PREVALENCE AND PATTERNS OF COGNITIVE IMPAIRMENT IN AMYOTROPHIC LATERAL SCLEROSIS AND CORRELATION WITH DISEASE OUTCOME

Dr. Manisha K Yalapalli

DM Neurology THESIS

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SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM

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A THESIS SUBMITTED BY

Dr. Manisha K Yalapalli

TO

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IN PARTIAL FULFILMENT OF THE

REQUIREMENTSFOR THE AWARD OF

DM Neurology

2021 - 2023

DECLARATION BY THE STUDENT

CERTIFICATE

I, Dr. Manisha K Yalapalli hereby certify that I had personally carried out the work depicted in the thesis titled, "Prevalence and Patterns of cognitive impairment in Amyotrophic Lateral Sclerosis and correlation with disease outcome".

No part of this thesis has been submitted for the award of any other degree or diploma prior to this date.

Date 23.08.2023

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The thesis entitled, "Prevalence and Patterns of cognitive impairment in Amyotrophic Lateral Sclerosis and correlation with disease outcome". was carried out under my direct supervision. No part of the thesis was submitted for the award of any degree or diploma prior to this date.

*Clearance was obtained from the Institutional Ethics Committee for carrying out the study.

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APPROVAL OF THE THESIS

The thesis entitled

Prevalence and Patterns of cognitive impairment in Amyotrophic Lateral Sclerosis and correlation with disease outcome

Submitted by

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for the degree of **DM**

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LIST OF ABBREVIATIONS (Optional)

S No	Abbreviation	Full Form
1	ACE III	Addenbrooke's cognitive evaluation III
2	RAVLT	Rey Auditory Verbal Learning Test
3	VOSP	Visual object and space perception battery
4	ALS- CBS	ALS- Cognitive behavioral screen
5	QoL	Quality of life
6	ALS - FRS	ALS -Functional Rating scale
7	MRC SUM	Medical Research Council- Sum score
8	TMT	Trail making test

SYNOPSIS

PREVALENCE AND PATTERNS OF COGNITIVE IMPAIRMENT IN AMYOTROPHIC LATERAL SCLEROSIS AND CORRELATION WITH DISEASE OUTCOME

SYNOPSIS

BY

Manisha K Yalapalli

for DM Neurology

of

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM

SYNOPSIS

Amyotrophic lateral sclerosis (ALS) is a relentlessly progressive disorder of upper and lower motor neurons which leads to muscle weakness and eventually paralysis. Though initially considered to be a purely neuromuscular syndrome, with the description of ALS-Plus syndromes constituting extrapyramidal involvement, cognitive dysfunction, autonomic dysfunction, oculomotor and sensory abnormalities, it was considered to be a neurodegenerative syndrome. Cognitive impairment is described in 55 to 75% of patients in various studies. However, there is scanty information regarding the natural history of cognitive decline in ALS and its incidence and prevalence. Even though various risk factors for cognitive impairment in ALS like old age, bulbar onset, and male sex have been proposed, they have not been reported consistently. There is no data so far to suggest if there is a definite impact of cognitive impairment in survival and motor progression, especially in the Indian population, where the data is extremely lacking.

Aims and objectives:

The aim of the study was to assess the prevalence and patterns of cognitive impairment in Amyotrophic Lateral Sclerosis and to determine the association of cognitive impairment with disease progression, change in quality of life and caregiver burden at 6-month follow-up.

Hypothesis:

Cognitive impairment affects a significant proportion of patients with ALS and worsens the disease progression, quality of life and caregiver burden at follow-up.

Methods:

Ours is a single-centre prospective observational study and all patients diagnosed with Amyotrophic Lateral Sclerosis by Gold Coast criteria attending the OPD and admitted

in wards of the Department of Neurology, Sree Chitra Tirunal Institute of Medical Sciences and Technology (SCTIMST) from 01.12.2021 to 01.01.2023 were enrolled in the study and followed up for 6 months. Patients with gross motor or bulbar impairment affecting neuropsychological test performances were excluded. The demographic, clinical, and electrophysiological data was collected and a detailed neuropsychological assessment involving domains of attention, execution, memory, fluency, visuospatial function and behaviour was done. Quality of life and caregiver burden were assessed at baseline and follow-up. The prevalence and patterns of cognitive impairment were determined and the effect of cognitive impairment on motor progression, functional assessment, quality of life and caregiver burden were determined.

Significant findings:

Out of the 88 patients, after applying inclusion and exclusion criteria, 60 were included, of which 46 patients were followed up for 6 months. The mean age of presentation was 55.5(±13) years. The male-to-female ratio was 1.8: 1. The mean ALS- Functional rating scale at presentation was 39.7(±6.36). Neuropsychological parameters showed predominant involvement in executive dysfunction, visuospatial function and memory. In our cohort, 63.3% were detected to be cognitively impaired with impairment in at least two non-overlapping tasks involving at least two domains. Increased age and decreased ALS- FRS scores at baseline were significantly associated with cognitive impairment. Patients with cognitive impairment were noted to have reduced quality of life ($P= 0.032$) and increased caregiver burden ($p< 0.001$). On follow-up cognitive impairment was associated with poor functional scores on ALS- FRS($p= 0.05$), impaired quality of life parameters – mainly for physical functioning ($p= 0.035$) and increased caregiver burden ($p= 0.046$). No association was noted with motor progression.

Implications:

- Our study showed cognitive impairment in about two-thirds in an Indian cohort of ALS
- The predominant cognitive domains involved are executive function, attention and visuospatial function, and memory in that order.
- Cognitive impairment was noted to have a significant impact on functional scores, quality of life, and caregiver burden at baseline and 6-month follow-up.
- There was no correlation with motor progression
- Our study further proves that the hitherto assumption that "ALS spares the mind" does not hold.
- A significant proportion had cognitive impairment despite there being no clinical symptoms, which affects the quality of life and the functional scores, as well, the capacity to make decisions regarding further life-prolonging interventions
- This indicates the need for detailed neuropsychology evaluation and formulation of culturally appropriate neuropsychological tests and early cognitive intervention in ALS patients
- This could improve the quality of life for both patients and caregivers managing this devastating disease.

1 INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a relentlessly progressive disorder of upper and lower motor neurons which leads to muscle weakness and eventually paralysis. Recent studies suggest that ALS is a complex genetic disorder with about 10% of cases being familial with Mendelian Pattern of inheritance, rest of the 90% are classified as sporadic, although there is evidence for common inherited susceptibility genes.(Greenway et al., 2006)

The initial presentation of ALS may be divided into spinal-onset disease (that is, the onset of muscle weakness of the limbs), and bulbar-onset disease, which is characterized by dysarthria (difficulty with speech) and dysphagia (difficulty swallowing)(Hardiman et al., 2017). Although the primary symptoms of ALS are associated with motor dysfunction (such as muscle weakness, spasticity and dysphagia), up to 50% of patients develop cognitive and/or behavioural impairment during the course of the disease, and 13% of patients present with concomitant behavioural variant frontotemporal dementia (FTD). (Elamin et al., 2013; Phukan et al., 2007) Among the various types of FTD, frontal dysexecutive syndrome is usually seen in ALS rather than other types of FTD. The high prevalence of cognitive and/or behavioural symptoms in patients with ALS, coupled with the finding of a hexanucleotide repeat expansion in C9orf72 has been identified as a major cause of ALS and FTD. (DeJesus-Hernandez et al., 2011). This altered the perception of ALS from a pure neuromuscular disorder to a neurodegenerative disorder.

There has been better characterization of ‘plus’ syndromes more recently. Co-existing parkinsonism, sensory syndromes, autonomic dysfunction, oculomotor

abnormalities, cerebellar involvement, cognitive impairment, geographical clustering constitute the plus syndromes. (Brooks et al., 2000)Cognitive impairment has been increasingly recognized as an important association.

ALS when associated with frontotemporal dysfunction, it is categorized as ALS – FTD based on the consensus criteria by Strong and Neary et al; (Neary et al., 1990; Strong et al., 2003, 2017). Also, the behavior or/ and cognitive features, not sufficient to meet the diagnosis of dementia, but sufficient to give rise to impairment were termed as ALS cognitive impairment(ALSci) and ALS behavioral impairment(ALSBi). (Strong et al., 2003). People who develop dementia not typical of FTD were categorized as ALS-Dementia. Early reports suggested cognitive impairment rates of 1 to 4% increasing to 55 to 75% recently (Phukan et al., 2007; Ringholz et al., 2005; Strong et al., 1999) probably due to better assessment with increased neuropsychological performance testing and a holistic assessment with development of new scales involving multiple domains.

Prior studies have shown impairment of attention, working memory, verbal fluency and frontal executive functions(Phukan et al., 2007; Robinson, 2006; Strong et al., 1999) corroborated by histopathological and functional imaging studies(Wilson et al., 2001). The ALS-specific patterns of cognitive impairment were considered to involve execution and attention and hence previous studies categorized this ALS- Sci spectrum as ALS- Executive impairment; non-executive cognitive impairment has been described in 34.1% and 17.4% of patients respectively. The executive impairment is due to involvement of the frontostriatal circuit, whereas the non-executive group predominantly including memory occurred due to impairment in hippocampal circuitry (Phukan et al., 2012). Older age, bulbar onset, and low education have been suggested as risk factors for ALS-associated dementia or cognitive

dysfunction, but the associations have been inconsistent across different studies. (Rippon et al., 2006).

The impact of cognitive dysfunction in ALS is considerable. Cognitive deficits could interfere with compliance with treatment, the ability to make end-of-life decisions, worsen the disease outcome, affect the quality of life of patients and increase carer distress. The pattern of cognitive dysfunction has never been studied in an Indian ALS cohort. In this background, we envisaged this study to examine the frequency and patterns of cognitive impairment in patients with ALS, its various associations, and the effect it has on motor progression, quality of life and caregiver burden.

AIMS AND OBJECTIVES:

1. To study the prevalence and patterns of cognitive impairment in Amyotrophic Lateral Sclerosis
2. To assess the association of cognitive impairment with disease progression
3. To determine the association of cognitive impairment on change in quality of life and caregiver burden at 6-month follow-up.

REVIEW OF LITERATURE

AMYOTROPHIC LATERAL SCLEROSIS- DEMOGRAPHICS

Amyotrophic lateral sclerosis (ALS), a prototypic motor neuron disease (MND), is a progressive disease of upper and lower motor neurons leading to varying degrees of muscle weakness, ultimately paralysis and death within 2-4 years in most cases.

It was originally delineated by Jean-Martin Charcot (1825–1893), a French neurologist, who described the clinical and pathologic aspects of ALS (Kumar et al., 2011). In the US, Lou Gehrig, a baseball legend first suffered ALS at the age of 38 years and died within 4 years, hence also named as Lou Gehrig's disease. The annual incidence rate of ALS is at 0.6 to 1.8, and prevalence is at 4 to 8 per 100,000 population. (Rowland and Shneider, 2001) The disease occurs in a random pattern throughout the world except for a clustering of patients among inhabitants of Guam, West New Guinea and the Kii Peninsula where ALS is often combined with dementia and parkinsonism. The ALS is about one-and-half times more common in men than women. Most patients are in the fifth decade and incidence increases with advancing age. (Hardiman et al., 2017).

Up to 20% of individuals with ALS have a family history of either ALS or FTD (familial ALS), and of these, four genes account for up to 70% of all cases of familial ALS, namely, C9orf72, TARDBP (encoding TAR DNA-binding protein 43, TDP43), SOD1 (encoding superoxide dismutase) and FUS (encoding RNA- binding protein FUS)· However, even in the case of these known Mendelian-inherited genes, familial forms of ALS are often characterized by <50% penetrance and genetic pleiotropy, with evidence of oligogenic and polygenic inheritance in individuals with seemingly sporadic disease.(Hardiman et al., 2017)

The traditional definitions of ALS sub-groups are based on the extent of involvement of upper and lower motor neurons, the other classification schemes are based on the site of onset (that is, bulbar-onset or spinal-onset disease), the level of certainty of diagnosis according to the revised El Escorial criteria and heritability (sporadic or familial disease)(Hardiman et al., 2017)

The treatment of ALS is primarily symptomatic management with currently only two available disease-modifying therapies like Riluzole and Edaravone; Phase I trials assessing the use of antisense oligonucleotides in SOD1-related and C9orf72-related ALS are underway. In view of the limited therapeutic options, main focus is on improving the quality of life of patients. (Hardiman et al., 2017)

DIAGNOSTIC CRITERIA OF ALS – EVOLUTION :

The original diagnostic criteria defined at El Escorial, Spain, in 1990 and their subsequent 1998 revision at Airlie House, USA, and in 2006 at Awaji-shima, Japan, employed categories based on the number of body regions (bulbar, cervical, thoracic and lumbosacral) with simultaneous UMN as well as LMN signs. The terms used were - 'suspected', 'possible', 'probable', 'probable laboratory-supported' and 'definite' ALS. The patients' evolution through each of these categories until they could be labelled definite was extremely slow; leading to patients dying with ALS without a "definite" diagnosis.

Even though EMG may detect LMN findings accurately, it falls deficient in UMN findings and may not be used as an isolated marker.

El Escorial and Airlie House criteria for the diagnosis of ALS(Brooks et al., 2000; Mitsumoto, 2017)

The presence of:

(a) Evidence of lower motor neuron degeneration by clinical, electrophysiological or neuropathological examination;

(b) Evidence of upper motor neuron degeneration by clinical examination; and (c) Progression of the motor syndrome within a region or to other regions,

as determined by history or examination; and,

The absence of:

(a) Electrophysiological and pathological evidence of other disease processes that might explain the signs of lower or upper motor neuron degeneration; and,

(b) Neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs.

Categories of Diagnostic Certainty (El Escorial criteria)

Definite ALS: Upper and lower motor neuron signs in three regions.

Probable ALS: Upper and lower motor neuron signs in at least two regions, with upper motor neuron signs rostral to (above) lower motor neuron signs.

Possible ALS: Upper and lower motor neuron signs in one region, upper motor neuron signs alone in two or more regions, or lower motor neuron signs above upper motor neuron signs.

Suspected ALS: Lower motor neuron signs in only two or more regions.

Categories of Diagnostic Certainty (Airlie House criteria)

Clinically definite ALS: clinical evidence alone of upper and lower motor neuron signs in three regions.

Clinically probable ALS: clinical evidence alone of upper and lower motor neuron signs in at least two regions with some upper motor neuron signs rostral to the lower motor neuron signs.

Clinically probable–laboratory-supported ALS: clinical signs of upper and lower motor neuron dysfunction in only one region, or upper motor neuron signs alone in one region with lower motor neuron signs defined by electromyography criteria in at least two limbs, together with proper application of neuroimaging and clinical laboratory protocols to exclude other causes.

Possible ALS: clinical signs of upper and lower motor neuron dysfunction in only one region, or upper motor neuron signs alone in two or more regions; or lower motor neuron signs rostral to upper motor neuron signs and the diagnosis of clinically probable–laboratory-supported ALS cannot be proven.

With the discovery of new potential biomarkers of subclinical UMN degeneration like blood neurofilament concentrations, diffusion tensor imaging, transcranial magnetic stimulation; and LMN degeneration, like muscle ultrasound detection of subclinical fasciculation and the futility of relying on the site of onset alone and EMG findings which have high variability and cannot detect UMN findings; new diagnostic criteria like the Gold Coast have been proposed that are multiaxial; where EMG may be used as adjunct for clinical decision making, rather than the sole criterion which helps in better identification, diagnosis , early intervention.(Martin R Turner, 2022a)

The Gold Coast criteria for the diagnosis of amyotrophic lateral sclerosis(Martin R Turner, 2022a)

1. Progressive motor impairment documented by history or repeated clinical assessment, preceded by normal motor function,

AND

2. The presence of upper and lower motor neurone dysfunction in at least ONE body region, with upper and lower motor neuron dysfunction noted in the same body region if only one region is involved, or lower motor neurone dysfunction in at least TWO body regions,

AND

3. Investigations excluding other disease processes.

ALS PLUS SYNDROMES/ UNCOMMON MANIFESTATIONS IN ALS

ALS when associated with atypical features, it is defined as ALS Plus syndromes. Even though there were few atypicalities described in a few case reports and series; it was recognised as a different entity in consensus modification El Escorial criteria. The clinical features seen in plus syndromes are extrapyramidal signs, cerebellar degeneration, dementia, autonomic nervous system involvement, objective sensory abnormalities, oculomotor abnormalities and mimics like delayed post-poliomyelitis; multifocal motor neuropathy with or without conduction block; endocrinopathies; lead intoxication; infections. (Brooks et al., 2000; Shannon Vandriel et al., 2014). In a study done by Vandriel et al; there is a high prevalence of ALS plus syndromes to as high as 13.6% and notably poorer prognosis, along with a high association with bulbar onset in this subset(Shannon Vandriel et al., 2014).

Among these, cognitive dysfunction has been recognised frequently with a progressive increase in prevalence. (Rippon et al., 2006; Wilson et al., 2001) The mechanism underlying the poor prognosis is the histopathologic abnormalities like TDP- 43 related pathology and increased ubiquitin which appears to correlate with cognitive decline.

COGNITIVE DYSFUNCTION IN ALS AND THE SPECTRUM OF ALS- FTD

Previously it was thought that ALS was purely a neuromuscular disorder. With the emergence of Plus syndromes, increased atypicalities were noted, of which cognitive dysfunction is a major part. Previously ALS was thought to spare the mind. However, studies in the early 1900s had shown some association between ALS and cognitive dysfunction, although it was never studied or prevalence was not ascertained until recently. Initially, motor neuronopathy developed in patients with frontotemporal dementia, suggesting an association. The earliest cases had shown reports of character change and behavioural alterations such as social disinhibition in patients with ALS; these have been labelled as ALS- Dementia. (Morita et al., 1987)

In one study of patients with dementia and MND, the pattern of mental change was shown to be indistinguishable from that of frontotemporal dementia (FTD) characterized by profound personality change and alteration in social cognition, features of primary progressive aphasia. There was a sparing of memory–recall and visuospatial function. These patients had executive dysfunction and exhibited poor abstraction, planning, set-shifting and organizational skills. Also profound changes in affect, with loss of basic and social emotions, and repetitive and ritualistic behaviours were noted. Thus suggesting the spectrum of FTD- ALS. The orbitofrontal and anterior temporal neocortex are the sites of earliest pathological change in FTD, with subsequent spread into other parts of the frontal lobe and subcortical structures with relative preservation of the hippocampal structures in

FTD / MND accounts for the absence of severe amnesia and the memory impairment is considered secondary to primary executive deficits. In patients not amounting to dementia, cognitive impairment in ALS was categorized as ALSci and behavioural impairment as ALSbi.(Strong et al., 2003) The ALS-specific domains involved were execution and attention and the non-specific domains involved were language and memory.

Patients with cMND /ALS (cognitive impairment in MND/ALS) have difficulty expressing their thoughts and feelings and controlling the emotional aspects of their behavior because of pseudobulbar and bulbar palsy. A lack of initiative and compliance in occupational and physical therapy was noted in patients with cMND /ALS suggesting the possibility of cognitive change in cMND/ALS, predominantly in the realm of executive functions. Deficits have been identified on the Wisconsin Card Sorting Test, Picture Sequencing and Verbal Fluency. (Massman et al., 1996; Neary et al., 2000; Ringholz et al., 2005; Strong et al., 1999)

Whereas some studies have reported impaired memory in cMND /ALS (Abrahams et al., 2005; Kew et al., 1993) others have demonstrated sparing of memory. (Neary et al., 2000; Talbot, 1996). Few studies have also reported impairment in language. A rapidly progressive aphasia has been described in relation to FTD- ALS; however complete aphasia is less likely in ALS with cognitive impairment. Deficits have been described in verbal fluency, semantics, and sentence comprehension. Poor verbal fluency has been shown to arise because of higher-order executive deficits rather than primary linguistic abilities. (Rakowicz and Hodges, 1998; Strong et al., 1996)

One of the earliest large prospective studies by Phukan et al; showed that ALS patients had frontotemporal dementia in 13.8% of patients. Among patients without dementia, predominant executive impairment as per consensus criteria was noted in 34.1% .

Non-executive cognitive impairment was noted in memory and language in 17.4%. The visuospatial function was however underrepresented noted in only 1.5% of patients.

In a study done by Ringholz et al; 50% of patients had some degree of cognitive impairment., the majority of the impaired patients in this study had deficits in attention, concentration, and working memory, with memory and confrontation naming, impaired to a lesser degree. This pattern has been described as a frontal/subcortical syndrome (Ringholz et al., 2005).

The cognitive impairment across ALS clinical stages has been studied by Chio et al; where 20.5% had ALS- FTD, 16.6% ALSci, 7.9%, ALS bi and non-executive impairment in 2%. They found that across Kings and MiToS(Milano Torino) staging, motor and cognitive components worsened in parallel and became more pronounced when the bulbar function was involved.

Early reports suggest a cognitive impairment of 1 to 4%,(3-5) however recent studies report as high as 55 to 75% cognitive impairment. ((Phukan et al., 2007; Ringholz et al., 2005; Strong et al., 1999). The increase could be due to the emergence of new neuropsychological tests and formulation of better cognitive batteries with holistic assessment leading to increased detection of cognitive impairment. The changes could also be due to selection bias and the stage of the population recruited.

PATTERN OF COGNITIVE DYSFUNCTION IN ALS

The range of cognitive impairment observed in ALS is striking, ranging from marked reduction in frontal executive skills to only mild cognitive deficits.(Lomen-Hoerth et al., 2003) The most common reported cognitive deficits are impairments in word fluency.(Abrahams et al., 2005; Strong et al., 1996) Other cognitive deficits such as the

inability to develop concepts and shift sets, perseveration of thought, impairment in planning, verbal and visual memory deficits, and impairment in visual perception and working memory have been described in patients with ALS.(Lomen-Hoerth et al., 2003; Strong et al., 1996).

EXECUTIVE FUNCTION:

Executive functions are thought of as higher- level mental processes that control and organise other cognitive processes. (Hoffmann, 2013) They are a heterogeneous set of skills that facilitate problem solving and responses to novelty. They are also implicated in regulation of behaviour, response initiation, motivation.

Impaired verbal fluency, a sensitive indicator of damage to frontal or striatofrontal areas that are involved in intrinsic initiation of responses, has been reported in almost all studies of cognitive impairment in ALS. Both letter fluency and category fluency may be affected. Simultaneous effects on both types of fluency implicate dysfunction in components of the executive system, whereas a disproportionate reduction in category fluency would suggest broader semantic impairment. (Massman et al., 1996),(Abrahams et al., 1997)

MEMORY:

There is wide variability in memory deficits of ALS so far in the literature. Immediate recall impairment was most commonly described, while delayed recall impairment is variable. This pattern favors that the abnormality lies in encoding rather than the executive component of memory and involves a neuronal circuit that arises in the left frontal lobe. One of the studies has also reported that free picture recall is affected in patients with ALS. (David and Gillham, 1986).

VISUOPERCEPTUAL FUNCTION:

Visuoperceptual functions include attention, object identification, and object recognition. They are largely preserved in many patients with ALS, (Kew et al., 1993; Robinson, 2006; Talbot, 1996) except for one by Strong et al; (Strong et al., 1999)

LANGUAGE:

Language networks were impaired in PET studies of ALS patients, suggesting the involvement of extra motor pathways. (Abrahams et al., 1996; Kew et al., 1993; Temp et al., 2021). Deficits noted in studies of ALS have reduced verbal output, deficits in the naming of objects (Robinson, 2006; Strong et al., 1999) and semantic paraphasia (substitution of words that relate closely to one another, e.g., sock for glove, or rabbit for squirrel)(Rakowicz and Hodges, 1998)

Patients with ALS can have features of progressive non-fluent aphasia, and semantic dementia (Caselli et al., 1993). Some of the patients had marked reductions in syntactic comprehension and naming.

Naming deficits have been reported in a few studies (Massman et al., 1996; Rakowicz and Hodges, 1998) which suggests that a language dysfunction underlies basic word-finding processes. However, in some patients, confrontation naming ability is intact. Processing of verbs has been reported to be greater than that of nouns in patients who have primary progressive aphasia or ALS with dementia(Hillis et al., 2004). Hillis and colleagues(Hillis et al., 2004) suggest that such differences in the patterns of language deterioration might relate to the degeneration of different brain areas, which implicates the posterior inferior frontal cortex and insula in motor speech and naming actions. Results from other studies have suggested that language deficits such as progressive slowing of word

retrieval form a continuum with aphasia in ALS. (Robinson, 2006)

Aphasia may be an early part of dementia or language deficits occur independently of cognitive impairment, and that patients with such deficits have a distinct subtype of ALS-related dementia. This suggests that the subtypes of ALS and frontotemporal dementia form a continuum, mutations in GRN have been associated with ALS, typical frontotemporal dementia, and a non-fluent progressive aphasia within a single family. (Snowden et al., 2006)

BEHAVIOUR:

Behavioural impairment is also considered as a feature in ALS. Rating scales such as the Neuropsychiatry Inventory, Frontal Behaviour Inventory, and Frontal Systems Behaviour Scale have shown that up to 63% of patients with ALS are apathetic, irritable, inflexible, restless, and disinhibited. Apathy and difficulties with social judgment seem to be more frequent in patients whose ALS has bulbar onset than in those whose ALS is non-bulbar. (Grossman et al., 2007)

The clinical presentation is thought to represent abnormalities that do not meet the Neary criteria for frontotemporal dementia.(Lomen-Hoerth et al., 2003) Behavioral impairment in ALS can be classified on the basis of presentation of frontal-lobe-type behavioral impairment in two or more areas, as measured from a standardized caregiver interview. (Grossman et al., 2007; Strong et al., 1996).

STUDY	PATIENTS (N)	TEST PERFORMANCE IMPAIRED	TEST PERFORMANCE SPARED
Gallassi, 1985 (Gallassi et al., 2009)	22	Verbal fluency, verbal reasoning, visual attention (Barrage test), short-term verbal memory (Rey's), short-term visual recall	Long-term verbal memory (Rey's verbal learning), memory spans (verbal and spatial)
Massman, 1996 (Massman et al., 1996)	146	Verbal fluency ,immediate free recall, continuous recognition memory , attention, set shifting	Delayed verbal recognition memory visuo-perception confrontation naming
Abrahams, 1997 (Abrahams et al., 1997)	52	Verbal fluency (written), executive function and intrinsic generation, planning and working memory, set shifting, word recognition memory test, Stroop negative priming (trend towards significance)	Episodic memory, recall memory
Ringholz, 2005	279	Verbal fluency, visual recall, logical memory, confrontation naming	Visuo-perceptual ability, MMSE, cognitive inhibition (Stroop)

(Ringholz et al., 2005)			
Cockford et al (2018)	161	Executive, language, letter fluency showed cross sectional effect across stages	Memory and visuospatial function

TABLE.1 - Notable studies on ALS- Cognitive impairment and modalities affected

PATHOLOGY IN ALS:

The pathological hallmark of ALS is ubiquitin-positive inclusions and TAR DNA binding protein- 43 (TDP- 43) inclusions. Ubiquitin-positive skein-like or dense, round structures in the cytoplasm of anterior horn cells that are not detected by H&E and other routine staining methods were described in ALS and also identified in FTD observed in neurons of the frontal cortex, temporal cortex, hippocampus and striatum, occasionally in glial cells. They are negative for proteins commonly associated with neurodegenerative inclusions, such as tau and alpha-synuclein.(Neumann et al., 2006)

TDP-43 was identified as the main component of ubiquitinated inclusions in both ALS and FTD patients termed as TDP-43 proteinopathies.TDP-43 is a heterogeneous nuclear ribonucleoprotein and has many different cellular functions, including mRNA stability, mRNA processing, mRNA transport and translation and negative regulation of alternative splicing.(Brettschneider et al., 2013) Under normal conditions, TDP-43 is expressed in many tissues including the nuclei of neurons and glial cells. In sporadic and most familial ALS as well as FTLD(Frontotemporal lobar degeneration)-TDP-43, there is a loss of nuclear TDP-43 and the formation of pathological aggregates in the cytoplasm**.** The mechanism behind this redistribution is poorly understood and could be either the

translocation of TDP-43 from the nuclei to the cytoplasm, or an impaired TDP-43 cytoplasm-to-nucleus shuttling process(Kawashima et al., 1998; Neumann et al., 2006; Saberi et al., 2015). In 2011, abnormally expanded GGGGCC hexanucleotide repeats in C9orf72 were identified as the most common genetic cause of Familial ALS and FTD. It displays the signature ubiquitin-positive, TDP-43-positive immunoreactive aggregates in neuronal cytoplasm(DeJesus-Hernandez et al., 2011)

Staging of ALS neuropathology has been proposed by Braak et al and Brettschneider et al. Stage 1 disease is characterized by a mild burden of pTDP-43 pathology involving motor cortex, brainstem motor nuclei, and spinal motoneurons. Stage 2 disease involves mild-moderate burden of pTDP-43 with dissemination into the prefrontal neocortex (middle frontal gyrus), reticular formation, and cerebellar nuclei. Stage 3 disease involves moderate burden of pTDP-43 with dissemination into basal ganglia and prefrontal and postcentral neocortex and striatum. Stage 4 disease involves severe burden of pTDP-43 including the hippocampal formation(Braak et al., 2013; Brettschneider et al., 2013)

The pathology of cognitive dysfunction is described mainly in frontal lobes in ALS ranging from frontal gyral atrophy, micro vacuolation of layer II cortex in frontal and temporal regions to gliosis of frontal subcortical white matter (Wilson et al., 2001). Also, ubiquitin-positive, tau-negative, and synuclein-negative neuronal inclusions in the cingulate gyrus and superficial linear spongiosis of the frontal cortex have been described predominantly in cingulate gyrus in cognitively impaired patients with ALS(Hoffmann, 2013). The predominant frontal distribution of abnormalities in histopathological studies corroborates with the clinical observations of impairment of attention, working memory, verbal fluency and predominant frontal executive functions(5,6).

IMAGING IN ALS- COGNITIVE IMPAIRMENT:

In patients with ALS, structural imaging shows hyperintensity along the Corticospinal tracts on T2-weighted or fluid-attenuated inversion recovery images in the posterior limb of the internal capsule, centrum semiovale and ventral brain stem . (Agosta et al., 2010) Voxel-based morphometry studies have shown that regional gray matter loss is not only confined to the motor cortex, but extends to the frontal, temporal, parietal, and limbic regions.(Kassubek et al., 2005) White matter loss in the corpus callosum, cerebellum, frontotemporal, and occipital regions has also been described.

A general pattern of cortical reorganization was found for motor function in patients with ALS when compared with that seen in normal subjects, with increased activation of the contralateral sensorimotor cortex, supplementary motor area, basal ganglia, and cerebellum demonstrated on fMR images during motor tasks. Reduced activation in the dorsolateral prefrontal cortex has been observed, providing further evidence for the existence of frontal lobe function deficits in patients with ALS (Stanton et al., 2007)

In patients with cognitive impairment, frontal atrophy on CT and MRI has been described,(Abrahams et al., 1996)and SPECT and PET studies have demonstrated reduced activation in dorsolateral and medial prefrontal cortices(Hoffmann, 2013)

In a study by Temp AGM et al; group differences in connectivity of the default mode network (DMN), motor network (MN), and ventral attention network (VAN) were investigated using a full-factorial model. Widespread decrease in functional connectivity in all three networks was noted when comparing ALS patients to healthy controls. Similar patterns of hypoconnectivity in the bilateral motor cortices and frontotemporal emerged when comparing the ALSci and ALS-FTD patients to those not cognitively impaired. Hyperconnectivity in the DMN temporal gyrus correlated with worse global cognition; moreover, hyperconnectivity in the thalamus, insula, and putamen correlated with worse shifting ability. Better-preserved motor function correlated with higher motor neuronal

connectivity. Resting-state functional connectivity differs between cognitive profiles of ALS and is directly associated with clinical presentation, specifically with motor function, and cognitive shifting.(Agosta et al., 2010; Temp et al., 2021)

COGNITIVE IMPAIRMENT- IMPACT ON QUALITY OF LIFE, OUTCOME

Cognitive impairment has major clinical implications, even though not studied so far in detail. When patient care is planned, problems with judgment, attention, inhibition, and generation of responses should be considered.

Deteriorating cognitive or executive function can affect the capacity to make decisions about health care or financial issues and the ability to engage with adequate competence in end-of-life decisions. Cognitive impairment can also reduce initiative and compliance with interventions such as occupational and physical therapy. As per study done by Olney RK. Et al; patients with ALS who also have FTLD are half as likely as are those who do not have FTLD to comply with non-invasive ventilation.(Olney et al., 2005) Awareness of safety issues, such as how to avoid or cope with falls or choking episodes, might also be compromised by cognitive impairment. The increasing use of brain–computer interfaces in patients with ALS means that the evaluation of cognitive impairment and decision-making capacity by such interfaces will become highly relevant, both scientifically and ethically.

ALS with dementia has not been shown in studies to affect carer burden or quality of life of patients. However, carer burden is consistently higher for patients with dementia than for patients with other disorders,(Thommessen et al., 2002) and this might also be the case when patients with ALS and dementia are compared with patients with ALS but no dementia. Cognitive impairment has a profound negative effect on patients' survival, ability to adapt to life-prolonging interventions, quality of life, and decision-making capacity (54).

In many neurodegenerative diseases, carer burden is directly related to the need for residential care. Moreover, time of survival seems to be significantly shorter for patients who have ALS and frontotemporal dementia.(Olney et al., 2005)

In particular, patients with bulbar-onset ALS with FTLD were more than twice as likely to die at any interval after ALS onset than were patients who had bulbar-onset classic ALS, which suggests that these disease variants have different clinical trajectories.(Portet et al., 2001)

The phenotype and natural course of cognitive impairment in ALS is unclear. The methods to assess impairment has also differed with no standardized protocol. Some of these studies did not account for the motor and speech impairment in ALS.

One of the largest studies of ALS so far detected cognitive impairment in 132 (47%) of 279 consecutive patients who attended an ALS clinic(Ringholz et al., 2005). Most notable of these impairments was executive dysfunction alongside mild memory decline. About 15% of patients had severe cognitive impairment with features that were consistent with frontotemporal dementia. However, there have been no large population-based clinical studies of the prevalence of cognitive decline in ALS.

There is scanty information regarding the natural history of cognitive decline in ALS than about the incidence and prevalence. Some longitudinal studies have characterized the progress of the cognitive decline. A longitudinal study of eight patients with ALS(Strong et al., 1999) noted progressive impairment of working memory, problem solving, cognitive flexibility, visual perception, and recognition memory for words and faces in patients with bulbar-onset ALS over a 6-month period. Subsequent neuropathological analysis of these patients showed neuronal loss in the anterior cingulate gyrus. In a separate study,(Robinson, 2006)seven of 19 patients with ALS developed cognitive deficits over a similar period,

although the between-group and within-group comparisons did not show significant differences in cognitive function over time. These findings were not replicated by a third longitudinal study,(Abrahams et al., 2005) in which all cognitive functions were stable over a 6-month period in patients who had ALS but no dementia.

