Neuropsychological deficits in amyotrophic lateral sclerosis (ALS): a South India experience

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Abstract

ALS is a terminal progressive degenerative neurological disorder studies suggest that approximately 35% to 52% of ALS patients experience cognitive deficits which may be identified early in the course of the disease. Cognitive deficits being the integral part of the disease has not been studied in the Indian setting. This is one of the first studies assessing the pattern of cognitive impairment in ALS in the Indian condition. The objective is to examine the neuropsychological profile of amyotrophic lateral sclerosis. Cognitive function was studied in 20 ALS patients: mean age 45.85 ± 13.9 years (22-65). Neuropsychological test battery was administered. In all 21 test were administered individually in 4-5 sessions which lasted for 7-8 hours. The results show that the majority of patients were from lower/middle socio-economic background. Scores were compared with gender, age and education specific norms, wherein scores falling below 15th percentile of the normative data were treated as deficits. ALS-associated cognitive impairments include deficiencies in visual attention, working memory, fluency, cognitive flexibility, response inhibition, planning, problem solving, and visual-perceptual skills. These impairments indicate executive dysfunction. In conclusion ALS is a disease that affects higher cognitive frontal functions, especially the EF.

Keywords: Cognitive function; Executive function; Neuropsychological assessment

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a pure motor disease; it is a progressive disorder of the upper and lower motor neurons Rowland and Shneider

(2001). Cognitive impairment in ALS ranges from mild impairment to fronto-temporal lobar dementia (Strong, Lomen-Hoerth, Caselli, Bigio & Yang, 2003). Cognitive abnormalities include deficiencies in frontal executive skills. Cognitive impairment occurs in sporadic and familial forms of ALS. Patients may present with cognitive deficits before, after, or at the onset of motor neuron disease. Neuropsychological studies have suggested that the predominant cognitive deficits are seen in the domain of executive functions and free recall indicating frontal lobe dysfunction (Gallassi et al., 1985; Abrahams, Goldstein, Lyoyd, Brooks & Leigh, 1995; David & Gillham, 1986; Massman et al., 1996; Frank, Haas, Heize, Stark & Munte, 1997; Abrahams et al., 2000). Electrophysiological studies (Gil et al., 1995; Münte et al., 1998 and 1999; Vieregge, Wauschkuh, Heberlein, Hageneh & Verleger, 1999) have provided evidence for extra-motor involvement in non-demented patients with ALS. Imaging studies have shown frontal atrophy and hypometabolism in the frontotemporal regions and the anterior cingulate gyrus in ALS patients with cognitive deficits (Ludolph, Langen & Regard, 1992; Kew, Goldstein, Leigh, Abrahams & Cosgrave, 1993; Tanaka et al., 1993; Talbot, 1995; Abe et al., 1997). Functional and structural imaging studies suggest frontal involvement in non-demented ALS patients (Ludolph et al., 1992; Kato, Hayashi & Yagishita, 1993; Kew et al., 1993; Abrahams, 1995; Abrahams et al., 2000; Lloyd, Richardson, Brooks, Al-Chalabi & Leigh, 2000). 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 (Mitsuyama, 1984; Anderson, Cairns & Leigh, 1995; Strong et al., 2003). The prevalence of cognitive impairment in ALS is unknown. It is estimated to be 2% to 5% (Jokelainen, 1977; Hudson, 1981) but they vary up to 35% to 52% (Massman et al., 1996; Lomen-Hoerth et al., 2003).

The aim of this study is to investigate the presence and pattern of cognitive dysfunction in, relatively less handicapped and non-demented ALS patients referred from the Department of Neurology, Neuromuscular Clinic, National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore, India.

2. Method

The study began after obtaining ethical clearance from the NIMHANS ethical committee and written informed consent from all the patients.

20 patients were referred from the Neuromuscular Clinic, Department of Neurology, NIMHANS, Bangalore, India. Patients were diagnosed by the Neurologist to have amyotrophic lateral sclerosis (ALS). There were 17 males and 3 females. The mean age at examination was 45.85 ± 13.9 years (22-65), and the mean duration of illness was 15.75 ± 15.0 months (2-60). Mean age of onset was 44.75 ± 14.1 years (19-65). Symptom at onset was bulbar dysfunction in 6 (30.0%) and limb onset in 14 (70.0%). On examination wasting and weakness of limbs was noted in 18 (90.0%) and bulbar involvement in 10 (50.0%). According to revised El Escorial criteria (Miller, Munsat, Swash & Brooks, 1999) seven patients had definite ALS and 13 had probable ALS. Majority of the patients hailed from lower/middle socio-economic status. All patients were right handed as assessed by the Edinburg's Handedness Inventory. Patients were excluded if they had any sensory abnormalities, and serious concomitant conditions, such as stroke, depression, and other psychiatric disease. All the patients were assessed individually. They were assessed in 3-4 sessions with adequate rest pauses.

