SHORT REPORT

Relation between cognitive dysfunction and reduced vital capacity in amyotrophic lateral sclerosis

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Background: Many patients with amyotrophic lateral sclerosis (ALS) with cognitive impairment have fronto-temporal dysfunction. Whereas in some patients with ALS the fronto-temporal dysfunction is undoubtedly due to the degenerative process associated with the disease, in others dysfunction cannot be accounted for by an irreversible degenerative process alone, as it also appears to involve a reversible process. We hypothesised that reduced vital capacity can be a key contributor to the fronto-temporal dysfunction observed in patients with ALS.

Objective: To investigate the association between fronto-temporal dysfunction and reduced vital capacity in ALS.

Methods: 16 consecutive patients who conformed to a diagnosis of definite or probable ALS (El escorial criteria) were grouped by vital capacity, and their clinical characteristics and cognitive functions, including disease duration, attention, executive function and memory, were measured.

Results: Patients with a reduced vital capacity performed significantly poorer in memory retention ($p=0.028$), retrieval efficacy ($p=0.003$), spoken verbal fluency ($p=0.03$) and spoken verbal fluency indexes ($p=0.016$) than those with a normal vital capacity.

Conclusion: The fronto-temporal dysfunction in ALS might be attributable to potentially reversible secondary effects associated with reduced vital capacity, as well as to the primary degenerative process.

Amyotrophic lateral sclerosis (ALS) is traditionally considered as a degenerative disease exclusively of the motor system, but recent studies revealed cognitive impairment in up to 50% of patients with ALS.^{1–3} Also, the most common pattern of cognitive impairment is fronto-temporal dysfunction.^{1–3}

Whereas in some patients with ALS the fronto-temporal dysfunction is undoubtedly due to the degenerative process associated with the disease, in others dysfunction cannot be accounted for by an irreversible degenerative process alone, as it also appears to involve a reversible process. The reasons for suspecting non-degenerative reversible causes of cognitive dysfunction in ALS include: (1) improved cognitive function by non-invasive positive pressure ventilation over 6 weeks in ALS,⁴ (2) significant difference in mean forced vital capacity (FVC) between patients with ALS with fronto-temporal lobar dementia and those without (66% vs 95% predicted),¹ (3) neuronal loss, gliosis, sponginess in the hippocampus and parahippocampal area which is vulnerable to hypoxia,⁵ according to the brain pathology of ALS patients with frontal lobe dysfunction⁶ and (4) cognitive impairment in patients with sleep disordered breathing, characterised as fronto-temporal dysfunction.⁷ These findings appear to indicate that not only a degenerative process but also ventilatory status can be a key contributor to the cognitive dysfunction observed in patients with ALS, and that the reversible secondary fronto-temporal

dysfunction might be misinterpreted as irreversible symptoms of degenerative process. Thus, in this study, we measured cognitive function related to the frontal and temporal lobes and investigated their associations with the ventilatory status of the patient.

METHODS

Patients were recruited from the ALS Clinic at the Seoul National University Hospital. All patients conformed to a diagnosis of definite or probable ALS (El escorial criteria).⁴ The following patients were excluded: those diagnosed more than 36 months before study commencement; age >75 years; history of respiratory support (tracheostomy, non-invasive ventilation or oxygen inhalation); inability to communicate; or failure to provide consent. Sixteen patients were eventually enrolled in the study. We measured clinical characteristics, ALS Functional Rating Scale Revised (ALSFRS_r), FVC and cognitive function, including attention, executive function and memory.

Neuropsychology

The neuropsychological battery used included the following: Mini-Mental State Examination (MMSE), Rey Auditory Verbal Learning Test, a spoken phonemic verbal fluency test (for Korean words starting with the sounds “s” and “k”), a written phonemic verbal fluency test (for Korean words with the initial sounds “b” and “z”) and a written categorical verbal fluency test (for animals, foods, flowers and grocery items). For each fluency test, we determined a fluency index (fi), which represents intrinsic response generation, and which was calculated by⁸

$$fi = (\text{time allowed} - \text{time taken to read out or copy all words generated}) / \text{total number of items generated}.$$

Statistics

To investigate the association between disease severity and fronto-temporal dysfunction, the 16 patients were grouped arbitrarily about an ALSFRS_r cut-off of 39. In addition, in order to examine the association between reduced vital capacity and fronto-temporal dysfunction, patients were also grouped about an FVC cut-off of 80% predicted.⁹ These dichotomous groups were compared using non-parametric Mann–Whitney U tests; a significance level of $p<0.05$ was used throughout.

