Comparison of Cognitive Impairment between Amyotrophic Lateral Sclerosis Patients and Healthy Controls in Neurological Institute of Thailand

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Abstract

Objectives: To determine the cognitive impairment in Thai amyotrophic lateral sclerosis patients (ALS) by using The Thai Mental State Examination (TMSE).

Material and Methods: This is a case-control study analysis of 15 ALS patients and 30 healthy control people from September 1st, 2021 to December 31st, 2021 at Neurological Institute of Thailand, Bangkok, Thailand. Demographic data, ALS symptoms, ALS disease severity score, laboratory investigations, medications, and TMSE score have been analyzed.

Results: TMSE total score in ALS group was significantly lower than control group (24 and 27.5, p-value = 0.015). Judging from the score of each domains, there were the orientation and language domains which had significant differences from the control group. The orientation median score was 6 (IQR5-6) and 6 (IQR6-6) (p-value = 0.015), while the language score had wider difference as 7 (IQR5-8) and 8.50 (IQR8-9) (p-value = 0.011). Since many ALS patients in this study (6/15) had severe upper limb weakness. This findings resulted in lower scores from both 3-step command and drawing parts in language domain. Therefore, we also analyzed the subgroup of ALS patients who still had good hand motor skills (9/15) compared to matched controls (18/30). The results showed that there were no significant differences in both TMSE total score and language score. Moreover, when we excluded the 3-step command and drawing parts out of the language assessment (total score after excluded = 5), we also found no differences between case and control groups. We also found that ALS disease severity had no correlation with

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cognitive impairment by ALS functional rating scale, Japanese ALS severity scale, and MRC sum score.

Conclusion: The result of this study illustrates that ALS patients have certain mild cognitive impairment in the orientation domain. this TMSE examination may not be suitable for cognitive screening for ALS patients due to their requirement of good hand function in some parts of the tests and it is insensitive for assessment of executive functions. Thus, this study may support that there should be a new Thai-translated cognitive test that properly assess the ALS patients.

Keywords: Cognitive Impairment, Dementia, ALS, Amyotrophic Lateral Sclerosis

Introduction

Amyotrophic lateral sclerosis (ALS) is an uncommon motor neuron disease which affects both upper and lower motor neuron in several body regions. These patients have progressive symptoms of weakness, dysphagia, respiratory insufficiency, and will have deficits in activities of daily living.[1] The overall crude worldwide incidence of ALS is about 2 new cases per 100,000 people annually.[2] ALS is mostly found in patients aged around 60-65 years old and it has age-dependent onset and duration.[3] Currently, ALS disease still has no specific treatment and patients would only get supportive care to prolong their survival.

ALS has wide phenotypic heterogeneity, it is not limited to only motor system, but other neurological systems can also be affected. The recent studies suggest that ALS patients may have mild cognitive impairment with subtle executive deficits. Around 5% of ALS patients have a clinical subtype of frontotemporal lobar degeneration (FTLD) called Frontotemporal Dementia (FTD).[4] In recent years, the gap between ALS and frontotemporal dementia has been bridged by genetic evidence, including abnormality in TDP-43 protein and, C9orf72 hexanucleotide repeats.[5,6] A combination of clinical, neuroimaging, and neuropathological data suggest that ALS and FTD may be one disease spectrum with clinical, pathological and genetic overlap.[7] ALS patients with mild cognitive impairment are not different from classic ALS but ALS-FTD patients have a worse prognosis than classic subtype.

Cognitive symptoms in ALS patients have been reported to have variable presentations. Some patients may have problem in only single domain, but several patients may have problem in multiple cognitive domains. However, the information about the frequency, severity, and progression of cognitive impairment in classic ALS is still unclear. The most consistently studied cognitive changes in ALS reported the deficits in executive functions (eg. verbal fluency and attention), whereas abnormalities in memory and language domains are more preserved.[4]

There are many neuropsychological tests for executive functions. However, due to the complexity of tests, the results can be confounded by bulbar or limb weakness in ALS. Then, there are some of the specific tests for ALS patients such as, the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) invented by Abrahams and colleagues. ECAS calculated a verbal fluency index using the time that the patients took to copy words they had written in fluency tests.[8] The Wisconsin card-sorting test is used to measure rule shifting and mental flexibility.[4] These batteries have high sensitivity and specificity, but they took very long time to perform. Short batteries such as the mini mental state examination (MMSE) is easier to use in clinical practice and can reveal some bahavioral

abnormalities such as perseveration, inattention, and disinhibition; but it cannot be used to screen for frontotempotal dementia because it has only few tests for Frontal lobe function. Currently in Thailand, there are two most widely used translated cognitive screening tests which are The Thai Mental State Examination (TMSE) and Montreal cognitive assessment (MOCA) Thai version, the TMSE is much easier for the patient to perform the test compared to MOCA, which used many manual skills to evaluate and may be too difficult for ALS patients.