There are also several risk factors proposed for dementia in ALS, like old age, male sex, poor education, family history, pseudobulbar palsy and bulbar site of onset, but they have not been reported consistently.(Abrahams et al., 1997; Massman et al., 1996; Portet et al., 2001)

As there are no large population-based studies of cognitive function in ALS, there is less analysis of clinical implications of cognitive impairment on disease management

3 MATERIALS AND METHODS

Study Design: Ours is a single-centre prospective observational study

Study Setting: All patients diagnosed as Amyotrophic Lateral Sclerosis by Gold Coast criteria attending the OPD and admitted in wards of Department of Neurology, Sree Chitra Tirunal Institute of Medical Sciences and Technology (SCTIMST) from 01.12.2021 to 01.01.2023 were enrolled in the study and followed up for 6 months. Informed written consent was obtained prior to recruitment

Sample Size Calculation:

Assuming a base population of ALS of 3000 (based on current population prevalence), and an expected prevalence of cognitive impairment of 30% (arrived at based on midpoint of range of 10%-40% observed from literature, with absolute precision of ±10%, setting alpha at 0.05, the sample size computed using Open Epi version 3 was 40. Assuming a non-response of 20%, the sample size was rounded up to 60.(Sullivan et al., 2009)

INCLUSION CRITERIA:

- Patients fulfilling the Gold Coast diagnostic criteria for ALS
- Kings College stage 3 or less (no nutritional or respiratory support)
- Age > 18 years and consenting for the study

EXCLUSION CRITERIA:

- Patients with nutritional or respiratory failure
- Current medical conditions or treatments that could compromise cognitive functions (i.e; Systemic illness, Psychosis)
- Gross bulbar or motor impairment with an ALS- -functional rating scale of < 2 (for speech and upper limb power) which could compromise the performance of neuropsychological tests
- Those fulfilling criteria for ALS – frontotemporal dementia

DATA COLLECTION:

The demographic, educational status, number of languages the patient can speak and clinical data including the duration of illness, type of onset bulbar vs limb, and stage of ALS, were collected with a structured proforma. The severity of weakness was assessed with a Medical Research Council (MRC) sum score. The functional impairment was assessed using the ALS functional rating scale (ALS- FRS).

ALS- FRS scale Revised: It captures 12 parameters of functional assessment. - Speech, salivation, swallowing, handwriting, cutting food and handling utensils, dressing and hygiene, turning in bed and adjusting bed clothes, walking, climbing stairs, dyspnoea, orthopnea and the need for ventilatory support. The score ranged from 0 to 48.

The severity of stages of ALS was described based on King's Clinical Staging of ALS.

STAGE	King's Clinical Staging of ALS.
1	Involvement of one clinical region
2	Involvement of second clinical region
3	Involvement of third clinical region
4	Nutritional or Respiratory failure
5	Death

Table: 2 - STAGING OF ALS- KING'S CLASSIFICATION

MUSCLE	SCORE LEFT	SCORE RIGHT
Shoulder abductors		
Elbow Flexors		
Wrist Extensors		
Hip Flexors		
Knee Extensors		
Foot Dorsiflexors		

GRADE	MRC SCALE FOR MUSCLE STRENGTH
5	Normal
4	Movement against gravity and resistance
3	Movement against gravity over the full range
2	Movement of the limb, but not against gravity
1	Visible contraction without movement of limb
0	No visible contraction

TABLE 3– MRC – MEDICAL RESEARCH COUNCIL SCALE FOR MUSCLE STRENGTH- SUM SCORE

INVESTIGATIONS:

Investigations like NCS, EMG and tests for secondary etiology like thyroid function tests, vasculitic screen, infective, heavy metal screening, MR Brain and spine imaging and genetic testing, if indicated and done in patients, were collected.

NEUROPSYCHOLOGICAL ASSESSMENT:

A detailed neuropsychological battery was administered to each patient covering the major cognitive domains. (Attention, Executive function, Memory, Visuospatial ability, Fluency). The battery also included behavioral assessment using cognitive behavioral screen and Quality of life assessment. The testing room was well lit, quiet and had minimal distractions. Patients who had severe motor disability or bulbar dysfunction affecting the performance in assessment have been excluded.

The following tests were administered

1. A multidomain test – Addenbrooke's cognitive evaluation III (ACE III) covering the domains of attention, memory, visuospatial ability, language, and fluency.

2. Executive function – Attention and set-shifting - Trail making tests A and B

3. Fluency - Phonemic fluency and categorical fluency

4. Language – Picture naming task

5. Memory – Rey's auditory verbal learning test (RAVLT)

6. Visuospatial function – Visual object space perception battery – Position discrimination

and cube analysis test

7. Behavior – ALS – Cognitive behavioral screen (ALS-CBS) and ALS -CBS – Caregiver behavioral questionnaire

8. Quality of Life - SF 36 questionnaire (Physical function, energy, emotional aspect, role limitation, social function, pain and general quality assessment).

9. Caregiver Burden score - Zarit Burden interview

ACE III:

The scoring in each domain involving attention, memory, fluency, language, and visuospatial ability was attained. The sum score was also obtained. The individual and sum scores were compared with normative Indian population age, education adjusted and then abnormality by 2 SD from normative data was considered as cognitive impairment.

Trail Making Tests A and B (TMT A and B) – Both tests were timed. TMT- A required the patient to connect 25 encircled numbers in ascending order, testing the visual scanning, numeric sequencing, and psychomotor speed.

TMT B- The person must connect the circles from 1 to 25, along with alternating between numbers in two colors(Black and White). It tests the executive function, mainly set-shifting.

The difference in performance between both was also derived to give an executive function index. The time required to complete the test is considered

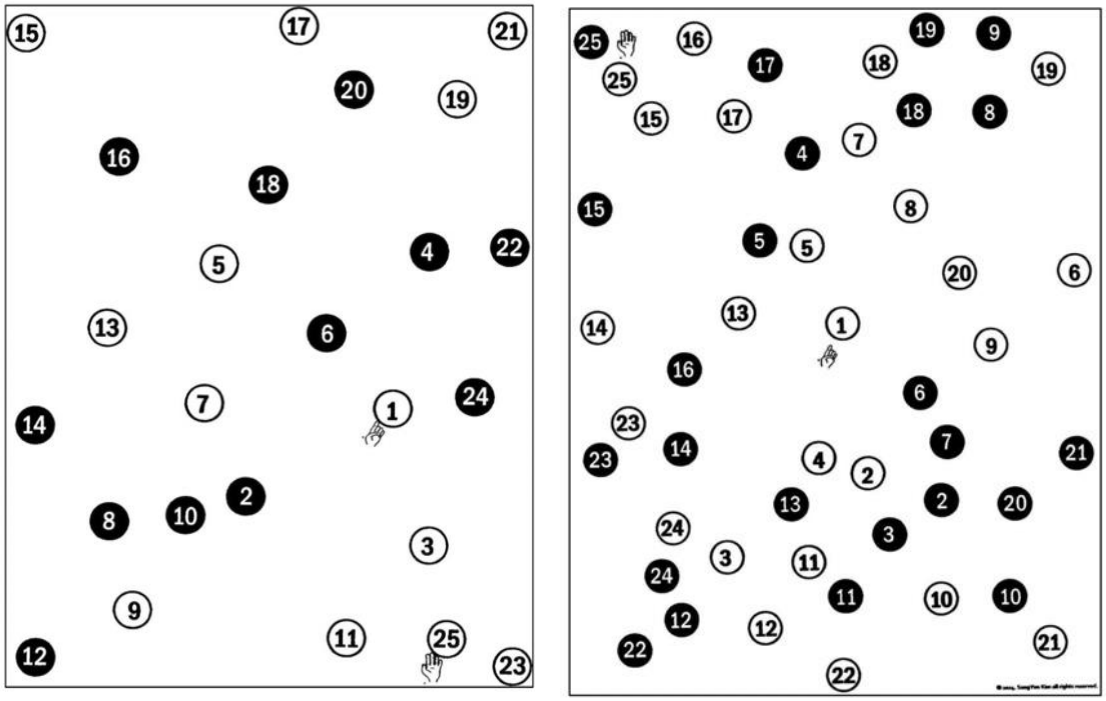


FIGURE 1 – TMT A and TMT B test proformas

Phonemic Fluency – This test assesses the executive function, ability to retrieve specific information using selective attention, mental set shifting. Patient is asked to recite as many words as he can starting with given syllables in 1 minute given for each letter – Ka, Ma, Pa and sum scores are obtained based on number of correctly named items after adjusting for errors.

Categorical Fluency – This test is used to assess executive function, language, semantic memory. They are asked to generate as many words as possible in a specific category. 1 min is given to each category and sum scores obtained based on correctly named items after adjusting for errors.

Picture naming Task- This measures language, word retrieval. 30 drawings are shown to patient, and he is asked to reproduce. If he fails to name or makes an error or needs category or phonemic cues to aid, scoring is adjusted for the errors and cues.

Rey Auditory Verbal Learning test (RAVLT) - This test assesses the immediate recall, verbal learning ability, delayed recall. We administered a 15-word battery, the immediate recall and trial 5 score and delayed recall after a distraction task after 20 min is noted. The responses are scored and decrease by 2 SD, after adjusting for age and education for normative Indian population is noted to define cognitive impairment.

Visual Object space perception (VOSP) Battery - We have used 2 tests for assessing the visuospatial function. In the position discrimination scored out of 20, spatial perception is assessed while the cube analysis scored out of 10 assesses the spatial and object perception. The normative scores for this are adjusted from age only and derived from Warrington et al

ALS Cognitive Behavioral Screen 20 (ALS- CBS 20)- This is scored on a scale up to 20 for domains involving attention, concentration, tracking and recall and a behavioral questionnaire scoring scored from 0 to 20 for ALS- CBS and 0 to 45 for Caregiver behavioral questionnaire to ascertain the patients behavioral status. It is a freely available questionnaire (Appendix-)

Quality of Life (QoL) – SF (Short Form survey) 36 Questionnaire- This is administered to a patient containing 36 questions assessing varied aspects of quality of life - Physical function, energy, emotional aspect, role limitation, social function, pain and general health. There was no time limit. (Appendix)

Caregiver Burden: Caregiver burden is assessed using Zarit Burden interview consisting of 22 items, score ranging from 0 to 88 (Appendix)

OUTCOME:

1. To assess the effect of cognitive impairment on disease progression
2. To assess the association of cognitive impairment on quality of life and caregiver burden on follow-up

All tests were administered uniformly by the same person and required 2 hours. All the tests have been administered and scored based on the user guidelines provided by the ICMR – cognitive battery manual, except for VOSP and ALS CBS. Most of the tests used in the cognitive battery in our cohort were selected specifically to overcome the motor and verbal deficits while performing visuospatial function tests and can be used until King's college stage 3 level of impairment. The cognitive impairment in each test was defined as per ICMR normative data for the patient population(Menon et al., 2020). (Alladi et al., 2014) Abnormality in cognitive score by 2 standard deviations (SD) from normative data of the Indian population adjusted for age and educational status was considered as impairment. The patients who underperformed in 2 non-overlapping tests involving at least 2 domains were considered to have cognitive impairment.(Phukan et al., 2012)

On follow-up at 6 months, patients' motor progression was tested using the MRC sum score, and functional status using the ALS- FRS scale. The quality of life and Caregiver burden was reassessed using the SF 36 and caregiver burden questionnaires respectively. The motor progression and the quality of life and care giver burden were assessed for any association with the cognitively affected population.

STATISTICAL ANALYSIS:

- Descriptives were done with mean and SD, confidence intervals, for ordinal variables and proportions and frequencies for categorical variables.
- Analysis at baseline- Bivariate analysis was done using the Chi-square test/ Fisher Exact for frequencies. In the case of ordinal/continuous variables, for parametric data, an unpaired T-test and if non-parametric, Mann Whitney U test were used. The normality of the data was assessed using the Shapiro-Wilk Test.
- The association between cognitive impairment and type of onset, linguistic status and disease severity was assessed in each domain of impairment.
- The quality of life and caregiver burden scores were assessed to see association with cognitive impairment at baseline.
- Analysis at follow up - Paired t-test for parametric and Wilcoxon signed-rank test for non-parametric data
- Repeated Measures ANOVA was done to assess the correlation of variables on follow-up in relation to cognitive impairment
- Multivariate regression was done to assess whether there is an independent association for cognitive impairment.

ETHICAL CONSIDERATIONS:

This study has the approval of the Institutional Ethics Committee (IEC /1795) and informed consent was obtained from all subjects .

4 RESULTS

Of the 88 patients with diagnosed ALS based on Gold Coast criteria, after applying exclusion criteria, a sample of 60 was studied. The excluded patients were those with gross bulbar impairment (n=18), significant systemic diseases affecting the performance on neuropsychological testing (n=12), ALS – FTD (n=6), and with secondary aetiologies on workup (n=7). Of which 14 were lost to followup and 46 were studied in 6 month followup.

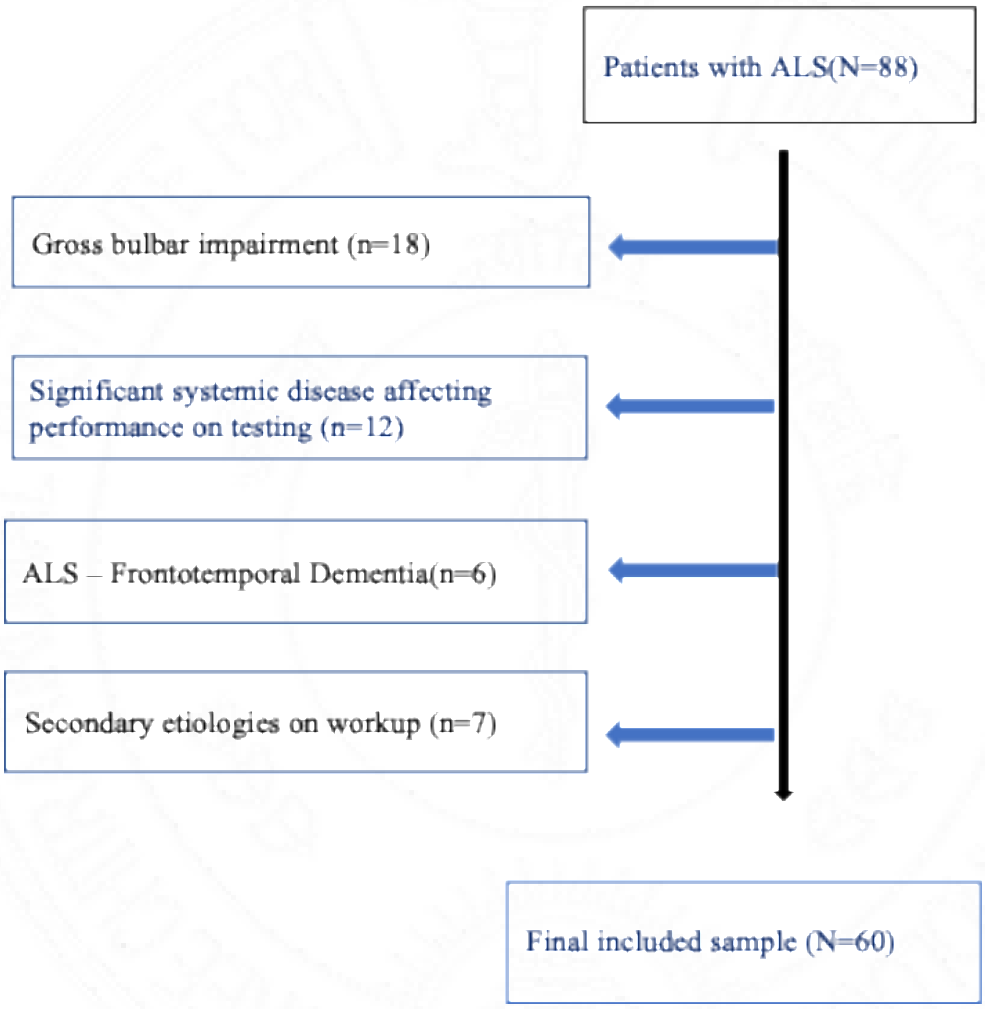


Figure:2: Flowchart Describing Enrolling of Patients

DEMOGRAPHIC DATA:

AGE:

The age distribution extended from 25 to 88 yrs. Mean age of presentation was 55.5 (±13) years. Majority of the patients were in 4th decade and 5th decade. Mean age was slightly higher in males, 56(±14) years compared to females 54.5 (±11)yrs. Bulbar onset patients tended to present at a later age with mean age of population 59.3 (±12.2) years compared to spinal onset at 53(±13) years .

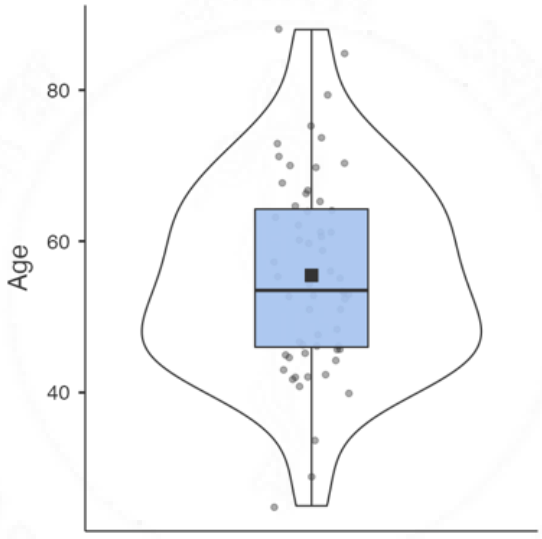


FIGURE:3: Box Plot – Violin diagram depicting age distribution across the cohort – Median ±IQR – 53.5±19

GENDER:

21 (35%) patients were males and 39 (65%) were females giving a male to female ratio of 1.8:1. The females and male patients were almost equally distributed in bulbar and spinal onset ALS.

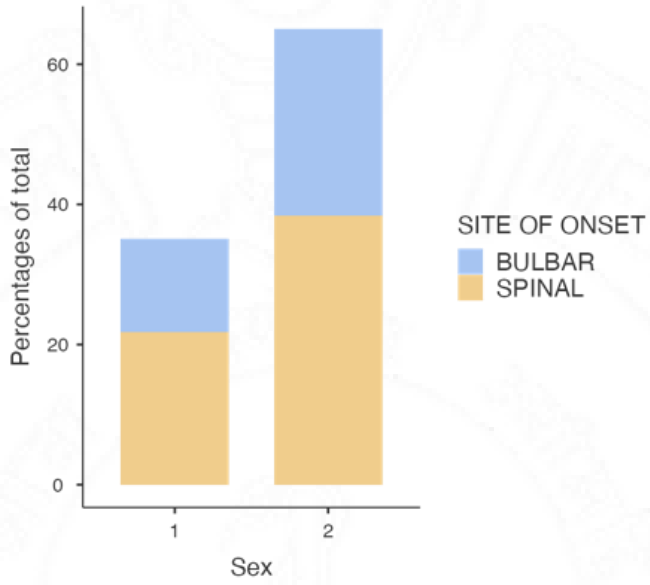


Figure: 4: Sex Distribution Across Onset Of ALS

EDUCATION AND LINGUISTIC STATUS:

39 (65%) had educational status of high school and above, whereas 21(35%) had lower education status. 17 (28.3%) were monolinguistic and 43 (71.7%) patients could speak more than one language.

SITE OF ONSET AND PATTERN:

Onset was bulbar in 24 (40%) of patients and spinal in 36 (60%).

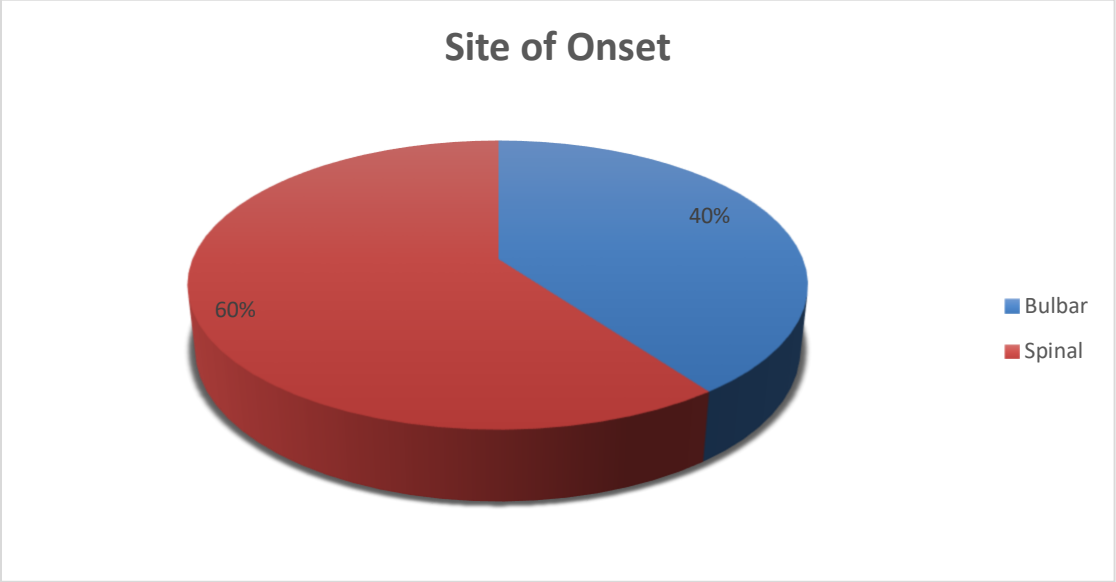


Figure:5: Pie chart depicting site of onset

BASELINE FUNCTIONAL ASSESSMENT:

ALS FUNCTIONAL RATING SCALE: Mean ALS- FRS at presentation was 39.7(±6.36). Patients with spinal onset ALS had poorer functional rating scale scores 38.1(±6.90) compared to bulbar onset; 42(± 4.68) (P=0.012).

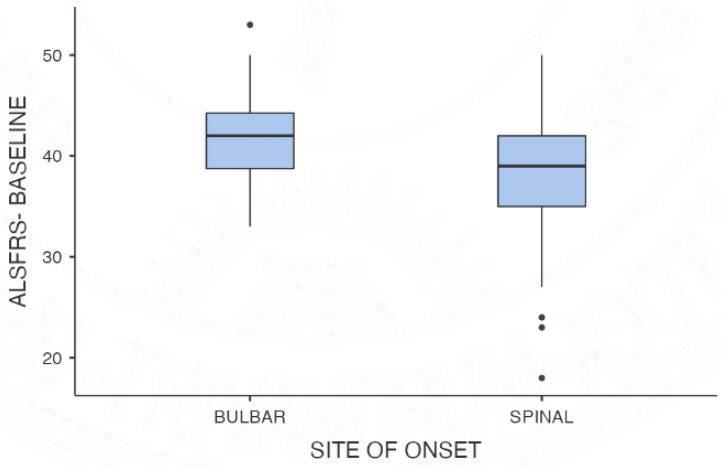


Figure: 6: Box Plot Showing ALS-FRS with respect to site of onset of ALS - Median±IQR (Bulbar – 42 ± 5.5; Spinal- 39 ±7)

MRC SUM SCORE:

Mean MRC sum score was 51(±8.97). They varied from a minimum of 23 to a maximum of 60. Male patients 53.1(±7.01) had higher mean MRC Sum scores compared to females.47.3(±10.9)

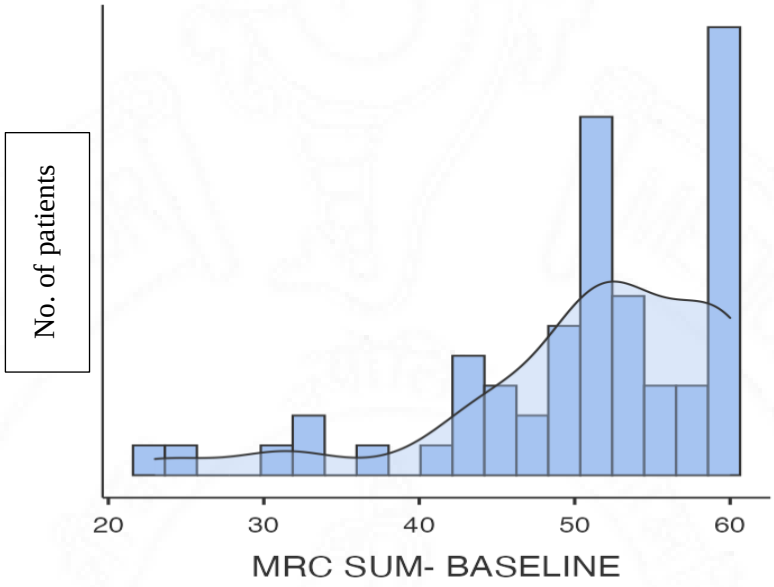


FIGURE: 7: Bar Diagram describing MRC SUM Scores distribution

DURATION OF ILLNESS

The mean duration of illness was 20.6 (± 30) months. It constituted duration ranging from 1 month to 15 yrs. The increased duration illness was noted to be higher in patients with severe ALS and in those with spinal onset ALS. 11.5(±8.35) months in Bulbar onset vs 26.7(± 38.3) in spinal onset ALS) months

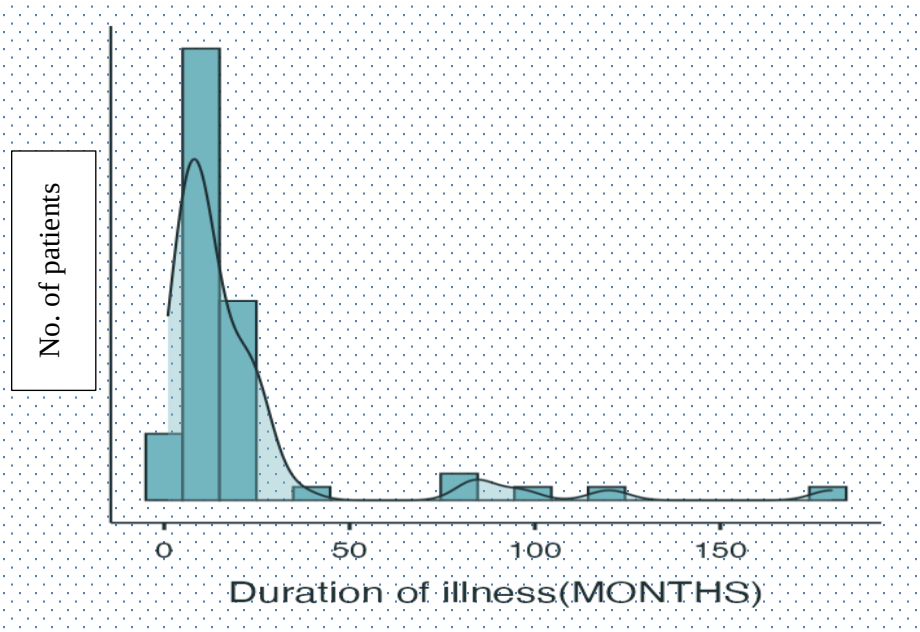


FIGURE: 8: Bar Diagram depicting duration of illness in ALS

KINGS STAGING AND SEVERITY OF ALS:

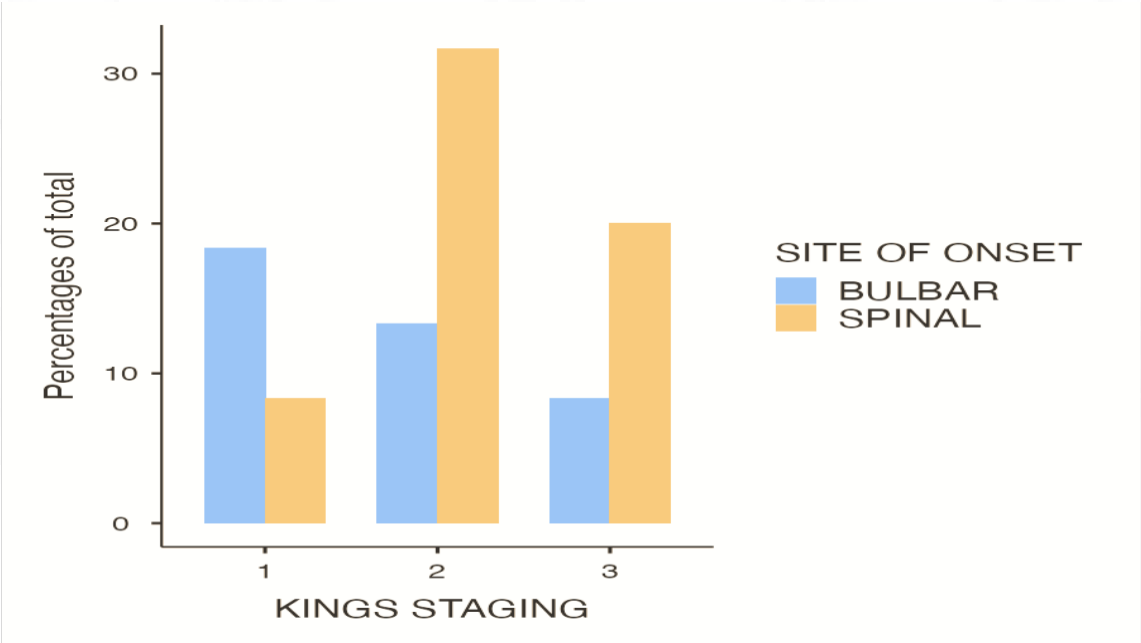


Figure.9: Distribution of Population Across Kings Staging

As per Kings staging, 16 patients (26.7%) were in stage 1, 27(45%) were stage 2 and 17 (28.3%) were stage 3. Patients with bulbar onset ALS were more likely to be in Stage 1 of Kings, whereas spinal onset were in stage 2 (p=0.023). 17(28.3%) patients had severe

disease, 43(71.7%) had mild severity. None of the patients in our cohort reported cognitive symptoms

ELECTROPHYSIOLOGICAL PARAMETERS:

Compound muscle Action Potentials of the more affected limb among median, ulnar, peroneal and tibial nerves were included. Among all, peroneal amplitudes were lowest and tibial were the least affected.

VARIABLE	Mean +/- SD	Minimum	Maximum
CMAP- MEDIAN	7.97(± 4.93)	0	20.2
CMAP- ULNAR	9.30(± 5.26)	0	20.3
CMAP - PERONEAL EDB	4.03 (± 3.84)	0	17.5
CMAP- PERONEAL TA	4.07(±3.60)	0	11
CMAP- TIBIAL	9.89(±6.64)	0	27.8

TABLE.4: Electrophysiological Data - Distribution Of CMAP

NEUROPSYCHOLOGY DATA:

ACE III DATA:

ACE III score comprised Attention, Memory, Fluency, Language and visuospatial function. Most common impairment was seen in memory domain 27 (45%), followed by attention 25(41.7%), visuospatial function 20 (33.7%), Fluency 16 (26.7%), Language 12(20%.

	N	Mean	Median	SD	IQR
ACE III (ATTENTION)	60	15.63	16.00	2.39	4.00
ACE III (MEMORY)	60	18.35	19.00	5.43	6.25
ACE III FLUENCY	60	8.72	8.50	2.52	3.00
ACEIII LANGUAGE	60	24.88	26.00	2.33	2.00
ACE III VISUOSPATIAL	60	13.87	14.50	2.87	3.00
ACE III SUM	60	86.48	89.00	11.94	13.25

Table 5- ACE III Mean Scores Of Each Domain

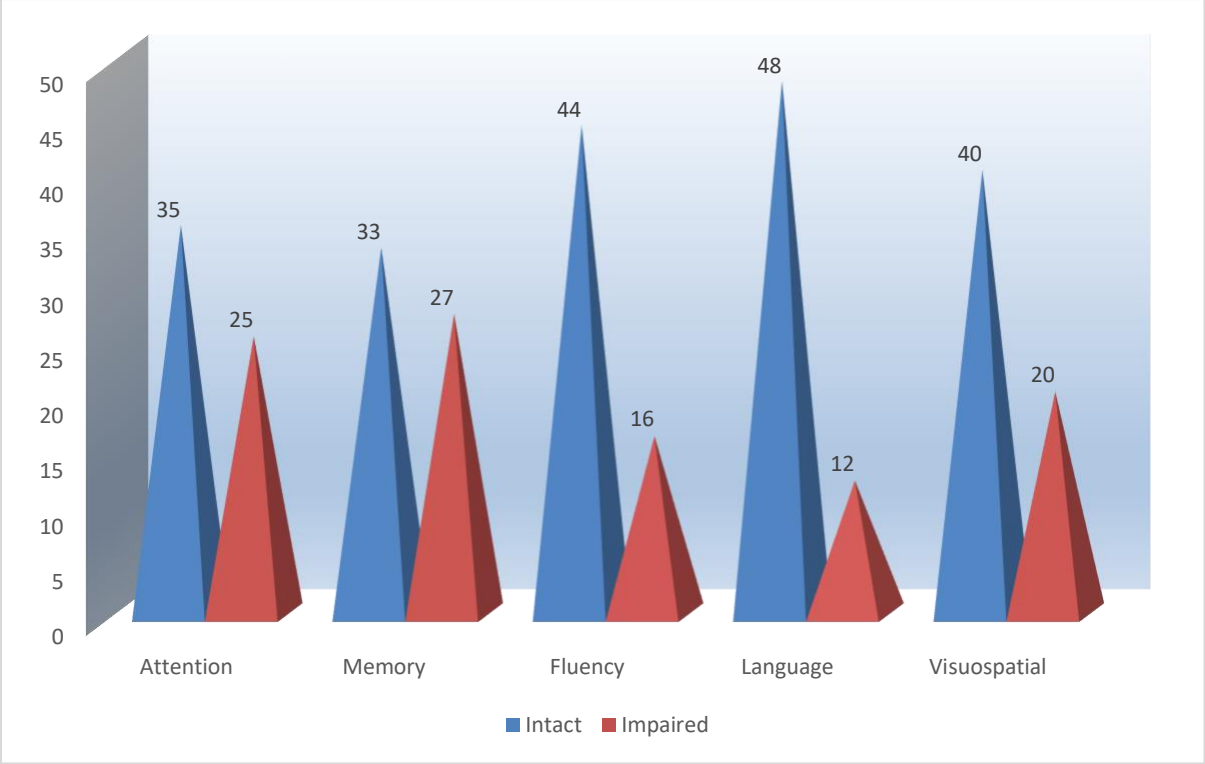


Figure.10 : Distribution of various domains Across ACE III

FLUENCY:

Phonemic fluency was more commonly affected compared to categorical; with 8 (13.3%) and 6 (10%) patients involved respectively. Phonemic fluency scores ranged from 9 to 56, whereas categorical from 20 to 54. The mean phonemic fluency score is 27.9(±10.6);

categorical fluency is 34.1 (±7.25).