2.1. Procedure

A comprehensive neuropsychological assessment was carried out by trained neuropsychologists to assess cognitive functioning. The following cognitive domains were assessed: motor speed, fluency (category and phonemic fluency), working memory (verbal and visual), planning, set-shifting, verbal learning, and verbal memory. Some of these were paper-pencil tests. The tests used for the present study have been standardized for use in the Indian population (Rao, Subbakrishna & Gopukumar, 2004).

Motor speed. To assess the domain of motor speed the *Finger Tapping Test* (Halstead, 1947) was administered. The test consists of a tapping key mounted on a box with an attached electronic counter. The subject was required to tap the key as many times as possible within a 10-s trial. Five 10-s trials were administered for both the right and left hand with a rest pause of 30-s after the third trial. Number of taps with the forefinger of each hand was recorded. The average number of taps across trials for the right hand and left hand was used for analyses.

Verbal fluency. To assess phonemic fluency, the *Phonemic Fluency Test* (Rao et al., 2004) was administered. This test is analogous to the *Controlled Oral Word Association Test* (Benton & Hamsher, 1989). To make the test suitable for use in Indian languages, the phonemes "Ka", "Pa", and "Ma" were used. The subject was required to generate words beginning with each of the phonemes. One-minute time was given for each phoneme. The score used

was the average number of words generated. The *Animal Names Test* (Lezak, 1995) was administered to assess category fluency. The subject was asked to generate animal names, excluding fish, birds, and snakes, for 1 minute. The score used was the total number of animal names generated.

Working memory. To assess the domain of verbal working memory, *Verbal N-Back Task* (Rao et al., 2004) was administered. The test is a modification of the task developed by Smith and Jonides (1999). Test stimuli comprise two lists of 30 randomly arranged phonemes, which are read aloud to the subject. In the 1-back task, the subject is instructed to say, "yes" whenever the phoneme is repeated. In the 2-back task, the subject is instructed to respond whenever a phoneme is repeated after an unrelated phoneme. The score is the number of correct responses in the 1-back and 2-back tasks. The *Visual N-Back Task* (Rao et al., 2004) was administered to assess visual working memory. The test is modified from the task developed by Smith and Jonides (1999). The 1-back and 2-back procedures are similar to that of the Verbal N-Back Task. The test stimuli are 36 cards containing dots printed randomly in positions around an imaginary circle. In the 1-back task, the subject is instructed to respond whenever the dot appears in the same position on two consecutive cards. In the 2-back task, the subject is required to respond whenever the dot appears in the same position on alternate cards. The score used for analyses is the number of correct responses on the 1- and 2-back tasks.

Planning. To assess the domain of planning, the *Tower of London Test* (TOL) was administered (Shallice, 1982). The test stimuli consist of two boards with three pegs of different sizes and three different colored balls (red, blue, and green). The subject is required to match the arrangement on the examiner's board using the minimum number of moves. A total of 14 problems of increasing complexity are given. The total number of problems solved with minimum moves (TNPMM) was used for analyses in the present study.

Verbal learning and memory. The *Auditory Verbal Learning Test* (AVLT) was administered, which assesses immediate memory span, new learning, susceptibility for interference, and recognition memory (Schmidt, 1996). Subjects were required to recall as many words as possible from a 15-word list that was read aloud to them. Five such learning trials were administered. Following this an interference trial was administered in a similar manner using a different word list. An immediate recall, a 20-min delayed recall without prior warning, and a recognition trial of the original list was also administered. The present study used the World Health Organization (WHO) word lists, which were translated into different Indian languages. The test was administered and scored according to the procedure given by Schmidt (1996). For analyses, the scores Trial I-V Total, Immediate Recall, and Delayed Recall of the word list were considered.

