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Screening for frontal lobe and general cognitive impairment in patients with amyotrophic lateral sclerosis

Richard A. Osborne [a], Ramnik Sekhon [b], Wendy Johnston [b], Sanjay Kalra [a,b,*]

[a] Centre for Neuroscience, University of Alberta, Canada
[b] Division of Neurology, Department of Medicine, University of Alberta, Canada

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ABSTRACT

Objectives: Cognitive impairment occurs in up to 50% of patients with amyotrophic lateral sclerosis (ALS). Simple tools are required to identify such individuals, as cognitive impairment adversely impacts quality of life and survival. Our objective was to determine the potential utility of the Frontal Assessment Battery (FAB) and the Montreal Cognitive Assessment (MoCA) in evaluating frontal lobe and general cognitive impairment, respectively. We also assessed the feasibility of screening for cognitive impairment in those patients with advanced physical disability by modifying selected FAB and MoCA subtasks.

Methods: Fifty-four consecutive ALS patients were screened; 44 completed the FAB and 39 completed the MoCA. We administered modified tasks to patients with severe hand weakness or dysarthria. The patients were classified as cognitively impaired on each measure based on published cut-off scores of 14.11 on the FAB and 26 on the MoCA.

Results: Twenty-one percent and 53% of patients were impaired on the FAB and the MoCA, respectively. Scores from patients receiving modified instructions did not differ from those completing standard versions. There were statistically significant correlations between the MoCA total scores and forced vital capacity (FVC) and ALSFRS-R scores. There was no correlation between these variables and the FAB.

Conclusions: Both the FAB and MoCA detected cognitive impairment in ALS patients. While the MoCA classified more patients as cognitively impaired than the FAB, the latter was more feasible for assessing patients with physical impairment. Simple task modifications proved effective in allowing patients with speech and motor impairments to undergo screening. Future studies are required to validate both measures, establish optimal cut-off scores, and validate modifications.

1. Introduction

While considered a predominantly motor syndrome, it is now recognized that cognitive and behavioural disturbances associated with frontotemporal lobar degeneration (FTLD) occur in up to 50% of patients with amyotrophic lateral sclerosis (ALS) [1,2].

The overlap between ALS and FTLD is supported by clinical, radiological, pathological, and genetic evidence [3]. Up to 15% of patients with ALS meet diagnostic criteria for frontotemporal dementia (FTD) [4], a variant of FTLD marked by profound changes in social behaviour and executive function. Among patients with FTD, 14% have features of widespread motor neuron degeneration warranting a diagnosis of probable or definite ALS, and an additional 36% meet diagnostic criteria for possible ALS [5]. Cognitive and behavioural abnormalities are also found in approximately 50% of non-demented ALS patients, suggesting that pure ALS and FTD syndromes exist along a continuum of a singular neurodegenerative disease [6].

Voxel-based morphometry [7] studies provide evidence of diffuse grey matter atrophy in ALS and ALS with FTLD, as well as reduced cortical activation during tests of frontal lobe function. Neuropathological investigations implicate a common pathophysiological mechanism underlying these findings, with abnormal aggregates of TDP-43 observed within neuronal inclusions in patients with both ALS and FTLD [8]. Recently, an expanded hexanucleotide repeat on gene C90RF72 of chromosome 9p21 has been identified as the cause of the majority of familial cases of ALS (fALS), FTD, and ALS-FTD [9–12].

Extra-motor changes in ALS are of considerable clinical significance, as cognitive and behavioural dysfunction are associated with reduced survival and compliance with treatments such as percutaneous endoscopic gastrostomy and non-invasive positive-pressure ventilation [13,14]. Recent studies have also reported increased burden and depression and decreased quality of life among caregivers of ALS patients with FTLD [15].

Despite the clinical and biological significance of extra-motor cerebral changes, cognitive deficits remain challenging to assess for several reasons. First, the time and resource-intensive nature of neuropsychological batteries prevents their widespread use in busy ALS clinics. Second, well-established screening tests such as the Mini-Mental Status

* Corresponding author at: 2E3.18 Walter C Mackenzie Health Sciences Centre, 8440-112 Street, Edmonton, AB T6G 2B7, Canada. Tel.: +1 780 407 7780.
E-mail address: sanjay.kalra@ualberta.ca (S. Kalra).

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Examination (MMSE) are insensitive to the executive deficits that predominate in ALS [4]. Third, motor and speech impairments may hinder adequate cognitive assessment.

The objective of this study was to explore the utility of two brief screening measures, the Frontal Assessment Battery (FAB) [16] and the Montreal Cognitive Assessment (MoCA) [17] as they potentially could address the limitations noted above.

The FAB was chosen because it can be completed in 5 to 10 min and predominantly tests frontal lobe functions that are disproportionately impaired in patients with ALS [1,4]. FAB scores correlate with performance on various executive tasks including the Wisconsin Card Sorting Test, verbal fluency tests, and the Trail Making Test [16,18]. There is also a correlation between FAB scores and perfusion in the bilateral medial and dorsolateral prefrontal cortices during single photon emission computed tomography [19]. Furthermore, the FAB has been widely used in patients with neurological diseases affecting frontal lobe function, including FTD [19,20], Parkinson's disease [18], and stroke [21]. However, its use as a screening measure in ALS has been limited [22–25].