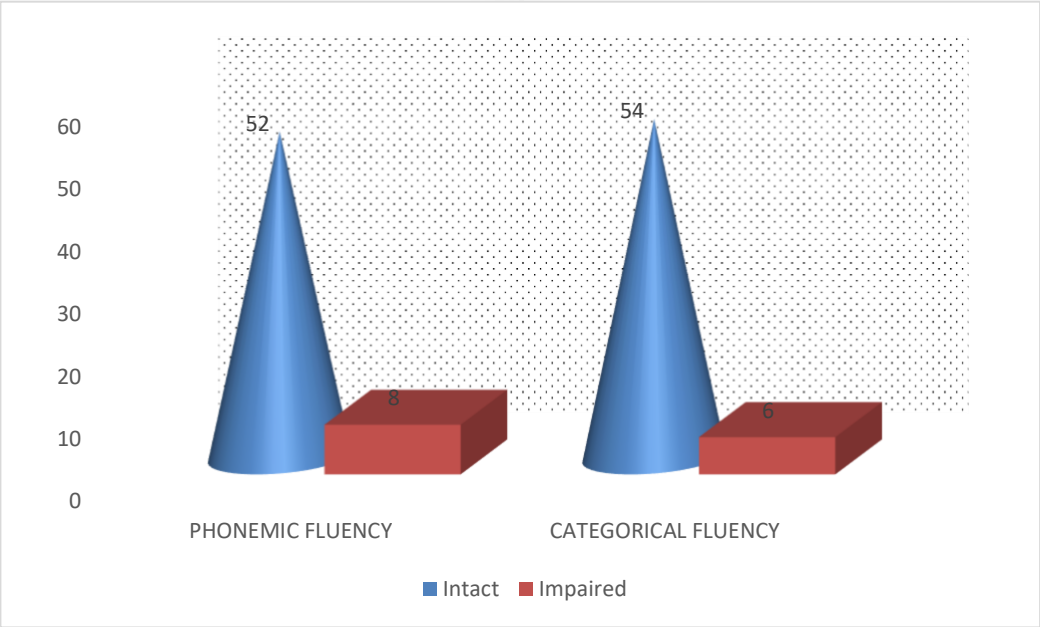


Figure.11: Pyramid Diagram Illustrating Phonemic and Categorical Fluency

EXECUTION:

Trail-making B test was more affected with 31(51.7%) patients showing impairment followed by 18 patients (30%) showing impairment in Trial A test. The mean time required for Trail A test was 100 (±94) sec; Trail B is 276(± 107) sec. The time to complete Trail A test ranged from 43 to 270s and Trail B from 111 to 612 s.

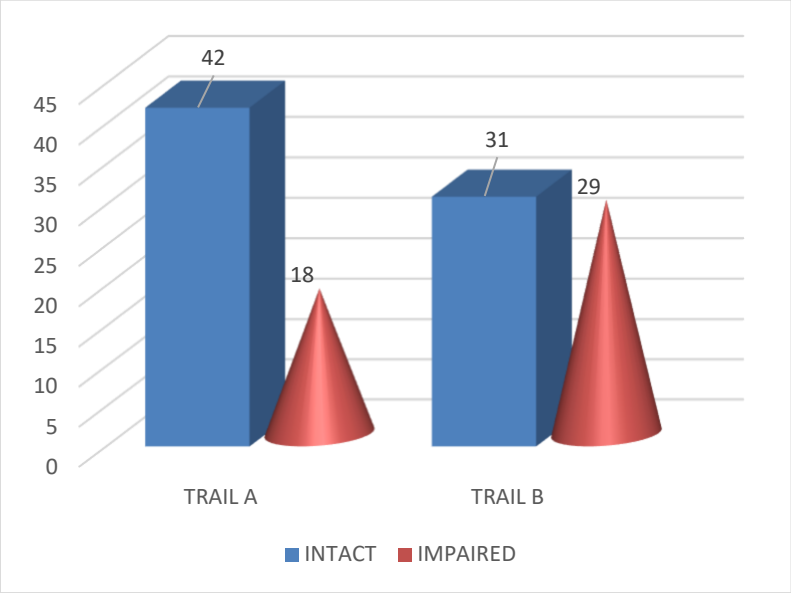


Figure: 12. Column Diagram Illustrating Trial A And B Impairment Scores

LANGUAGE:

Picture naming task was assessed for language. The scores ranged from 57 to 90. Majority performed better on picture naming task with only 6 (10%) patients affected. The mean scores being 82.2 (±7.07).

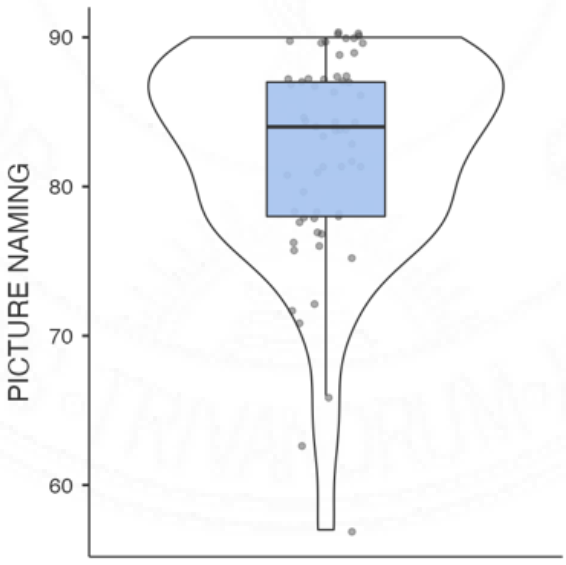


Figure: 13. Violin Diagram Illustrating Scores In Picture Naming Task (Median±IQR - 84±9)

RAVLT:

Immediate registration, learning and memory were ascertained using immediate score, Trial 5 score, and delayed recall, respectively. Majority showed impairment in learning aspect in 12 (20%) patients, compared to registration and memory impairment in 7(11.7%) patients. The mean of RAVLT total score 36.7(±12.7); ranging from 6 to 66.

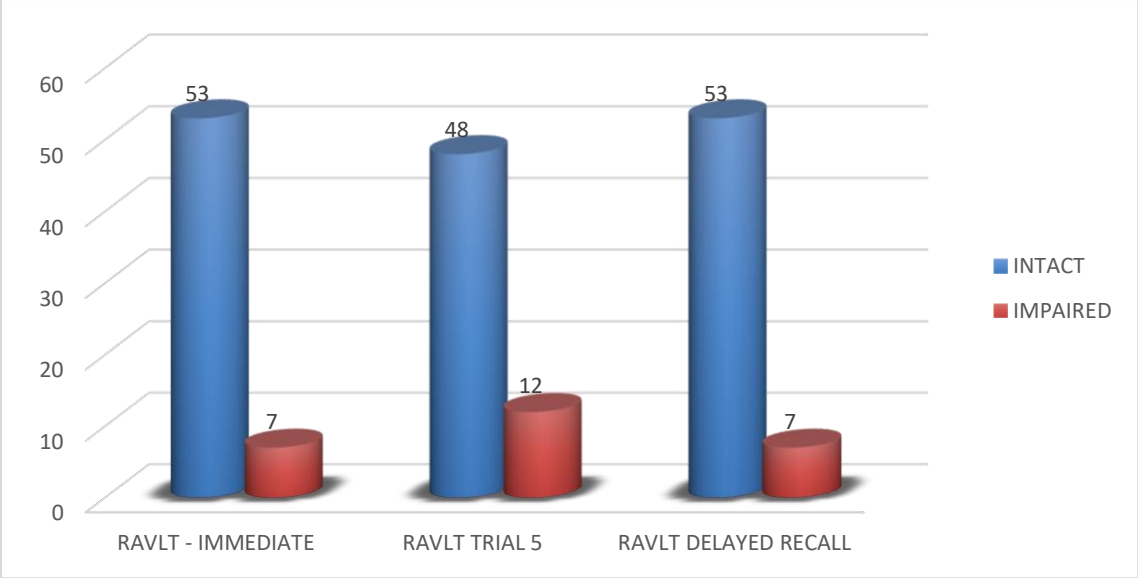


Figure.14 : Column Diagram – Representing RAVLT Scores

VISUOSPATIAL FUNCTION:

Among the tests used for assessing visuospatial function, majority showed impairment in position discrimination; 29 (48.3%) patients compared to 6(10%) patients in cube analysis. The scores for position discrimination ranged from 10 to 20, with mean of 17(±1.78) and from 2 to 10 for cube analysis with mean of 7.9 (±1.68)

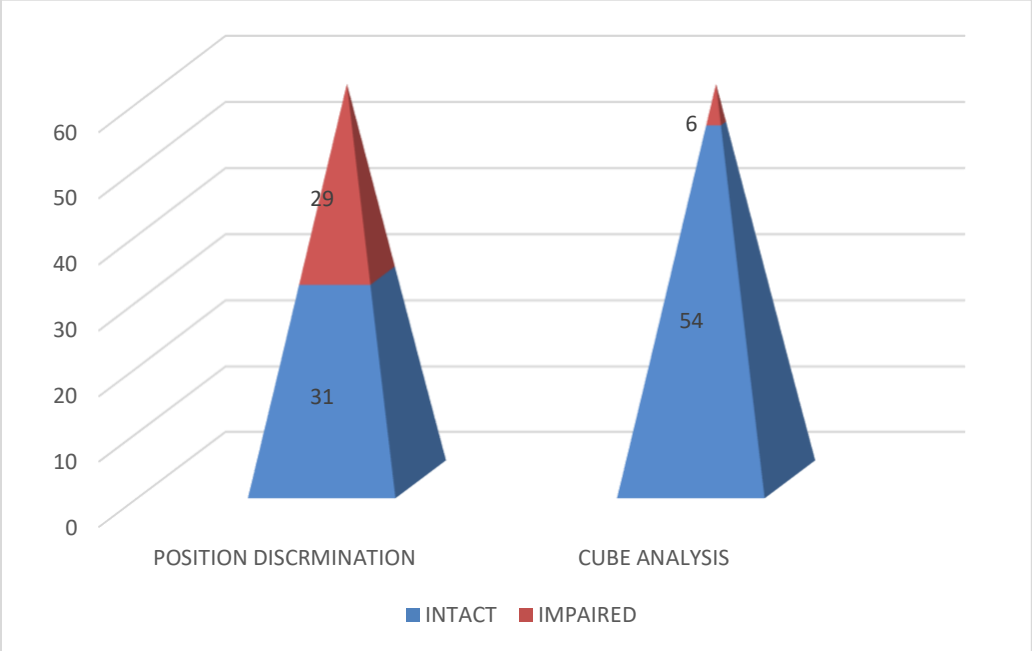


Figure.15: Pyramid Diagram Illustrating Distribution of Visuospatial Scores

COGNITIVE IMPAIRMENT:

Overall cognitive impairment which included patients with impairment in at least two non-overlapping tasks of at least 2 domains was seen in 38 (63.3%) patients. All the cognitively impaired patients in our cohort had multidomain MCI.

COGNITIVE BEHAVIOURAL SCREEN:

Cognitive behavioral scores were assessed from ALS – CBS both with patient and caregiver. ALS CBS score ranged from 6 to 20 with mean of 13.6 (±3.51), whereas ALS – CBS caregiver burden score ranged from 22 to 46 with mean of 34.8 (±5.25)

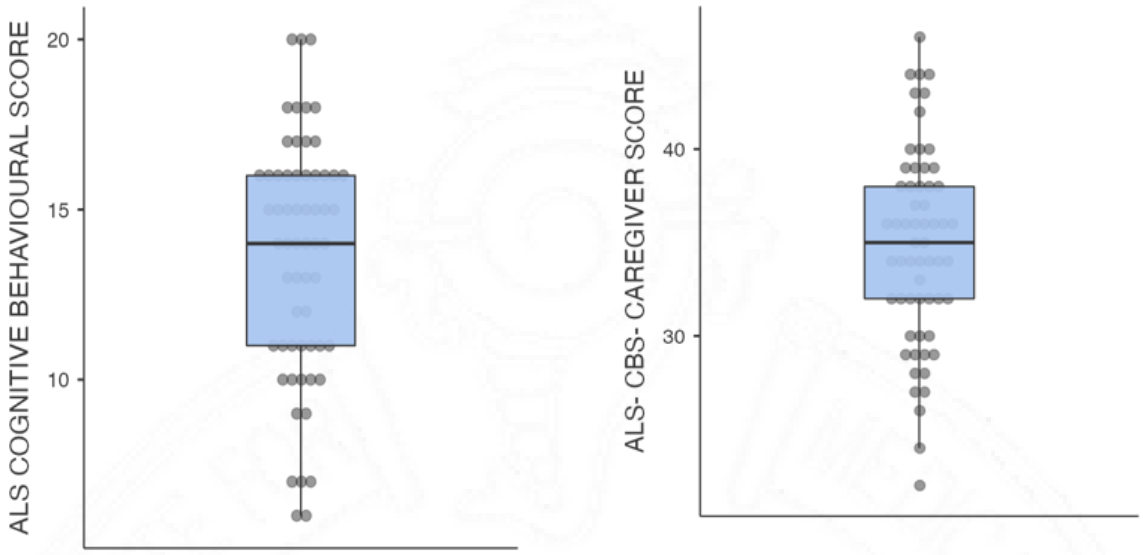


Figure.16: Box Plot Showing Distribution Of ALS- Cognitive behavioral Scores (Median±IQR- 14±5) And Caregiver Burden Scores (Median±IQR -35±6)

QUALITY OF LIFE:

Quality of life showed the least scores in role limitation due to physical health while role limitation due to emotional problems with social function was relatively less affected.

QoL PARAMETERS	LOW SCORES	HIGH SCORES
Physical Functioning	38 (63.3%)	22(36.7%)
Role limitation due to physical health	46(76.7%)	14(23.3%)
Role limitation due to emotional problems	40(66.7%)	20(33.3%)
Energy/ Fatigue	38(63.3%)	22(36.7%)

Emotional well being	36(60%)	24(40%)
Social Function	21(35%)	39(65%)
Pain	30(50%)	30(50%)
General Health	37(61.7%)	23(38.3%)

Table.6 : Quality of Life Scores- Distribution

CAREGIVER BURDEN:

Caregiver burden was high in 25 patients (41.7%). The scores ranged from minimum of 14 to maximum of 66 with mean 37.3(±14.4)

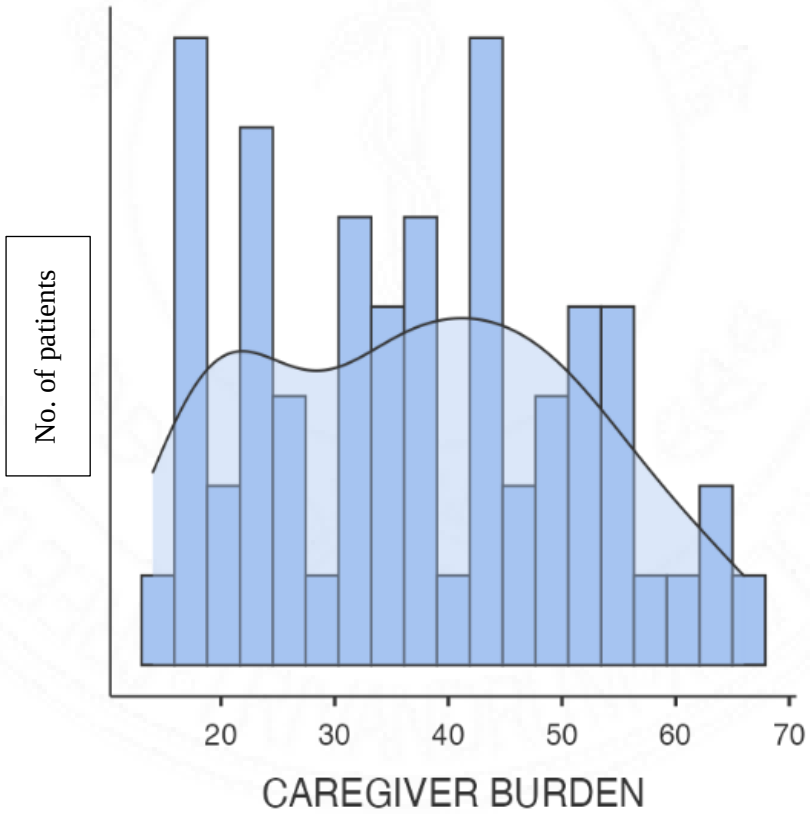


Figure. 17: Bar Diagram Depicting the Distribution Of Caregiver Burden Scores

FOLLOW UP DATA:

Functional scores, Quality of life parameters and caregiver burden data was collected at 6 month Follow up in 46 patients.

ALS FRS SCORE and MRC SUM SCORES:

Mean ALSFRS and MRC sum score on follow up decreased significantly compared to baseline values. As the data violated tests of normality by Shapiro Wilk, follow up scores were assessed using Wilcoxon.

	BASE LINE	FOLLOW UP	Shapiro Wilk	Wilcoxon W
ALS FRS	40.0(±6.3)	33.7(±7.7)	<0.001	P < 0.001
MRC SUM	52.2(±7.6)	46.9(± 9.8	<0.001	P< 0.001

Figure.7: Table Describing ALS- FRS and MRC Sum Scores On Follow-up

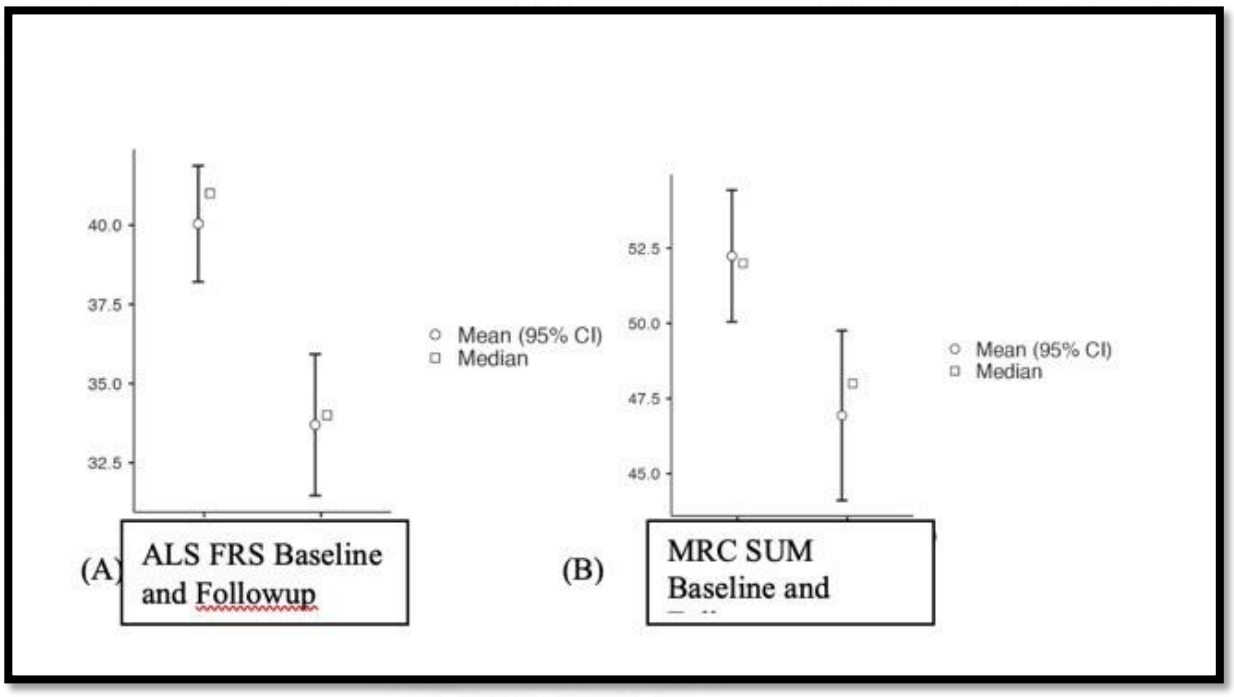


FIGURE.18 : (A) ALS- FRS Baseline and Follow up (B) MRC Sum – Baseline and Follow-up

QUALITY OF LIFE:

Quality of life parameters had significantly worsened on 6 month follow up , the most affected were physical functioning, Role limited due to emotional problems and role limited due to physical function.

QoL PARAMETERS	POOR QoL	Good QoL	P value (Wilcoxon W)
Physical Function	42 (91.3%)	4 (8.7%)	<0.001
Role limitation due to physical	44 (95.7%)	2 (4.3%)	0.003
Role limitation due to energy	35 (76.1%)	11 (23.9%)	0.014
Energy	32 (69.6%)	14 (30.4%)	0.004
Emotional	39 (84.8%)	7(15.2%%)	<0.001
Social Function	26 (56.5%)	20 (43.5%)	<0.001
Pain	35 (76.1%)	11 (23.9%)	<0.001
General Health	39 (84.7%)	8 (15.2%)	<0.001

TABLE.8 : QoL Parameters among cognitively intact and impaired patients

CAREGIVER BURDEN:

On follow-up increased caregiver burden was seen 27 (60%) of patients which is higher compared to 41.7% at baseline. The mean caregiver burden scores on follow up were 45.2+/- 18.1 compared to baseline score of 36.4+/-14.9, statistically significant. (p< 0.001)

MORTALITY

3 patients had expired constituting 5.1% . Of them, the cause of death was respiratory failure in two patients, one patient died of unidentified cause. The patients died at 3-, 5- and 6-month follow-up.

COMPARISON OF DEMOGRAPHIC VARIABLES AMONG COGNITIVELY AFFECTED AND INTACT PATIENTS:

The sex of the patient, education status, language, site of onset of MND did not show significant association with cognitive impairment.

VARIABLE	**COGNITIVELY INTACT**	**COGNITIVELY AFFECTED**	**P VALUE**
Sex – Females	8 (38.1%)	13 (61.9%)	P= 0.866
Males	14 (35.9%)	25 (64.1%)	
Education			
High school and above	17 (43.6%)	22 (56.4%)	P= 0.129
Less than high school	5 (23.8%)	16 (76.2%)	
Language			
Single language	4 (23.5%)	13 (76.5%)	P= 0.184
Multiple languages	8 (41.9%)	25 (58.1%)	
Stage of MND			
1	5 (31.3%)	11 (68.8%)	P= 0.223
2	13 (48.1%)	14 (51.9%)	
3	4 (23.5%)	13 (76.5%)	
Severity			

Mild Moderate	18 (41.9%) 4 (23.5%)	25 (58.1%) 13 (76.5%)	P= 0.184
Diabetes	1 (12.5%)	7 (87.5%)	P= 0.128
Hypertension	4 (22.2%)	14 (77.8%)	P= 0.129
Hypothyroidism	2 (66.7%)	1 (33.3%)	P=0.249
Dyslipidemia	1 (33.3%)	2 (66.7%)	P=0.902
Malignancy	1 (33.3%)	2 (66.7%)	P= 0.902
Site of onset Bulbar Limb	 7 (29.2%) 15 (41.7%)	 17 (70.8%) 21(58.3%)	 P= 0.325

Table.9: Comparison of Baseline Demographic Variables Between Cognitively Intact and Impaired Patients

VARIABLE	COGNITIVELY INTACT	COGNITIVELY IMPAIRED	P Value	Shapiro Wilk
Age (yrs)	49.9(± 11.6)	58.71 (±2.78)	0.010*	0.824
ALS FRS Baseline	42.2 (±4.56)	38.2 (± 6.84)	0.010#	0.011
MRC SUM SCORE	51.4(± 8.61)	50.8 (±9.28)	0.944#	<0.001
Caregiver Burden scores	29.5(±11.4)	44(±14.1)	0.001*	0.690

***Unpaired T Test**

 # Mann Whitney U test

TABLE 10 : Comparison of continuous variables at baseline between cognitively intact and impaired patients

QUALITY OF LIFE PARAMETERS:

Quality of life was significantly reduced in patients with cognitive impairment, with pain being a major abnormality, which was statistically significant (p= 0.032). Though the other parameters suggested poor QoL in cognitively impaired people, none of them were statistically significant.

QoL PARAMETERS (Poor QoL)	**COGNITIVELY INTACT**	**COGNITIVELY IMPAIRED**	**P VALUE**
Physical Functioning	13 (34.2%)	25 (65.8%)	0.604
Role limitation due to physical health	17 (37%)	29 (63%)	0.933
Role limitation due to emotional problems	13 (32.5%)	27 (67.5%)	0.344
Energy/ Fatigue	14 (36.8%)	38 (63.2%)	0.970
Emotional well being	12 (33.3%)	38 (66.7%)	0.512
Social Functioning	6 (26.6%)	15 (71.4%)	0.340
Pain	7 (23.3%)	23 (76.7%)	0.032
General Health	12(32.4%)	25(67.6%)	0.388

TABLE 11: Table describing Quality of Life Parameters distribution along cognitively intact and impaired patients

CAREGIVER BURDEN

Cognitively impaired patients reported increased caregiver burden scores; statistically significant at P < 0.001. Mean caregiver burden score ranged from 44+/- 14.1

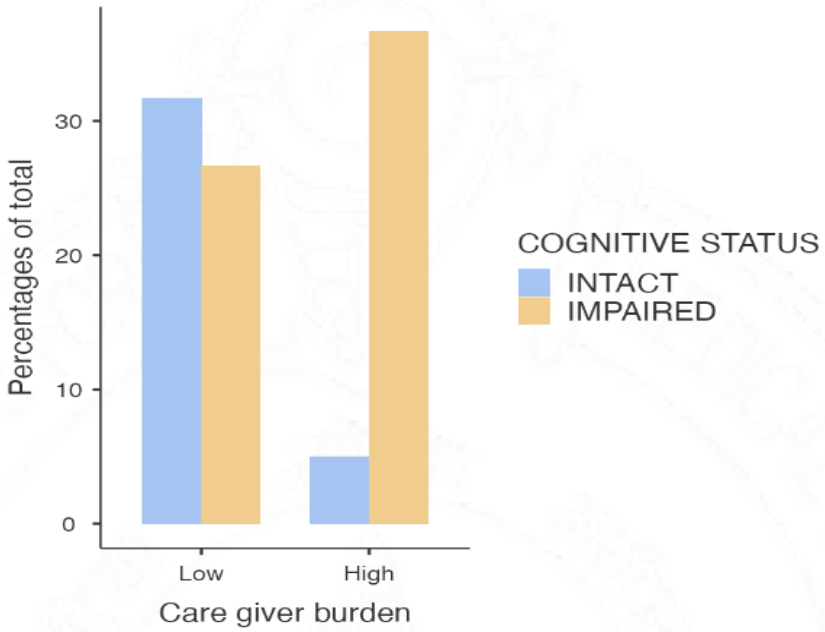


Figure.18 : Care giver burden in relation with cognitive impairment

Among the demographic and functional variables, increased age (P= 0.010) and poor ALS FRS scores (P= 0.010) at baseline, were found to be significantly associated with cognitive impairment.

Patients with cognitive impairment were likely to have poor quality of life for aspect of pain (P= 0.032) and association with increased caregiver burden. (P<0.001)

ELECTROPHYSIOLOGICAL PARAMETERS:

VARIABLE	COGNITIVELY INTACT	COGNITIVELY IMPAIRED	P value	Shapiro Wilk
CMAP- MEDIAN	9.66(±4.79)	6.92(±4.79)	0.044*	0.142
CMAP- ULNAR	10.13(± 5.45)	8.8(±5.15)	0.364*	0.097
CMAP- PERONEAL EDB	5.24(± 4.52)	3.30(±3.21)	0.168#	0.012
CMAP PERONEAL TA	3.71(±3.47)	4.25(±4.2)	0.744#	<0.001
CMAP- TIBIAL	11.4(±7.47)	8.98(±6.0)	0.189*	0.364

*- Unpaired T test

Shapiro Wilk test

TABLE 12: Table showing electrophysiological parameters – comparison between cognitively intact and impaired patients.

Among the electrophysiological parameters, low CMAP amplitudes from median nerve were noted to be significantly associated with cognitively impaired patients

CORRELATION BETWEEN DEMOGRAPHICS AND VARIOUS COGNITIVE PARAMETERS:

Age:

Increased age is significantly associated with cognitive impairment (p=0.01); the neuropsychological parameters that have been shown to have association were Trail B, RAVLT- immediate and cube analysis; the mean age was increased in the patients with impaired test performance in all of the above.

NEUROPSYCHOLOGICAL PARAMETER	INTACT	IMPAIRED	P VALUE
TRAIL B	52(±14)	58.6 (±10.4)	0.05
RAVLT – IMMEDIATE	54.13(±12.7)	65.71 (±11.4)	0.02
CUBE ANALYSIS	54.35(±11.6)	67.5 (± 20)	0.04

TABLE 13 : Comparison of neuropsychological parameters in relation to Age

SEX:

The gender of the patient had shown no significance with the overall cognitive status of the patient; however female gender has been shown to have significant impairment in neuropsychological test performance in Trail- making B test and in RAVLT memory assessment.

NEUROPSYCHOLOGICAL PARAMETER	INTACT	IMPAIRED	P VALUE
TRAIL B			
Males	23 (59%)	16(41%)	0.025
Females	6(28.6%)	15(71.4%)	
RAVLT – MEMORY			
Males	38(97.4%)	1(2.6%)	0.003
Females	15(71.4%)	6 (28.6%)	

TABLE 14 : Comparison of neuropsychological parameters in relation to Sex

Education:

Education was shown to be significantly associated with ACEIII. Less educated people had poor performance in both ACE III – Memory and Fluency

NEUROPSYCHOLOGICAL PARAMETER (	INTACT	IMPAIRED	P VALUE
ACE III Memory			
10th standard and above	26(66.7%)	13(33.3%)	P <0.013
Less than 10 th standard	7(33.3%)	14(66.7%)	
ACE III Fluency			
10th standard and above	35(89.7%)	4 (10.3%)	P <0.001
Less than 10 th standard	9 (42.9%)	12(57.1%)	

TABLE 15 : Comparison of neuropsychological parameters in relation to Education

LANGUAGE

Language was shown to be significantly associated with fluency and performance in Trail-making test A. People who were multilingual performed better in phonemic, categorical fluency and Trail-making test A assessment

NEUROPSYCHOLOGICAL PARAMETER	INTACT	IMPAIRED	P VALUE
Phonemic Fluency			
Single Language	11(22.2%)	41 (78.8%)	P = 0.002
Multilingual	6 (75%)	2 (25%)	
Categorical Fluency			

Single Language Multilingual	13 (24.1%) 4 (66.7%)	41 (75.9%) 2 (33.3%)	P= 0.028
TRAIL A Single Language Multilingual	8 (47.1%) 34(79.1%)	9 (52.9%) 9 (20.9%)	P= 0.015

TABLE 16: Comparison of neuropsychological parameters in relation to Language

ALS FRS Score:

Poor ALS FRS at baseline is associated with overall cognitive impairment. The main neuropsychological parameters affected are Picture naming task

NEUROPSYCHOLOGICAL PARAMETER	**INTACT**	**IMPAIRED**	**P VALUE (Mann Whitney)**
PICTURE NAMING	40 (± 6.16)	35.17(±6.9)	P= 0.05

TABLE 17: Comparison of neuropsychological parameters in relation to ALS – FRS Scores

KINGS STAGING AND SEVERITY:

Kings staging / severity of ALS did not show any association with overall cognitive impairment. However, patients who had severe ALS had higher impairment in picture naming task, which was statistically significant

NEUROPSYCHOLOGICAL PARAMETER	INTACT	IMPAIRED	P VALUE
PICTURE NAMING			
Mild	41(95.3%)	2 (4.7%)	P= 0.028
Severe	13(76.5%)	4(23.5%)	

TABLE 18: Comparison of neuropsychological parameters in relation to staging of ALS

ELECTROPHYSIOLOGICAL PARAMETERS:

CMAP amplitudes of median nerve have significant association with overall cognitive impairment. Peroneal EDB low amplitudes; 38(± 3.8) vs 18 (± 3.37) were shown to be associated with decreased performance in ACE – Visuospatial domain assessment. ($p < 0.033$).

QUALITY OF LIFE PARAMETERS:

QoL parameters especially pain has been associated with overall cognitive impairment. However various other aspects like predominantly pain and emotional well-being were affected in Fluency and Trail making.

NEUROPSYCHOLOGY PARAMETER	QoL parameter affected	P value
ACEIII MEMORY	Role limitation due to emotional problems	P= 0.044
	Pain	P= 0.034

ACE III VISUOSPATIAL	General Health	P= 0.004
CATEGORICAL FLUENCY	Social Function Pain	P= 0.042 P= 0.004
TRAIL A	Pain	P= 0.018
TRAIL B	Emotional well being Pain	P= 0.017 P=0 .002
RAVLT – Immediate	General Health	P= 0.014
RAVLT – Trial 5	Emotional well being General Health	P=0.032 P=0.011

TABLE 19: Comparison of neuropsychological parameters in relation to Quality-of-Life Parameters

MULTIVARIATE REGRESSION ANALYSIS- PREDICTORS OF COGNITIVE IMPAIRMENT:

Multivariate regression analysis models' fitness was assessed using Naegelkerke R square at 0.534 indicating a strong fit. Increased age of the patient, ALSFRS baseline scores, QoL parameter role limitation due to emotional problems and caregiver burden were shown to have independent associations with cognitive impairment.

PREDICTOR	**P Value**	**ODDS RATIO**	**95%CONFIDENCE INTERVAL**
Higher Age	0.013	1.110	1.022- 1.207

ALSFRS – Baseline	0.007	0.818	0.707-0.948
QoL- Role limitation due to emotional problems	0.035	1.012	1.001- 1.024
Caregiver Burden	0.023	1.072	1.010- 1.137

TABLE 20: Multivariate Regression analysis to assess the independent association of variables

FOLLOWUP RESULTS:

ASSOCIATION OF COGNITIVE IMPAIRMENT WITH FOLLOW-UP FUNCTIONAL PARAMETERS:

***FUNCTIONAL SCORES*:**

There was a significant association of cognitive impairment with ALS – FRS scores on follow up; (P< 0.044). The neuropsychological parameters known to be significantly associated with cognitive impairment were ACE III Scores (P= 0.024)

MOTOR PROGRESSION:

There was no significant association of MRC sum score on follow-up with cognitive impairment.