In Thailand, there is no known study about cognitive symptoms in ALS patients before. Therefore, this study aims to find out whether ALS patients in Thailand have significant cognitive impairment or not, and if they have, which domains are the most affected.

Materials and Method

1. Study design

This study was a case control study in Neurological Institute of Thailand, Bangkok, Thailand. The participants were enrolled from the outpatient departments in between September 1st, 2021 and December 31st, 2021. ALS patients and control subject was enrolled in 1:2 ratio (ALS : control). Both group were matched with age and educational status. The medical records and data from ALS registry were reviewed to assess demographic, clinical data, amyotrophic lateral sclerosis functional rating scale (ALS-FRS), MRC Grading Score and Japanese ALS Severity Scale.

2. Inclusion criteria

Inclusion criteria for ALS group

- Age ≥ 18 years old
- Have the diagnosis of ALS (including only Probable ALS Laboratory Supported, Probable ALS, or Definite ALS by The Revised El Escorial criteria[9])
- Able to communicate in verbal or written language
- Never been diagnosed with cognitive disorders

Inclusion criteria for control group

- Age ≥ 18 years old
- Never been diagnosed with cognitive disorders

3. Exclusion criteria

- Patients and controls who were unable to complete neuropsychological tests

4. Assessment tools

Every participants in both ALS and control group had been informed about the study before participated. The Thai Mental State Examination (TMSE), a validated cognitive screening test that being used widely in Thailand, is a neuropsychological test in this study. The test is used to analyze each cognitive domain of the participants and took approximately 10-15 minutes to complete. All of the tests were examined by the experienced neuropsychologist in Neurological institute of Thailand (K.S.).

The total score of TMSE test is 30 points, which contains of 6 domains ; orientation, registration, attention, calculation, language, and recall memory.

The revised ALS functional rating scale (ALSFRS-R) is a validated questionnaire-based scale for monitoring the progression of disability in ALS patients. It is composed of 12 questions that cover functions in 4 domains: gross motor tasks, fine motor tasks, bulbar function, and respiratory function. The score for each question is summed for an overall score ranging from 0 to 48, the higher the score the more function is retained.[10]

The Japanese ALS severity classification scale was used in the edaravone trials to evaluate the severity of ALS in patients.[11] The level of functionality is classified into one of five categories on an ordinal scale, with 1 representing the least amount of functional impairment associated with severity of disease, and 5 representing the most. Information regarding the validity and reliability of this assessment tool were not identified.

The Medical Research Council sum score (MRC-SS) is a measure of global peripheral muscle strength, which ranges from 0 (complete paralysis) to 60 (normal strength).[12] Manual strength of six muscle groups (shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, and ankle dorsiflexion) is evaluated on both sides using MRC scale (muscle strength is scored 0-5 in each muscle).[13] This score was originally developed for detecting early strength alterations in patients with Guillain-Barré syndrome

4. Outcomes

Primary outcome : To find the proportion of cognitive impairment in ALS patients and cognitive impairment characteristics. Then, evaluate the comparison of TMSE total score and each domain score between ALS patient group and control groups.

Secondary outcome : To determine the correlation between ALS severity scale and cognitive impairment

5. Ethical issue

The study was approved by Neurological Institute of Thailand ethic committee

6. Statistical analysis

Descriptive statistical analysis has been performed on all demographic data and clinical characteristics. Because of small sample size, the median and interquartile range were compared for numerical data between groups. Qualitative data is described using percentage. Group comparison is performed using Mann-Whitney U test for numerical ordinal variables. Spearman correlation is performed to investigate the association between ALS severity score and TMSE score. Any 2-sided $P<0.05$ is considered statistically significant. Data analysis is performed using SPSS for window version 17.0 (SPSS Inc, Chicago, Illinois, USA).