3. Results

Cognitive functioning in the ALS sample was compared with normative data derived from a group of 540 normal healthy volunteers (Rao et al., 2004). Healthy volunteers were recruited from relatives of patients admitted at the hospital, students, and from the community at large. Healthy volunteers who obtained a score of > 2 on the General Health Questionnaire (GHQ-12) developed by Goldberg and Williams (1988) were excluded, as these persons met criteria for psychological distress, which could influence cognitive functioning. Healthy volunteers were also excluded if they had a previous history of neurological, neurosurgical, or psychiatric illness or substance dependence and family history of alcohol dependence, schizophrenia or bipolar disorder. The sample was divided into three age ranges (16-30, 31-50, and 51-65 years) and three education groups (no formal schooling, 1 to 10 years, and greater than 10 years of formal education) separately for males and females. For each test variable, percentile scores were calculated. The 15th percentile score (1 SD below the mean) was taken as the cut off score (Heaton et al., 1995). Cutoff scores were calculated for each group based on age, education, and gender. A deficit was defined as a test score falling below the 15th percentile (Heaton et al., 1995). Validation for each of the tests has been carried out on patient groups with focal lesions, refractory epilepsy, head injury, and Parkinson disease (Rao et al., 2004). In order to examine the prevalence of cognitive deficits, a cognitive profile was obtained for each patient in the ALS group by comparing test performance with the normative data described above. Based on the number of test variables falling below the 15th percentile, the severity of cognitive impairment was established.

Table 1. I showing age and education of the ALS patients N = 20

	Age	Education School	Education College	No Education
Male	16-65 years	Total-12	Total-5	
	16-30 years	5	3	
	31-50 years	5	1	
	51-65 years	2	1	
Female	16-65 years	Total-3	Total-0	
	16-30 years	2	–	–
	31-50 years	1	–	–
	36-40 years	–	–	–
	51-65 years	–	–	–

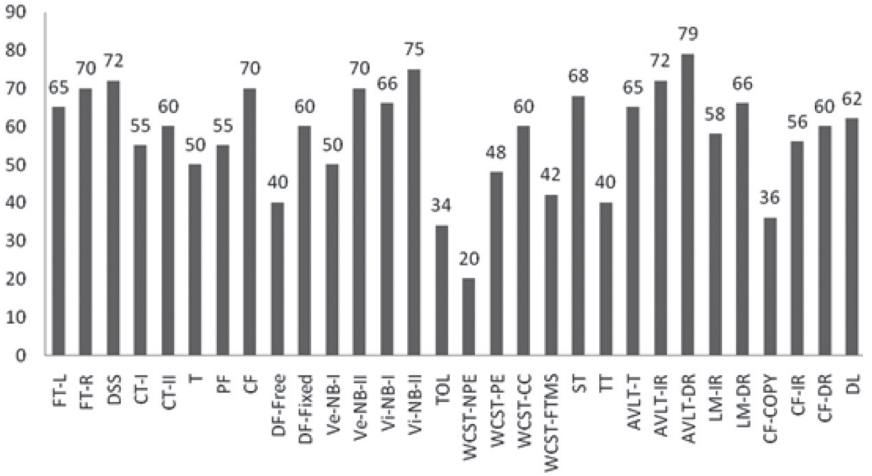

Figure 1. I showing the percentage of deficits on each of the test N-20

Above 50% indicates the number of patients with deficits.

Finger tapping-left, right (FT), Digit symbol substitution (DSS), Color trials-I, II (CT), Triads (T), Phonimic fluency (PF), Category fluency (CF), Design fluency (DF), Verbal N-Back (Ve-NB), Visual N-Back (Vi-NB), Tower of London (TOL), Wisconsin card sorting test - Non preservative errors, Preservative errors, Category completed, Failure to maintain set (WCST-NPE, PE, CC, FTMS), Stroop test (ST), Token test (TT), Auditoty verbal learning test-Total, Immediate recall, Delayed recall (AVLT-T, IR, DR), Logical memory - Immediate recall, Delayed recall (LM-IR, DR), Complex figure test-copy, Immediate recall, Delayed recall (IR, DR), Design learning (DL).

The graph shows the percentage of deficits of the 20 ALS patients on the neuropsychological battery. Sensitive of the test in ALS patients was considered when more than 50% patients showed deficits on a particular test. Deficits were seen in the following domains, motor and mental speed, attention, executive functions-fluency, working memory, set shifting, verbal and visual learning and memory.

