SHORT REPORT

Cognitive functioning in sporadic amyotrophic lateral sclerosis: a six month longitudinal study

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J Neurol Neurosurg Psychiatry 2006;**77**:668–670. doi: 10.1136/jnnp.2005.073403

Objective: To observe changes in cognition over six months in subjects with recently diagnosed sporadic amyotrophic lateral sclerosis (ALS).

Methods: The study used a between-group and within-group longitudinal design. Nineteen ALS subjects and eight matched caregivers were recruited to participate in baseline neuropsychological assessments that were repeated six months later. Between group comparisons for these variables were undertaken at baseline and six months later. Within group/across time comparisons for these variables were carried out for both groups. Individual analyses for the neuropsychological variables using *z* scores were done for the ALS subjects using their baseline performance as the basis for comparison with their six month performance.

Results: The between-group and within-group comparisons did not show significant differences in cognitive function over time. In individual analyses, however, seven of 19 ALS subjects (36.84%) developed abnormal neuropsychological performance over six months.

Conclusions: Early in the disease course, over one third of the ALS subjects developed cognitive deficits over six months. These findings support the hypothesis that cognitive deficits in ALS become more prominent over time.

Frontotemporal dementia (FTD) is now considered a common finding in amyotrophic lateral sclerosis (ALS). Although the presentation of ALS as dementia was reported historically to be rare (1–2% in sporadic ALS),[1 2] it is now recognised that dementia is a common finding in ALS, with a prevalence of at least 30%.[3–6]

Cognitive deficits in sporadic ALS, without dementia, have been found in up to 50% of samples studied.[7–9] These deficits have been reported to be localised primarily in the frontotemporal cortices.[2 7 8 10–13] The optimum methodology to be applied when investigating cognition in ALS has evolved. Several cross sectional studies have used timed tasks to support their findings, and they have excluded individuals with ALS who have severe articulatory and fine motor control difficulties that prevent adequate participation in neuropsychological testing.[7 8 10 12 13] Other cross sectional studies, however, have accommodated these problems by using neuropsychological tests that were untimed and required choice strategies. Findings of these studies, again, support the observation that non-demented individuals with ALS develop cognitive deficits in a frontotemporal pattern.[9 14–19] On reviewing these studies, Strong and colleagues,[20] have articulated guidelines to direct ongoing investigation of cognition in ALS. Most importantly, longitudinal studies are needed because it has not been established whether the cognitive deficits associated with ALS become more prominent over time. Strong and colleagues' subsequent longitudinal observation of cognition in those who had ALS showed a decline across several cognitive domains including word retrieval, visual recognition memory, and visuoperception over a six month period, particularly in those who were bulbar predominant.[21] These findings suggested more diffuse cerebral involvement, given the presence of deficits in visuoperception.

For this study, we observed cognitive functioning during a longitudinal study of sporadic ALS patients. Our study allowed maximum participation of subjects irrespective of their abilities to speak or write, by using cognitive probes that were not timed, and which required choice strategies rather than retrieval strategies. We hypothesised that ALS patients will show a decline in cognitive function in a frontotemporal pattern when compared with a group of age and education matched control subjects over a six month period, and when comparing the baseline and six month performance of the ALS subjects.

METHODS

This study was approved by the institutional review board at the University of Pennsylvania.

Subjects

We recruited a sample of 19 ALS subjects (10 men and nine women; mean (SD) age 62.84 (13.90) years; mean length of education 15.84 (3.27) years) and eight age ($p = 0.515$) and education ($p = 0.284$) matched controls (four men and four women; mean age 66.75 (14.33) years; mean length of education 14.38 (2.92) years). Subjects were recruited at the southeast Pennsylvania Amyotrophic Lateral Sclerosis Association (ALSA) programme, based at the Pennsylvania Hospital in Philadelphia. Control subjects were caregivers (spouses, partners, and friends). ALS subjects were recruited consecutively as new referrals to the ALSA programme, but they were not approached to participate until after their second outpatient visit. This occurred within three months of confirmation of diagnosis and within one year of the onset of neurological symptoms and signs. All ALS subjects were considered to have sporadic disease. Three of the ALS subjects were bulbar predominant and 16 were limb predominant in their clinical presentations. Exclusionary criteria included non-native English speakers; presence of a concurrent neurological condition; a sitting vital capacity less than 50% of predicted in ALS subjects; and any behaviours or clinical findings indicative of cognitive deficits and depression, as observed by the multidisciplinary team.