Results

1. Demographic Characteristics

A total of 15 ALS patients and 30 control participants were enrolled from September 1st, 2021 to December 31st, 2021 at Neurological Institute of Thailand. The demographic and clinical characteristics have been shown in Table 1. There were no significant difference in sex (male:female) (6:9, 15:15, p = 0.752), age (median age) (57.76, 58.51, p = 0.516), and educational level (p=1.00) between both groups.

Median age of onset of symptom in ALS patients was 56.16 years, and mostly presented with upper limb weakness (60%). Median of MRC grading score was decreased from 47 to 43 between first visit and on day of TMSE examination, while median of total ALS-FRS scale and Japanese ALS severity scale were the same in both days. In addition, there were 2 patients who take Riluzole for the treatment of ALS. For imaging results, four patients had negative result of MRI brain, 1 patient had abnormal finding as Pontocerebellar atrophy, while MRI brain had not been done in most patients (66.67%). In contrast, MRI C-spine had been done in most ALS patients (93.33%) and all of them had negative results. The diagnosis of ALS patients were mostly defined as Probable ALS with laboratory support (73.33%), followed by Probable ALS (13.33%), and Definite ALS (13.33%).

Table 1 Baseline characteristics of study population

Associated factors	ALS group (n = 15)	Control group (n= 30)	p-value
1. Sex (Male / Female), no. (%)	6(40) / 9(60)	15(50) / 15(50)	0.752
2. Age at evaluation (years); median (IQR 25,75)	57.8 (49.1,60.7)	58.5 (49.0,63.4)	0.516
3. Educational Level, no. (%)			1.00
• Grade 1-6	6 (40)	13 (43.33)	
• Grade 7-12	3 (20)	5 (16.67)	
• Diploma degree and above	6 (40)	12 (40)	
4. Age at symptom onset (years); median (IQR25,75)	56.2 (46.7,60.2)		
5. First Presentation, no. (%)			
• Bulbar weakness	3 (20)		
• Upper limb weakness	9 (60)		
• Lower limb weakness	3 (20)		
6. MRC Grading Score (points); median (IQR25,75)			
• First visit	47 (38,53)		
• TMSE test day	43 (38,53)		
7. ALSFRS-R (points); median (IQR25,75)			
• First visit	37 (23,44)		
• TMSE test day	37 (21,44)		
8. Japanese ALS Severity Scale (points); median (IQR25,75)			
• First visit	3 (2,4)		
• TMSE test day	3 (2,4)		
9. On Riluzole, no. (%)	2 (13.33)		
10. MRI Brain, no. (%)			
• Negative result	4 (26.67)		
• Abnormal	1 (6.67)		
• Not done	10 (66.67)		
11. MRI C-Spine, no. (%)			
• Negative result	14 (93.33)		
• Abnormal	0 (0)		
• Not done	1 (6.67)		
12. Diagnosis, no. (%)			
• Definite ALS	2 (13.33)		
• Probable ALS	2 (13.33)		
• Probable ALS with laboratory support	11 (73.33)		

2. Primary outcome

Based on TMSE standard cut-off, there were 5 patients in ALS group (33.33%) who were in cognitive impairment range (TMSE score ≤ 23) and 10 patients (66.67%) in normal range (TMSE score > 23). TMSE total score had statistically significant difference comparing between both ALS and control groups (median (IQR) ; 24 (23-26) and 27.5 (24.75-28.25), p-value = 0.015). Judging from the score of each domain, there were orientation and language domains that had significant differences from the control group. The orientation median score were 6 (IQR5-6) and 6 (IQR6-6) (p-value = 0.015), while the language score had wider

difference which were 7 (IQR5-8) and 8.50 (IQR8-9) (p-value = 0.011). The other domains had no significant differences between ALS and control groups. The results are shown in Table 2.

In the orientation part, there were 4 patients who failed to recall the time, 2 patients failed to recall the place, and 1 patient failed to remember the person.

As for the results of language domain of ALS patients, there were 6 patients who had weak hand muscles and failed to perform the 3-step command and drew misshaped house due to their muscle weakness. There were 4 patients who couldn't answer in abstract thinking part by failing to identify similarity of cats and dogs. There was 1 patient who fail to perform the reading part by doing different movement from the instruction. Another patient performed one wrong step in the 3-step command.