VARIABLE	INTACT	IMPAIRED	P VALUE
ALS FRS – ON FOLLOW UP	36.8(±7.27)	32(±7.6)	P = 0.044
MRC SUM SCORE-FOLLOW UP	48.4(±9.39)	47(±10.6)	P= 0.439

TABLE 21: Assessment of follow-up ALS – FRS and MRC SUM score on Follow up

QUALITY OF LIFE PARAMETERS:

The Quality-of-life parameters which were affected on follow up were emotional well-being (P=0.013) and physical functioning (P=0.015)

QoL PARAMETERS (Poor QoL)	COGNITIVELY INTACT	COGNITIVELY IMPAIRED	P VALUE
Physical Functioning	326.5(±196.4)	481(±200.18)	P= 0.015
Role limitation due to physical health	288.2(± 78.12)	294.8(±96.7)	P= 0.812
Role limitation due to emotional problems	200(± 86.6)	234.5(±76.9)	P=0.168
Energy/ Fatigue	112.9(± 33.12)	126.2(± 47.8)	P= 0.318
Emotional well being	109.4(±30.92)	131(± 24.83)	P= 0.013
Social Functioning	125(±44.19)	139.5(± 46.12)	P= 0.302
Pain	125.9(± 38.9)	148.8(±41.44)	P= 0.071
General Health	133.8(± 55.8)	163.8(± 60.72)	P= 0.103

TABLE 22: Quality of Life parameters on follow-up - Association with Cognitive impairment

CAREGIVER BURDEN:

Cognitively impaired patients had increased caregiver burden on follow-up (p= 0.001)

	INTACT	IMPAIRED	P VALUE
CAREGIVER BURDEN – ON FOLLOW UP	34.5(±16.48)	51.7(±15.9)	P= 0.001

TABLE 23– Caregiver Burden on Follow up – Association with cognitive impairment

REPEATED MEASURES ANOVA:

Repeated measures ANOVA of follow up data showed significant association for ALS FRS scale($p<0.001$) and MRC SUM score ($p< 0.001$) – however no statistically significant difference within subjects and between subjects in relation to cognitive impairment

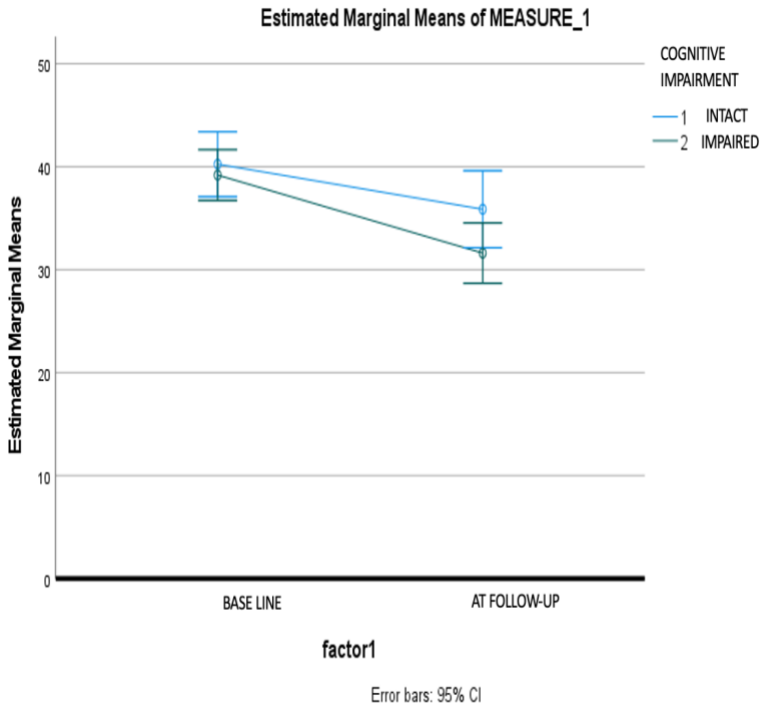


FIGURE 19: Repeated measures ANOVA explaining association of cognitive impairment with ALS FRS Baseline and follow up

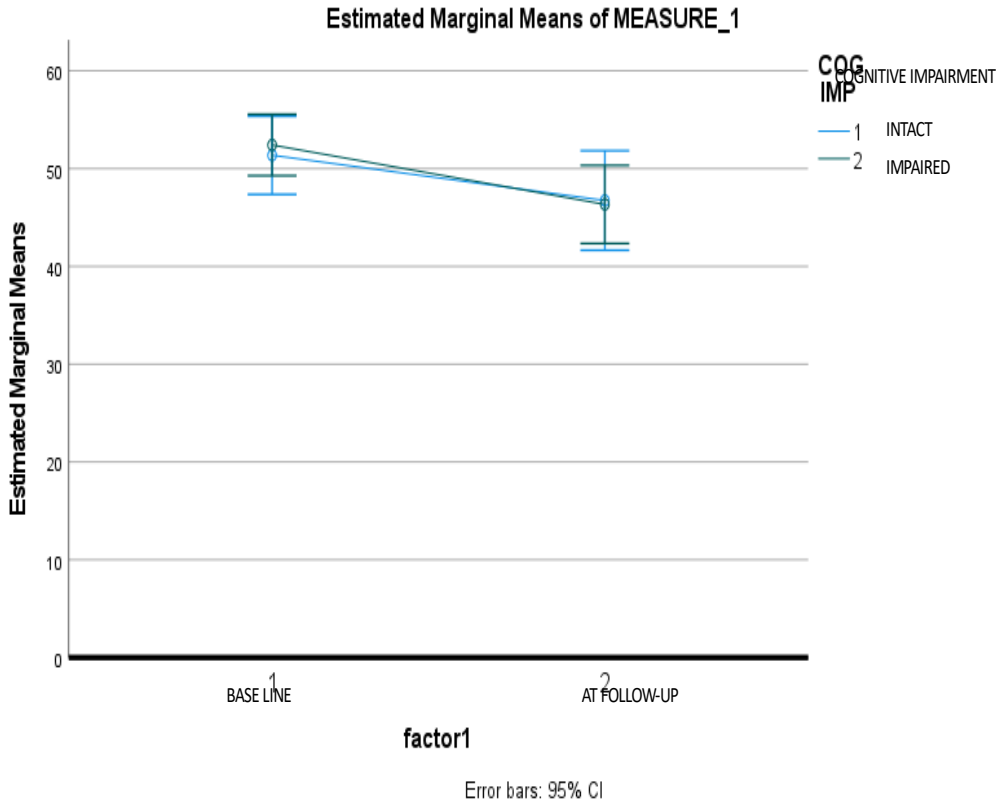


FIGURE 20: Repeated measures ANOVA explaining association of cognitive impairment with MRC SUM Baseline and follow up

QUALITY OF LIFE PARAMETERS:

Among quality-of-life parameters, both within subjects and between subjects, showed statistically significant results for Physical functioning, social function and General health**.**

QoL parameters	P value	Intrasubject	Intersubject
Physical Functioning	< **0.001**	<**0.043**	< **0.001**
Role limitation due to physical health	**0.002**	**0.104**	**0.798**

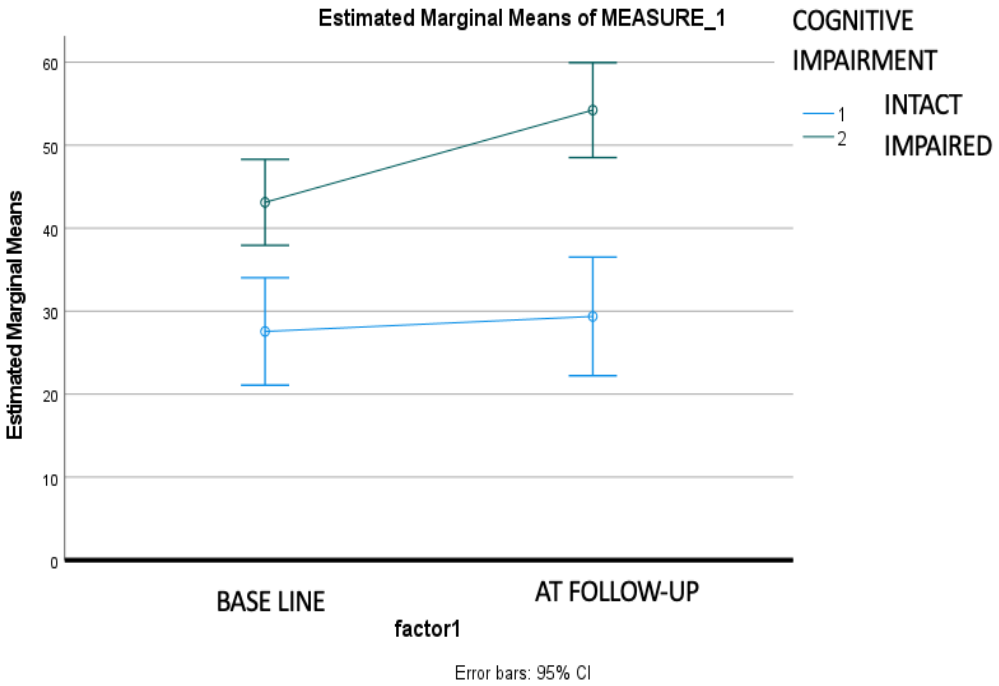
Role limitation due to emotional problems	**0.003**	**0.747**	**0.013**
Emotional well being	**0.003**	**0.087**	**0.150**
Energy /Fatigue	**0.003**	**0.079**	**0.066**
Social Function	**<0.001**	**0.028**	**0.002**
Pain	**<0.001**	**0.855**	**< 0.001**
General Health	**<0.001**	**0.002**	**< 0.001**

TABLE 24: Repeated measures ANOVA explaining association of cognitive impairment with QoL parameters on follow up

CAREGIVER BURDEN:

Repeated measures ANOVA of follow up data showed significant association for caregiver burden both within subjects and between subjects in relation to cognitive impairment**.**

FIGURE 21: Repeated measures ANOVA explaining association of cognitive



impairment with Caregiver Burden Baseline and follow up

MULTIVARIATE REGRESSION ANALYSIS- FOLLOW UP:

The factors that were associated with independent association with cognitive impairment on follow-up were ALS- FRS, QoL parameter- Physical Functioning, and Caregiver Burden.

PREDICTOR	P value	Odds Ratio	95% CONFIDENCE INTERVALS
ALS - FRS	P= 0.05	0.904	0.815- 1.00
PHYSICAL FUNCTIONING	P=0.035	1.004	1.0003- 1.01
CAREGIVER BURDEN	P=0.046	4.832	1.028- 22.71

TABLE 25 – Multivariate Regression analysis assessing the independent association of variables on follow-up in relation to cognitive impairment

5 DISCUSSION

This is one of the few prospective follow-up studies assessing cognitive impairment in patients with ALS in an Indian cohort; and has uniquely delineated the various aspects of cognition, its predictors and effect on disease progression in ALS, where the data so far has either been inadequate or inconsistent.

We have assessed the incidence of cognitive impairment in ALS, described the patterns of cognitive dysfunction and assessed the association of ALS with motor progression, functional scores and caregiver burden after 6 months. We have used Gold Coast criteria for the selection of our patients as it is more practical and better delineated the prognostication. The original diagnostic criteria defined at El Escorial, Spain, in 1990 and their subsequent 1998 revision at Airlie House, USA, and in 2006 at Awaji-shima, Japan, employed categories based on the number of body regions (bulbar, cervical, thoracic and lumbosacral) with simultaneous UMN as well as LMN signs. The terms used in the various iterations included some or all of: 'suspected', 'possible', 'probable', 'probable laboratory-supported' and 'definite' ALS.

The categories have been shown to have little independent prognostic value and patients with MND deemed to have 'insufficient' UMN signs clinically were denied entry to trials, despite similar rates of disability progression. (Martin R Turner, 2022b)

Hence, we included our patients based on the more liberal Gold Coast criteria for better inclusion. Replacing only a single factor influencing overall prognosis like the site of onset, with a multiaxial classification based on the rate and pattern of progression of disability might provide a better stratification.

Even though on screening we had 88 patients with ALS, we excluded 28 of them for various reasons. Those with gross bulbar impairment and severe disability which affect the verbal and written neuropsychological test performances were excluded in this initial study. We also excluded patients with definite ALS- FTD, as this study was aimed at delineating

the subgroup of people who had no overt symptoms, and a possible alternate pathology. With that, we had a final sample of 60, of which 46 were available for follow up at 6 months.

DEMOGRAPHIC DATA:

In our study mean age of presentation was slightly lower than the previously reported studies on cognitive impairment in ALS. In the cognitively impaired group, the mean age was higher compared to intact individuals. This result was statistically significant and was proven in multivariate regression to be an independent predictor. This occurred despite using age-adjusted scores when comparing normative data for assessing neuropsychological parameters. The test performance was significantly affected for Trail making test-B, RAVLT -Registration and Cube analysis (Visuospatial assessment) tests. This is in concurrence with Phukan et al. and Massman et al. where they found higher age in cognitively impaired patients, though this did not achieve statistical significance. (Massman et al., 1996; Phukan et al., 2007)

Male patients constituted the majority and no statistically significant difference was noted between cognitively impaired and intact groups for gender. This is in concurrence with prior studies (Massman et al., 1996; Phukan et al., 2007). A few studies like Chio et al., 2019(Chiò et al., 2019) had shown preponderance in female patients. In this study, we noted that the performance of females was poorer in Trail making B test and RAVLT memory assessment.

Educated people above high school constituted about two-thirds of our cohort. Patients who had less education were seen to have higher cognitive impairment after adjusting normative data for education. This was however not statistically significant, whereas prior studies have shown statistical significance (Chiò et al., 2019; Phukan et al., 2012). Decreased years of education were shown to have an increased prevalence of executive dysfunction in a study by Phukan et al. In our study, significant impairment was

noted in memory domain and fluency assessment with respect to education status. Education is thought to create a reserve capacity that allows better performance despite frontotemporal degeneration (Chiò et al., 2019)

The influence of language on cognition has not been studied so far in ALS. Our study found that patients with multilinguistic status performed better in both phonemic and categorical fluency. Mechanisms have been described in other types of dementia which showed that learning a foreign language and bilingualism enhance brain functional connectivity between regions involved in language processing and result in enhanced executive functions. Other mechanisms like preserving white matter integrity and increased grey matter density that lead to better neural reserve have also been described. (Kim et al., 2019) The mechanism per se in ALS has not been well studied and needs further pathophysiological studies.

The mean duration of illness at the time of presentation in our study was associated with the severity of motor deficits but did not affect the cognitive impairment. Although the duration of illness at presentation was marginally higher, it was not statistically significant. This was consistent with previous studies which did not show a significant association for duration with executive dysfunction (Massman et al., 1996; Phukan et al., 2012). However, Massman et al had shown that the duration of illness was shorter in the impaired group favoring a rapid progression, although this association was not statistically significant.

FUNCTIONAL SCORES:

The patients with poor functional scores in ALS-FRS at baseline were more likely to have cognitive impairment. The individual domain that was shown to be affected in our study were picture naming task. The findings were similar to those noted by Massman et al and Robinson et al, which showed worse scores in the cognitively impaired population. Some others failed to show a correlation between ALS- FRS scores and cognitive

impairment. (Phukan et al., 2012)

MRC Sum scores however showed no correlation in contrast to some studies that showed significant cognitive impairment with increasing motor progression like Massman et al.(Massman et al., 1996)

ONSET OF ALS:

Bulbar and spinal onset did not show any significant association with cognitive impairment concurrent with some of the previous studies like Massman et al. (Massman et al., 1996) However studies like Strong et al (Strong et al., 2003), Abrahams et al, (Abrahams et al., 1997) and Lomen-Hoerth et al (Lomen-Hoerth et al., 2003) showed significant association of bulbar onset with cognitive impairment. The lack of significance in our study could be due to the fact that we excluded patients with significant bulbar impairment. A hypothesis proposed was that the topography of the motoneuron degeneration in bulbar ALS patients results in more extensive disruption of cognitive pathways due to widespread degeneration. (Schreiber et al., 2005). Also, association has been described due to connections between the prefrontal cortex and areas controlling facial and speech muscles, which could favor the dissemination of TDP- 43 lesions from the motor to the cognitive area. (Brettschneider et al., 2013; Lomen-Hoerth et al., 2003)

STAGING AND SEVERITY:

A study by Crockford et al., which was done to assess the cognitive impairment across various stages of ALS had shown that cognitive dysfunction increased with a progressive increase in the severity of ALS. (Crockford et al., 2018). This was predominantly described in functions like execution, language and letter fluency, but not with memory or visuospatial domains. (Crockford et al., 2018)

The mechanism proposed was the probable spread of degenerative cortices in the frontal

cortex with increasing severity. In our study, no correlation was noted across various Kings stages or severity and cognitive impairment. Our exclusion of patients who had a severe gross bulbar or respiratory impairment that affects neuropsychological test performances, thus restricting stage 3 and stage 4 population enrollment, could have contributed to this observation.

ELECTROPHYSIOLOGICAL PARAMETERS:

The electrophysiological parameters have not been studied so far in relation to cognitive impairment. The low CMAP amplitudes of the median nerve are shown to be associated with cognitive impairment. Decreased peroneal CMAP amplitudes had reduced performance in the ACE-Visuospatial domain. The CMAP is an indirect marker for motor progression but could not explain the association with cognitive impairment.

QUALITY OF LIFE:

In our studies, cognitive impairment has been shown to affect the quality of life mainly in general health, physical functioning, aspect of pain, emotional well-being and social function. The predominant neuropsychological parameters affected were fluency, execution, memory, and visuospatial domains. This was concurrent with other studies like Goldstein et al, where health and social health were affected. (Goldstein et al., 2002) The variations could be due to the different scoring systems used. Apart from this, there are no studies that compare quality of life about cognition and impact on long-term QoL.

CAREGIVER BURDEN:

Caregiver burden refers to the feelings of loss, loneliness and other emotional

changes perceived by caregivers due to the provision of home care, which comes at a physical, mental, emotional, social and economic cost to the caregiver. (Burke et al., 2015) Caregiver burden in our study was high in our study in almost half of the patients and correlated with cognitive impairment. This was similar to the study by Lilo et al (Lillo et al., 2012) which showed that neurobehavioral symptoms in ALS, contributed to high caregiver burden. Another study by Burke et al has shown that increased level of knowledge, severity of illness and anxiety correlated positively with high caregiver burden (Burke et al., 2015)

MORTALITY:

Only 3 patients died in the 6-month follow-up. There was no correlation between cognitive impairment and mortality. The mortality was less compared to other studies which is attributable to the exclusion of severe patients with stage disease and short follow up duration. The cause of death in two patients was respiratory failure and one unidentified.

PREVALENCE AND PATTERNS OF COGNITIVE IMPAIRMENT:

Cognitive impairment was noted in two-thirds of the population with all the patients having multidomain affliction. The high proportion is despite stringent criteria of mean +/- 2 SD used for defining cognitive impairment. The previous studies had noted cognitive impairment ranging from 35% to 52% (Lomen-Hoerth et al., 2003; Massman et al., 1996; Phukan et al., 2012; Ringholz et al., 2005; Strong et al., 2003; Wilson et al., 2001) . The still higher prevalence in our cohort could be due to the type of neuropsychological tasks we have used, which was not uniform in the studies done so far. The most common domains affected were executive function, attention, visuospatial function, and memory. The executive function and attention were the predominant domains involved so far in previous

studies. (Phukan et al., 2012; Ringholz et al., 2005; Strong et al., 2003) The predominant involvement in executive function and attention could be explained by the early prefrontal cortex involvement. Studies have shown that Tar DNA Binding Protein – 43 inclusions are known to spread in ALS from the primary motor cortex, spinal cord, and cranial nerves to reticular formation of the brainstem, and prefrontal cortex thus explaining the predominant executive and attention involvement which were considered to be ALS-specific domains. (Brettschneider et al., 2013) Our study differed regarding the significant involvement of memory and visuospatial function which have not been frequently described so far and were considered to be ALS nonspecific domains. However, the spread of inclusions has been finally to the hippocampus also, which has not been studied in detail as patients were not followed up until memory deficits started in the above studies. The other reason could be the difference in neuropsychological tests used. Among the two tests used to assess the visuospatial dysfunction in our cohort, position discrimination was impaired in the majority compared to cube analysis suggesting variation based on the type of tests used.

FOLLOW UP:

Very few longitudinal studies assessing the follow-up have been done in ALS patients.

In our cohort, follow-up analysis done using repeated measures of ANOVA and regression has shown that patients with cognitive impairment had worsening of ALS-FRS scores. Even though motor progression as assessed by MRC SUM scores did show intrasubject variation, no significant Intersubject variation was noted suggesting that the cognitive impairment may not affect motor progression, but negatively impacts the functional scores on follow-up. It is considered from the literature so far that motor and cognitive components of ALS may worsen in parallel (Crockford et al., 2018). ALS pathology disseminates in a regional ordered sequence through a cortical efferent spreading model. (Chiò et al., 2019; Strong et

al., 2003). However, we could not prove this hypothesis in our study probably due to the loss of some patients due to attrition, and also because of lack of functional studies. Moreover, the quality-of-life parameters especially for physical functioning and social function showed a negative correlation with cognitive impairment. The caregiver burden was also significantly high on follow-up. This is in contrast to a previous study by Bock et al, which has shown that there was no significant correlation between ALS – FRS, and QoL in cognitively intact or impaired patients. However, caregiver burden scores showed a significant association with cognitive impairment. (Bock et al., 2017). The significant findings in our study could be explained by the effect of cognition in various aspects of quality of life affecting the patients' emotional well-being, social functioning and health status,(Goldstein et al., 2002) and the emotional issues faced by the caregiver while dealing with ALS patients. (Lillo et al., 2012)

STRENGTHS AND LIMITATIONS:

STRENGTHS:

1. Ours is a prospective, longitudinal study that assessed the patients at baseline and follow-up, which compare the effect of cognitive dysfunction on motor progression, quality of life and caregiver burden. Currently data is lacking on longitudinal studies in this aspect.
2. We have a relatively large sample of patients
3. We have considered neuropsychological parameters involving all domains and at least a minimum of two tests for each domain.
4. We have also delineated the effect of each variable on individual neuropsychological parameters which has not been done so far.
5. Moreover, there is no data in the Indian population, where the pattern of cognitive impairment is likely to differ when compared to the Western population.

LIMITATIONS:

1. Selection bias as we have excluded patients with significant bulbar impairment and other systemic factors affecting performance on neuropsychological tests.
2. This is the initial study to identify the domains which are affected in ALS patients. For future studies, we would further need to modify the battery to include culturally appropriate studies which can be used even in patients with severe bulbar or limb weakness.
3. We had selected tests which had been validated in our population using normative data in the published population data. These tests were necessarily different from the previously published studies from Western population. A uniform comparison between the studies was not possible due to this.

4. The duration of follow up was kept as 6 months which is short considering the natural course of ALS.

Despite these limitations, ours is the only study that has emphasized the effect of individual demographic and functional variables on various aspects of cognitive impairment; and also, the only study in the Indian population that compared the effect of cognition on follow-up in relation to motor progression.

Our data regarding the pattern of cognitive impairment may help in early specific interventions that could improve the cognitive status, when administered earlier and thus improve the functional status and quality of life both for the patient and the caregiver burden of the bystanders. This also calls for timely assessment of detailed cognitive status despite no reported cognitive symptoms by the patient. The study adds to the insight on the wider pathological abnormalities in ALS.

6 SUMMARY AND CONCLUSIONS

1. Our study showed cognitive impairment in about two-thirds in an Indian cohort of ALS
2. The predominant cognitive domains involved are executive function, attention and visuospatial function, and memory in that order.
3. Cognitive impairment was noted to have a significant impact on functional scores, quality of life, and caregiver burden at baseline and 6-month follow-up.
4. There was no correlation between cognitive impairment and survival or motor progression.
5. Our study further proves that the hitherto assumption that “ALS spares the mind” does not hold.
6. A significant proportion had cognitive impairment despite there being no clinical symptoms, which affects the quality of life and the functional scores, as well, the capacity to make decisions regarding further life-prolonging interventions.
7. The study suggests the need for detailed neuropsychology evaluation in ALS patients and use of culturally appropriate and comprehensive set of neuropsychological tests to help in uniformity while comparing trials
8. The study also enunciates the need for early cognitive intervention.
9. This could improve the quality of life for both patients and caregivers managing this devastating disease.

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1. POSTER PRESENTATION: An unusual cause of gross hematuria; Apicon Guntur 2019

2. PAPER PRESENTATION: Etiology and clinical profile of pregnancy-related acute kidney injury; Apicon Guntur 2019

3. PAPER PRESENTATION: Prevalence, Predictors and Outcome of Stuttering Lacunar Strokes in Travancore Neurocon, 2022

4. Poster Presentation- Grisel syndrome presenting as Pseudo dystonia- A twist in the neck in Travancore Neurocon, 2022

5. SHORT COMMUNICATIONS: Prevalence, Predictors and Outcome of Stuttering Lacunar Strokes; World Stroke Congress, Singapore - 2022

6. AWARD PAPER PRESENTATION: Diagnostic Utility of Next generation Sequencing in Leukodystrophies and genetic leukoencephalopathies in AOCN- IANCON 2022

7. PAPER PRESENTATION: Thrombus Histology – Correlation with stroke aetiology and recanalization in KAN MONSOON SUMMIT – INTERNATIONAL UPDATE – 2023

8. AWARD PAPER PRESENTATION: Gelastic Seizures beyond Hypothalamic hamartomas – Prevalence, predictors, and Outcome in ECON 2023

PUBLICATIONS IN JOURNALS

1. **Rowell's syndrome- A rare clinical entity,Indian journal of Applied Research,volume 10, issue 2, February, 2020**
2. **IBA 57 Mutation associated Infantile Cavitating Leucoencephalopathy – Neurology**
3. **Hypomagnesemia induced encephalopathy with transient torsionalnystagmus evolving into downbeat nystagmus: A rare complication of ileostomy – Acta Neurological Belgica**

MD DISSERTATION

A STUDY OF CLINICAL PROFILE OF HYPERTENSIVE EMERGENCIES IN A TERTIARY CARE INSTITUTE

Current project/s at hand:

1. **Prevalence and Patterns of cognitive dysfunction in Amyotrophic Lateral Sclerosis and correlation with disease progression**
2. **Prevalence, Predictors and Outcome of Stuttering Lacunar Strokes – Completed ; under review**

for publication **3. Gelastic Seizures beyond Hypothalamic hamartomas – Prevalence, predictors, and Outcome** **4. Diagnostic Utility of Next generation Sequencing in Leukodystrophies and genetic leukoencephalopathies** **5. Thrombus Histology – Correlation with stroke aetiology and recanalization**	
Signature: 	**Date:** **31.08.2023** **Place:** **Thiruvananthapuram, Kerala**

CV OF THE INVESTIGATOR

Nair	**Sruthi**	**S**
Last Name	First Name	Middle Name
Date of Birth (dd/mm/yy) **25/09/1982**		Sex **Female**
Study Site Affiliation: **Principal Investigator**		
Professional Mailing Address (Include Institution name)		Study Site Address (Include Institution name)
Associate Professor , Neurology Department, Sree Chitra Tirunal Institute for Medical Science And Technology, Trivandrum, Kerala-695011		**Neurology Department, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, Kerala-695011**
Telephone (Office): **0471-2524488**		Mobile Number: **9895045032**
Telephone (Residence): Nil		Email : **sruthisn@sctimst.com**

Academic Qualifications (Most recent qualification first)

Degree/Certificate	Year	Institution, Country
DM(Neurology)	2014	Sree Chitra Tirunal Institute for Medical Science and Technology, India
MD(Medicine)	2009	Government Medical College, Trivandrum, India
MBBS	2005	Government Medical College, Trivandrum, India

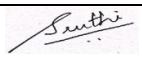
Details of professional registration : (MCI/State Registration/Bar Council/DCI/etc including Registration Number and Year of Registration: **TCMC 34737, dated 22.10.2005**

Current and previous positions (most recent position first)

Month and Year	Title	Institution/Company, Country
May 2018 till date	Associate Professor of Neurology	Sree Chitra Tirunal Institute for Medical Science and Technology, India
May 2015 to May 2018	Assistant Professor of Neurology	Sree Chitra Tirunal Institute for Medical Science and Technology, India

Brief summary of relevant research experience:
Research interests in multiple sclerosis and related diseases, neuromuscular diseases and electromyography. Investigator in completed and ongoing studies on motor neuron disease, myasthenia gravis, motor unit number estimation, and multiple sclerosis.

Current project/s at hand:
(A) Principal Investigator of the DST funded project 'Structural and functional imaging correlates of cognitive dysfunction in relapsing remitting multiple sclerosis' – completed
(B) Site PI of ICMR funded project 'Indian Multiple Sclerosis and Allied Demyelinating Disorders Registry and Research Network' – under IEC review

Signature: 	Date: 26.08.2020 Place: Thiruvananthapuram

CURRICULUM VITAE - DR. SYAM KRISHNAN NAIR

Last Name NAIR	First Name SYAM	Middle Name KRISHNAN
Date of Birth (dd/mm/yy) 10/04/75		Sex MALE
Study Site Affiliation (e.g. Principal Investigator, Co-Investigator, Coordinator) PRINCIPAL INVESTIGATOR		
Professional Mailing Address (Include Institution name)		Study Site Address (Include Institution name)
Professor, Department Of Neurology Sree Chitra Tirunal Institute for Medical Sciences and Technology Thiruvananthapuram – 695011, Kerala, India		Professor, Department Of Neurology Sree Chitra Tirunal Institute for Medical Sciences and Technology Thiruvananthapuram – 695011, Kerala, India
Telephone (Office): 0471-2524-262, 0471-2524268		Mobile Number:+91-9847310745 +91-9496252344
Telephone (Residence):		Email: drsyamknair@yhoo.co.in , drsyam@sctimst.ac.in

Academic Qualifications (Most recent qualification first)

Degree/Certificate	Year	Institution, Country
DM (NEUROLOGY)	2005	SreeChitraTirunal Institute for Medical Sciences and Technology (SCTIMST), Thiruvananthapuram, Kerala, India
MD (INTERNAL MEDICINE)	2002 (Passed out as the "**Best Outgoing Student**")	Government Medical College, Thiruvananthapuram, Kerala (University of Kerala), India
MBBS	1997 (Finished Internship in 1998) **Passed out with Second Rank in the University**	Government Medical College, Kottayam, Kerala (Mahatma Gandhi University) , India

Details of professional registration: (MCI/State Registration/Bar Council/DCI/etc including Registration Number and Year of Registration

REG NO. 26740 (Travancore-Cochin Medical Council – Kerala) -1998

Current and previous positions (most recent position first)		
Month and Year	Title	Institution/Company, Country
December 2018 - continuing	Professor of Neurology	Sree Chitra Tirunal Institute For Medical Sciences And Technology Thiruvananthapuram – 695011, Kerala, India.
December, 2014 – December 2018	Additional Professor of Neurology	Sree Chitra Tirunal Institute For Medical Sciences And Technology Thiruvananthapuram – 695011, Kerala, India.
December, 2011 – December, 2014	Associate Professor of Neurology	Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), Thiruvananthapuram, Kerala, India
December, 2008 – December, 2011	Assistant Professor of Neurology	Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), Thiruvananthapuram, Kerala, India
August, 2008- December, 2008:	Senior Lecturer in Neurology,	Government Medical College, Calicut, Kerala, India
February, 2008- July, 2008:	Adhoc Consultant [Present Designation – Assistant Professor (Adhoc)], Department of Neurology	Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), Thiruvananthapuram, Kerala, India
February 2006- January 2008	Consultant Neurologist	St. Mary's Hospital, Thodupuzha, Kerala

Brief summary of relevant research experience:

Research Projects Undertaken
Externally Funded Projects

1. **Principal Investigator** of the project "Exploring the human gut microbiome, metabolome and alpha synuclein in health and Parkinson's disease (PD) – a window to the gut microbiota-brain axis alterations in PD". **SCTIMST IEC Approval Number**: SCT/IEC/1307- DECEMBER 2018. **Funding Agency:** Indian Council of Medical Research (ICMR). **Collaborator:** Cochin University of Science and Technology (CUSAT)
2. **Principal Investigator** of the project "Quantitative estimation of regional brain iron deposition- a potential biomarker for Parkinson's disease and other neurodegenerative conditions causing atypical Parkinsonism". **SCTIMST IEC Approval Number**: SCT/IEC/857- FEBRUARY 2016. **Funding Agency:** Department of Biotechnology, Government of India.
3. **Principal Investigator** of the Project "Validation of the Malayalam version of Montreal Cognitive Assessment (MoCA) scale and a prospective evaluation of mild cognitive impairment in Parkinson's disease using the Malayalam version (MoCA-M)". **SCTIMST IEC Approval Number**: SCT/IEC/438/DECEMBER 2012. **Funding Agency**: Indian Council of Medical Research
4. **Co-Investigator** of the project "Deciphering the genetic architecture of Parkinson's disease in Indian population". **SCTIMST IEC Approval Number**: SCT/IEC/540/AUGUST 2016. **Funding Agency:**

Michael J Fox Foundation, USA

5. **Co-Investigator** for the project "The effects of Yoga on Motor Cortex Plasticity, Motor Learning and the Motor Deficits of Parkinson's disease" **SCTIMST IEC Approval Number**: SCT/IEC/937/AUGUST 2016. **Funding Agency**: Department of Science and Technology, Government of India

Funded Research and Development Projects in Collaboration with the Biomedical Technology Wing

1. **Co-Investigator** for the TRC funded project (8125 GN) "Development of Deep Brain Stimulator System for Movement Disorders". **Total Project Cost:**Rs. 21.6 Million. **Collaborators**: Comprehensive Care Centre for Movement Disorders, SCTIMST; BMT wing, SCTIMST and Bhabha Atomic Research Centre, Mumbai.
2. **Co-Investigator** for the Project "Development and Implementation of Tele-consultation facility for patients with Movement Disorders". **Collaborators**: Comprehensive Care Centre for Movement Disorders (CCCMD), SCTIMST; Computer Division, SCTIMST and BMT wing, SCTIMST. **Funding**: In- house project of CCCMD

Institute Funded Projects

1. **Principal Investigator** for the Institute Funded (Dir/INT. PROJ/SCTIMST/2010, dated 27/07/2010) Project "Comparison of the Sleep Disorders in Familial Vs Sporadic Parkinson's disease- a Prospective study". **SCTIMST IEC Approval Number**: IEC/310, dated 18/09/2010.

International Multicentre Clinical Trials

1. **Co-Investigator** for the Clinical Trial "Protocol 28850. Open label trial to determine the long-term safety of XXXX in Parkinson's disease patients." of Neurology). **SCTIMST IEC Approval Number**: IEC/217. **Status**: Completed.
2. **Co-Investigator** for the clinical trial "Protocol SP 921- A multicentre, randomized, placebo controlled, 5-arm parallel group trial to assess XXXX transdermal system dose response in subjects with advanced-stage Parkinson's disease". **SCTIMST IEC Approval Number**: IEC/ 256. **Status**: Completed.
3. **Co-Principal Investigator** for the clinical trial "Protocol P04938- A Phase 3, 12-week, double blind, placebo and active controlled efficacy and safety study of XXXX in subjects with moderate to severe Parkinson's disease". **SCTIMST IEC Approval Number**: SCT/IEC/339/SEPTEMBER-2011. **Status:** Completed.
4. **Co-Principal Investigator** for the clinical trial "A phase 3 double blind placebo and active controlled dose-range finding efficacy and safety study of XXXX in subjects with early Parkinson's disease". **SCTIMST IEC Approval Number**: SCT/IEC/340/SEPTEMBER-2011. **Status:** Completed.