Procedures

Neuropsychological testing was undertaken in the ALS and control subjects' homes within one month of recruitment (baseline) and six months later. Cognitive functions across several domains were probed using a comprehensive, selective neuropsychological battery encompassing eight tests:

Abbreviations: ALS, amyotrophic lateral sclerosis; ALSA, Amyotrophic Lateral Sclerosis Association; FTD, frontotemporal dementia

- Selective verbal attention: Recognition Digit Span Forward.[22] The highest span achieved was used as the measure.
- Verbal working memory: Recognition Digit Span Reverse.[22] The highest reverse span achieved was used as the measure.
- Verbal memory: multiple choice version of the Rey Auditory Verbal Learning Task (RAVLT).[23] Performance accuracy during trial 1 (short term recognition memory), trial 5 (verbal learning) and the delayed recognition trial (long term recognition memory) were used as the measures.
- Language/vocabulary: Peabody Verbal Learning Test (PVLT).[24] The percentage of correctly match items was used as the measure.
- Visuoperception: Object Decision Test[25] and Efron Shapes Discrimination test.[26] The percentage of correctly selected items was used as the measure on the former test, and the highest level of difficulty of visual discrimination achieved on the latter.
- Executive functions/visual organisation: Raven's Coloured Progressive Matrices.[27] The percentage of correctly matched items was used as the measure.
- Executive functions/visual problem solving and hypothesis generation: Wisconsin Card Sorting Test (WCST).[28] The largest number of categories achieved, up to a maximum of 6, and the percentage of correct responses were used as the measures.

To minimise the influence of dysarthria, impaired motor control, and fatigue, the following testing conditions were applied: no timed tests were used; choice strategies were used that encompassed visually presented stimuli on all tests; and the presentation of tests was counterbalanced across subjects and time. All subjects were able to complete the test battery within two hours.

Analyses

ALS and control group performances were summarised with mean scores for each variable which were used to carry out multiple analyses of variance (MANOVAs) to assess whether there were group differences (ALS subjects, control subjects) or time differences (baseline, six months later), and interaction (group×time) effects that were significant. If meaningful and significant group differences were found, between-group *t* tests would be carried out to explore group differences at baseline and six months later. If meaningful and significant time differences on the MANOVAs were found, within-group *t* tests would be done to explore differences between performance at baseline and six months later for both groups. Significance was defined at a p value $\leqslant 0.05$.

Within-group individual analyses of the ALS subjects were carried out using *z* scores as another approach to detect longitudinal differences between testing at baseline and six months later. Mean performance of ALS subjects for each cognitive variable at baseline was used as the basis for comparison of performance six months later during the individual analyses. A *z* score of $\geqslant -1$ standard deviation on converted score during testing at six months was used to define impairment.

RESULTS

Group analyses

During MANOVAs undertaken for each of the variables, no significant and meaningful between-group differences were found at baseline testing and six months later. Moreover, no significant and meaningful within-group differences were found between testing at baseline and six months later for either group. Finally, no significant interaction effects were demonstrated.

Individual analyses

Seven ALS subjects (36.84%) showed progression of abnormal cognitive performance over the six month period of the study. Of these seven subjects, only one had abnormal performance on a majority of the neuropsychological tests at the six month testing. This subject's abnormal performance occurred on all measures except for the visual discrimination task; the subject was bulbar predominant at baseline, and clinically progressed to develop dementia after the period of observation of this study. Another six ALS subjects (32%) had abnormal performance in up to three of the tests at six months, and none of these subjects developed dementia during the period of the study. One of these subjects was bulbar predominant at baseline. Abnormal performance at six months among these six ALS subjects was observed on tests that probed verbal short term recognition memory (3), hypothesis generation (3), verbal working memory (1), verbal learning (1), verbal long term recognition memory (1), visual organisation (1), and visual perception/object decision (1). These findings are summarised in table 1. The remaining 12 ALS subjects had stable performance over time. One of these subjects was bulbar predominant at baseline.

