-point difference.

Our data do not support previous studies of special susceptibility of bulbar-onset ALS for dementia. Although the sample size was small, only 1 bulbar-onset case was found in the demented group. Selection bias may have played a role in the inconsistent results across studies regarding bulbar-onset disease and dementia. Our attempt at consecutive enrollment should be less susceptible to systematic bias than previous studies that used convenience samples[28,46,47] or that exclusively evaluated bulbar-onset patients.[26] A study[48] of consecutive patients with ALS referred to a regional neurology service included a disproportionate number of bulbar-onset cases (78%) for unclear reasons, although only 2 of those 14 bulbar-onset cases were diagnosed as having dementia. Although patients with bulbar onset were not overrepresented in our sample, selection bias may have played a role in this study as well. We do not have data on the patients with ALS

Table 3. Comparison of Motor and Functional Status Between Nondemented and Demented ALS Groups

Sign/Score	No Dementia (Healthy + Mildly Impaired) (n = 31)	Dementia (Possible + Probable) (n = 9)	*P* Value
Dysphagia, No. (%)	7 (23)	4 (44)	.19
Dysarthria, No. (%)	11 (35)	4 (44)	.45
Respiratory involvement, No. (%)	5 (16)	1 (11)	.59
Masticatory weakness, No. (%)	6 (19)	3 (33)	.32
Facial weakness or fasciculations, No. (%)	14 (45)	5 (56)	.43
Abnormal volitional palate movement, No. (%)	5 (16)	2 (22)	.50
Abnormal reflex palate movement, No. (%)	7 (23)	2 (22)	.68
Tongue atrophy, No. (%)	15 (48)	4 (44)	.57
EMG c/w MND, No. (%)	29 (94)	9 (100)	.60
Appel scale score, mean (range)*			
Swallowing	4.2 (3-9)	7.0 (3-15)	.14
Speech	4.5 (3-9)	6.0 (3-15)	.32
Bulbar	8.6 (6-18)	13.0 (6-30)	.40
Respiratory	12.4 (6-24)	12.7 (6-24)	.91
Muscle strength	15.0 (6-32)	18.1 (11-32)	.19
Lower extremity function	16.9 (6-29)	17.9 (10-24)	.65
Upper extremity function	16.9 (6-33)	15.0 (7-33)	.62
Total	68.3 (37-110)	76.7 (41-115)	.32

Abbreviations: ALS, amyotrophic lateral sclerosis; EMG c/w MND, electromyographic findings consistent with motor neuron disease.

*Data are from the ALS Rating Scale (Appel et al[29]); scores increase with increasing disability.

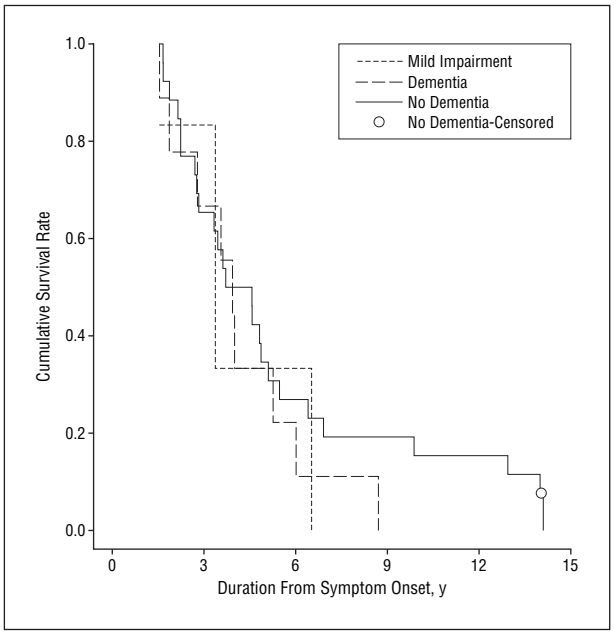

Figure. Kaplan-Meier survival curves by cognitive status.

who were not included in this study, and the Eleanor and Lou Gehrig MDA/ALS Research Center typically evaluates 300 new patients with ALS per year.

Table 4. Cognition, ALS Severity, and Survival in the Study Cohort: Univariate Analyses

	No Dementia (n = 29)	Dementia (n = 9)	*P* Value
Survival period, median [mean] (range), y			
Overall	3.7 [5.3] (1.5-14.1)	3.9 [4.2] (1.6-8.7)	.43
Before neuropsychologic testing	1.4 [1.7] (0.6-4.8)	1.2 [1.6] (0.6-3.0)	.83
After neuropsychologic testing	2.3 [3.6] (0.4-12.4)	2.2 [2.6] (0.3-7.9)	.44

Abbreviation: ALS, amyotrophic lateral sclerosis.