Internally funded/ non-funded, IEC approved research projects:

1. **Principal Investigator** of the project "Effect of subthalamic nucleus Deep Brain Stimulation Surgery on impulsivity in Parkinson's disease patients." **SCTIMST IEC Approval Number**: SCT/IEC/770/JUNE-2015.
2. **Principal Investigator** of the project "Do baseline clinical and Neuropsychological factors predict the occurrence of dementia on follow-up in patients with Parkinson's disease undergoing Deep Brain Stimulation surgery?" **SCTIMST IEC Approval Number**: SCT/IEC/921/JUNE 2016.
3. **Principal Investigator** of the project "Improvement of non-motor fluctuations in Parkinson's disease with Deep Brain Stimulation – a prospective controlled study" **SCTIMST IEC Approval Number**: SCT/IEC/920/ JUNE 2016.
4. **Principal Investigator** of the project "Effect of bilateral subthalamic stimulation on the non-motor symptoms in Parkinson's disease" **SCTIMST IEC Approval Number**: SCT/IEC/504/ NOVEMBER 2013.
5. **Co-Principal Investigator** for the project "Cognitive profile and prevalence of mild cognitive impairment in early onset Parkinson's disease". **SCTIMST IEC Approval Number**: SCT/IEC/1084/AUGUST 2017.
6. **Co-Principal Investigator** for the project "Apraxia of eyelid opening in Parkinson's disease following bilateral subthalamic nucleus deep brain stimulation". **SCTIMST IEC Approval Number**: SCT/IEC/1159/DECEMBER 2017.
7. **Co-Principal Investigator** for the project "Prevalence and determinants of non-motor fluctuations in Indian patients with Parkinson's disease experiencing motor fluctuations". **SCTIMST IEC Approval Number**: SCT/IEC/939/AUGUST 2016.
8. **Co-Principal Investigator** for the project"Non-conventional programming paradigms – indications, efficacy and clinical outcomes in subthalamic stimulation for PD. **SCTIMST IEC Approval Number**: SCT/IEC/938/AUGUST 2016.
9. **Co-Principal Investigator** for the project "Do DRD 3 genetic polymorphisms contribute to impulsivity in Parkinson's disease patients?". **SCTIMST IEC Approval Number**: SCT/IEC/769/JUNE 2015
10. **Co-Principal Investigator** for the project "Resting state connectivity between the basal ganglia and cerebellum in health and Parkinson's disease- a combined functional MRI and Diffusion Tensor Imaging study". **SCTIMST IEC Approval Number**: SCT/IEC/816/OCTOBER 2015.
11. **Co-Investigator** of the project "Cerebellar modulation of depotentiation at the primary motor cortex in health and during levodopa induced dyskinesias in Parkinson's disease". **SCTIMST IEC Approval Number**: SCT/IEC/708/DECEMBER 2014.
12. **Co-Principal Investigator** for the project "Is hearing impairment a non-motor symptom in Parkinson's disease? A prospective study". **SCTIMST IEC Approval Number**: SCT/IEC/719/DECEMBER 2014.
13. **Co-Principal Investigator** of the project "Long-term follow-up of bilateral subthalamic nucleus deep brain stimulation for advanced Parkinson's disease patients". **SCTIMST IEC**

Approval Number: SCT/IEC/503/NOVEMBER 2013.

14. **Co-Principal Investigator** of the project "Non-invasive cerebellar inhibition by transcranial magnetic stimulation for the treatment of Levodopa induced dyskinesias in Parkinson's disease." **SCTIMST IEC Approval Number**: SCT/IEC/363/ SEPTEMBER 2011.

15. **Co- Investigator** of the project "Evaluation of non-motor symptoms in patients with Parkinson's disease from Kerala using Non-Motor Symptoms Scale (NMSS). **SCTIMST IEC Approval Number:** SCT/IEC/261/ FEBRUARY 2010.

PUBLICATIONS

1. **Krishnan S** (Corresponding author), Shetty K, Puthanveedu DK, Kesavapisharady K, Thulaseedharan JV, Sarma G, Kishore A. Apraxia of Lid Opening in Subthalamic Nucleus Deep Brain Stimulation for Parkinson's Disease-Frequency, Risk Factors and Response to Treatment. Mov Disord Clin Pract. 2021 Apr 12;8(4):587-593. doi: 10.1002/mdc3.13206. PMID: 33981792.
2. Saraf U, Chandarana M, Puthenveedu DK, Kesavapisharady K, Krishnan S (Corresponding author), Kishore A. Childhood-Onset Dystonia Attributed to Aicardi-Goutières Syndrome and Responsive to Deep Brain Stimulation. Mov Disord Clin Pract. 2021 Apr 19;8(4):613-615. doi: 10.1002/mdc3.13205. PMID: 33981798
3. Mitesh Chandarana, Udit Saraf, Divya K.P., **Syam Krishnan** (Corresponding Author), Asha Kishore. Myoclonus – a review. Ann Indian Acad Neurol. 2021 Epub ahead of print. DOI: 10.4103/aian.AIAN_1180_20
4. Cherian A, KP Divya, Paramasivan NK, Krishnan S. Pearls and Oysters: Levodopa Responsive Adult NCL (Type B Kufs Disease) Due to *CLN6* Mutation. Neurology. 2021 Apr 19:10.1212/WNL.0000000000011997. doi: 10.1212/WNL.0000000000011997. Online ahead of print.
5. Mahale RR, Krishnan S, Divya KP, Jisha VT, Kishore A. Gender differences in progressive supranuclear palsy. Acta Neurol Belg. 2021 Feb 17. doi: 10.1007/s13760-021-01599-0. PMID: 33595832
6. Mahale RR, **Krishnan S**, Divya KP, Jisha VT, Kishore A. Subtypes of PSP and prognosis: A retrospective analysis. Ann Ind Acad Neurol 2021. DOI: 10.4103/aian.AIAN_611_20.
7. Zafar SM, Rajan R, **Krishnan S**, Kesavapisharady K, Kishore A. Interleaved Stimulation for Freezing of Gait in Advanced Parkinson's Disease. Neurol India. 2021 Mar-Apr;69(2):457-460. doi: 10.4103/0028-3886.314570. PMID: 33904475.
8. Cherian A, Paramasivan NK, Puthanveedu DK, **Krishnan S**, Nair AR. Generalized Chorea Due to Secondary Polycythemia Responding to Phlebotomy. J Mov Disord. 2021 Jan;14(1):89-91. doi: 10.14802/jmd.20081. PMID: 33121224.
9. **Syam Krishnan**, Asha Kishore. Parkinson's disease. In: Shirly G, S K Kunnath, Anne Varghese, Vinitha Mary George (Editors) Disability: An Overview, In the Context of the Rights of Persons with Disabilities (RPwD) Act, 2016. 1st Edition, Published by NISH (National Institute of Speech and Hearing), Thiruvananthapuram, 2019. ISBN: 9788193985007
10. **Krishnan S**, Pisharady KK, Rajan R, Sarma SG, Sarma PS, Kishore A. Predictors of dementia-free survival after bilateral subthalamic deep brain stimulation for Parkinson's disease. Neurol India. 2019 Mar-Apr;67(2):459-466. doi: 10.4103/0028-3886.258056.
11. Shetty K, **Krishnan S**, Thulaseedharan JV, Mohan M, Kishore A. Asymptomatic Hearing Impairment Frequently Occurs in Early-Onset Parkinson's Disease. J Mov Disord. 2019 May;12(2):84-90. doi: 10.14802/jmd.18048.

12. Kishore A, Ashok Kumar Sreelatha A, Sturm M, von-Zweydorf F, Pihlstrøm L, Raimondi F, Russell R, Lichtner P, Banerjee M, **Krishnan S**, Rajan R, Puthenveedu DK, Chung SJ. Understanding the role of genetic variability in LRRK2 in Indian population. Mov Disord. 2018 Nov 28. doi: 10.1002/mds.27558. [Epub ahead of print]. PMID 30485545
13. Rajan R, **Krishnan S**, Sarma G, Sarma SP, Kishore A. Dopamine Receptor D3 rs6280 is Associated with Aberrant Decision-Making in Parkinson's Disease. Mov Disord Clin Pract. 2018 Jul 19;5(4):413-416. doi: 10.1002/mdc3.12631. PMID: 30363458
14. Popa T, Hubsch C, James P, Richard A, Russo M, Pradeep S, **Krishan S**, Roze E, Meunier S, Kishore A. Abnormal cerebellar processing of the neck proprioceptive information drives dysfunctions in cervical dystonia. Sci Rep. 2018 Feb 2;8(1):2263.
15. **Krishnan S**, Pisharady KK, Divya KP, Shetty K, Kishore A. Deep Brain Stimulation for Movement disorders. Neurol India. 2018 Mar-Apr;66 (Supplement): S90-S101.
16. **Krishnan S**, Rajan R, Kishore A. Deep brain stimulation for movement disorders. In: Mukherjee A (Editor-in-Chief). IAN Textbook of Neurology. 1st Edn. New Delhi. Jaypee Brothers Medical publishers; 2017.
17. **Krishnan S**, Pisharady KK. Surgical Treatment of Levodopa-induced Dyskinesia in Parkinson's Disease. Ann Indian Acad Neurol. 2017 Jul-Sep;20(3):199-206.
18. Kishore A, Popa T, James P, **Krishnan S**, Robert S, Meunier S. Severity of Writer's Cramp is Related to Faulty Motor Preparation. Cereb Cortex. 2017 Sep 11:1-14.
19. Joseph PS, **Syam Krishnan**, Narayanappa G, Nair M. Young onset Parkinsonism in a patient with familial central core disease. Neurol India. 2017 Mar-Apr;65(2):386-388.
20. Kishore A, James P, **Krishnan S**, Yahia-Cherif L, Meunier S, Popa T. Motor cortex plasticity can indicate vulnerability to motor fluctuation and high L-DOPA need in drug-naïve Parkinson's disease. Parkinsonism Relat Disord. 2017 Feb; 35:55-62.
21. Krishnamoorthy S, Rajan R, Banerjee M, Kumar H, Sarma G, **Krishnan S**, Sarma S, Kishore A. Dopamine D3 receptor Ser9Gly variant is associated with impulse control disorders in Parkinson's disease patients. Parkinsonism Relat Disord. 2016 Sep; 30:13-7.
22. Rajan R, **Krishnan S**, Kesavapisharady KK, Kishore A. Malignant subthalamic nucleus deep brain stimulation withdrawal syndrome in Parkinson's disease. Movement Disorders Clinical Practice 2016. Published online in Wiley InterScience (www.interscience.wiley.com). DOI:10.1002/mdc3.12271.
23. **Krishnan S**, Prasad S, Pisharady KK, Sarma G, Sarma SP, Kishore A. The decade after subthalamic stimulation in advanced Parkinson's disease: A balancing act. Neurol. India 2016; 64(1):81-9.
24. **Krishnan S**, Justus S, Meluveettil R, Menon RN, Sarma SP, Kishore A. Validity of Montreal Cognitive Assessment in Non-English-speaking patients with Parkinson's disease. Neurol India. 2015 Jan-Feb;63(1):63-7.
25. Syambabu Chandran, **Syam Krishnan**, Gangadhara Sarma S, Sankara Sarma P, Asha Kishore. Gender influence on selection and outcome of deep brain stimulation for Parkinson's disease. Ann Indian Acad Neurol 2014; 17:66-70.
26. Sarathchandran S, Soman S, Sarma SG, **Krishnan S**, Kishore A. Impulse control disorders in Indian patients with Parkinson's disease. Mov Disord 2013; 28: 1901-1902.
27. Kishore A, Popa T, Balachandran A, Chandran S, Pradeep S, Backer F, **Krishnan S**, Meunier S Cerebellar sensory processing alterations impact motor cortical plasticity in Parkinson's disease: clues from dyskinetic patients. Cereb Cortex. 2014 Aug;24(8):2055-67.
28. Binitha Rajeswari, **Syam Krishnan**, Sarada C, Kusumakumary Parukuttyamma. Guillain Barre

Syndrome with acute lymphoblastic leukemia. Indian Pediatrics 2013; 50: 791-792.
29. **Krishnan S**, Sarma G, Sarma S, Kishore A. Do nonmotor symptoms in Parkinson's disease differ from normal aging? Mov Disord. 2011 Sep;26(11):2110-3.
30. Behari M, Bhattacharyya KB, Borgohain R, Das SK, Ghosh B, Kishore A, **Krishnan S,** Mridula KR, Muthane U, Pal PK, Sankhla C, Shukla G. Parkinson's disease. Ann Indian Acad Neurol 2011; 14(Suppl 1):S2-6.
31. Kishore A, Rao R, **Krishnan S** et al. Long term stability of effects of subthalamic stimulation in Parkinson's disease: Indian experience. Mov Disord. 2010 Oct 30;25(14):2438-44.
32. Lekha Pandit, Maria Ban, Stephen Sawcer, Bhim Singhal, **Syam Nair**, Kurupath Radhakrishnan, Rajesh Shetty, Z Misri, Suresh Hegde, Irruvathur Gopalakrishna Bhat. Evaluation of the established non-MHC Multiple Sclerosis loci in an Indian population. Mult Scler. 2011 Feb;17(2):139-43.
33. Mahesh Pundlik Kate, Chandrasekharan Kesavadas, Muralidharan Nair, **Syam Krishnan**, Manoj Soman, Atampreet Singh. Late-onset Boucher-Neuhäuser Syndrome (late BNS) associated with white-matter changes: a report of two cases and review of literature. J Neurol Neurosurg Psychiatry. 2011 Aug;82(8):888-91.
34. Neeraj N. Baheti, **Syam Krishnan**, Bejoy Thomas, Chandrasekharan Kesavadas, Ashalatha Radhakrishnan. Stroke like episodes in Sturge-Weber syndrome. Neurol India. 2010 Sep-Oct;58(5):797-9.
35. Baheti NN, Hassan H, Rathore C, **Krishnan S**, Kesavadas C. Acquired hepatolenticular degeneration: is the T1 hyperintensity due to manganese deposition? Neurol India. 2009 Nov-Dec;57(6):812-3.
36. Baheti NN, Cherian A, Kate M, **Krishnan S**, Thomas B. Intracerebral haemorrhages in Vogt-Koyanagi-Harada disease. Neurol India. 2009 Nov-Dec;57(6):815-7.
37. **Syam Krishnan**, PS Mathuranath, Sankara Sarma, Asha Kishore. Neuropsychological functions in progressive supranuclear palsy, multiple system atrophy and Parkinson's disease. Neurol India. 2006 Sep;54(3):268-72.
38. Khan SF, Ashalatha R, **Syam K**. Periodic EEG pattern in neuro-dengue -- a novel observation. Eur J Neurol. 2005 Dec;12(12):1009.
39. Somarajan A, Ashalatha R, **Syam K**. Moya Moya disease: an unusual clinical presentation. J Assoc Physicians India. 2005 Jan;53:49-51.

Current project/s at hand as PI / Co-PI:

1. Exploring the human gut microbiome, metabolome and alpha synuclein in health and Parkinson's disease (PD) – a window to the gut microbiota-brain axis alterations in PD
2. Validation of the Malayalam version of Montreal Cognitive assessment scale (MoCA) and a prospective evaluation of Mild Cognitive Impairment in Parkinson's disease using the Malayalam Version.
3. Quantitative estimation of Regional Brain Iron Deposition – A Potential biomarker for Parkinson's Disease and other Neurodegenerative Conditions Causing Atypical Parkinsonism.
4. Cognitive profile and prevalence of mild cognitive impairment in early onset Parkinson's

disease.

5. Apraxia of eyelid opening in Parkinson's disease following bilateral subthalamic nucleus deep brain stimulation.

Signature: 	July 20, 2021 Thiruvananth- -apuram

Format for CV of the Investigators

Last Name: Menon	First Name: Ramshekhar	Middle Name: N
Date of Birth (dd/mm/yy) 25/09/1978		Sex M
Study Site Affiliation (e.g. Principal Investigator, Co-Investigator, Coordinator) Principal Investigator		
Professional Mailing Address (Include Institution name)		Study Site Address (Include Institution name)
Epilepsy Office, 4th floor , Block 2, SCTIMST, Trivandrum-11		Department of Neurology, SCTIMST, Trivandrum 11
Telephone (Office): 0471- 2524481		Mobile Number: 9946916769
Telephone (Residence):0471- 2734040		Email: rsnmenon@sctimst.ac.in

Academic Qualifications (Most recent qualification first) Epilepsy Fellowship, DM, DNB, MD, MBBS

Degree/Certificate	Year	Institution, Country
MBBS	2002	University of Pune, India
MD, DNB Medicine	2006	University of Mumbai, India
DM Neurology	2009	Maharashtra University of Health Sciences, India
Epilepsy Fellowship	2010	SCTIMST

Details of professional registration : (MCI/State Registration/Bar Council/DCI/etc including Registration Number and Year of Registration- TCMC- 30958/2002

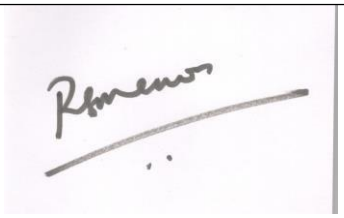
Current and previous positions (most recent position first) Additional professor, Department of Neurology

Month and Year	Title	Institution/Company, Country
2017 till present	Additional Professor	SCTIMST
2015-2017	Associate Professsor	SCTIMST
2011-2015	Assistant Professor	SCTIMST

Brief summary of relevant research experience:
Research and clinical experience in epilepsy, cognitive neurology, autoimmune disorders, status epilepticus and general neurology
No. of publications and book chapters: 61
No. of extramural funded projects: 15

Current project/s at hand:

1) PI: Effect of yoga on neuropsychological functions and brain connectivity networks in mild cognitive impairment and cognitively normal subjects.3 years. Commenced on 30/07/2016; Status ongoing.
2) Project PI: The influence of sleep architecture on the severity of memory disruption in amnestic MCI- Funded by Kerala State Council for Science, Technology and Environment. INR 8,41,500. Status completed in November 2016.
3) Project PI: Validation of memory fMRI paradigms and its utility in pre-surgical evaluation of patients with refractory TLE. Funded by Department of Science & Technology. INR 14,85,000. Status- completed on 31/03/2017
4) Site Project PI: Development and validation of a comprehensive clinical and neuropsychological test battery for use in the Indian context for patients with Vascular Cognitive Impairment. Funded by ICMR. INR 14,00,000. Status completed on 31/12/2015
5) Project PI: The human brain mapping project- a resting state fMRI study of healthy controls and patients with MCI & AD. Funded by cognitive science initiative of DST. INR 18, 77,600. Status ongoing.
6) Technology development- Site Project PI: Biomedical signal analyzer for seizure prediction, in collaboration with Centre for development of Advanced Computing, Trivandrum. Funded by Department of Electronics & Information Technology. INR 4,62,000 out of INR 30,38,000. Commenced on 30/06/2014. Pilot phase completed on 30/06/2015
7) Collaboration with BMT wing projects- Development of intracranial electrodes for use in acute and chronic electrocorticography for periods up to 15 days.- Clinical PI
8) Co-PI: Non-linear analysis of EEG signals in Alzheimer's Disease through DST funding provided to collaborating centre, NIT Kozhikode. Commenced on 04/07/14. Status completed on 30/06/2015
9) Co-PI: Biochemical and functional investigation of dorsolateral prefrontal cortex in mild cognitive impairment using functional magnetic resonance spectroscopy and functional magnetic resonance imaging. Commenced on 2/7/2016;INR 14,40,000 (DST-SERB); status completed on 01/07/2018.
10) Co-PI: A resting state fMRI and task based fMRI study: Optimization, language lateralization, memory lateralization and connectivity in normal subjects versus patients with epilepsy. Commenced on 1/7/2014; Status Ongoing; DBT
11) Co-investigator: In vitro beta-amyloid uptake by peripheral blood macrophages: predictor for progression of mild cognitive impairment to Alzheimer's disease. Commenced on 1/3/2015; ICMR- Rs. 40,99,400; Status Ongoing.
12) Co-investigator: Study of genetic risk factors associated with inflammation, autophagy and oxidative stress in Alzheimer's Disease and Frontotemporal Dementia; DST-SERB Postdoc fellowship- INR 19,20,000

Signature:  Ramshekhar N Menon	Date: 10/05/2020 Place: Trivandrum

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013/RR-21)

SCT/IEC/1795/JANUARY/2022 21.02.2022

Dr. Manisha K Yalapalli
Senior Resident
Department of Neurology
SCTIMST, Thiruvananthapuram

Dear Dr. Manisha Yalapalli,

The Institutional Ethics Committee held on 29th January, 2022, reviewed and discussed your application to conduct the study titled "**PREVALENCE AND PATTERNS OF COGNITIVE IMPAIRMENT IN AMYOTROPHIC LATERAL SCLEROSIS AND CORRELATION WITH DISEASE OUTCOME**" (IEC/1795).

The following members of the Ethics Sub-committee were present at the meeting held on 29th January, 2022.

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. Kala Kesavan P	MBBS,MD	Female	Basic Medical Scientist	No
2.	Adv. N Anand	BAL, L.LB	Male	Legal Expert	No
3.	Dr. Harikrishna Varma P. R	Ph.D (Materials Sciences)	Male	Medical Technology	Yes
4.	Dr. Manikandan.S	MBBS,MD,PDCC	Male	Clinician	Yes
5.	Dr. Ashalatha R	MBBS, MD,DM	Female	Clinician	Yes
6.	Dr. Biju Soman	MBBS,MD, DPH, MSc, DLSHTM	Male	Basic Medical Scientist	Yes
7.	Dr. Srinivas G	PhD	Male	Basic Medical Scientist (Member Secretary)	Yes

The following documents were reviewed:

1. *Responses made based on the reviewer's comments*
2. *Checklist Form*
3. *Covering letter addressed to the Chairman, IEC, SCTIMST dated 02.09.2021*
4. *IEC Application Form*
5. *Research Proposal*
6. *Declaration form*
7. *Informed Consent Form in English and Malayalam*
8. *Patient Information Sheet in English and Malayalam*
9. *CV of PI and Co-PI*
10. *Proforma*
11. *SRC Recommendation*

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Dr. G. Srinivas
Member Secretary, IEC

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES & TECHNOLOGY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST
THIRUVANANTHAPURAM

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST, THIRUVANANTHAPURAM

PROFORMA

Unique identification number

Date of evaluation

1. Patient biodata

1.1 Age (in years) ……..

1.2 Sex (Male/Female) ……..

1.3 Occupation …….

1.4 Education

1.5 Languages known

2. Clinical details

2.1 Year of symptom onset …….

2.2 Duration of illness ……years… .....months

2.3 Onset Site – Bulbar vs Spinal

2.3.1 Lower limb onset

2.3.1.1 Proximal/distal

2.3.2 Upper limb onset

2.3.2.2 Proximal/Distal

2.4 Motor symptoms

2.5 Non motor symptoms

2.6 Kings staging

2.7 Severity

3. ALSFRS-R Scoring – Baseline and Followup

3.1 Speech

3.2 Salivation

3.3 Swallowing

3.4 Handwriting

3.5 a Cutting food and handling utensils (patients without gastrostomy)

b. Cutting food and handling utensils (alternate scale for patients with gastrostomy)

3.6 Dressing and hygiene

3.7 Turning in bed and adjusting bed clothes

3.8 Walking

3.9 Climbing stairs

3.10 Dyspnea

3.11 Orthopnea

3.12 Respiratory insufficiency

3.13 **Total ALSFRS-R score**- Baseline

4. MRC- SUM Score - Baseline and Followup

4.1.1 Arm abduction

4.1.2 Elbow flexion

4.1.3 Wrist extensors

4.1.4 Hip Flexion

4.1.5 Knee extension

4.1.6 Ankle Dorsiflexion

5. Neuropsychology Evaluation

5.1 General tests

5.1.1 Addenbrooke's cognitive evaluation lll

5.1.2 Domains – Attention, Memory, Fluency, Language, Visuospatial function, ACE III Sum

5.2 Executive function

5.2.1 Trail A and B test

5.3 Language

5.3.1 Picture naming task

5.4 Letter fluency

5.4.1 Phonemic Fluency

5.4.2 Categorical Fluency

5.5 Memory

5.5.1 Rey Auditory Verbal Learning test

5.6 Visuospatial function

5.6.1 Position discrimination

5.6.2 Cube Analysis

5.7 Behavioral Problems

5.7.1 ALS Cognitive Behavioral screen and ALS -CBS Caregiver behavioral questionnaire

6.Questionnaires- Baseline and Followup

6.1 QoL Questionnaires

6.1.1 The Short form health survey -36 (SF-36)

6.2 Caregiver Questionnaire

6.2.1 Zarit Caregiver burden interview

7.Investigations

7.1 Nerve conduction study

5.1.2 CMAP- Median

5.1.2 CMAP – Ulnar

5.1.3 CMAP- Peroneal Extensor Digitorum Brevis

5.1.4 CMAP- Peroneal Tibialis Anterior

5.1.5 CMAP- Tibial

7.2 Electromyography

8.Tests for secondary etiology (if indicated)

8.1 MRI Brain with spine

8.2 Thyroid function tests

8.3 Tumor markers

8.4 Vasculitic screen

8.5 Metabolic screen

8.6 . Infective screen

8.7 Anticholinesterase Receptor Antibody

8.8 Anti-Musk antibody

8.9 Anti-Ganglioside Antibodies

8.10 Genetic Testing

INFORMED CONSENT FORM

TITLE OF STUDY:

PREVALENCE AND PATTERNS OF COGNITIVE IMPAIRMENT IN AMYOTROPHIC LATERAL SCLEROSIS AND CORRELATION WITH DISEASE OUTCOME

I confirm that I have read and understood the information sheet attached to this informed consent form for the above study and have had the opportunity to ask questions. [ ]

(i) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(ii) I understand that the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the study. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iii) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) [ ]

(iv) I agree to take part in the above study. [ ]

Name of Participant:	Name of witness:
Signature:	Signature:
Date:	Relation to participant:
	Date:

DECLARATION BY THE PRINCIPAL INVESTIGATOR

I attest that the requirements for informed consent for the medical research project described in this form have been satisfied. I have discussed the research project with the participant and explained to him / her in non-technical terms all of the information contained in this informed consent form. I further certify that I encouraged the participant to ask questions and that all questions asked were answered. A copy of the informed consent form has been given to the study participant.

Place: Trivandrum Principal Investigator

Manisha K.Y

Date: 02.09.21

Name of the PI: Dr Manisha K Yalapalli
Address and Contact Details: Senior Resident, Department of Neurology
Sree Chitra Tirunal Institute for Medical Sciences and Technology,
Medical College PO, Trivandrum -11
Phone: 9949201366 , E-mail: manisha@sctimst.ac.in

Signature of the PI:
For any clarifications regarding the study's ethics clearance you may contact –
Dr.Srinivas.G
Member Secretary of the SCTIMST-IEC.
Phone number is: 0471-2524689
email id : iec.mem.sec@sctimst.ac.in

കാര്യബോധത്തോടെയുള്ളസമ്മതപത്രം

പഠനശീർഷകം

അമിയോട്രോഫിക് ലാറ്ററൽ സ്ലിറോസിസിലെ അവബോധ ക്ഷയത്തിന്റെ വ്യപ്തിയും മാതൃകകളും രോഗത്തിന്റെ പരിണിതഫലവുമായുള്ള അവയുടെ പരസ്പരബന്ധവും

(കോളങ്ങൾ അടയാളപ്പെടുത്തുക)

i. മുകളിൽ പറഞ്ഞ പഠന സംബന്ധമായ പങ്കെടുക്കുന്നവർക്കുള്ള കാര്യവിവരണപത്രം വായിച്ചതായി ഞാൻ സമ്മതിക്കുന്നു. ചോദ്യങ്ങൾ ചോദിക്കാൻ എനിക്ക് അവസരം ലഭിച്ചു [ ]

ii. എന്റെ പങ്കാളിത്തം സ്വമേധയായാണെന്നും, കാരണമൊന്നും നൽകാതെയും എന്റെ വൈദ്യപരിചരണത്തെ ബാധിക്കാതെയും ഏതു സമയത്തും എനിക്ക് പിൻമാറാൻ സ്വാതന്ത്ര്യമുണ്ടെന്നും മനസ്സിലാക്കുന്നു. [ ]

iii. ഞാൻ പഠനത്തിൽനിന്നും പിൻമാറിയാലും പഠനം നടത്തുന്നവർക്കും നൈതീകകമ്മിറ്റിക്കും എന്റെ ആരോഗ്യരേഖകൽ പരിശോധിക്കാൻ എന്റെ സമ്മതം ആവശ്യമില്ലെന്ന് ഞാൻമനസ്സിലാക്കുന്നു, അതിന് ഞാൻ സമ്മതിക്കുന്നു. എന്തായാലും, പഠനഫലമായി ശേഖരിച്ച വിവരങ്ങൾ പ്രസിദ്ധീകരിക്കുമ്പോഴോ മൂന്നാം കക്ഷികൾക്ക് നൽകുമ്പോഴോ എന്നെ തിരിച്ചറിയാനിടയാകുന്നതൊന്നും വെളിപ്പെടുത്തുകയില്ലെന്ന് ഞാൻ മനസ്സിലാക്കുന്നു. [ ]

iv. ശാസ്ത്രീയ ഉദ്ദേശത്തോടെ പഠനഫലമായി ലഭിക്കുന്ന വിവരങ്ങളോ ഫലങ്ങളോ പങ്കുവെയ്ക്കുന്നതിന് പരിധിയൊന്നും വയ്ക്കില്ലെന്ന് ഞാൻ സമ്മതിക്കുന്നു. [ ]

v. മുകളിൽ പറഞ്ഞ പഠനത്തിൽ പങ്കെടുക്കാൻ സ്വമേധയാ ഞാൻ സമ്മതിക്കുന്നു. [ ]

പേര്
ഒപ്പ്
തിയതി
സാക്ഷിയുടെ പേര്
ഒപ്പ്
തിയതി

പ്രധാന ഗവേഷകയുടെ പ്രസ്താവന

മെഡിക്കൽ റിസർച്ച് പ്രോജക്ടിനാവശ്യമായ സമ്മതപത്രത്തിനു വേണ്ടുന്ന എല്ലാ ഘടകങ്ങളും തൃപ്തികരമായി നിർവഹിച്ചിരിക്കുന്നുവെന്ന് ഞാൻ ബോധ്യപ്പെടുത്തുന്നു. പഠനപങ്കാളിയുമായി ഗവേഷണ പദ്ധതിയെപ്പറ്റി സാങ്കേതികേതര പദങ്ങളുപയോഗിച്ച് എല്ലാ വിവരങ്ങളെപ്പറ്റിയും ചർച്ച നടത്തുകയും പ്രതീക്ഷിക്കാവുന്ന അപകട സാധ്യതകളും പാർശ്വഫലങ്ങളും വിശദീകരിക്കുകയും ചെയ്തു. പങ്കാളിയെചോദ്യങ്ങൾ ചോദിക്കാൻ പ്രേരിപ്പിക്കുകയും എല്ലാ ചോദ്യങ്ങൾക്കും ഉത്തരം നൽകുകയും ചെയ്തു എന്നും ഞാൻ സാക്ഷ്യപ്പെടുത്തുന്നു.

സമ്മതം വാങ്ങുന്നയാളുടെ പേര്
ഒപ്പ്
തീയതി

മേൽവിലാസവും ബന്ധപ്പെടാനുള്ളവിവരങ്ങളും

ഡോ. മനീഷ യാലപ്പള്ളി,

സീനിയർറെസിഡന്റ്, ന്യൂറോളജി ഡിപ്പാർട്ട്മെന്റ്,
ശ്രീ ചിത്ര തിരുനാൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഫോർ മെഡിക്കൽ സയൻസസ് ആന്റ് ടെക്നോളജി, മെഡിക്കൽ കോളേജ് പിഒ, തിരുവനന്തപുരം 695011
ഫോൺ 9949201366, ഇമെയിൽ: manisha@sctimst.ac.in

ഗവേഷണത്തെപ്പറ്റി താങ്കൾക്ക് ചോദ്യങ്ങൾ, ഉത്കണ്ഠ അല്ലെങ്കിൽ പരാതി എന്നിവയുണ്ടെങ്കിൽ ദയവായി ബന്ധപ്പെടുക:

ഡോ. ശ്രീനിവാസ് ജി
മെമ്പർസെക്രട്ടറി, ഇൻസ്റ്റിറ്റ്യൂഷണൽ എത്തിക്സ് കമ്മിറ്റി
ശ്രീചിത്ര തിരുനാൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഫോർമെഡിക്കൽ സയൻസസ് ആന്റ് ടെക്നോളജി
ഫോൺ 0471- 2524689, ഇമെയിൽ: iec.mem.sec@sctimst.ac.in

PATIENT INFORMATION SHEET

Sree Chitra Tirunal Institute for Medical Sciences and Technology

Thiruvananthapuram, Kerala-695011

TITLE OF THE STUDY:

Prevalence and patterns of Cognitive impairment in amyotrophic lateral sclerosis and correlation with disease outcome

Principal Investigator:

Dr. Manisha K Yalapalli, Senior Resident, Department of Neurology, SCTIMST

Co-Principal Investigators:

Dr.Sruthi S.Nair, Associate Professor, Department of Neurology, SCTIMST

Dr.Syam Krishnan,Professor,Department of Neurology ,SCTIMST Co-Investigator :

Dr.Ram Shekar Menon,Professor,Department of neurology,SCTIMST

Sir/ madam,

We invite you to take part in our study titled 'Prevalence and patterns of Cognitive impairment in amyotrophic lateral sclerosis and correlation with disease outcome .'

Before you agree to participate in this research study, it is important that you read and understand this information sheet which will provide you with all the information needed for participation in this study so that you can make a well informed and considered decision about participation. In addition, if you have any questions, the investigator and his team members will be happy to answer them and explain to you more about this research study, the procedure involved and the related issues. You may ask them any questions you may have regarding the study or ask them to explain any word or information that you don't clearly understand. In this study we aim to find out the prevalence of cognitive impairment in patients with Amyotrophic lateral sclerosis attending SCTIMST , to assess if cognitive impairment affects the outcome in ALS in disease progression; quality of life and caregiver burden

Why is this study being done?

You are invited to take part in this study as you have a condition called Amyotrophic lateral sclerosis. Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder characterized by the degeneration of both upper and lower motor neurons in the brain and spinal cord leading to motor and extra-motor symptoms.

Although traditionally considered a pure motor disease, recent evidences suggest that ALS is a multisystem disorder affecting even the cognitive domain .Cognitive impairment , in fact, is observed in 30- 50% of patients . Detecting and monitoring ALS cognitive and behavioral impairment even at early disease stages is likely to affect outcome of the illness. Regarding this there are very few studies in world and none from India.

What is the purpose of this study?

There are scant longitudinal data on extra-motor impairment in ALS.The possible association between cognition and outcome in ALS has not been well studied. Study of cognitive impairment and assessing the outcome can thus ,help to initiate aggressive management with a tailored regimen for each patient .Hence the need for the current study .

Objectives of the study:

1. To study the frequency and patterns of cognitive impairment in ALS.
2. To compare the disease progression ,change in quality of life and caregiver burden at 6 months in cognitively impaired versus cognitively preserved patients with ALS

How many people will take part in the study?

All the patients diagnosed with Amyotrophic lateral sclerosis from 1/1/2022 -31/06/2023 attending the SCTIMST OPD or admitted in wards.