DISCUSSION

The findings of our longitudinal study support the hypothesis that cognitive deficits in individuals with ALS can develop over six months. Given that visuoperception was uniformly spared in five of our seven ALS subjects with abnormal findings, the pattern of cognitive impairment can be viewed primarily but not exclusively as frontotemporal. This interpretation of our findings largely concurs with those of another longitudinal study undertaken by Strong and colleagues.[21] There are several similarities between these studies. Both attempted to minimise the influence of dysarthric speech production and impaired fine motor control during their testing of small

Table 1 Neuropsychological performance for the seven subjects with amyotrophic lateral sclerosis who had abnormal findings over a six month period early in their disease course

	Subject No						
Cognitive domain	**1**	**2**	**7**	**15**	**16**	**17**	**19**
Selective verbal attention							x
Verbal working memory		x					x
Verbal short term memory	x	x	x				x
Verbal learning					x		x
Verbal long term memory					x		x
Visuoperception–object decision	x						x
Visuoperception–visual discrimination							
Executive–visual organisation	x						x
Executive–hypothesis generation				x	x	x	x

x: *z* score $\geqslant -1$ standard deviation.

samples (n = 19 in this study (three bulbar predominant/16 limb predominant) versus n = 13 in the study by Strong and colleagues (five bulbar predominant/eight limb predominant)). Both studies detected cognitive decline early in the course of the disease and both showed a decline in cognition broadly across several domains, primarily localised to the frontotemporal lobes but also including the parietal lobes. However, there are differences between the two studies. In our study, the individual analyses of the ALS subjects were critical for observing decline in cognitive function in every domain probed. In contrast, in the study by Strong *et al*, the between-group comparisons (ALS *v* control subjects) at six months after baseline testing exclusively revealed a decline in cognition for the ALS subjects in selected domains (word retrieval, visual memory, visuoperception). Moreover, Strong *et al* observed that ALS subjects who were bulbar predominant at clinical presentation had relatively more cognitive impairment over time than their limb predominant subjects. We were unable to confirm this observation as only three of our 19 subjects were bulbar predominant, thus precluding meaningful comparisons of this subgroup with either the control subjects or the limb predominant subgroup of ALS subjects.

The prevalence of cognitive impairment in sporadic ALS reported in our present study is lower than previously reported (37% in this study *v* 52% in the study by Lomen-Hoerth *et al*[9]). This difference can be explained by the fact that the ALS subjects (n = 100) observed by Lomen-Hoerth and colleagues were not uniformly recruited early in their disease course, some having been diagnosed with ALS up to two years before recruitment in the study. The study by Lomen-Hoerth *et al*, while not longitudinal, assessed many ALS subjects later in their disease course, explaining their reported higher prevalence of cognitive impairment. We speculate that several of our 12 ALS subjects who remained stable over six months may eventually have developed cognitive impairment, and perhaps FTD, if they had been followed for longer.

In summary, in this longitudinal study we observed that cognitive impairment develops in subjects with sporadic ALS early in the course of disease. Formal cognitive testing that is minimally demanding of speech production, fine motor control, speed of cognitive processing, and peripheral motor reaction time can be used successfully to identify cognitive deficits that are not apparent clinically. Verification of these findings will require future exploration with longitudinal studies that include larger sample sizes, follow ALS subjects over longer periods of time, and link neuropsychological performance with concurrently performed dynamic cerebral imaging and necropsy examination.

ACKNOWLEDGEMENTS

This research was supported by pilot funding from the Center for Neurodegenerative Research at the University of Pennsylvania, Philadelphia. Subject recruitment was supported by the Amyotrophic Lateral Sclerosis Association (ALSA) clinical programme at the Pennsylvania Hospital. We are grateful for the assistance of MaryAnn Patchen MA, Research Assistant, University of Pennsylvania Health System, Department of Rehabilitation Medicine, Pennsylvania Hospital, 801 Spruce Street, Third Floor, Philadelphia, PA 19107, USA.

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Competing interests: none declared

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Received 5 July 2005
In revised form 23 November 2005
Accepted 4 December 2005

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