The MoCA was included in our screening protocol, as cognitive impairment in ALS is not restricted to frontal lobe functions. Impairment in other cognitive domains, including memory and confrontation naming, have also been reported [26,27]. These findings suggest that maximum sensitivity to cognitive impairment in ALS would be achieved using a comprehensive screening instrument that evaluates frontal and non-frontal cognitive domains. As the majority of ALS patients are over the age of 50, an assessment of general cognition may be useful in identifying co-morbid conditions affecting cognition such as vascular diseases and Alzheimer's disease (AD). The MoCA possesses excellent sensitivity to even mild cognitive impairment (MCI) [17], and is superior to the MMSE in the detection of cognitive dysfunction in patients with stroke [28], MCI [17,29], Parkinson's disease [30], AD [17,29], and Huntington's disease [31]. Several advantageous features of the MoCA, relative to the MMSE, contribute to its enhanced sensitivity, including: the lack of a prominent ceiling effect [30], the inclusion of frontal executive tasks, and a more challenging delayed recall component.

Previous studies have found that speech and motor impairments prevent a substantial portion of ALS patients from completing the FAB and that adjusting total scores for missed items may compromise the instrument's reliability and validity. [25,32] To address these concerns, we modified selected subtasks of both the FAB and MoCA to facilitate screening in those with advanced disability.

2. Methods

2.1. Subjects

Fifty-four consecutive patients at the ALS clinic at the University of Alberta in Edmonton were screened for cognitive impairment as part of their routine clinical care. Patients meeting diagnostic criteria for possible, probable, or definite ALS (according to the revised El Escorial criteria [33]) were scheduled for 20 min of cognitive testing within their regular 3-hour clinic visit. Six patients could not perform testing due to both anarthria and severe hand weakness, as this combination of deficits precluded completion of several tasks on the FAB and MoCA. One patient declined participation and 3 were excluded due to major psychiatric disturbances. A total of 44 patients were tested (Table 1). Patients who underwent screening with both instruments completed the FAB first. Ethics approval was obtained from the Health Research Ethics Board of the University of Alberta for a retrospective analysis of the data abstracted from clinic charts.

Patients with severe hand weakness or dysarthria did not complete tasks requiring handwriting or verbal output, respectively. As a result, 6 patients were tested on only five of the 6 domains of the FAB (3 did not complete verbal fluency, 2 did not complete motor programming, and 1 did not complete prehension behaviour). Nine patients were unable to complete all tasks on the MoCA (7 patients did not complete the visuospatial/executive tasks and 2 patients did not complete the language tasks). In 5 patients, the MoCA was not performed due to unforeseen in-clinic time constraints (e.g., patient had to leave early, unexpectedly prolonged visits with other health care professionals).

Table 1
Summary of patient clinical and demographic data (mean ± SD). ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised, FVC = forced vital capacity.

	FAB	MoCA	p-value
N (N with Complete test, %)	44 (38, 86%)	39 (30, 77%)	
Age	63.9 ± 15.0	68.0 ± 12.4	n.s.
Male:female	2.8:1	2.8:1	n.s.
Onset bulbar (percent)	25	19	n.s.
Education (years)	12.4 ± 2.7	12.0 ± 2.7	n.s.
ALSFRS-R (range = 0–48)	31.5 ± 9.0	33.3 ± 8.6	n.s.
FVC (% of predicted)	78.1 ± 25.0	78.7 ± 23.8	n.s.
Disease Duration (Months)	48.3 ± 56.5	40.2 ± 51.4	n.s.

2.2. Screening instruments

2.2.1. The Frontal Assessment Battery

The FAB takes approximately 5 to 7 min to administer and consists of the following tasks: abstraction, verbal fluency, motor programming, conflicting instructions, inhibitory control, and prehension behaviour. A maximum of 3 points is allocated for each of the six tasks, for a total maximum score of 18. Scores were corrected for age and education according to previously published normative data and patients with corrected scores below 14.11 were classified as abnormal [34].

2.2.2. The Montreal Cognitive Assessment

The MoCA takes approximately 10–15 min to administer and assesses cognitive functions in the following domains: visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall, and orientation. A maximum total score of 30 is possible, with scores below 26 indicative of cognitive impairment [17]. Patients with 12 or less years of education are allocated an additional point.

2.2.3. Task modifications

Modifications were made to accommodate those with advanced hand weakness or dysarthria. A modified FAB was administered to 7 patients, 6 of whom completed the entire FAB. Three of these patients provided written answers to the abstraction task to compensate for dysarthria. Due to hand weakness, 2 patients tapped their feet and 2 patients clicked their teeth on the conflicting instructions and inhibitory control tasks. A modified MoCA was completed by five patients. Two patients with severe hand weakness used their dominant foot for tapping during the attention subsection and 3 patients with severe dysarthria provided written responses to the naming, memory, attention, abstraction, and orientation tasks.

2.3. Statistical analysis

Pearson and Spearman correlations assessed the relationship between FAB and MoCA scores and clinical and demographic variables, including age, education, ALSFRS-R scores, FVC, and disease duration. Statistical significance was accepted at $p < 0.05$, one-tail test.

3. Results

3.1. Frontal Assessment Battery

Eight (21%) of the 38 patients that completed the entire FAB were classified as impaired. There was considerable variability in FAB scores (Fig. 1).