RESULTS

Sixteen patients (10 men and six women, aged 43–75 years, ALSFRS_r 27–44, FVC 61–100%) were eligible. When patients were grouped based on disease severity (ALSFRS_r), no significant difference in cognitive function was observed (see supplementary table; the supplementary table can be viewed on

Abbreviations: ALS, amyotrophic lateral sclerosis; ALSFRS_r, Amyotrophic Lateral Sclerosis Functional Rating Scale Revised; FVC, forced vital capacity; MMSE, Mini-Mental State Examination

Table 1 Clinical features and neuropsychology test results for patients with reduced vital and intact vital capacity

	With reduced FVC	Without reduced FVC	Total	p Value
Sex (M:F)	5:3	5:3	10:6	
Age (y)	57.13 (11.52)	58 (10.13)	57.56 (10.49)	
Mean period of education (y)	10	10	10	
FVC (%)	70.38 (6.26)	94.13 (6.42)	82.25 (13.71)	
No of patients with bulbar symptoms	1	3	4	0.442
No of patients with mild dyspnoea or orthopnoea	4	5	9	1.00
ALSFRS _r	38.13 (5.24)	37.25 (4.71)	37.69 (4.84)	0.574
Disease duration (months)	21.5 (12.11)	20.13 (8.82)	20.82 (10.31)	
MMSE	27.38 (1.76)	26.25 (2.76)	26.81 (2.31)	0.649
RAVLT				
Learning trial				
1	12.75 (2.49)	12.75 (3.69)	12.75 (3.04)	0.574
2	12.50 (3.50)	11.50 (3.21)	12.00 (3.29)	0.645
3	12.25 (3.33)	12.50 (1.41)	12.38 (2.47)	0.721
4	12.62 (1.92)	13.13 (2.64)	12.88 (2.25)	0.505
5	12.50 (2.73)	12.38 (3.07)	12.44 (2.80)	0.878
Delayed recall	10.87 (2.85)	12.38 (3.54)	11.63 (3.20)	0.328
Multiple choice	11.50 (2.27)	10.13 (3.83)	10.81 (3.12)	0.195
Learning curve	51.66 (31.81)	55.67 (22.89)	52.55 (26.79)	0.959
Memory retention	22.88 (16.70)	55.68 (29.80)	39.28 (28.83)	0.028
Retrieval efficacy	29.15 (23.67)	72.84 (30.21)	34.59 (34.59)	0.003
Spoken verbal fluency s (index)	7.42 (3.59)	12.00 (2.12)	9.33 (3.77)	0.030
Spoken verbal fluency k (index)	(7.94 (3.51))	(3.79 (0.32))	(6.10 (3.32))	(0.016)
Written verbal fluency b (index)	6.00 (3.06)	10.00 (3.53)	7.67 (3.72)	0.106
Written verbal fluency z (index)	(8.65 (3.23))	(5.71 (2.50))	(7.35 (3.16))	(0.190)
Category fluency animal (index)	6.50 (3.10)	6.67 (1.63)	6.60 (2.17)	0.610
Category fluency food (index)	(5.60 (2.83))	(5.71 (2.09))	(5.66 (2.26))	(0.914)
Category fluency flower (index)	6.00 (3.55)	6.50 (2.43)	5.67 (2.75)	0.610
Category fluency supermarket (index)	(7.01 (5.24))	(6.07 (3.53))	(6.30 (4.04))	(0.914)
Category fluency animal (index)	13.00 (1.83)	13.57 (4.86)	13.29 (3.54)	0.902
Category fluency food (index)	(3.93 (0.92))	(3.83 (1.46))	(3.88 (1.18))	(0.792)
Category fluency flower (index)	10.71 (3.15)	10.71 (3.86)	10.71 (3.38)	0.902
Category fluency supermarket (index)	(5.34 (2.60))	(4.52 (3.86))	(4.89 (1.86))	(1.000)
Category fluency animal (index)	8.20 (3.11)	6.75 (2.19)	7.31 (2.56)	0.622
Category fluency food (index)	(2.37 (1.46))	(4.15 (2.32))	(3.50 (2.17))	(0.230)
Category fluency flower (index)	8.60 (2.32)	8.25 (2.37)	8.38 (2.26)	0.833
Category fluency supermarket (index)	(3.20 (1.16))	(3.93 (1.69))	(3.66 (1.50))	(0.527)

ALS, amyotrophic lateral sclerosis; ALSFRS_r, Amyotrophic Lateral Sclerosis Functional Rating Scale Revised; FVC, forced vital capacity; MMSE, Mini-Mental State Examination; RAVLT, Rey Auditory Verbal Learning Test.

Patients were grouped based on an FVC of <80% or ≥80%. A significant difference was found between these two groups in memory retention ($p=0.028$), retrieval efficacy ($p=0.003$), spoken verbal fluency ($p=0.03$) and spoken verbal fluency indexes ($p=0.016$).

Significant results are presented in bold typeface.

All data are expressed as mean (SD) or number of patients.