How is the study done?

The study will be done in 2 parts.At first Cognitive battery will be administered to assess frequency and patterns of cognitive dysfunction.And on followup visit after 6 months ;outcome on disease progression and quality of life and caregiver burden will be assessed

This shall be planned either during your routine follow up visit to the NM Clinic or any other out patient visit at your date of convenience.

Will any biological sample(s) be stored and used in the future?

This study involves collection of demographic and clinical data,disease symptoms,progression ,investigations to rule out secondary etiology like NCS and EMG and a cognitive battery. No biological sample will be analyzed other than routine investigations done as a standard protocol in ALS patients.

What are the risks of the study?

This study involves only assessment of medical reports and interviewing. No add on risks as only standard protocol investigations are done as for all ALS patients. This study does not involve any procedures or administering of drugs specifically for the study.

Will the information pertaining to my illness be shared with others?

Your privacy is very important to us and the results of the tests performed on you will be treated as highly confidential, and nobody other than the investigators listed above will be knowing the test results. Your name or any other identifiable detail will not be published in any research paper or scientific presentation arising out of the study.

Will the study results be shared with me?

The investigators will share the details with you if any correctable abnormality is found and advice on remedial measures if present. The scientific information resulting from the study also will be shared with you after completion, if you wish to know it.

How will I benefit from the study?

Taking part in this research study is unlikely to benefit you immediately in any manner. However, we do hope that this study will shed light on the outcomes in patients with ALS and cognitive dysfunction and further research.

What other choices do I have if I don't take part in this study?

The study is only being done to gather scientific information. It is completely voluntary and you may choose not to take part in this study without any consequences and without it affecting your treatment in SCTIMST in any manner.

What are the costs of the tests and the procedures?

You will not have to pay for any tests or procedures, which are done as a part of the research study. The tests will be done as standard protocol for all ALS patients. Hence you will not have any travelling / other study related expenses for participation. No other incentives will be provided.

Will I lose my rights if I do not take part in this study?

You do not give up any of your rights by taking part in this study. Taking part in this research study is your decision. You do not have to take part in this study if you are unwilling and you will not be losing any of your rights if you choose not to participate. Your further treatment in the institute will in no way be affected. You will also be at the liberty to withdraw from the study at any stage (even after signing this consent form) of the study in case you want to withdraw.

Will my personal details be kept confidential?

The results of this study will be published in a medical journal but you will not be identified by name in any publication or presentation of results. Your clinical details and results of the tests may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

Whom should I contact for any doubts pertaining to the study?

If you have any further questions, please ask

Dr Manisha K Yalapalli

Senior Resident, Department of Neurology,

Tel: 9949201366, Email: manisha@sctimst.ac.in

Name of the PI: Dr Manisha K Yalapalli

Address and Contact Details:

Senior Resident, Department of Neurology

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രോഗിക്കുള്ള കാര്യവിവരണപത്രം

ശ്രീ ചിത്ര തിരുനാൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഫോർ മെഡിക്കൽ സയൻസസ് ആന്റ് ടെക്നോളജി , തിരുവനന്തപുരം 695011

പഠനശീർഷകം

അമിയോട്രോഫിക് ലാറ്ററൽ സ്ലിറോസിസിലെ അവബോധ ക്ഷയത്തിന്റെ വ്യപ്തിയും മാതൃകകളും രോഗത്തിന്റെ പരിണിതഫലവുമായുള്ള അവയുടെ പരസ്പരബന്ധവും

പ്രധാന ഗവേഷക

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ശ്രീ/ശ്രീമതി,

അമിയോട്രോഫിക് ലാറ്ററൽ സ്ലിറോസിസിലെ അവബോധ ക്ഷയത്തിന്റെ വ്യപ്തിയും മാതൃകകളും രോഗത്തിന്റെ പരിണിതഫലവുമായുള്ള അവയുടെ പരസ്പരബന്ധവും എന്ന പഠനത്തിൽ പങ്കെടുക്കൻ താങ്കളെ ഞങ്ങൾ ക്ഷണിക്കുന്നു.

ഈ പഠനത്തിൽ പങ്കെടുക്കുവാൻ താങ്കൾ സമ്മതിക്കുന്നതിനുമുമ്പ് ഈ പഠന സംബന്ധമായി അറിയേണ്ടുന്ന പ്രസക്തമായ എല്ലാ വിവരങ്ങളും നൽകുന്ന ഈ കാര്യവിവരണപത്രം വായിക്കുകയും മനസ്സിലാക്കുകയും ചെയ്യേണ്ടത് കാര്യബോധത്തോടെ സമ്മതം നൽകാൻ തീരുമാനമെടുക്കുന്നതിൽ പ്രധാനമാണ്. അതിനൊപ്പം താങ്കൾക്കെന്തെങ്കിലും ചോദ്യങ്ങളുണ്ടെങ്കിൽ അവ വിശദീകരിച്ചുതരുവാൻ ഗവേഷകയും സംഘാംഗങ്ങളും സന്തോഷത്തോടെ തയാറാകുകയും ഗവേഷണ പഠനം, ഉൾപ്പെട്ട നടപടികൾ ബന്ധപ്പെട്ട വിഷയങ്ങൾ എന്നിവയെപ്പറ്റി കൂടുതൽ വിശദീകരണം നൽകുകയും ചെയ്യും. പഠനത്തെപ്പറ്റി താങ്കൾക്കെന്തെങ്കിലും ചോദ്യങ്ങളോ വ്യക്തമായി മനസ്സിലാകാത്ത ഏതെങ്കിലും വാക്കുളോ വിവരങ്ങളോ ഉണ്ടെങ്കിൽ പഠനം നടത്തുന്നവരോട് ചോദിക്കുക.

ഈ പഠനത്തിൽ, ശ്രീചിത്രയിൽ വരുന്ന രോഗികളിലെ അമിയോട്രോഫിക് ലാറ്ററൽ സ്ലിറോസിസിലെ (എഎൽഎസ്) അവബോധ ക്ഷയത്തിന്റെ വ്യപ്തിയും മാതൃകകളും രോഗത്തിന്റെ പരിണിതഫലവുമായുള്ള അവയുടെ പരസ്പരബന്ധവും കണ്ടെത്താനും, അവബോധക്ഷയം എഎൽഎസ് രോഗപുരോഗതിയെയും, ജീവിതഗുണനിലവാരത്തെയും പരിചരണം നൽകുന്നവരുടെ ജോലിഭാരത്തേയും ബാധിക്കുന്നോ എന്നും വിലയിരുത്തുകയാണ് ഈ പഠനത്തിന്റെ ലക്ഷ്യം.

എന്തുകൊണ്ടാണ് ഈ പഠനം നടത്തുന്നത്?

താങ്കൾക്ക് അമിയോട്രോഫിക് ലാറ്ററൽ സ്ലിറോസിസ് എന്ന അവസ്ഥയുള്ളതിനാലാണ് ഈ പഠനത്തിൽ പങ്കെടുക്കാൻ ക്ഷണിക്കുന്നത്. തലച്ചോറിന്റെ മുകൾ ഭാഗത്തും താഴ്ഭാഗത്തും

നട്ടെല്ലിലുമുള്ള മോട്ടോർ ന്യൂറോണുകൾ ക്ഷയിക്കുന്ന, മോട്ടോർ, എക്സ്ട്രാ-മോട്ടോർ ലക്ഷണങ്ങളിലേയ്ക്ക് നയിക്കുന്ന, അമിയോട്രോഫിക് ലാറ്ററൽ സ്ലിറോസിസ് ഒരു നാഡീക്ഷയ രോഗമാണ്.

പരമ്പരാഗതമായി, മോട്ടോർ ന്യൂറോൺ രോഗമായി പരിഗണിക്കപ്പെട്ടിരുന്ന എഎൽഎസ് ഒരു ബഹുശരീരവ്യവസ്ഥാ തകരാറും, അവബോധ മേഖലയെപോലും ബാധിക്കുന്നതു മാണെന്ന് സമീപകാല തെളിവുകൾ ചൂണ്ടിക്കാണിക്കുന്നു. യഥാർത്ഥത്തിൽ 30 മുതൽ 50 ശതമാനം രോഗികളിൽ അവബോധക്ഷയം നിരീക്ഷിക്കപ്പെട്ടിട്ടുണ്ട്. എഎൽഎസ് അവബോധ, പെരുമാറ്റ തകരാർ, രോഗത്തിന്റെ ആദ്യഘട്ടത്തിൽ തന്നെ കണ്ടെത്തുകയും നിരീക്ഷിക്കുകയും ചെയ്യുന്നതിലൂടെ രോഗത്തിന്റെ പരിണിതഫലത്തെ സ്വാധീനിക്കാ നിടയുണ്ട്. ഈ വിഷയത്തിൽ ലോകത്ത് വളരെ കുറച്ച് പഠനങ്ങളേ ഉണ്ടായിട്ടുള്ളു, ഇൻഡ്യയിൽ നിന്നും ഒന്നുമില്ല.

ഈ പഠനത്തിന്റെ ഉദ്ദേശമെന്ത്?
എഎൽഎസ്സിലെ എക്സ്ട്രാ മോട്ടോർ ക്ഷയം സംബന്ധിച്ച തിരശ്ചീന വിവരങ്ങൾ വിരളമാണ്. എഎൽഎസ്സും അവബോധക്ഷയവും തമ്മിലുള്ള ബന്ധവും പരിണിതഫലവും വേണ്ടും വിധത്തിൽ പഠനം നടത്തിയിട്ടില്ല. അവബോധക്ഷയവും അതിന്റെ പരിണിതഫലവും വിലയിരുത്തുന്നതിലൂടെ ഓരോ രോഗിക്കും അനുയോജ്യമായവിധം രൂപപ്പെടുത്തുന്ന സജീവമായ ചികിത്സാതന്ത്രം തയാറാക്കുന്നതിനെ സഹായിച്ചേക്കാം. അതിനാലാണ് ഈ പഠനം നടത്തുന്നത്.

പഠനത്തിന്റെ ഉദ്ദേശം:

- എഎൽഎസ്സ്സിലെ അവബോധക്ഷയത്തിന്റെ വ്യാപ്തിയെപ്പറ്റി പഠിക്കുക
- എൽഎസ്സ്റ്റെ പരിണിതഫലത്തിൽ അവബോധക്ഷയം സ്വാധീനിക്കുന്നുണ്ടോയെന്ന് വിലയിരുത്തുക. (1) രോഗപുരോഗതി, (2) ജീവിതഗുണനിലവാരം, (3) പരിചരണം നൽകുന്നവരുടെ ജോലിഭാരം

ഈ പഠനത്തിൽ എത്ര ആളുകൾ പങ്കെടുക്കും?

SCTIMST ഒപിഡിയിൽ വന്നതോ വാർഡിൽ പ്രവേശിപ്പിച്ചതോ ആയ, അമിയോട്രോഫിക് ലാറ്ററൽ സ്ലിറോസ് രോഗനിർണ്ണയം നടത്തപ്പെട്ട 1/1/2022 മുതൽ 31/06/2023 വരെയുള്ള എല്ലാ രോഗികളെയും.

പഠനം എങ്ങനെയാണ് നടത്തുന്നത്?
ഈ പഠനം രണ്ട് ഭാഗമായാണ് നടത്തുന്നത്. ആദ്യം അവബോധത്തകരാറിന്റെ ആവർത്തനവും മാതൃകകളും വിലയിരുത്തും, 6 മാസത്തിനുശേഷമുള്ള തുടർ ചികിത്സാ സന്ദർശന സമയത്ത് രോഗപുരോഗതിയും, ജീവിതഗുണനിലവാരവും, പരിചരണം നൽകുന്നവരുടെ ജോലിഭാരവും അതിന്റെ പരിണിതഫലവും വിയിരുത്തും. ഇത് താങ്കളുടെ ന്യൂറോ മെഡിസിൻ ക്ലിനിക്കിലെ പതിവ് തുടർചികിത്സാ സന്ദർശനസമയത്തോ താങ്കൾക്ക് സൗകര്യപ്രദമായ ദിവസമോ ചെയ്യാൻ ആസൂത്രണം ചെയ്യും.

ഏതെങ്കിലും ജൈവ സാമ്പിളുകൾ സൂക്ഷിക്കുകയും ഭാവിയിൽ ഉപയോഗിക്കുകയും ചെയ്യുമോ?

എൻസിഎസ്, ഇഎംജി അവബോധ പരമ്പര എന്നീ രണ്ടാംനിര രോഗകാരണങ്ങൾ ഇല്ല എന്ന് ഉറപ്പാക്കാനാണ് ഈ പഠനത്തിൽ സാമൂഹിക വ്യക്തിവിവരങ്ങൾ ക്ലിനിക്കൽ വിവരങ്ങൾ രോഗലക്ഷണങ്ങൾ, പുരോഗതി, പരിശോധനകൾ എന്നിവയുടെ വിവരങ്ങൾ ശേഖരിക്കുന്നത്. എഎൽഎസ് രോഗികളിൽ ആംഗീകൃതമായ നടപടിക്രമപ്രകാരം നടത്തുന്ന പതിവ് പരിശോധനകൾക്ക് പുറമേ, ഏതെങ്കിലും ജൈവ സാമ്പിളുകൾ ശേഖരിക്കലോ സൂക്ഷിക്കലോ ആവശ്യമില്ല.

പഠനത്തിലെ അപായ സാദ്ധ്യത എന്താണ്?
പഠനത്തിൽ ചികിത്സാ രേഖകളുടെ വിലയിരുത്തലും അഭിമുഖവും മാത്രമേ ഉള്ളു. എല്ലാ എഎൽ എസ് രോഗികളിലും നടത്തുന്ന അംഗീകൃതമായ നടപടിക്രമപ്രകാരമുള്ള പരിശോധനകളേ നടത്തുന്നുള്ളു എന്നതിനാൽ അപായസാദ്ധ്യത വർദ്ധിപ്പിക്കുന്നില്ല. ഈ പഠനത്തിനായി പ്രത്യേകമായ നടപടികളോ മരുന്ന് നൽകലോ ഉൾപ്പെടുന്നില്ല.

എന്റെ രോഗവുമായി ബന്ധപ്പെട്ടവിവരങ്ങൾ മറ്റുള്ളവരുമായി പങ്കുവെയ്ക്കുമോ?
താങ്കളുടെ സ്വകാര്യത ഞങ്ങൾക്ക് പ്രധാനമാകയാൽ താങ്കളിൽ നടത്തിയ പരിശോധനകളുടെ ഫലങ്ങൾ വളരെ രഹസ്യമായിരിക്കും, മുകളിൽ പറഞ്ഞ ഗവേഷകർ ഒഴികെ മറ്റാർക്കും പരിശോധനാഭലങ്ങൾ അറിയുകയില്ല. ഈ പഠനഫലമായി ഉണ്ടാകുന്ന ഗവേഷണ പ്രസിദ്ധീകരണത്തിലോ പ്രദർശനത്തിലോ താങ്കളുടെ പേരോ തിരിച്ചറിയാനിടയാക്കുന്ന മറ്റേതെങ്കിലും വിശദാംശങ്ങളോ പ്രസിദ്ധീകരിക്കുകയുമില്ല.

പഠനഫലങ്ങൾ എന്നോട് പങ്കുവെയ്ക്കുമോ?

പരിഹരിക്കാവുന്ന ഏതെങ്കിലും അസാധാരണത്വം കണ്ടെത്തിയാൽ പരിഹാരം ലഭ്യമെങ്കിൽ വേണ്ടുന്ന നിർദ്ദേശത്തോടെ ഗവേഷകർ താങ്കളുമായി വിശദാംശങ്ങൾ പങ്കുവെയ്ക്കും. താങ്കൾക്കറിയാൻ താത്പര്യമുണ്ടെങ്കിൽ പഠനം പൂർത്തിയായ ശേഷം ലഭ്യമാകുന്ന ശാസ്ത്രീയ വിഷയങ്ങളും താങ്കളോട് പങ്കുവെയ്ക്കും.

പഠനത്തിൽ എങ്ങനെയാണ് എനിക്ക് നേട്ടമുണ്ടാകുക?

ഈ ഗവേഷണപഠനത്തിൽ പങ്കെടുക്കുന്നതുകൊണ്ട് ഉടനെ താങ്കൾക്ക് നേട്ടമൊന്നും ഉണ്ടാകില്ല. എന്നിരുന്നാലും അവബോധക്ഷയമുള്ള എഎൽഎസ് രോഗികളുടെ പരിണിതഫലങ്ങളിൽ ഈ പഠനം വെളിച്ചം വീശുമെന്നും ഭാവി ഗവേഷണങ്ങളെ സഹായിക്കുമെന്നും ഞങ്ങൾ പ്രതീക്ഷിക്കുന്നു.

ഞാൻ പഠനത്തിൽ പങ്കെടുക്കുന്നില്ലെങ്കിൽ എനിക്ക് മറ്റു മാർഗ്ഗമെന്ത്?
ഈ പഠനം ശാസ്ത്രിയ വിവരങ്ങൾ ശേഖരിക്കാൻ മാത്രമാണ്. ഇത് പൂർണ്ണമായും സ്വമേധയായാണ്, ഒരു പ്രത്യാഘാതങ്ങളും ഇല്ലാതെ SCTIMSTയിലെ താങ്കളുടെ ചികിത്സയെ ഒരു വിധത്തിലും ബാധിക്കാതെ ഈ പഠനത്തിൽ താങ്കൾക്ക് പങ്കെടുക്കാതിരിക്കാം.

പരിശോധനകളുടെയും നടപടികളുടെയും ചിലവെത്ര?
ഗവേഷണപഠനവുമായി ബന്ധപ്പെട്ട് നടത്തുന്ന പരിശോധനകൾക്കും നടപടികൾക്കും താങ്കൾ പണം മുടക്കേണ്ടതില്ല. പരിശോധനകളെല്ലാം അംഗീകൃതമായ നടപടിക്രമപ്രകാരം എല്ലാ എഎൽഎസ് രോഗികൾക്കും നടത്തുത്തേണ്ടുന്നതാണ്. ആകയാൽ താങ്കൾക്ക് യാത്ര/മറ്റ് പഠനസംബന്ധമായ ചിലവുകൾ എന്നിവയുണ്ടാകില്ല. മറ്റ് പ്രോത്സാഹന ങ്ങളൊന്നും നൽകില്ല.

ഞാൻ പങ്കെടുക്കുന്നില്ലെങ്കിൽ എന്റെ അവകാശങ്ങൾ നഷ്ടപ്പെടുമോ?

ഈ പഠനത്തിൽ പങ്കെടുക്കുന്നതുകൊണ്ട് താങ്കളുടെ അവകാശങ്ങളൊന്നും നഷ്ടപ്പെടില്ല. ഈ പരീക്ഷണത്തിലെ താങ്കളുടെ പങ്കാളിത്തം സ്വമേധയായാണ്. താങ്കൾക്ക് സമ്മതമില്ലെങ്കിൽ ഈ പഠനത്തിൽ പങ്കെടുക്കേണ്ടതില്ല, പങ്കെടുക്കുന്നില്ലെന്ന് തീരുമാനിച്ചാലും താങ്കളുടെ ഇൻസ്റ്റിറ്റ്യൂട്ടിലെ ചികിത്സയെ ഒരുവിധത്തിലും ബാധിക്കില്ല. പഠനത്തിന്റെ ഏത് ഘട്ടത്തിലും (സമ്മതപത്രം ഒപ്പിട്ടശേഷവും) താങ്കൾക്ക് പഠനത്തിൽ നിന്നും പിൻമാറാവുന്നതാണ്.

എന്റെ വ്യക്തി വിവരങ്ങൾ രഹസ്യമായിരിക്കുമോ?

പഠനഫലം ഒരു വൈദ്യശാസ്ത്ര പ്രസിദ്ധീകരണത്തിൽ പ്രസിദ്ധീകരിക്കുമെങ്കിലും താങ്കളെ പേരുകൊണ്ട് തിരിച്ചറിയാനിടയാക്കുന്നതൊന്നും പ്രസിദ്ധീകരണത്തിലോ പ്രദർശനത്തിലോ ഉണ്ടാകില്ല. താങ്കൾ പഠനത്തിൽ പങ്കെടുക്കാൻ സമ്മതിച്ചാൽ, വീണ്ടുമുള്ള സമ്മതമില്ലാതെ പഠനവുമായി ബന്ധപ്പെട്ടവർ താങ്കളുടെ ക്ലിനിക്കൽ വിവരങ്ങൾ അവലോകനം ചെയ്തേക്കാം.

ബന്ധപ്പെടാനുള്ള വിവരങ്ങൾ

താങ്കൾക്കെന്തെങ്കിലും ചോദ്യങ്ങളുണ്ടെങ്കിൽ ദയവായി ബന്ധപ്പെടുക

ഡോ. മനീഷ യാലപ്പള്ളി, സീനിയർ റെസിഡന്റ്,

ഫോൺ 9949201366, ഇമെയിൽ: manisha@sctimst.ac.in

പ്രധാന ഗവേഷകയുടെ പേര്

ഡോ. മനീഷ യാലപ്പള്ളി

സീനിയർ റെസിഡന്റ്, ന്യൂറോളജി ഡിപ്പാർട്ട്മെന്റ്,
ശ്രീ ചിത്ര തിരുനാൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഫോർ മെഡിക്കൽ സയൻസസ് ആന്റ് ടെക്നോളജി

ഫോൺ 9949201366, ഇമെയിൽ: manisha@sctimst.ac.in

മേൽവിലാസവും ബന്ധപ്പെടാനുള്ള വിവരങ്ങളും

ഡോ. മനീഷ യാലപ്പള്ളി,

സീനിയർ റെസിഡന്റ്,

സീനിയർ റെസിഡന്റ്, ന്യൂറോളജി ഡിപ്പാർട്ട്മെന്റ്,
ശ്രീ ചിത്ര തിരുനാൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഫോർ മെഡിക്കൽ സയൻസസ് ആന്റ് ടെക്നോളജി

ഫോൺ 9949201366, ഇമെയിൽ: manisha@sctimst.ac.in

പ്രധാന ഗവേഷകയുടെ ഒപ്പ്

ഗവേഷണത്തെപ്പറ്റി താങ്കൾക്ക് ചോദ്യങ്ങൾ, ഉത്കണ്ഠ അല്ലെങ്കിൽ പരാതി എന്നിവയുണ്ടെങ്കിൽ ദയവായി ബന്ധപ്പെടുക:

ഡോ. ശ്രീനിവാസ് ജി
മെമ്പർ സെക്രട്ടറി, ഇൻസ്റ്റിറ്റ്യൂഷണൽ എത്തിക്സ് കമ്മിറ്റി
ശ്രീ ചിത്ര തിരുനാൾ ഇൻസ്റ്റിറ്റ്യൂട്ട് ഫോർ മെഡിക്കൽ സയൻസസ് ആന്റ് ടെക്നോളജി
ഫോൺ 0471- 2524689, ഇമെയിൽ: iec.mem.sec@sctimst.ac.in

ALS Functional Rating Scale Revised (ALS-FRS-R)

Date:……..Name patient:……Date of Birth:……

Patient's number……..Right-/left-handed

Item 1: SPEECH

- 4 ☐ Normal speech process
- 3 ☐ Detectable speech disturbance
- 2 ☐ Intelligible with repeating
- 1 ☐ Speech combined with non-vocal communication
- 0 ☐ Loss of useful speech

Item 2: SALIVATION

- 4 ☐ Normal
- 3 ☐ Slight but definite excess of saliva in mouth; may have nighttime drooling
- 2 ☐ Moderately excessive saliva; may have minimal drooling (during the day)
- 1 ☐ Marked excess of saliva with some drooling
- 0 ☐ Marked drooling; requires constant tissue or handkerchief

Item 3: SWALLOWING

- 4 ☐ Normal eating habits
- 3 ☐ Early eating problems – occasional choking
- 2 ☐ Dietary consistency changes
- 1 ☐ Needs supplement tube feeding
- 0 ☐ NPO (exclusively parenteral or enteral feeding)

Item 4: HANDWRITING

- 4 ☐ Normal
- 3 ☐ Slow or sloppy: all words are legible
- 2 ☐ Not all words are legible
- 1 ☐ Able to grip pen, but unable to write
- 0 ☐ Unable to grip pen

Item 5a: CUTTING FOOD AND HANDLING UTENSILS
Patients <u>without</u> gastrostomy → Use 5b if >50% is through g-tube

- 4 ☐ Normal
- 3 ☐ Somewhat slow and clumsy, but no help needed
- 2 ☐ Can cut most foods (>50%), although slow and clumsy; some help needed
- 1 ☐ Food must be cut by someone, but can still feed slowly
- 0 ☐ Needs to be fed

Item 5b: CUTTING FOOD AND HANDLING UTENSILS
Patients <u>with</u> gastrostomy → 5b option is used if the patient has a gastrostomy and only if it is the primary method (more than 50%) of eating .

- 4 ☐ Normal
- 3 ☐ Clumsy, but able to perform all manipulations independently
- 2 ☐ Some help needed with closures and fasteners
- 1 ☐ Provides minimal assistance to caregiver
- 0 ☐ Unable to perform any aspect of task

Item 6: DRESSING AND HYGIENE

- 4 ☐ Normal function
- 3 ☐ Independent and complete self-care with effort or decreased efficiency
- 2 ☐ Intermittent assistance or substitute methods
- 1 ☐ Needs attendant for self-care
- 0 ☐ Total dependence

Item 7: TURNING IN BED AND ADJUSTING BED CLOTHES

- 4 ☐ Normal function
- 3 ☐ Somewhat slow and clumsy, but no help needed
- 2 ☐ Can turn alone, or adjust sheets, but with great difficulty
- 1 ☐ Can initiate, but not turn or adjust sheets alone
- 0 ☐ Helpless

Item 8: WALKING

- 4 ☐ Normal
- 3 ☐ Early ambulation difficulties
- 2 ☐ Walks with assistance
- 1 ☐ Non-ambulatory functional movement
- 0 ☐ No purposeful leg movement

Item 9: CLIMBING STAIRS

- 4 ☐ Normal
- 3 ☐ Slow
- 2 ☐ Mild unsteadiness or fatigue
- 1 ☐ Needs assistance
- 0 ☐ Cannot do

Item 10: DYSPNEA

- 4 ☐ None
- 3 ☐ Occurs when walking
- 2 ☐ Occurs with one or more of the following: eating, bathing, dressing (ADL)
- 1 ☐ Occurs at rest: difficulty breathing when either sitting or lying
- 0 ☐ Significant difficulty: considering using mechanical respiratory support

Item 11: ORTHOPNEA

- 4 ☐ None
- 3 ☐ Some difficulty sleeping at night due to shortness of breath, does not routinely use more than two pillows
- 2 ☐ Needs extra pillows in order to sleep (more than two)
- 1 ☐ Can only sleep sitting up
- 0 ☐ Unable to sleep without mechanical assistance

Item 12: RESPIRATORY INSUFFICIENCY

- 4 ☐ None
- 3 ☐ Intermittent use of BiPAP
- 2 ☐ Continuous use of BiPAP during the night
- 1 ☐ Continuous use of BiPAP during day & night
- 0 ☐ Invasive mechanical ventilation by intubation or tracheostomy

Interviewer's name.....

Addenbrooke's Cognitive Examination-III (ACE-III)- Malayalam

ADDENBROOKE'S COGNITIVE EXAMINATION –ACE III - Malayalam

NAME :_____	HOSP. NO : _____
D.O.B: _____	TESTING DATE(S): ____/_____/_____
AGE : _____	EDUCATION (YEARS):_____
Handedness:_____	Tested in (Language) : _____
Gender:_____	Urban/Rural:_____

Orientation/ Attention — Total Score (0-10)

1. (a) What is the	ഇത്/ഇന്ന് ആഴ്ചയിലെ ഏതു ദിവസമാണ് day	തിയതി എത്രയാണ് *date	ഏതു മാസമാണ് month	ഏതു വർഷമാണ് year	ഏതു കാലമാണ് season
b) Where are we	ഇത് ഏതാണ്/എത്രാമത്തെ നില (വീട്ട് പേര്/നമ്പർ) *** Floor (or house name /no.)	ആശുപത്രി (റോഡ്) *** Hospital (or street/ road)	നഗരം City	സംസ്ഥാനം State	രാജ്യം ** Country

Scoring: Score 1 point for each correct answer.
**Allow an error of + 2.*
*** Give the example of **Sri Lanka** if the subject gives the name of the state when asked the country*
**** The items in the brackets are to be used if the subject is being tested in his/her house*

2. Attention/ Concentration — Score (0-3)

ഞാൻ നിങ്ങളോട് മൂന്ന് സാധനങ്ങളുടെ പേര് പറയും.

പറഞ്ഞ് നിർത്തുമ്പോൾ അത് ഓർത്ത് വച്ച് ഏറ്റു പറയുക.

(ആവശ്യമുണ്ടെങ്കിൽ മൂന്ന് തവണ വരെ ആവർത്തിക്കാം.)

നാരങ്ങ, താക്കോൽ, പന്ത്.

ഏറ്റു പറഞ്ഞതിനുശേഷം പറയുക: " ഇത് ഓർത്തു വയ്ക്കുവാൻ ശ്രമിക്കുക, എന്തുകൊണ്ടെന്നാൽ, ഞാൻ കുറച്ച് കഴിഞ്ഞ് അത് നിങ്ങളോട് ചോദിക്കും."

3. ATTENTION-Serial 7 Subtraction — Score (0-5)

പരിശോധിക്കപ്പെടുന്ന വ്യക്തിയോട് നൂറിൽ നിന്നും ഏഴ് കുറയ്ക്കുവാൻ പറയുക, ഉത്തരം കുറിച്ച് ഇടുക, എന്നിട്ട് നിർത്താൻ പറയുന്നതുവരെയും ഓരോ പുതിയ അക്കത്തിൽ നിന്നും ഏഴ് കുറച്ച് കൊണ്ടിരിക്കാൻ പറയുക. പരിശോധിക്കപ്പെടുന്ന വ്യക്തി അഞ്ച് തവണ കുറച്ച് കഴിയുമ്പോൾ നിർത്താൻ പറയുക.

(93, 86, 79, 72, 65)

4. MEMORY-Recall of 3 Items

Score (0-3)

പരിശോധിക്കപ്പെടുന്ന വ്യക്തിയോട് നേരത്തെ ആവർത്തിക്കാൻ പറഞ്ഞ മൂന്ന് സാധനങ്ങളുടെ പേരു ഓർമ്മിച്ച് പറയുവാൻ പറയുക.

നാരങ്ങ,
താക്കോൽ
പന്ത്

5. VERBAL FLUENCY- Letter and Category

*** Letters** Score (0-7)

പരിശോധിക്കപ്പെടുന്ന വ്യക്തിയോട് പറയുക, *''ഞാൻ നിങ്ങളോട് ഒരു അക്ഷരം പറയുവാൻ പോകുകയാണ് അതിൽ തുടങ്ങുന്ന പരമാവധി വാക്കുകൾ പറയുക അവ സ്ഥലത്തിന്റെയോ, ആളിന്റെയോ പേര് ആകരുത്. ഉദാഹരണത്തിന് ഞാൻ ''ക'' എന്ന അക്ഷരം തരുകയാണെങ്കിൽ കാട്, കൃതജ്ഞത, കിലുക്കം എന്നിങ്ങനെയുള്ള വാക്കുകൾ പറയാം പക്ഷേ കമലാക്ഷി, കേരളം മുതലായവ പറയരുത്. തയാറാണോ? നിങ്ങൾക്ക് ഒരു മിനിറ്റ് സമയം ഉണ്ട്. നിങ്ങൾ ''പ''എന്ന അക്ഷരം കൊണ്ട് തുടങ്ങുന്ന കുറച്ചു വാക്കുകൾ പറയുക.''*

				>18	7
				14 - 17	6
				11-13	5
				8-10	4
				6-7	3
				4-5	2
				2-3	1
				0-1	0
				total	correct

Animals

Score (0-7)

പരിശോധിക്കപ്പെടുന്ന വ്യക്തിയോട് പറയുക, ''നിങ്ങൾക്ക് അറിയാവുന്ന മൃഗങ്ങളുടെയെല്ലാം പേര് പറയുക. അവ ഏത് അക്ഷരം കൊണ്ടും തുടങ്ങാം.''

				➢ 22	7
				17-21	6
				14-16	5
				11-13	4
				9-10	3
				7-8	2
				5-6	1
				<5	0
				total	correct

6. MEMORY-Anterograde Memory-Name and Address Score (0-7)

പരിശോധിക്കപ്പെടുന്ന വ്യക്തിയോട് പറയുക, " *ഞാൻ പറയുന്ന പേരും വിലാസവും ഏറ്റു പറയുക. നിങ്ങൾക്ക് പഠിക്കുവാനായിട്ട് അത് മൂന്ന് തവണ ഞാൻ ആവർത്തിക്കും. ഞാൻ നിങ്ങളോട് കുറച്ച് കഴിഞ്ഞ് പേരും വിലാസവും ചോദിക്കും.*" പരിശോധിക്കപ്പെടുന്ന വ്യക്തി നിങ്ങളോട് ഒപ്പം ഏറ്റു പറയുക ആണെങ്കിൽ നിങ്ങൾ പൂർണ്ണമായും പറഞ്ഞ് തീരുന്നത് വരെ കാത്തിരിക്കാൻ പറയുക.

	Elements	Trial 1	Trial 2	Trial 3	Delayed
Velayudhan Thampi വേലായുധൻ തമ്പി	**2**				
42 Kovil Road 42 കോവിൽ റോഡ്	**3**				
Chengammanad ചെങ്ങമനാട്	**1**				
Elanji ഇലഞ്ഞി	**1**				
Total	/7	/7	/7	/7	

7. MEMORY-Retrograde Memory-Famous People Score (0-4)

പരിശോധിക്കപ്പെടുന്ന വ്യക്തിയോട് ചോദിക്കുക:

ഠകാരളത്തിന്റെ മുഖ്യമന്ത്രി .....
ഇന്ത്യയുടെ പ്രധാനമന്ത്രി .....
ചെമ്മിൻ സിനിമയിലെ മുഖ്യകഥാപാത്രം .....
ഇന്ത്യയുടെ രാഷ്ട്രപിതാവ് .....

8. LANGUAGE-Comprehension- Score (0-3)

പരിശോധിക്കപ്പെടുന്ന വ്യക്തിയുടെ മുമ്പിൽ ഒരു പെൻസിലും കടലാസ് കഷണവും വയ്ക്കുക. പരിശീലനത്തിന്റെ ഭാഗമായി പരിശോധിക്കപ്പെടുന്ന വ്യക്തിയോട് ആദ്യം **പെൻസിലും കടലാസ്സും എടുക്കുവാൻ** പറയുക . ശരിയായി ചെയ്തില്ലെങ്കിൽ സ്കോർ "0" കൊടുക്കുക, എന്നിട്ട് പരിശോധന നിർത്തുക. പരിശോധിക്കപ്പെടുന്ന വ്യക്തി പരിശീലനം ശരിയായി ചെയ്തെങ്കിൽ തഴെകൊടുത്തിരിക്കുന്ന മൂന്ന് നിർദ്ദേശങ്ങളും തുടർന്നു ചെയ്യാവുന്നതാണ്. ഓരോ നിർദ്ദേശവും കൊടുക്കുന്നത്തിനു മുൻപ് പരിശോധിക്കപ്പെടുന്ന വ്യക്തിയുടെ മുമ്പിൽ ഒരു പെൻസിലും കടലാസ് കഷ്ണവും വയ്ക്കുക.