Table 5. Cognition, ALS Severity, and Survival in the Study Cohort: Multivariate Analyses*

Predictor Variable	Hazard Ratio (95% CI)	*P* Value
Cognition and Survival		
Dementia status	0.7 (0.3-1.5)	.32
mMMSE	1.0 (0.9-1.1)	.75
Letter fluency	1.0 (0.9-1.1)	.89
Category fluency	1.0 (0.9-1.0)	.44
Naming	0.9 (0.7-1.1)	.28
SRT total	1.0 (0.9-1.0)	.58
BVRT recognition	0.9 (0.6-1.2)	.40
Overall performance†	0.9 (0.9-1.0)	.23
ALS Severity and Survival		
Swallowing	1.1 (1.0-1.3)	.02‡
Speech	1.1 (1.0-1.2)	.19
Respiratory	1.0 (1.0-1.1)	.23
Total score	1.0 (0.9-1.0)	.12
Cognition, ALS Severity,§ and Survival		
Dementia status	0.7 (0.3-1.7)	.48
mMMSE	1.0 (0.9-1.0)	.84
Letter fluency	1.0 (0.9-1.1)	.86
Category fluency	1.0 (0.9-1.0)	.42
Naming	0.8 (0.7-1.1)	.28
SRT total	1.0 (0.9-1.0)	.82
BVRT recognition	0.9 (0.6-1.2)	.36
Overall performance†	1.0 (0.9-1.1)	.35

Abbreviations: ALS, amyotrophic lateral sclerosis; BVRT, Benton Visual Retention Test; CI, confidence interval; mMMSE, modified Mini-Mental State Examination; SRT, Selective Reminding Test.

*Cox proportional hazards models controlling for age, sex, education, and duration of illness at testing.

†Using summary variable as described in the "Methods" section of the text.

‡Statistically significant at $P<.05$.

§Data shown are for analyses using the Appel scale[29] total score as the severity indicator. Analyses using the Appel swallowing subscore revealed similar results.

The largest neuropsychologic study[9] evaluating cognitive impairment in sporadic ALS used a convenience sample of 146 patients from a teaching hospital and neuromuscular clinic. Patients underwent a similar neuropsychologic test battery and the Appel rating scale and had similar age, education, and Appel scale total scores. More than 35% of patients with ALS in their sample showed significant im-

pairment on neuropsychologic testing, with predominant difficulty in abstraction, word generation, and free recall. Other studies[4,6,25,26,28,48-50] have shown impairment in these tasks, most consistently with letter fluency. Similar to Massman et al,[9] we found relative preservation of recognition memory, but other researchers have found impaired performance.[27,28,50] Naming impairment has been reported as present[28,50] or absent[6,9] in other studies. As in the present study, verbal recognition memory, psychomotor speed, and visuospatial functioning were preserved in their group. Similar to our findings, the study by Massman et al found no differences between cognitively impaired and unimpaired groups in age, sex, duration of symptoms, site of onset, or presence of respiratory dysfunction. We did not find the increased frequency of dysarthria or the increased ALS severity seen in their cognitively impaired group. We did observe an association between increasing ALS severity and declining verbal fluency that was not attributable to increasing severity of dysarthria. Contrary to our findings, patients with ALS as a group in that study performed poorly across the neuropsychologic test battery. Apparent group differences in test performance between the 2 studies could be the result of selection bias or methodological differences: our comparison with an age-, education-, and sex-matched control group and their reliance on test-specific normative data. Sampling variation may have played a role in our study because ALS patients without dementia performed superior to controls on several neuropsychologic tests despite the matching procedure.

Decreased performance on neuropsychologic tests in ALS could result from the effects of oral motor dysfunction on the performance of time-dependent tests, such as letter and category fluency.[6,25] Comparison of bulbar and respiratory status between demented and nondemented ALS groups did not reveal significant differences. Independent of dementia status, bulbar and respiratory dysfunction did not show an association with verbal fluency or other neuropsychologic test performance in this study. Given that we administered these tests without modification to accommodate motor dysfunction, we attempted to account for bulbar and respiratory dysfunction by subclassifying demented patients, and we performed additional statistical analyses using a more conservative case definition that excluded demented patients with bulbar dysfunction. These analyses also showed no associations. Although a reasonable concern when performing cognitive testing in this population, a similar lack of effect of bulbar dysfunction on fluency and other neuropsychologic tasks has been noted by other researchers.[9,25]