Table 2 Comparison of TMSE score between ALS and control groups

TMSE score	ALS group (N = 15)	Control group (N = 30)	P-value
1. TMSE Total Score; median (IQR25,75)	24 (23,26)	27.5 (24.7,28.3)	**0.015***
2. Orientation; median (IQR25,75)	6 (5,6)	6 (6,6)	**0.015***
3. Registration; median (IQR25,75)	3 (3,3)	3 (3,3)	0.956
4. Attention; median (IQR25,75)	5 (5,5)	5 (5,5)	0.157
5. Calculation; median (IQR25,75)	2 (1,3)	3 (2,3)	0.082
6. Language; median (IQR25,75)	7 (5,8)	8.50 (8,9)	**0.011***
7. Recall memory; median (IQR25,75)	2 (2,3)	2 (1,3)	0.929

3. Subgroup analysis by excluding weak hand muscles cases and matched controls

In addition, we performed the subgroup analysis by excluding 6 ALS cases who had weak hand muscles and 12 matched control of those cases. We excluded patients who had MRC score of both wrist and finger muscle groups below than grade 3, which they would not be able to grip the pen or fold the paper. The results are shown in Table 3. The results were different from previous results as the TMSE total score and Language parts were not show significant difference from the control group (p-value = 0.533 and 0.810 perspectively). However, the orientation part still has as statistically significant difference between case and control groups (p-value = 0.047) as before.

Table 3 Subgroup analysis of TMSE score comparing between ALS and control group by excluding weak hand muscles cases and matched controls

	ALS group (N = 9)	Control group (N = 18)	P-value
1. TMSE total score; median (IQR25,75)	25 (23,28)	26 (24,28)	0.533
2. Orientation; median (IQR25,75)	6 (5,6)	6 (6,6)	**0.047***
3. Language; median (IQR25,75)	8 (7.5,9)	8 (7,9)	0.810

4. Language domain subgroup analysis by excluding 3-step command and drawing parts

Drawing part and 3-step command are parts of language domain. In ALS patients, both parts were affected by hand weakness and mislead to impair language domain in ALS patients. Another subgroup analysis was run by eliminating the 3-step command and drawing part from Language

segment in TMSE. The results are shown in Table 4. As a result, the total score of this domain decreased from 10 points to 5 points which resulted in no longer significant difference in language part. (p-value = 0.513)

Table 4 Comparison of TMSE language score (3-step command and drawing part were excluded) between ALS and Control groups

	ALS group (N = 15)	Control group (N = 30)	P-value
TMSE Language (cut version); median (IQR25,75)	5 (4,5)	5 (4.8,5)	0.513

5. Secondary outcome

The median value of revised ALS-FRS in first visit was 37 (IQR 23-44), which was the same as on TMSE examination day. According to Spearman Correlation Analysis, ALS-FRS and TMSE score had no significant correlation (Correlation coefficient = 0.427, p-value = 0.113). The result is shown in Figure 1. Moreover, in each function of ALSFRS-R including bulbar, gross motor, fine motor, and respiratory functions had not correlate with TMSE total score, the results are shown in Figure 2-5.

For the results of Japanese ALS severity scale, according to Chi-Square analysis there was no significant difference in TMSE total score between ALS patients in grade 1-5 (p-value = 0.440), which implied that Japanese ALS severity scale had no correlation to TMSE total score. The results are shown in Figure 6.

As for the MRC sum score, according to Spearman Correlation Analysis it also had no significant correlation between MRC sum score and total TMSE score of ALS patients (Correlation coefficient = 0.069, p-value = 0.806). The results are shown in Figure 7.

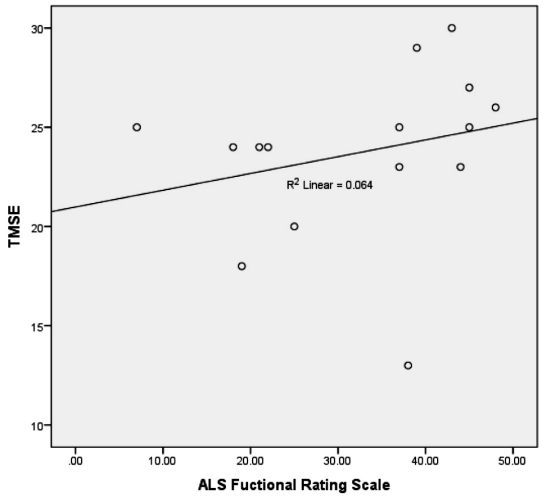

Figure 1 Relationship between ALS functional rating scale total score and TMSE total score