*** കടലാസ് പെൻസിലിന്റെ മുകളിൽ വയ്ക്കുക**

*** പെൻസിൽ എടുക്കുക പക്ഷേ കടലാസ് എടുക്കരുത്**

*** കടലാസിൽ തൊട്ടതിനുശേഷം പെൻസിൽ എനിക്ക് തരിക**

9. LANGUAGE- Sentence Writing Score (0-2)

പരിശോധിക്കപ്പെടുന്ന വ്യക്തിയോട് അവന്റെ/അവളുടെ കഴിഞ്ഞ അവധിക്കാലം/ ആഴ്ചാവസാനം ഏതെങ്കിലും ആഘോഷം/പരിപാടിയെ കുറിച്ച് രണ്ട് (അതിലധികമോ) പൂർണ്ണമായ വാചകങ്ങൾ എഴുതുവാൻ പറയുക. ചുരുക്കെഴുത്ത് ഉപയോഗിക്കുവാൻ പാടില്ല.

.....

.....

.....

.....

.....

10. LANGUAGE- Single Word Repetition Score (0-2)

പരിശോധിക്കപ്പെടുന്ന വ്യക്തിയോട് നിങ്ങൾ ഓരോന്നായി പറയുന്ന വാക്കുകൾ പറഞ്ഞതിനുശേഷം ആവർത്തിക്കുവാൻ പറയുക.

പ്രവണത

ആഡംബരം

കാര്യഗൗരവം

ശാസ്ത്രസാങ്കേതികം

11. LANGUAGE-Proverb Repetition Score (0-2)

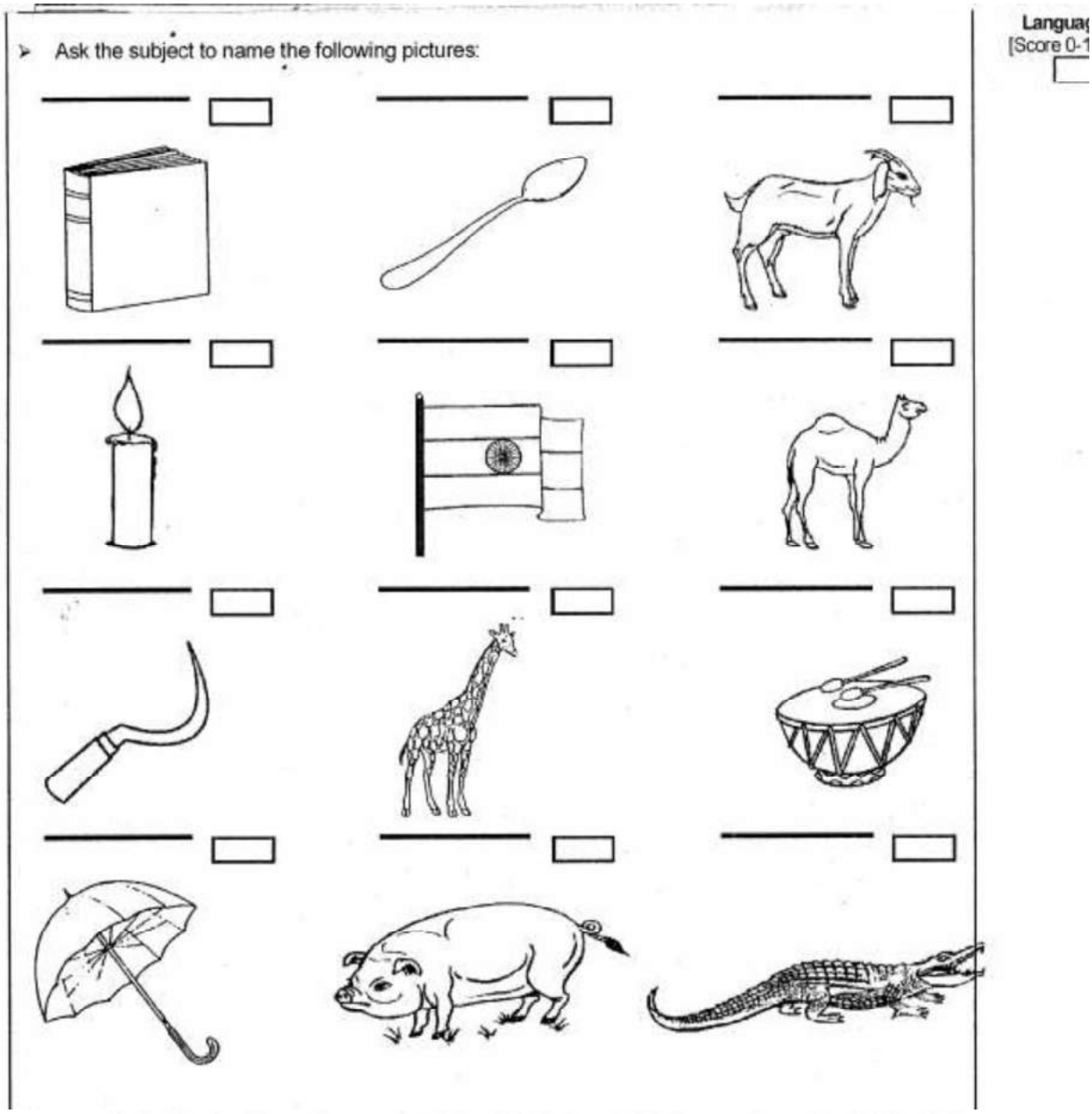
പരിശോധിക്കപ്പെടുന്ന വ്യക്തിയോട് വാക്യങ്ങൾ ആവർത്തിക്കുവാൻ പറയുക.

*** അവർ ഇവിടെ വന്നിരുന്നുവെങ്കിൽ എനിക്ക് അവരെ കാണാമായിരുന്നു.**

*** ഒഴിവുകഴിവുകളൊന്നും പറയരുത്.**

12.LANGUAGE-Object Naming Score (0-12)

പരിശോധിക്കപ്പെടുന്ന വ്യക്തിയോട് ഓരോ ചിത്രത്തിന്റെയും പേരു പറയുവാൻ പറയുക.



13. LANGUAGE- Comprehension Score (0-4)

നിങ്ങൾ വായിക്കുന്ന വാക്യം കേട്ടിട്ട് പരിശോധിക്കപ്പെടുന്ന വ്യക്തിയോട് തക്കതായ ചിത്രങ്ങൾ ചൂണ്ടിക്കാണിക്കുവാൻ പറയുക. വാക്കുകളുടെ അർത്ഥത്തെ കുറിച്ച് ഒരു സൂചനയും നൽകാൻ പാടില്ല.

- മഴയത്ത് ഉപയോഗിക്കുന്നത്
- പ്രകാശം പരത്തുന്നത്.
- ടകായ്ത്തുമായി ബന്ധപ്പെട്ടത്.
- അരുഭൂമിയിൽ കാണപ്പെടുന്നത്.

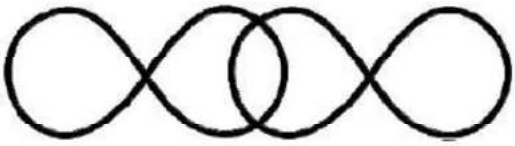
14. LANGUAGE-Reading Score (0-1)

പരിശോധിക്കപ്പെടുന്ന വ്യക്തിയോട് വാക്കുകൾ ഉറക്കെ വായിക്കുവാൻ പറയുക.

സഞ്ചി
സുന്ദരി
ഫലിതം
ഉത്കണ്ഠ
ബ്രഹ്മാണ്ഡം

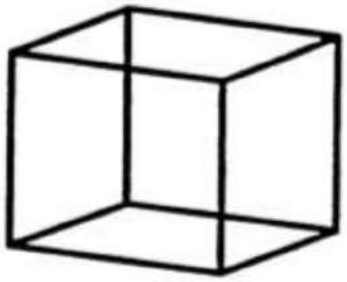
15. VISUOSPATIAL ABILITIES- Intersecting Infinity Loops Score (0-1)

പരിശോധിക്കപ്പെടുന്ന വ്യക്തിയോട് ചിത്രം പകർത്തി വരയ്ക്കുവാൻ പറയുക.



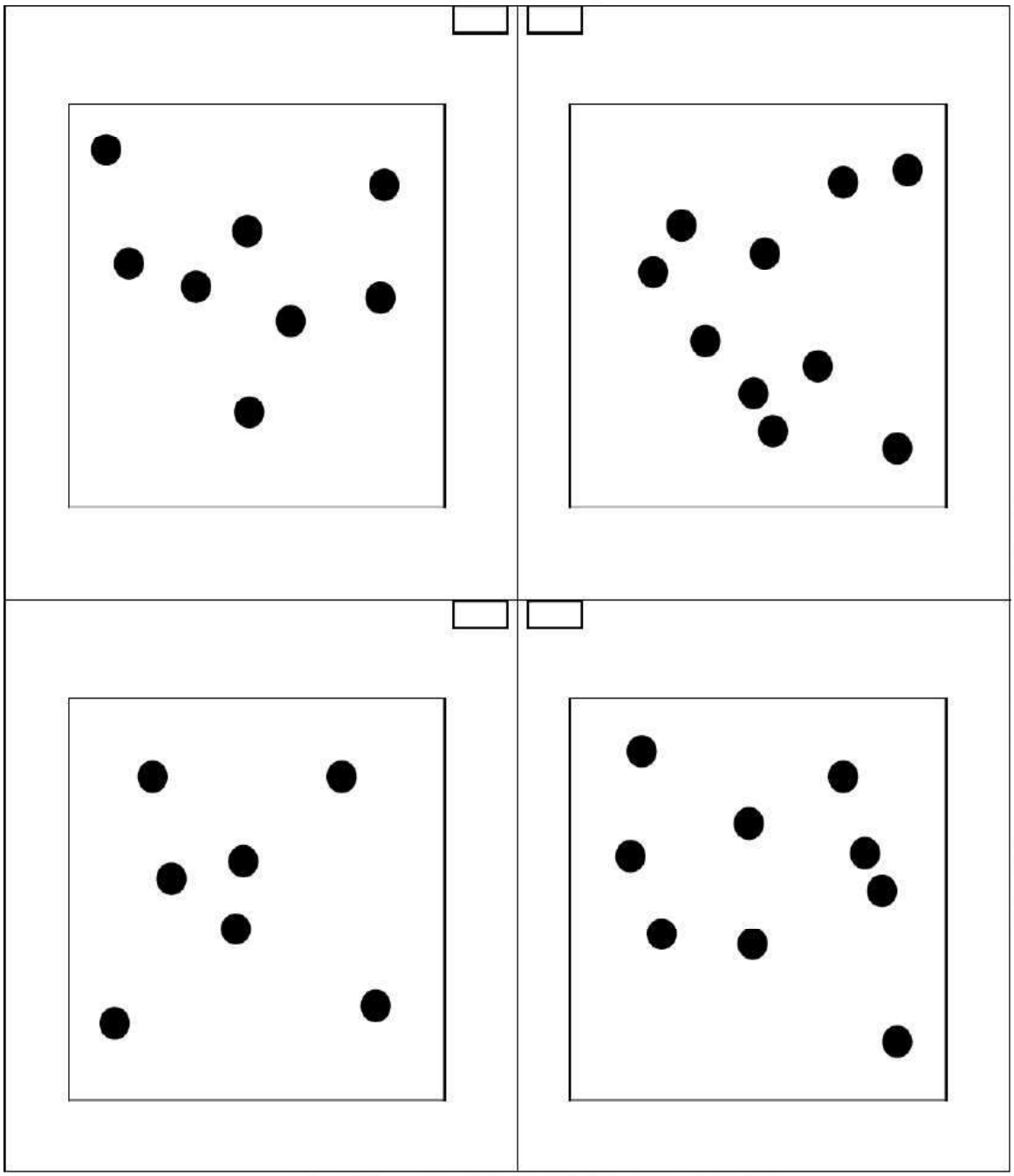
16. VISUOSPATIAL ABILITIES-3D Wire Cube Score (0-2)

പരിശോധിക്കപ്പെടുന്ന വ്യക്തിയോട് ചിത്രം പകർത്തി വരയ്ക്കുവാൻ പറയുക.



17. PERCEPTUAL ABILITIES-Counting Dots Score (0-4)

പരിശോധിക്കപ്പെടുന്ന വ്യക്തിയോട് ചിത്രത്തിൽ തൊടാതെ ഓരോ സമചതുരത്തിനുള്ളിൽ എത്ര കുത്തുകൾ ഉണ്ട് എന്ന് എണ്ണി പറയുവാൻ പറയുക.



Scoring: Score1 point for each correct answer. Correct answers: 8, 10, 9 and 7.

18. VISUOSPATIAL ABILITIES- Clock

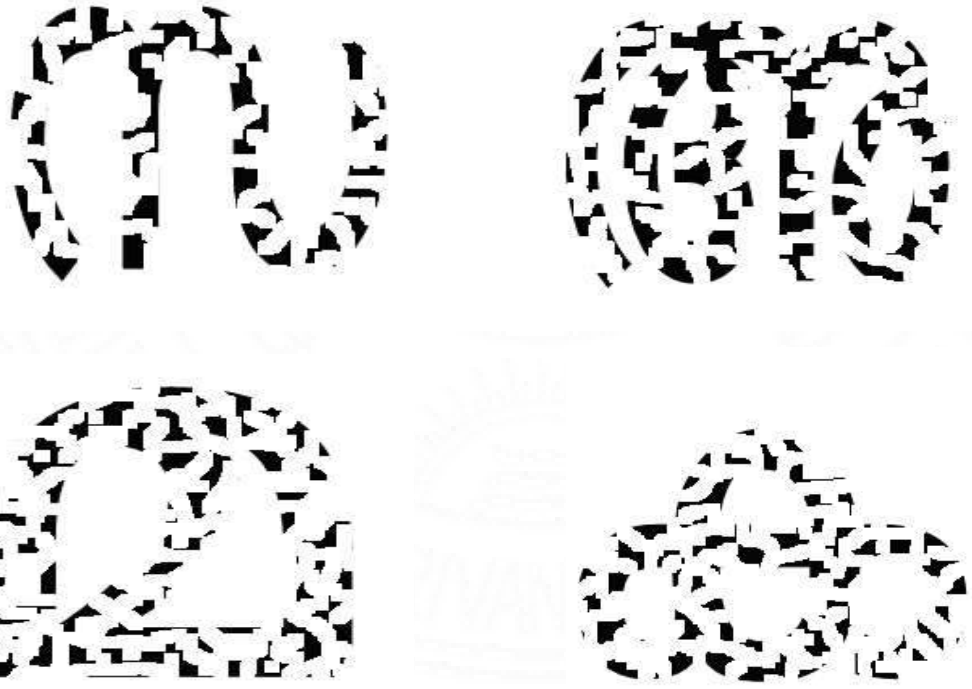
Score (0-5)

പരിശോധിക്കപ്പെടുന്ന വ്യക്തിയോട് എല്ലാ അക്കങ്ങളുമുള്ള ഒരു ക്ലോക്ക് വരയ്ക്കുവാൻ പറയുക. വരച്ച് കഴിയുമ്പോൾ അതിൽ **5:10** എന്ന സമയം വരച്ച് കാണിക്കുവാൻ പറയുക. പരിശോധിക്കപ്പെടുന്ന വ്യക്തിക്ക് ആദ്യം വരച്ചത് ഇഷ്ടമായില്ലെങ്കിൽ രണ്ടാമത് വരക്കുവാൻ അനുവദിക്കാം, എന്നിട്ട് രണ്ടാമത് വരച്ചത് പരിഗണിക്കാം.

19. PERCEPTUAL ABILITIES-Identifying Letters

Score (0-4)

പരിശോധിക്കപ്പെടുന്ന വ്യക്തിയോട് ഓരോ അക്ഷരങ്ങളും തിരിച്ചറിയുവാൻ പറയുക. പരിശോധിക്കപ്പെടുന്ന വ്യക്തി ചിത്രത്തിൽ ചൂണ്ടി കാണിക്കുവാൻ അനുവദിക്കാം.



21. MEMORY-Recall of Name and Address Score (0-7)

Memory

പരിശോധിക്കപ്പെടുന്ന വ്യക്തിയോട് പറയുക, *'' നേരത്തേ ഞാൻ പറഞ്ഞ പേരും മേൽവിലാസവും നിങ്ങൾ ഓർത്തു പറയുക.''*

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.....

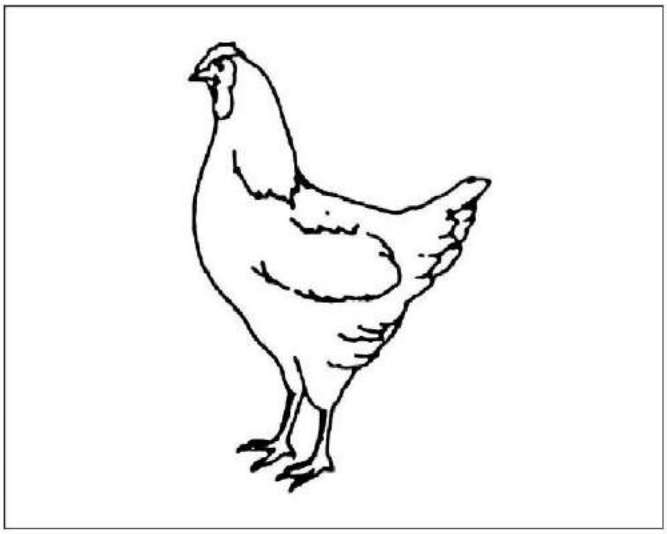
21. MEMORY– Recognition of Name and Address Score (0-5)

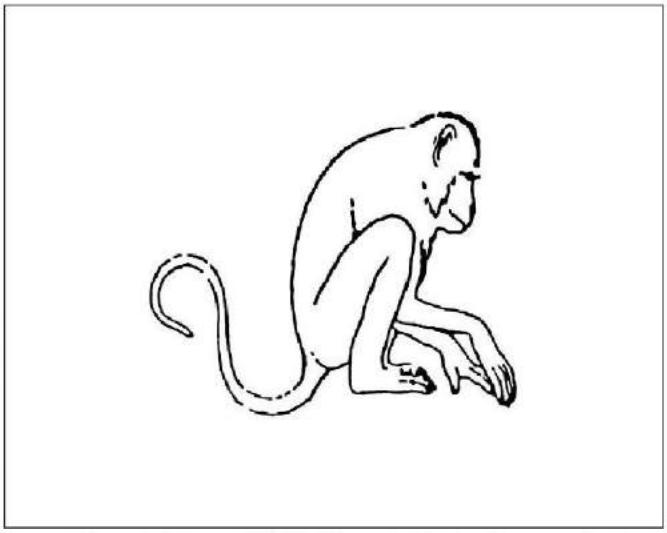
പരിശോധിക്കപ്പെടുന്ന വ്യക്തി ഒന്നോ അതിലധികമോ കാര്യങ്ങൾ ഓർത്തു പറഞ്ഞില്ലെങ്കിൽ താഴെ തന്നിരിക്കുന്ന പരിശോധന ചെയ്യേണ്ടതാണ്. എല്ലാകാര്യങ്ങളും ഓർത്തു പറയുകയാണെങ്കിൽ സ്കോർ 5 നൽകാവുന്നതാണ് എന്നിട്ട് പരിശോധന നിർത്താം. അല്പം മാത്രമേ ഓർമ്മിച്ചിട്ടുള്ളുവെങ്കിൽ അവയെ വലത് ഭാഗത്തെ ചായമടിച്ച നിരകളിൽ ശരിയായിട്ട് അടയാളപ്പെടുത്തേ□ താണ്. അതിനുശേഷം, ഓർമ്മിച്ചെടുക്കാത്തവയ്ക്ക് സൂചനകൾ നല്കുക. ഉദാഹരണത്തിന് ആ പേര് X, Y അല്ലെങ്കിൽ Z എന്ന് ആയിരുന്നോ? സൂചനയിലൂടെ ഓർത്തെടുത്തവയ്ക്ക് ഒരു പോയന്റ് നല്കുക. സൂചന കൂടാതെ ഓർമ്മിച്ചെടുത്തവയുമായി ഈ സ്കോറിനെ കൂട്ടിയെടുക്കേ□ താണ്.

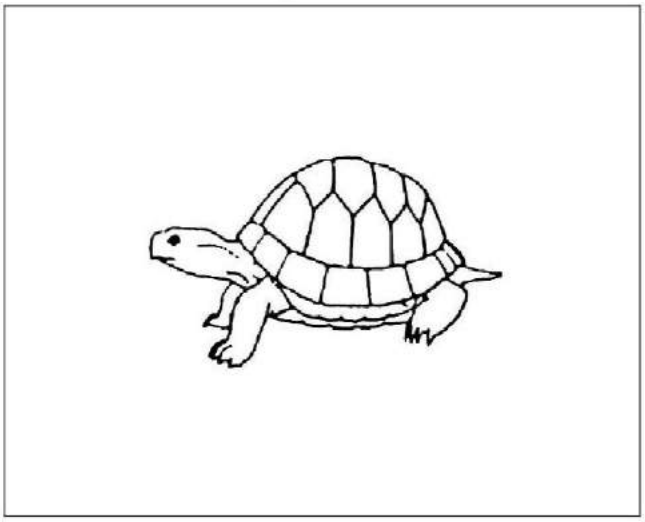
മാധവൻ തമ്പി	**വേലായുധൻ തമ്പി**	വേലായുധൻ നായർ	Recalled
24	**42**	46	Recalled
കോവിൽ തെരുവ്	കോന്നി റോഡ്	**കോവിൽ റോഡ്**	Recalled
ചെങ്ങന്നൂർ	**ചെങ്ങമനാട്**	ചേർത്തല	Recalled
ഇലഞ്ഞി	ഈറോഡ്	ഈരാറ്റുപേട്ട	Recalled

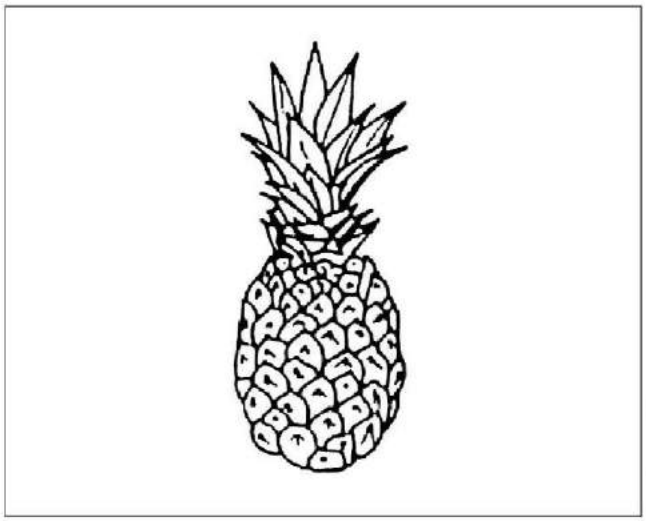
Scoring: Every item recognized correctly scores 1 point. Add the correctly recalled and recognized item to give a total of 5 points for this condition.

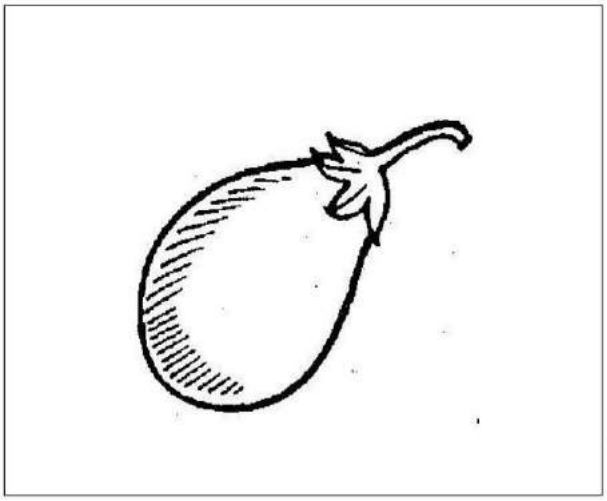
Total ACE-III SCORE	**/ 100**
Attention	**/18**
Memory	**/26**
Fluency	/14
Language	/26
Visuaspatial	/16