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However, when patients were grouped by FVC, those with an FVC <80% predicted ($n=8$, mean ALSFRS_r = 36.6) performed significantly poorer for memory retention ($p=0.028$), retrieval efficacy ($p=0.003$), spoken verbal fluency ($p=0.03$) and spoken verbal fluency index ($p=0.016$) than those with an FVC ≥80% predicted ($n=8$, mean ALSFRS_r = 37.3). Patients with a reduced vital capacity (FVC <80% predicted) and those with normal vital capacity (FVC ≥80% predicted) did not differ significantly in terms of sex, age, education, disease duration or ALSFRS_r, or bulbar or respiratory symptoms (table 1)

DISCUSSION

In this study, we found that reduced vital capacity in patients with ALS, but not disease severity, was correlated with a poor performance, as determined by fronto-temporal functional testing. This suggests that the fronto-temporal dysfunction in ALS might be attributable to potentially reversible secondary effects, as well as to the primary degenerative process.

Reduced vital capacity can affect the brain in several ways, such as chronic persistent hypoxia (continuous hypoventilation), chronic intermittent hypoxia (intermittent hypoventilation with sleep disordered breathing) and disturbance of sleep structure (with sleep disordered breathing), all of which can affect cognitive function independently.¹⁰ As patients with ALS

have a deregulated response to hypoxia,¹¹ hypoxia can be one of the contributors to cognitive dysfunction in patients with ALS, but further studies are needed to determine the mechanism most responsible.

Obviously, reduced vital capacity per se cannot be the sole cause of cognitive dysfunction in ALS, given that some patients develop fronto-temporal dysfunction before the onset of ALS,¹² and that many patients with ALS with cognitive dysfunction do not have significant respiratory difficulty.⁴ However, in some patients with ALS, the fronto-temporal dysfunction is associated with reduced vital capacity, whereas in others it is associated with a primary degenerative process. In addition, primary degenerative cognitive impairment may be aggravated by secondary causes such as hypoxia or sleep fragmentation associated with reduced vital capacity. Thus a detailed evaluation of the ventilatory status of patients seems warranted in assessing patients with ALS with cognitive impairment.

In the present study, ALS patients with a reduced vital capacity did not have lower MMSE scores than those with a normal vital capacity. However, MMSE is not a sensitive means of detecting fronto-temporal dysfunction,¹³ and may not be optimal for assessing cognitive status in ALS, because the most common type of cognitive impairment in ALS is fronto-temporal dysfunction.¹⁻³ On the other hand, verbal fluency was particularly sensitive to cognitive impairment in ALS in previous studies,⁸ and we confirmed the importance of verbal

fluency tests and the fluency index for evaluating cognitive dysfunction in ALS (table 1).

Patients enrolled in the present study were in the early disease stage. Mean disease duration was 21 months and mean FVC in those with reduced vital capacity was 70% of the reference value. However, even in early stage disease when respiratory muscles have not weakened sufficiently to cause significant problems during the day, patients with ALS may suffer from serious nocturnal hypoventilation or sleep fragmentation during REM (rapid eye movement) or deep sleep, as a result of the combined effects of sleep disordered breathing (apnoea and hypopnoea), hypotonia of the accessory muscles of respiration, a weak diaphragm and a supine position (orthopnoea).⁴

For the fluency test (spoken and written, category and verbal), only the spoken verbal fluency test "s" word and index were significant in our study. Although many studies reported that the fluency test is sensitive in detecting cognitive dysfunction in ALS, their results were not consistent in detail. Previously, spoken word fluency deficit was reported in patients with ALS.¹⁴ In contrast, some reported no deficit in spoken fluency but deficits in written verbal fluency and in category fluency.⁸ Others reported a deficit in spoken and written verbal fluency tests, but not in category fluency test.¹⁵ The reason for this discrepancy is not yet clear, although some claimed the presence of dysarthria may partly be responsible.⁸

Our study had several limitations. Firstly, because we performed cross sectional analysis, it is possible that fronto-temporal dysfunction and reduced vital capacity have a common aetiology, and that reduced vital capacity might be the result of fronto-temporal dysfunction. Also, patients with cognitive impairment might perform the FVC test less well, which needs the volition and cooperation of the patient. However, previous reports have demonstrated an improvement in fronto-temporal functions after correction of hypoventilation and sleep fragmentation,⁴ and thus it appears reasonable to view reduced vital capacity as a causative factor of fronto-temporal dysfunction. Secondly, while reduced FVC may cause hypoventilation and/or sleep fragmentation in patients with ALS, other factors, such as, sialorrhoea, bulbar dysfunction or weakness of the upper airway may also induce such symptoms in ALS. Thirdly, because our patients were in the early disease stage and fully ambulatory, they were reluctant to be admitted for an overnight polysomnography study. Hence we could not find out the mechanism (hypoxia, apnoea/hypopnoea or sleep fragmentation, etc) by which reduced vital capacity influenced cognitive function. Fourthly, the study population was small.

Nevertheless, our finding that fronto-temporal dysfunction in ALS is in part attributable to reduced vital capacity indicates the need for a large long term prospective study with respiratory support (such as non-invasive ventilation) to provide further information on the relationship between ventilatory status and cognitive function in patients with ALS. Such a study is currently in progress at the Seoul National University Hospital ALS Clinic.

The supplementary table can be viewed on the *J Neurol Neurosurg Psychiatry* website at <http://www.jnnp.com/supplemental>

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