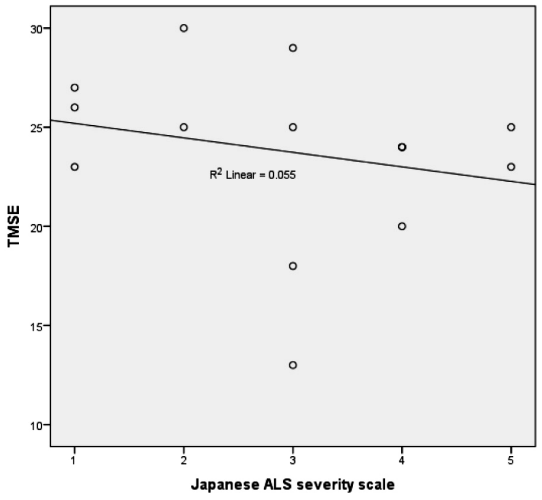

Figure 2 Relationship between ALS functional rating scale of bulbar function and TMSE total score

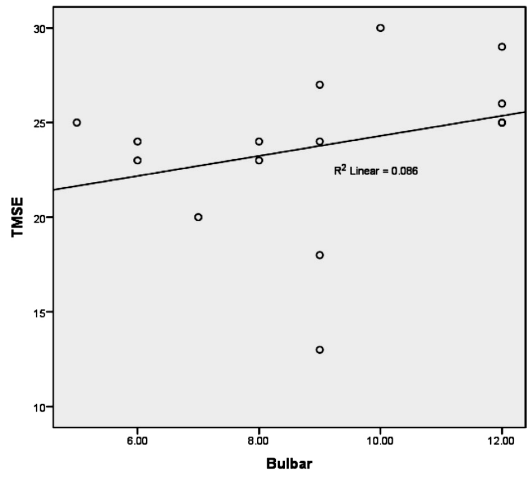

Figure 3 Relationship between ALS functional rating scale of fine motor function and TMSE total score

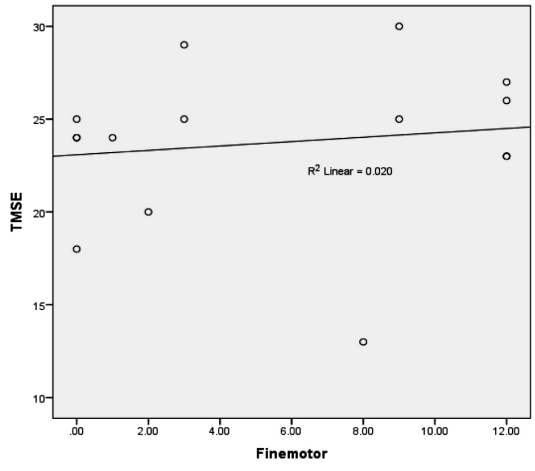

Figure 4 Relationship between ALS functional rating scale of gross motor function and TMSE total score

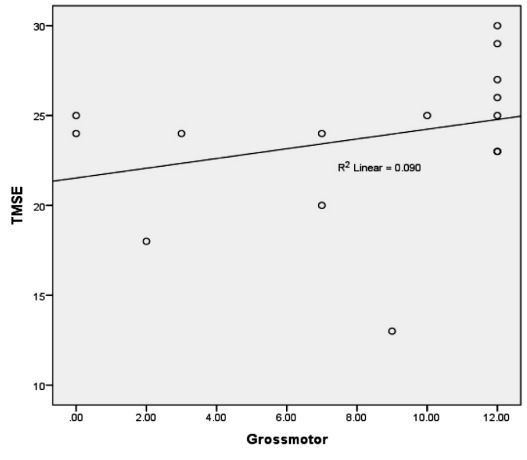

Figure 5 Relationship between ALS functional rating scale of respiratory function and TMSE total score