The neuropsychologic testing in this study was performed before widespread knowledge of the overlap between motor neuron disease and FTLD existed. The test battery was not designed to be particularly sensitive to dysfunction of the frontal executive system. We did not systematically assess patients for symptoms or signs of behavioral dysfunction (other than emotional lability), and we did not incorporate these features into the diagnostic impression. We used a classification system that considers memory impairment as the core feature of a dementia diagnosis. Although this approach may be less sensitive to the pattern of deficits seen in FTLD, the value in this approach is 2-fold: avoidance of overdiagnosis bias and confirmation that a proportion of patients with ALS given a standard test battery warrant a conventional neuropsychologic diagnosis of dementia. Limitations of our approach include retrospective assignment of diagnosis based on operationalized neuropsychologic criteria, without a measure of the impairment in social functioning required for a clinical diagnosis of dementia. This may have lead to overdiagnosis of dementia. Conversely, our lack of a behavioral inventory and additional frontal/executive tasks likely resulted in decreased diagnostic sensitivity. The exclusion of patients with known psychiatric disease may have lead to underascertainment of cases with the behavioral changes of FTLD. Despite these limitations, our patients with ALS exhibited deficits typical of FTLD: predominant impairment of free recall, executive function, and naming. Given the clinical overlap between FTLD and ALS, using neuropsychologic test batteries, behavioral inventories, and diagnostic criteria designed for the identification of FTLD may reveal an even greater burden of cognitive impairment in the ALS population. One study[25] using this approach found that nearly all the patients with ALS and diminished verbal fluency on screening who had neuropsychologic testing met the research diagnostic criteria for FTLD. However, only approximately 15% of our patients with ALS showed impaired verbal fluency according to the criteria of that study.

The possible association between cognition and survival in ALS has not been well studied. Clinical trials of ALS have tended not to include cognitive assessments and have excluded potential patients with signs of dementia. One observational study found a 10-month shorter median survival among demented vs nondemented patients with ALS that did not reach statistical significance.[26] Although our study was exploratory in this regard and underpowered to detect a survival difference of less than 3 years between demented and nondemented groups, our data do not suggest a difference in median survival. Larger prospective studies with interval cognitive assessments would more fully address the possibility of differential survival. We did not address the impact of impaired cognition on end-of-life decision making or use of life-prolonging measures in this study.

In conclusion, using a conventional test battery, 30% of a consecutive series of patients with ALS demonstrated cognitive impairment, and nearly a quarter qualified for a neuropsychologic diagnosis of dementia. Free recall, executive function, and naming were most impaired in ALS patients with dementia, consistent with the pattern seen in FTLD. Increasing ALS severity showed an association with declining verbal fluency, not accounted for by dysarthria. Cognitive test performance was not associated with site of onset or survival. The use of test batteries, behavioral inventories, and diagnostic criteria specific to FTLD may reveal an even greater burden of cognitive dysfunction in the ALS population.

Accepted for Publication: August 23, 2005.
Correspondence: Yaakov Stern, PhD, Gertrude H. Sergievsky Center, PH-18, Columbia University College of Physicians and Surgeons, 630 W 168th St, New York, NY 10032 (ys11@columbia.edu).

Author Contributions: *Study concept and design:* Rippon, Gordon, Albert, Marder, Rowland, and Stern. *Acquisition of data:* Gordon, Murphy, Rowland, and Stern. *Analysis and interpretation of data:* Rippon, Scarmeas, Gordon, Albert, Mitsumoto, and Stern. *Drafting of the manuscript:* Rippon, Gordon, Marder, and Rowland. *Critical revision of the manuscript for important intellectual content*: Scarmeas, Gordon, Murphy, Albert, Mitsumoto, Rowland, and Stern. *Statistical analysis:* Rippon, Albert, and Stern. *Obtained funding:* Marder and Rowland. *Administrative, technical, and material support:* Rippon, Gordon, and Murphy. *Study supervision:* Scarmeas, Gordon, Mitsumoto, Rowland, and Stern.
Funding/Support: This study was supported in part by Ruth L. Kirschstein National Research Service Award 5-T32-NSO753-21 from the National Institutes of Health, Bethesda, Md (Dr Rippon).
Acknowledgment: We gratefully acknowledge the contribution of Scott Goldstein (deceased), who initiated this study and collected the neuropsychologic test data. We also thank Maura Del Bene, MS, RN, NP-P, for assistance with data collection and Ming-Xin Tang, PhD, for assistance with the control sampling procedure.