4. Discussion

The objective of the study was to assess cognitive deficits and determine the presence of a specific neuropsychological profile in patients with ALS. The sample consisted of 20 patients diagnosed with ALS by the Neurologist. Mean age was 45.85 and mean education was 10.40. There were 17 male

patients and 3 female patients. On the Neuropsychological tests the ALS patients performance is as follows, on the speed test there was impairment on both motor L = (65%) R = (70%). The finger tapping test is used to measure motor speed. There are several brain structures mediating motor speed. The prefrontal cortex mediates motor planning, the supplementary motor area mediates initiation of motor acts, while the premotor cortex, basal ganglia and the cerebellum mediate fine motor control motor speed therefore requires integration among multiple centers, which mediate movement in ALS. Mental speed was measured by the Digit symbol substitution (72%). Mental speed requires coordination of different areas of the brain, mainly frontal and parietal cortices. Attention was measured by the Color trails I and II and triads, deficits were seen on both the test 55%, 60% and 50% of the patients respectively. Fluency was tested for both verbal and design fluency. It is an aspect of mental flexibility. Phonemic fluency refers to the capacity to generate new words in a regulated manner and category fluency refers to the capacity to generate words belonging to a category imposed by regulation. 55% and 70% of the patients showed deficits respectively. Neuroimaging studies have shown temporal lobe involvement in category fluency (Frith et al., 1991). On the design fluency only in the fixed condition 60% patients showed deficit. Verbal working memory using N-Back task I-Back (50%) II-Back (70%), this test activates Broca's area and left supplementary motor and premotor areas (Smith & Jonides, 1999). The verbal items appear to be represented in the left posterior temporal areas, short term storage of phonological information is in the left supramarginal gyrus, the left dorsolateral prefrontal cortex maintains the temporal order and the Broca's area supports articulatory processes (Henson, Burgess & Frith, 2000) visual working memory using N-Back task I (66%) II-Back (75%). The visual sketchpad is a buffer responsible for the initial registration of visual material (Baddeley, 1986). Activation in dorsolateral prefrontal cortex reflects manipulation and transformation rather than the storage or retrieval. Set shifting was tested by the WCST. It is the ability to change a mental set in response to environmental contingencies (Spreen & Strauss, 1998). It is the ability to adapt to response to a changing environment. Set shifting ability regulates attention, thought, speech, emotion, and social behavior. It requires cognitive flexibility both in the formation of mental set and in the subsequent shifting of the set. Recent evidence suggests that set shifting ability is also important in selection of appropriate tasks for execution. 60% of the patients showed deficit only in the number of categories completed. Response inhibition was measured by stroop test. It refers to the ease with which a perceptual set can be shifted both to conjoin changing demands and by suppressing a habitual response in favor of an unusual one. Contribution of the medial orbitofrontal cortex

to response inhibition and stimulus-based switching of attention, has been indicated Szatkowska (2007). Imaging studies with PET have shown activation of anterior right hemisphere lesions and medial frontal structures in stroop task (Bench et al., 1993). Casey et al. (1997) concluded that disruption of the basal ganglia, thalamo cortical circuits at the level of basal ganglia appears to be involved with response inhibition. 68% of the patients showed deficits on this test. Verbal learning and memory was tested using the Auditory Verbal Learning Test, and Logical Memory Test. It is the capacity to learn and remember verbal material. The right prefrontal lobe is involved to a greater extent in retrieval from episodic memory, Tulving (1999). Prefrontal cortices are important for the organization of the material, verification of recalled material and formulating heuristic strategies for learning, while the hippocampal structures are important for associations between events discrete in time and space. Lesions in the left temporal lobe disrupt verbal memory and excision of left hippocampal structures impairs verbal memory to a greater extent (Smith & Milner, 1981; Jones-Gotman, 1997). Deficits were seen in immediate recall (72%) on AVLT and 58% on LM, delayed recall on AVLT (79%) and (66%) on LM. Visual Learning and Memory was tested using the Rey's complex figure test and design learning test. It is the capacity to construct a design or to translate a visually perceived form into a three dimensional object or two dimensional figure. Visuo constructive ability requires attention, visuospatial perception, visuomotor coordination, planning and error correction ability. This ability is composite function of which is mediated by bilateral parietal structures, predominantly by the right parietal structure. The prefrontal structures also mediate the planning and error correction required for visuo constructive ability (Lezack, 1995). Deficits were seen in both the test CFT-IR (56%) and CFT-DR (60%) and on DL (62%). In summary results of the neuropsychological profile in ALS patients indicate impairment in motor and mental speed, attention, executive functions-fluency, working memory, planning, set shifting, response inhibition, verbal and visual learning and memory. ALS is a disease that affects higher cognitive function especially the executive functions.

Conclusion. We conclude that there is a fronto-temporal pattern of cognitive dysfunction in ALS expressing itself early in the course of the disease. The cognitive deficits do not progress in synchrony with motor decline, but distinctly more slowly since some of the cognitive functions were preserved. The cognitive profile also indicates that the higher cognitive function especially the executive functions were impaired.

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