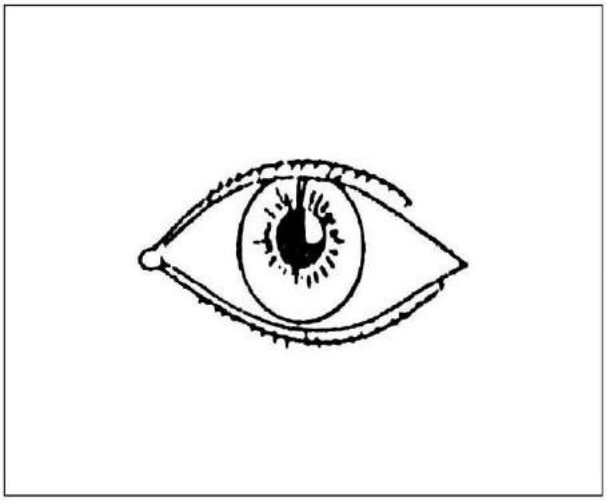


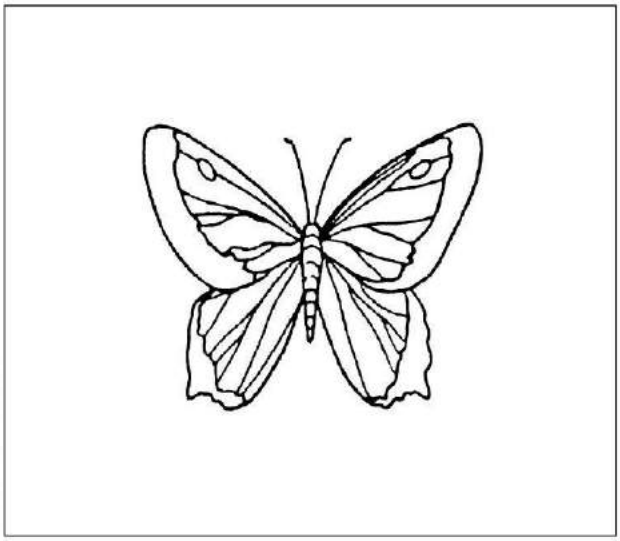


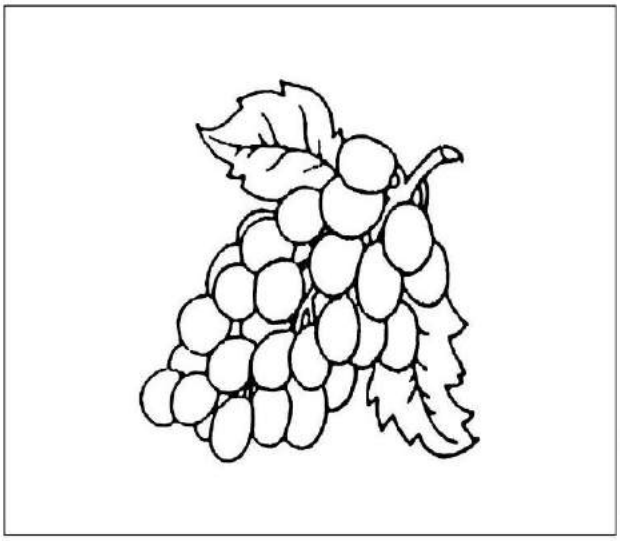


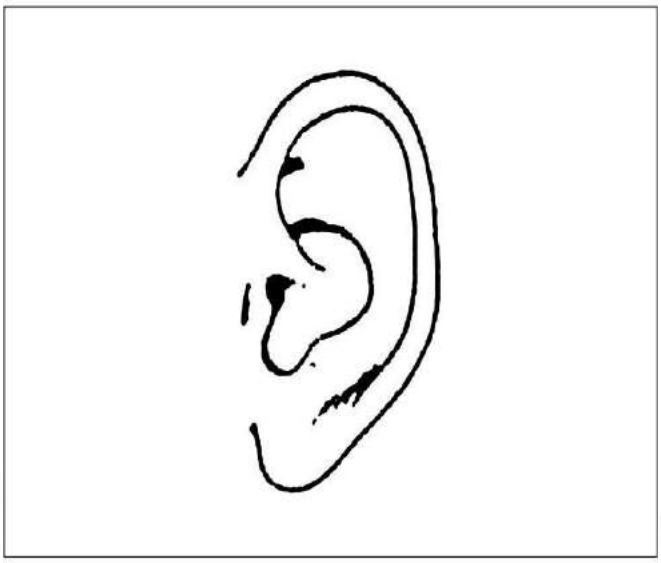


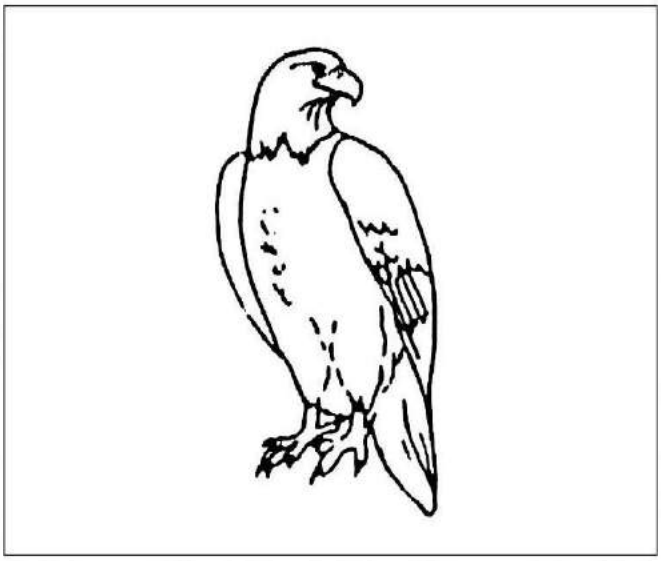


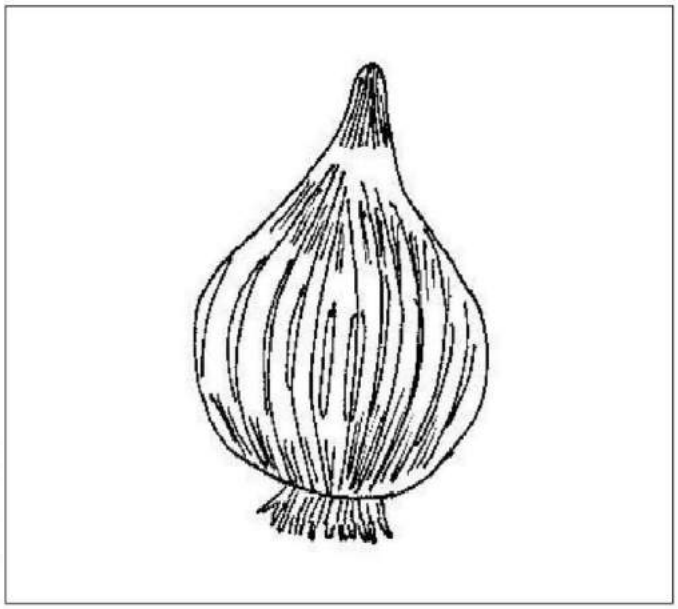


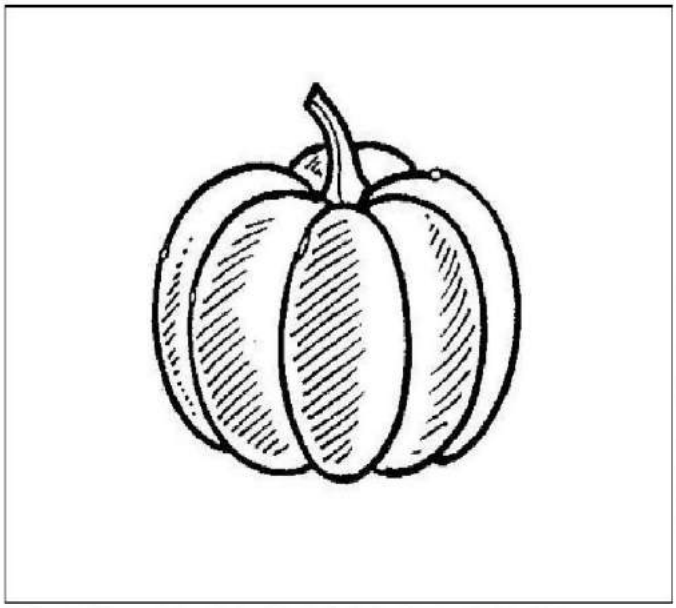


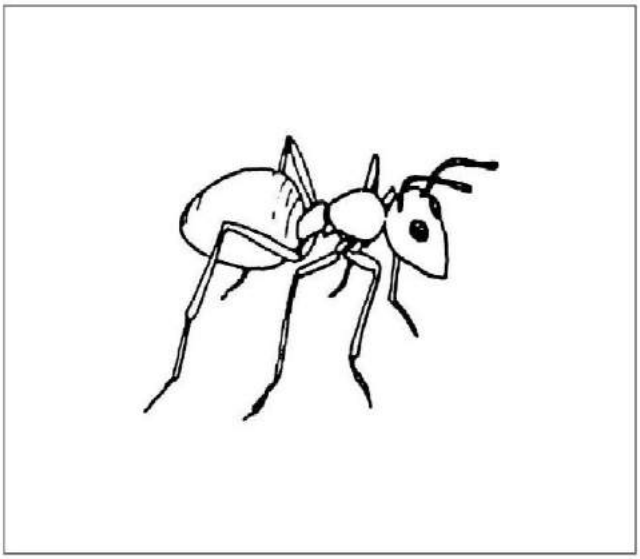


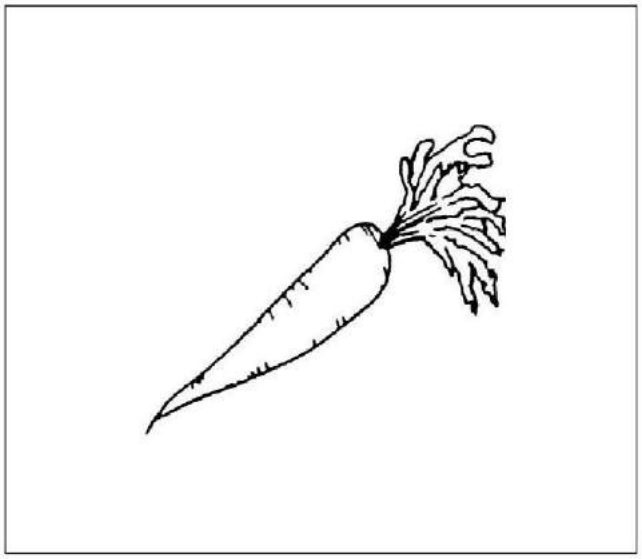


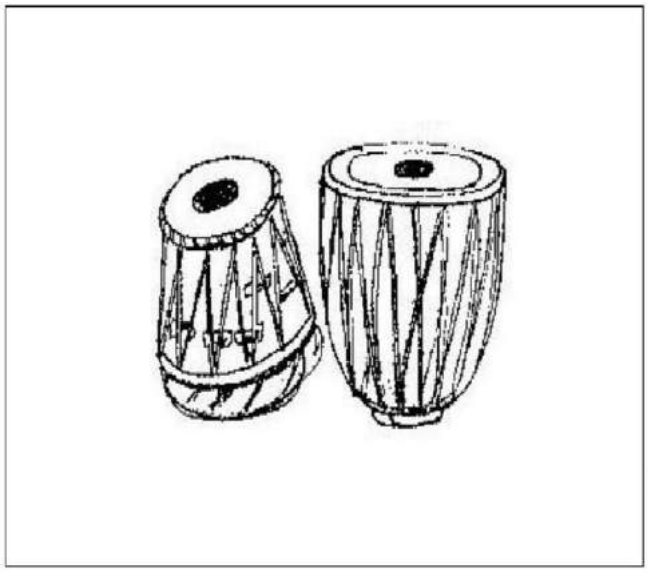


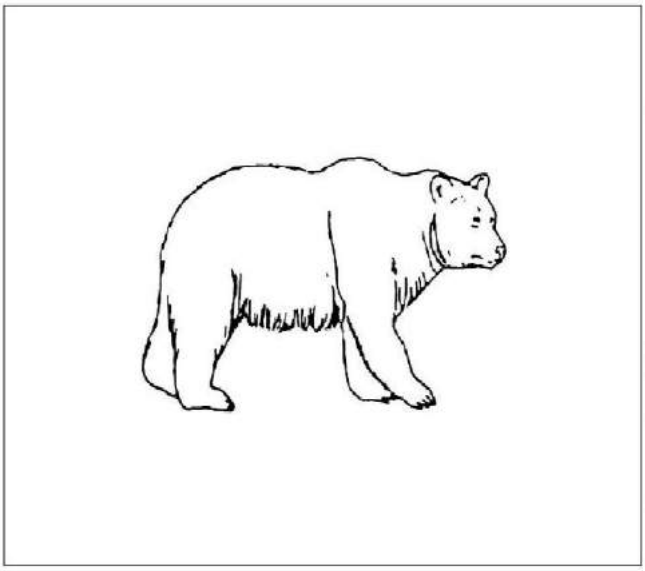


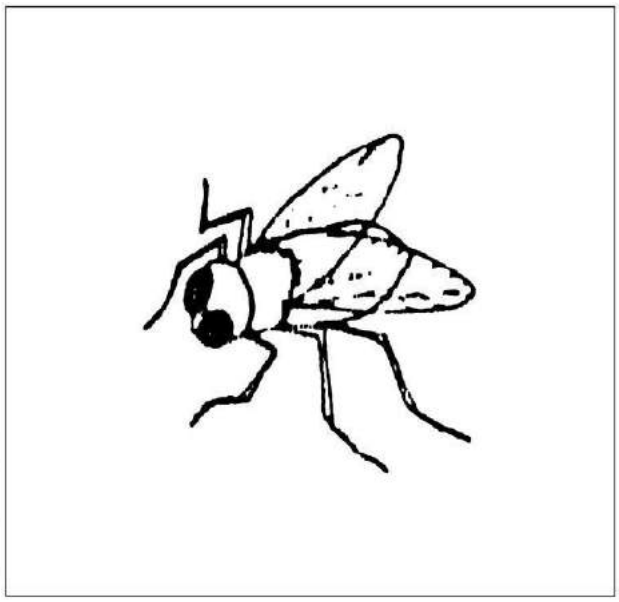


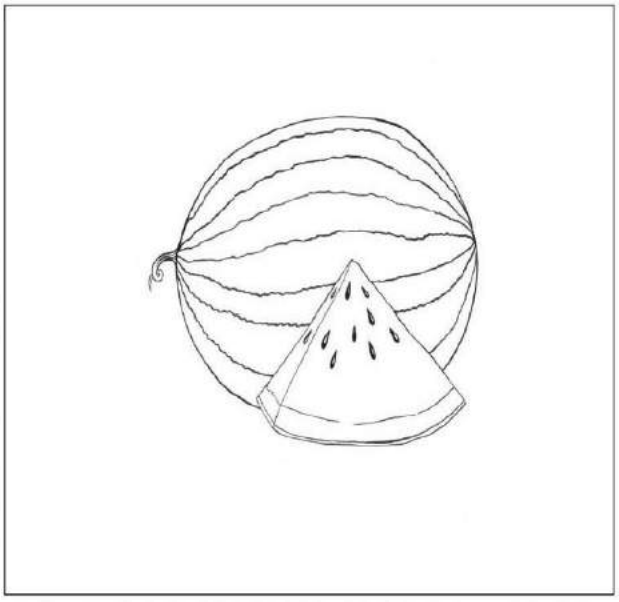


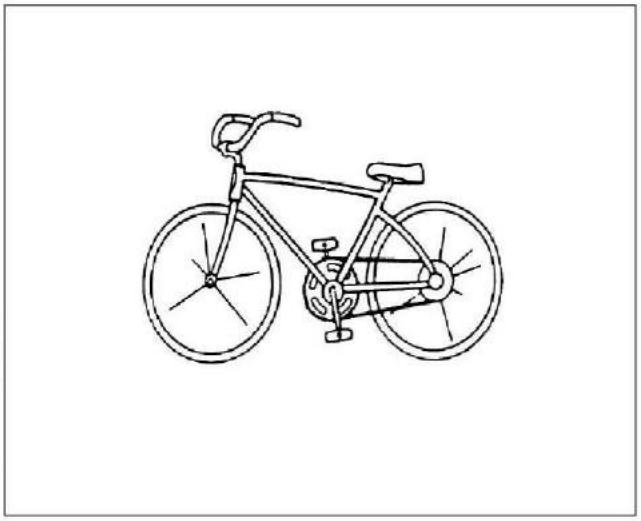


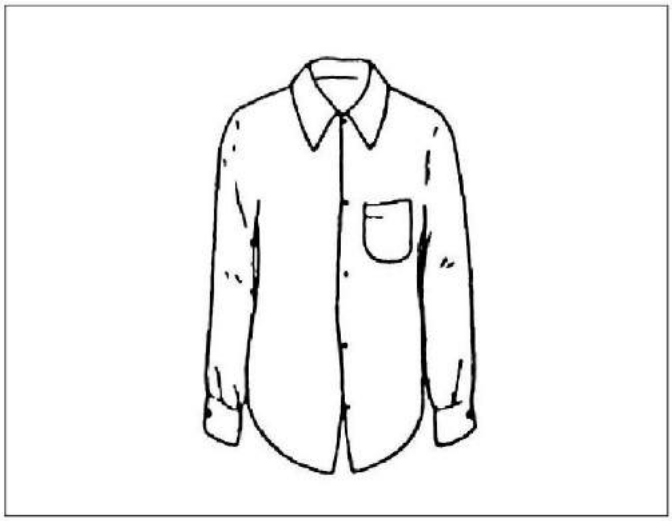


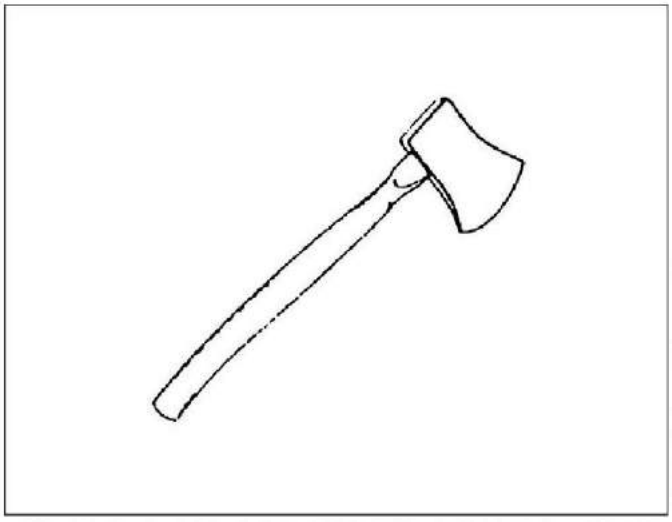


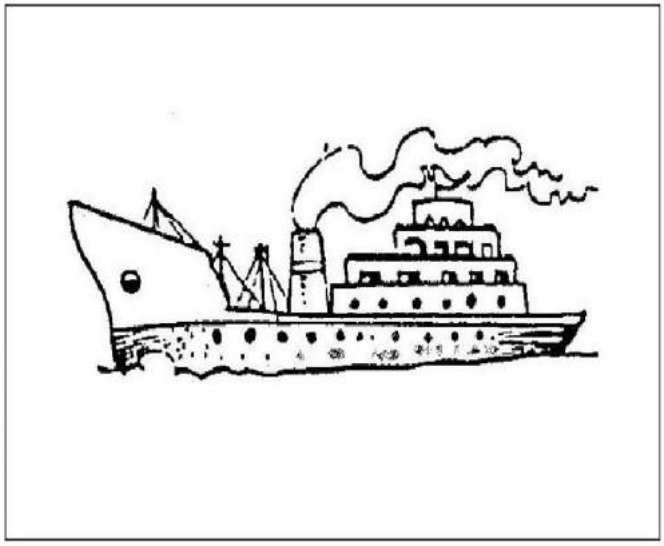


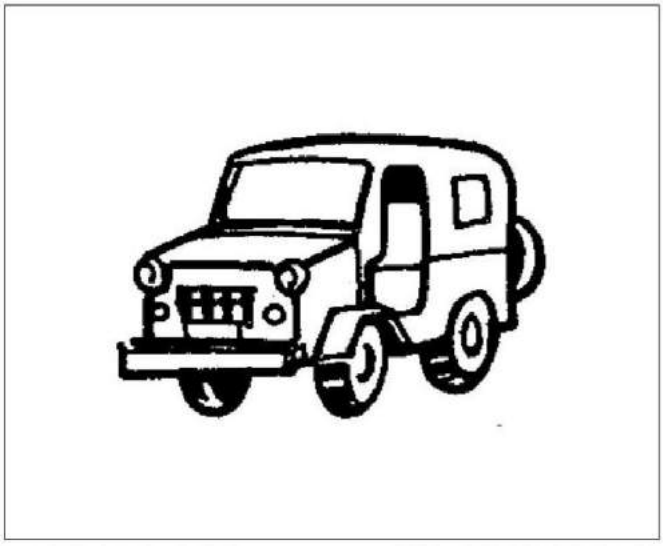


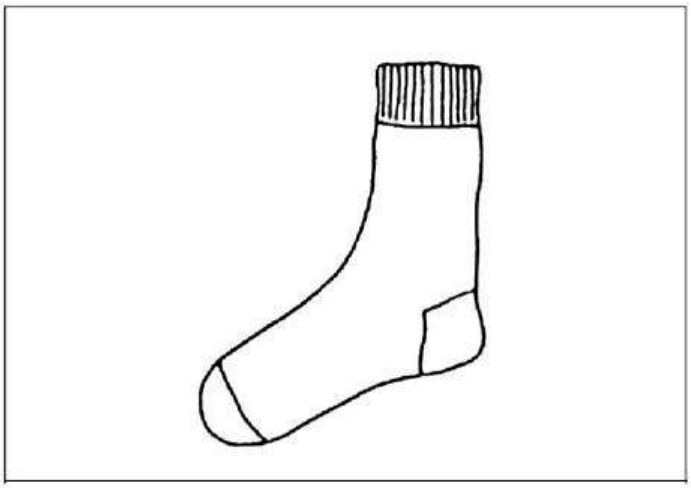


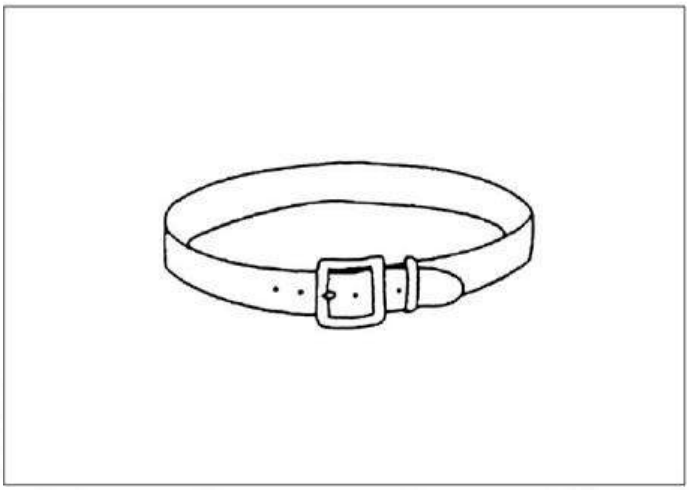


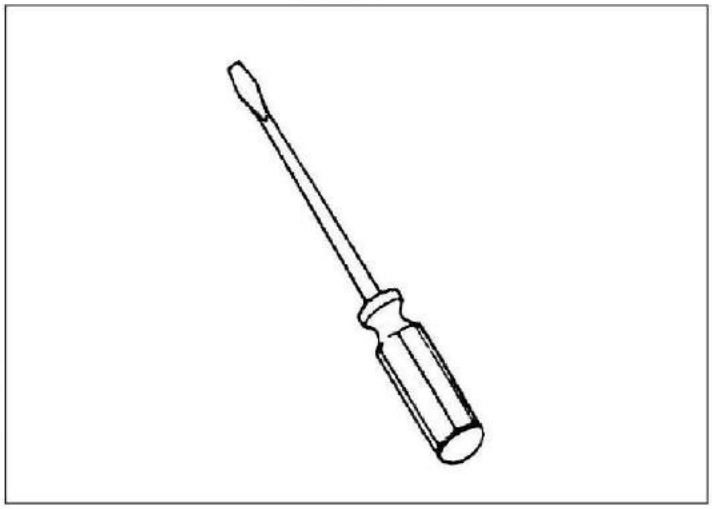


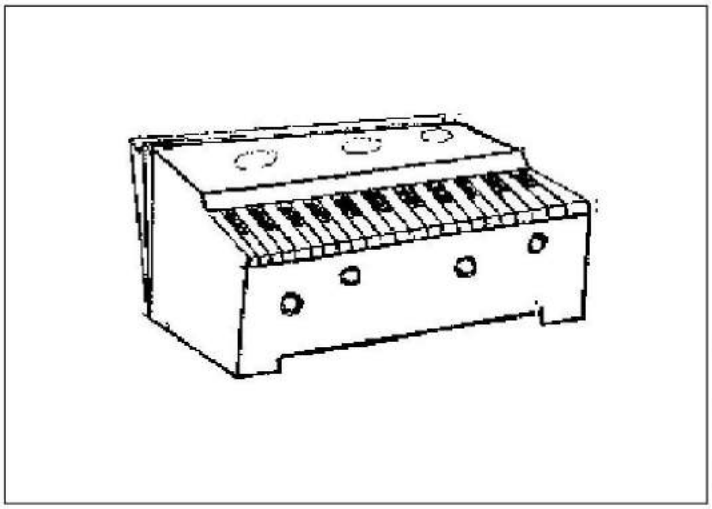


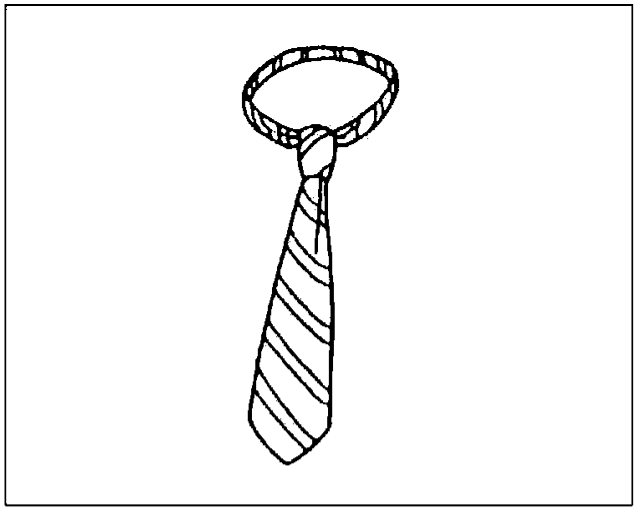


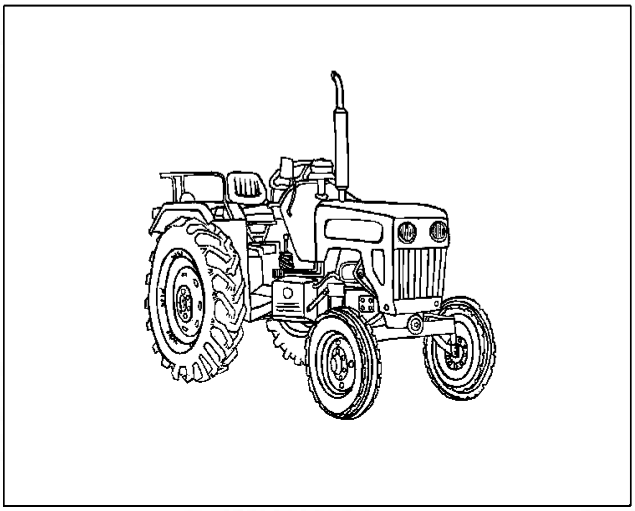












Appendix A: Semantic and Phonological Cues for Picture Naming Test

S. No	Stimulus	Below 10 seconds	Semantic cue (this is a /an)	After semantic cue	Phonemic cue (name of the picture begins with)	After phonemic cue
1	Hen		Bird		/h/	
2	Monkey		Animal		/m/	
3	Turtle		Animal		/t/	
4	Pineapple		Fruit		/p/	
5	Brinjal/ Eggplant		Vegetable		/b/(/e/)	
6	Eye		Part of the face		/ai/	
7	Butterfly		Insect		/p/	
8	Grapes		Fruit		/g/	
9	Ear		Part of the face		/I/	
10	Eagle		Bird		/i/	
11	Onion		Vegetable		/a/	
12	Pumpkin		Vegetable		/p/	
13	Ant		Insect		/ae/	
14	Carrot		Vegetable		/k/	
15	Tabala		Musical instrument		/ṭ/	
16	Bear		Animal		/b/	
17	Housefly		Insect		/h/	
18	Watermelon		Fruit		/w/	
19	Umbrella		Used when it rains		/a/	
20	Bicycle		Vehicle		/b/	
21	Shirt		Clothing		/Sh/ or /ʃ/	
22	Axe		Tool		/ae/	
23	Ship		Vehicle		/Sh/ or /ʃ/	
24	Jeep		Vehicle		/dz/	
25	Socks		Clothing		/s/	
26	Belt		Accessory		/b/	
27	Screwdriver		Tool		/s/	
28	Harmonium		Musical instrument		/h/	
29	Tie		Clothing		/t/	
30	Tractor		Vehicle		/t/	

Total Correct Response in native language (NL)

Total Correct Response in other language (OL)

Total=NL+OL=

QUALITY OF LIFE SCALE SF-36 (RAND)

QUESTIONNAIRE

Quality of life (QOL) measures have become a vital and often required part of health outcomes appraisal. For populations with chronic disease, measurement of QOL provides a meaningful way to determine the impact of health care.

Instructions for completing the questionnaire: *"Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully by ticking the option that best represents your response*."

Patient Name:_____SSN#: _____

Person helping to complete this form:_____ Date:___

1. In general, would you say your health is:

- Excellent
- Very good
- Good
- Fair
- Poor

2. Compared to one year ago, how would you rate your health in general now?

- Much better now than a year ago
- Somewhat better now than a year ago
- About the same as one year ago
- Somewhat worse now than one year ago
- Much worse now than one year ago

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

3. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.

- Yes, limited a lot.
- Yes, limited a little.
- No, not limited at all.

4. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf?

- Yes, limited a lot.
- Yes, limited a little.
- No, not limited at all.

5. Lifting or carrying groceries.

- Yes, limited a lot.
- Yes, limited a little.
- No, not limited at all

6. Climbing several flights of stairs.

- Yes, limited a lot.
- Yes, limited a little.
- No, not limited at all.

7. Climbing one flight of stairs.

- Yes, limited a lot.
- Yes, limited a little.
- No, not limited at all.

8. Bending, kneeling or stooping.

- Yes, limited a lot.
- Yes, limited a little.
- No, not limited at all.

9. Walking more than one mile.

- Yes, limited a lot.
- Yes, limited a little.
- No, not limited at all.

10. Walking several blocks.

- Yes, limited a lot.
- Yes, limited a little.
- No, not limited at all.

11. Walking one block.

- Yes, limited a lot.
- Yes, limited a little.
- No, not limited at all.

12. Bathing or dressing yourself.

- Yes, limited a lot.
- Yes, limited a little.
- No, not limited at all.

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

13. Cut down the amount of time you spent on work or other activities?

- Yes
- No

14. Accomplished less than you would like?

- Yes
- No

15. Were limited in the kind of work or other activities?

- Yes
- No

16. Had difficulty performing the work or other activities (for example, it took extra time)?

- Yes
- No

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

17. Cut down the amount of time you spent on work or other activities?

- Yes
- No

18. Accomplished less than you would like?

- Yes
- No

19. Didn't do work or other activities as carefully as usual?

- Yes

- No

20. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

- Not at all
- Slightly
- Moderately
- Quite a bit
- Extremely

21. How much bodily pain have you had during the past 4 weeks?

- None
- Very mild
- Mild
- Moderate
- Severe
- Very severe

22. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

- Not at all
- Slightly
- Moderately
- Quite a bit
- Extremely

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks?

23. Did you feel full of pep?

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- None of the time

24. Have you been a very nervous person?

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- None of the time

25. Have you felt so down in the dumps nothing could cheer you up?

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- None of the time

26. Have you felt calm and peaceful?

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- None of the time

27. Did you have a lot of energy?

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- None of the time

28. Have you felt downhearted and blue?

- All of the time
- Most of the time
- A good bit of the time

- Some of the time
- A little of the time
- None of the time

29. Did you feel worn out?

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- None of the time

30. Have you been a happy person?

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- None of the time

31. Did you feel tired?

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- None of the time

32. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

Ware, J., Snow, K., Kosinski, M., & Gendek, B. (1993). RAND 36- Item Health Survey: Manual and Interpretation Guide. Boston, MA: The Health Institute, The New England Medical Center. © Ware, J.

Scoring:

Table 1

Step 1: Recoding Items

Item numbers	**Change original response category ***	**To recoded value of:**
1, 2, 20, 22, 34, 36	1 →	100
	2 →	75
	3 →	50
	4 →	25
	5 →	0
3, 4, 5, 6, 7, 8, 9, 10, 11, 12	1 →	0
	2 →	50
	3 →	100
13, 14, 15, 16, 17, 18, 19	1 →	0
	2 →	100
21, 23, 26, 27, 30	1 →	100
	2 →	80
	3 →	60
	4 →	40
	5 →	20
	6 →	0
24, 25, 28, 29, 31	1 →	0
	2 →	20
	3 →	40
	4 →	60
	5 →	80
	6 →	100
32, 33, 35	1 →	0
	2 →	25
	3 →	50
	4 →	75
	5 →	100

Table 2

Step 2: Averaging Items to Form Scales

Scale	Number of items	After recoding per Table 1,average the following items
Physical functioning	10	3 4 5 6 7 8 9 10 11 12
Role limitations due to physical health	4	13 14 15 16
Role limitations due to emotional problems	3	17 18 19
Energy/fatigue	4	23 27 29 31
Emotional well- being	5	24 25 26 28 30
Social functioning	2	20 32
Pain	2	21 22
General health	5	1 33 34 35 36

Table 3: Reliability, Central Tendency, and Variability of Scales in the Medical Outcomes Study

Scale	Items	Alpha	Mean	SD
Physical functioning	10	0.93	70.61	27.42
Role functioning/physical	4	0.84	52.97	40.78
Role functioning/emotional	3	0.83	65.78	40.71
Energy/fatigue	4	0.86	52.15	22.39
Emotional well-being	5	0.90	70.38	21.97
Social functioning	2	0.85	78.77	25.43
Pain	2	0.78	70.77	25.46
General health	5	0.78	56.99	21.11
Health change	1	—	59.14	23.12

Ware, J.E., Jr., & Sherbourne, C.D. "The MOS 36-Item Short-Form Health Survey (SF-36): I. Conceptual Framework and Item Selection,". *Medical Care*, 30:473-483, 1992.

ALS CBS
ALS Cognitive Behavioral Screen

Susan C. Woolley, Ph.D.

Patient Id: _____ **DOB/Age:** _____ **Gender:** _____
Onset Date: _____ **FVC:** _____ **Education:** _____

Onset Region: bulbar, arm, leg, trunk, respiratory (circle one)

☐ Mark if pt responses were written, attach sheet

HAND PAGE 2 TO CAREGIVER.

Attention

a. Commands: *I am going to say some commands. Please listen carefully and then do what I say. (If patient is unable to indicate with finger, movement can be substituted with eyes, arm or other means).*

1. Point/indicate (with your finger) to the ceiling and then to your left.
2. Touch your shoulder, point to the floor, and then make a fist.

errors 0 1+
Score (circle) **1** **0**

b. Mental Addition/Language: *I am going to say some phrases. I want you to tell me the number of syllables in each phrase. For example, "the table" has 3 syllables. (Repetition of each phrase is allowed once).*

1. The weather is nice. (correct response: 5) answer _____
2. Tomorrow will be sunny. (correct response: 7) answer _____

errors 0 1+
Score (circle) **1** **0**
(score 0 if >20 seconds on either)

c. Eye Movements: *Saccades and Antisaccades.*

# of Correct Saccades out of 8: ____/**8** Score: 8/8 =**1** points, ≤7/8 = **0** points
# of Correct Antisaccades out of 8: ____/**8** Score: 8/8 =**2** points, 7/8 = **1** points, ≤ 6/8 = **0 points**

/5

Concentration

I am going to say some numbers. After I say them, I want you to say them to me backwards, or in reverse order. For example, if I say 3-6, you would say 6-3. (If written, do not allow pt to write forward span. Discontinue after failure on two consecutive trials).

		Correct	Incorrect			Correct	Incorrect
2-9	(9-2)	__	__	7-8-6-4	(4-6-8-7)	__	__
6-4	(4-6)	__	__	5-4-1-9	(9-1-4-5)	__	__
3-7-2	(2-7-3)	__	__	8-2-5-9-3	(3-9-5-2-8)	__	__
5-8-1	(1-8-5)	__	__	5-7-6-3-9	(9-3-6-7-5)	__	__

Maximum Span Correct: (Enter score)

/5

Tracking/Monitoring

a. Months: *Please say the months of the year backwards, starting with December. (circle omissions/mark repetitions & intrusions)*

Dec Nov Oct Sep Aug Jul Jun May Apr Mar Feb Jan

errors 0 1 2+
Score (circle) **2** **1** **0**

b. Alphabet: *Please say/write the alphabet for me. (mark uncorrected errors, omissions or intrusions)*

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

errors 0 1+
Score (circle) **1** **0**

c. Alternation Task: *I want you to alternate between numbers and letters, starting with 1-A, and then 2-B, 3-C, and so on. Please continue from there, alternating between number-letter, number- letter, in order, without skipping any until I tell you to stop. (Errors: Any mistake in sequencing, i.e., 7-H, or 8-9).*

4-D 5-E 6-F 7-G 8-H 9-I 10-J 11-K 12-L 13-M

errors 0 1 2
Score (circle) **2** **1** **0**

/5

Initiation and Retrieval

Say (write) as many words as you can starting with the letter F, as quickly as you can, in 1 minute. (Show pt Fluency Rules) You cannot say/write the names of people, places or numbers. Please do not say/write the same word with just a different ending, like truck, trucks. (S words can be substituted for F words). Errors: repetitions, rule violations.

1. _____	9. _____	17. _____
2. _____	10. _____	18. _____
3. _____	11. _____	19. _____
4. _____	**12.** _____	20. _____
5. _____	13. _____	
6. _____	14. _____	
7. _____	15. _____	
8. _____	16. _____	

correct words >12 12-8 <8 ≤ 4
Score (circle): **3** **2** **1** **0***

plus

errors 0 1 2+
Score (circle): **2** **1** **0**

*if ≤4 words, total verbal fluency score = **0** regardless of # of errors

/5

TOTAL SCORE

/20

ALS CBS
ALS Cognitive Behavioral Screen

Susan C. Woolley, Ph.D.

ALS Caregiver Behavioral Questionnaire

These questions pertain to possible changes that you have noticed since the onset of ALS symptoms. As best you can, consider changes that are unrelated to physical weakness. For example, question #1 asks about interest in activities. If the person can no longer play tennis but still seems interested in it (i.e. talks about it, watches it on television), then you would circle 3 for no change in level of interest.

If the person has always had the trait in question, please respond No Change, since there has been no change over time.

Compared to before ALS, does he/she:

	No Change	Small Change	Medium Change	Large Change
1. Have less interest in topics/events that used to be important to them?	3	2	1	0
2. Show little emotion, or seem less responsive emotionally?	3	2	1	0
3. Seem more agreeable or pleasant than in the past with fewer worries?	3	2	1	0
4. Fail to think things through before acting?	3	2	1	0
5. Seem more withdrawn from others but not sad?	3	2	1	0
6. Get confused or distracted more easily?	3	2	1	0
7. Have less ability to deal with frustration or stress?	3	2	1	0
8. Seem less concerned about the feelings or concerns of others than before?	3	2	1	0
9. Get angry or irritable more easily than before?	3	2	1	0
10. Seem more sarcastic or childlike than before?	3	2	1	0
11. Eat more or have a new preference for particular foods (i.e. sweets)?	3	2	1	0
12. Have more trouble changing opinions or adapting to new situations?	3	2	1	0
13. Show less judgment or more problems making good decisions (i.e. regarding safety, finances, etc)?	3	2	1	0
14. Have less awareness of obvious problems or changes, or deny them?	3	2	1	0
15. Have new problems with language, such as saying the wrong word more often, making up new words, or declines in spelling ability?	3	2	1	0

TOTAL SCORE: _____/45

The following questions relate to current symptoms, not changes over time:

Do you think your loved one:	**YES**	**NO**
• Seems depressed on most days?	[ ]	[ ]
• Seems anxious on most days?	[ ]	[ ]
• Seems extremely fatigued on most days?	[ ]	[ ]
• Suffers from unexpected crying or laughing spells?	[ ]	[ ]

Susan C. Woolley, Ph.D.

Eye Movement Instructions

Saccades: *I am going to hold my fingers up. Please keep your head straight and look at me. When I wiggle a finger, I want you to look at that finger and then look back at me* (examiner should execute this eye moment themselves to demonstrate). *Look at my finger by moving your eyes only, trying to keep your head still. Each time I wiggle a finger, look at it and then back to me. (*Do 2-3 trials with the patient as practice*) We will do that a few times. Ready? (*Do 8 random trials, pause for 1-2 seconds between each trial*).*

Antisaccades: Good, next I am going to wiggle a finger again, but this time, I want you to look AWAY from the finger that moves. For example, if I move this finger (wiggle one) then I want you to look at the other finger, not the one that moves, ok? (Examiner should demonstrate for patient) *Let's try it (*do 2-3 trials*). Just like before, try to keep you head still and just move your eyes. After each one, look back at me. Ready? (*Do 8 random trials, pause for 1-2 seconds between each trial*).*

FLUENCY RULES

NO NAMES OF PEOPLE

NO NAMES OF PLACES

NO NUMBERS

DO NOT USE SAME WORD WITH DIFFERENT ENDING

Zarit Caregiver Burden Assessment **(Revised, 22-items)**

Name: _____ Date: _____

The following is a list of statements that reflect how people sometimes feel when taking care of another person. After reading each statement, indicate how often you experience the feelings listed by circling the number that best corresponds to the frequency of these feelings.

	Never	Rarely	Sometimes	Frequently	Nearly Always
1) Do you feel stressed between caring for your relative and trying to meet other responsibilities for your family or work?	0	1	2	3	4
2) Do you feel embarrassed you're your relative's behavior?	0	1	2	3	4
3) Do you feel angry when you are around your relative?	0	1	2	3	4
4) Do you feel that your relative currently affects your relationship with other family members or friends in a negative way?	0	1	2	3	4
5) Are you afraid what the future holds for your relative?	0	1	2	3	4
6) Do you feel strained when you are around your relative?	0	1	2	3	4
7) Do you feel that you do not have as much privacy as you would like because of your relative?	0	1	2	3	4
8) Do you feel that your social life has suffered because you are caring for your relative?	0	1	2	3	4
9) Do you feel uncomfortable about having friends over because of your relative?	0	1	2	3	4
10) Do you feel that you have lost control of your life since your relative's illness?	0	1	2	3	4
11) Do you wish you could just leave the care of your relative to someone else?	0	1	2	3	4
12) Do you feel uncertain about what to do about your relative?	0	1	2	3	4

Over

	Never	Rarely	Sometimes	Frequently	Nearly Always
13) Do you feel that you should be doing more for your relative?	0	1	2	3	4
14) Do you feel you could do a better job in caring for your relative?	0	1	2	3	4
15) Overall, how burdened do you feel in caring for your relative?	0	1	2	3	4
16) Do you feel that your relative asks for more help than (s)he needs?	0	1	2	3	4
17) Do you feel that because of the time you spend with your relative that you do not have enough time for yourself?	0	1	2	3	4
18) Do you feel your relative is dependent upon you?	0	1	2	3	4
19) Do you feel your health has suffered because of your involvement with your relative?	0	1	2	3	4
19) Do you feel your health has suffered because of your involvement with your relative?	0	1	2	3	4
20) Do you feel that your relative seems to expect you to take care of him/her as if you were the only one he/she could depend on?	0	1	2	3	4
21) Do you feel that you will be unable to take care of your relative much longer?	0	1	2	3	4
22) Do you feel that you do not have enough money to care for your relative in addition to the rest of your expenses?	0	1	2	3	4

Scoring Instructions: Add Items 1-12 **Total 1-12 (maximum score = 48)** _____

Add Items 13-21 **Total 13-21 (maximum score = 36)** _____

Score #22 (maximum score = 4) _____

Total Score (88) _____

Source: Zarit SH, Reever KE, Bach-Peterson J. Relatives of the impaired elderly: correlates of feelings of burden. The Gerontologist 1980; 20:649-655.

Prevalance and patterns of cognitive impairment in Amyotrophic lateral sclerosis and correlation with disease outcome

by Dr. Manisha Karamala Yalapalli

General metrics

71,134	10,611	591	42 min 26 sec	1 hr 21 min
characters	words	sentences	reading time	speaking time

Score

93

This text scores better than 93% of all texts checked by Grammarly

Writing Issues

328	100	228
Issues left	Critical	Advanced

Plagiarism

6 %

45 sources

6% of your text matches 45 sources on the web or in archives of academic publications