REFERENCES

1. Rowland LP, Shneider NA. Amyotrophic lateral sclerosis. *N Engl J Med*. 2001;344:1688-1700.
2. Strong MJ. Progress in clinical neurosciences: the evidence for ALS as a multisystems disorder of limited phenotypic expression. *Can J Neurol Sci*. 2001;28:283-298.
3. Gallassi R, Montagna P, Ciardulli C, Lorusso S, Mussuto V, Stracciari A. Cognitive impairment in motor neuron disease. *Acta Neurol Scand*. 1985;71:480-484.
4. Ludolph AC, Langen KJ, Regard M, et al. Frontal lobe function in amyotrophic lateral sclerosis: a neuropsychologic and positron emission tomography study. *Acta Neurol Scand*. 1992;85:81-89.
5. Talbot PR, Goulding PJ, Lloyd JJ, Snowden JS, Neary D, Testa HJ. Inter-relation between "classic" motor neuron disease and frontotemporal dementia: neuropsychological and single photon emission computed tomography study. *J Neurol Neurosurg Psychiatry*. 1995;58:541-547.
6. Abrahams S, Leigh PN, Harvey A, Vythelingum GN, Grise D, Goldstein LH. Verbal fluency and executive dysfunction in amyotrophic lateral sclerosis (ALS). *Neuropsychologia*. 2000;38:734-747.
7. David AS, Gillham RA. Neuropsychological study of motor neuron disease. *Psychosomatics*. 1986;27:441-445.
8. Abe K, Fujimura H, Toyooka K, Sakoda S, Yorifuji S, Yanagihara T. Cognitive function in amyotrophic lateral sclerosis. *J Neurol Sci*. 1997;148:95-100.
9. Massman PJ, Sims J, Cooke N, Haverkamp LJ, Appel V, Appel SH. Prevalence and correlates of neuropsychological deficits in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry*. 1996;61:450-455.
10. Strong MJ, Lomen-Hoerth C, Caselli RJ, Bigio EH, Yang W. Cognitive impairment, frontotemporal dementia, and the motor neuron diseases. *Ann Neurol*. 2003;54(suppl 5):S20-S23.
11. Kew JJ, Goldstein LH, Leigh PN, et al. The relationship between abnormalities of cognitive function and cerebral activation in amyotrophic lateral sclerosis: a neuropsychological and positron emission tomography study. *Brain*. 1993;116:1399-1423.
12. Tanaka M, Kondo S, Hirai S, Sun X, Yamagishi T, Okamoto K. Cerebral blood flow and oxygen metabolism in progressive dementia associated with amyotrophic lateral sclerosis. *J Neurol Sci*. 1993;120:22-28.
13. Mitsuyama Y. Presenile dementia with motor neuron disease in Japan: clinicopathological review of 26 cases. *J Neurol Neurosurg Psychiatry*. 1984;47:953-959.
14. Okamoto K, Hirai S, Yamazaki T, Sun XY, Nakazato Y. New ubiquitin-positive intraneuronal inclusions in the extra-motor cortices in patients with amyotrophic lateral sclerosis. *Neurosci Lett*. 1991;129:233-236.
15. Wightman G, Anderson VE, Martin J, et al. Hippocampal and neocortical ubiquitin-immunoreactive inclusions in amyotrophic lateral sclerosis with dementia. *Neurosci Lett*. 1992;139:269-274.
16. Anderson VE, Cairns NJ, Leigh PN. Involvement of the amygdala, dentate and hippocampus in motor neuron disease. *J Neurol Sci*. 1995;129(suppl):75-78.
17. Neary D, Snowden JS, Gustafson L, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology*. 1998;51:1546-1554.
18. Lomen-Hoerth C, Anderson T, Miller B. The overlap of amyotrophic lateral sclerosis and frontotemporal dementia. *Neurology*. 2002;59:1077-1079.
19. Jackson M, Lennox G, Lowe J. Motor neurone disease-inclusion dementia. *Neurodegeneration*. 1996;5:339-350.
20. 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.
21. 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.
22. Wilhelmsen KC, Lynch T, Pavlou E, Higgins M, Nygaard TG. Localization of disinhibition-dementia-parkinsonism-amyotrophy complex to 17q21-22. *Am J Hum Genet*. 1994;55:1159-1165.
23. Jokelainen M. Amyotrophic lateral sclerosis in Finland, II: clinical characteristics. *Acta Neurol Scand*. 1977;56:194-204.
24. Hudson AJ. Amyotrophic lateral sclerosis and its association with dementia, parkinsonism and other neurological disorders: a review. *Brain*. 1981;104:217-247.
25. 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.
26. Portet F, Cadilhac C, Touchon J, Camu W. Cognitive impairment in motor neuron disease with bulbar onset. *Amyotroph Lateral Scler Other Motor Neuron Disord*. 2001;2:23-29.
27. Abrahams S, Goldstein LH, Al-Chalabi A, et al. Relation between cognitive dysfunction and pseudobulbar palsy in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry*. 1997;62:464-472.
28. Strong MJ, Grace GM, Orange JB, Leeper HA, Menon RS, Aere C. A prospective study of cognitive impairment in ALS. *Neurology*. 1999;53:1665-1670.
29. Appel V, Stewart SS, Smith G, Appel SH. A rating scale for amyotrophic lateral sclerosis: description and preliminary experience. *Ann Neurol*. 1987;22:328-333.
30. Haverkamp LJ, Appel V, Appel SH. Natural history of amyotrophic lateral sclerosis in a database population: validation of a scoring system and a model for survival prediction. *Brain*. 1995;118:707-719.
31. ALS CNTF Treatment Study (ACTS) Phase I-II Study Group. The Amyotrophic Lateral Sclerosis Functional Rating Scale: assessment of activities of daily living in patients with amyotrophic lateral sclerosis. *Arch Neurol*. 1996;53:141-147.
32. Stern Y, Sano M, Paulson J, Mayeux R. Modified Mini-Mental State Examination: validity and reliability [abstract]. *Neurology*. 1987;37:179.
33. Stern Y, Andrews H, Pittman J, et al. Diagnosis of dementia in a heterogeneous population: development of a neuropsychological paradigm-based diagnosis of dementia and quantified correction for the effects of education. *Arch Neurol*. 1992;49:453-460.
34. Pittman J, Andrews H, Tatemichi T, et al. Diagnosis of dementia in a heterogeneous population: a comparison of paradigm-based diagnosis and physician's diagnosis. *Arch Neurol*. 1992;49:461-467.
35. Buschke H, Fuld PA. Evaluating storage, retention, and retrieval in disordered memory and learning. *Neurology*. 1974;24:1019-1025.
36. Benton A. *The Visual Retention Test*. New York, NY: Psychological Corp; 1955.
37. Wechsler D. *Wechsler Adult Intelligence Scale-Revised (Manual)*. New York, NY: Psychological Corp; 1981.
38. Mattis S. Mental status examination for organic mental syndrome in the elderly patient. In: Bellak L, Karasu T, eds. *Geriatric Psychiatry*. New York, NY: Grune & Stratton; 1976:77-121.
39. Benton A, Hamsher KD. *Multilingual Aphasia Examination (Manual)*. Iowa City: University of Iowa; 1976.
40. Goodglass H, Kaplan E. *The Assessment of Aphasia and Related Disorders*. 2nd ed. Philadelphia, Pa: Lea & Febiger; 1983.
41. Vliet EC, Manly J, Tang MX, Marder K, Bell K, Stern Y. The neuropsychological profiles of mild Alzheimer's disease and questionable dementia as compared to age-related cognitive decline. *J Int Neuropsychol Soc*. 2003;9:720-732.
42. Kaplan E, Goodglass H, Weintraub S. *The Boston Naming Test*. Boston, Mass: E Kaplan & H Goodglass; 1978.
43. Rosen W. *The Rosen Drawing Test*. Bronx, NY: Veterans Administration Medical Center; 1981.
44. Brooks BR; Subcommittee on Motor Neuron Diseases/Amyotrophic Lateral Sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases and the El Escorial "Clinical Limits of Amyotrophic Lateral Sclerosis" Workshop Contributors. El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. *J Neurol Sci*. 1994;124(suppl):96-107.
45. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychological Association; 2000.
46. Cavalleri F, De Renzi E. Amyotrophic lateral sclerosis with dementia. *Acta Neurol Scand*. 1994;89:391-394.
47. Caselli RJ, Windebank AJ, Petersen RC, et al. Rapidly progressive aphasic dementia and motor neuron disease. *Ann Neurol*. 1993;33:200-207.
48. Rakowicz WP, Hodges JR. Dementia and aphasia in motor neuron disease: an underrecognised association? *J Neurol Neurosurg Psychiatry*. 1998;65:881-889.
49. 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.
50. Mantovan MC, Baggio L, Dalla Barba G, et al. Memory deficits and retrieval processes in ALS. *Eur J Neurol*. 2003;10:221-227.