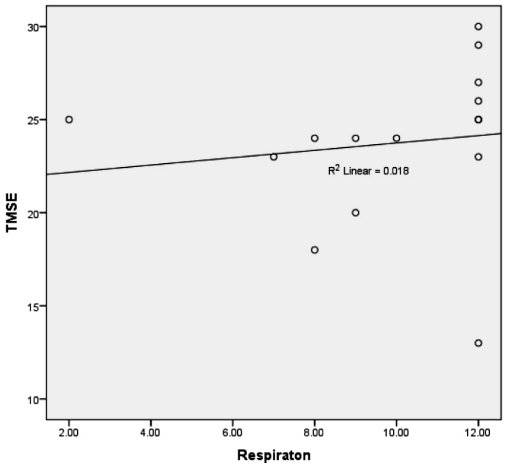

Figure 6 Relationship between Japanese ALS severity scale and TMSE total score

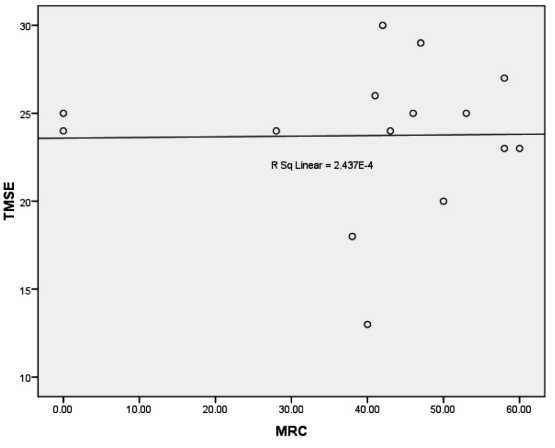

Figure 7 Relationship between MRC sum score and TMSE total score

Discussion

In the past, patients with ALS disease were believed to have normal cognitive function due to its pure motor neuron disease. Later on with updated data, we know that ALS and FTD may be in the same disease continuum through abnormal accumulation of TDP-43 protein in neural tissues of many patients.[5] Recent studies also found that there are common cognitive deficits in ALS patients including impaired verbal fluency, impaired attention, or executive dysfunction.[4] Since there is

no known study about cognitive symptoms in ALS patients in Thailand before, then we have decided to work in this research topic in Neurological Institute of Thailand.

Baseline characteristics in both groups were similar (sex, age, and educational level). There was no ALS patient who fullfilled the criteria of bvFTD. However, there was 1 ALS patient who had only disinhibition and frontal releasing signs whom scored 26 points in total TMSE score. From the cognitive test results, ALS patient group had significant lower total TMSE score than the control group. The significantly affected domains were the orientation and the language parts.

Language part of TMSE comprises of tests in multiple subdomains including language comprehension (3-step command), repetition, naming, reading (read and perform "close your eyes"), visuospatial (house drawing), and frontal executive function (abstract thinking). Some sections are not meant to use mainly for language assessment but need good language function to perform. Another factor that may affect the assessment is hand function, especially in 3-step command and house drawing parts. Since many ALS patients in this study (6/15) had severe upper limb weakness at the day of assessment (defined by MRC score of wrist and finger muscle groups below than grade 3 of both hands).This resulted in lower scores from both parts. Therefore, we also analyzed the subgroup of ALS patients who still had good hand motor skills (9/15) compared to matched controls (18/30). The results showed that there were no significant differences in both TMSE total score and language score. Moreover, when we excluded the 3-step command and drawing parts out of the language assessment (total score after excluded = 5), we also found no differences between case and control groups. We can assume from this finding that lower score of ALS patients in language part was mainly due to motor weakness confounder, not the cognitive impairment.

From this study, the truly significant affect domain was the orientation part, which was different from previous study. Some ALS patients did not oriented about the time, place, and person. There is no certain lesion for disorientation that it can be caused by multiple cortical lesions. But it is still inconclusive that the impairment was due to the cause that patients did not pay attention to the place or unable to remember the name of the hospital and current date, as the attention and memory segment were both normal. The patients might not be aware of the current date or place due to their disability to move around independently in the environment. Apart from that, the result was slightly inconclusive because the median scores were equal, but the significant difference was from the different IQR of both groups.

Apart from the hand weakness, there were 4 ALS patients (26.67%) who failed to perform the abstract thinking part, but it was not statistically significant. It may imply that there were some degree of executive dysfunction in ALS group, but it did not have significant difference because TMSE only have two tests for frontal lobe function. We may need more detailed neuropsychological test for Frontal lobe cognitive function.

We also found that ALS disease severity had no correlation with cognitive impairment, including ALS functional rating scale, Japanese ALS severity scale, and MRC sum score. This findings suggests that more severe motor disability may not associated with more severe cognitive function.

TMSE requires shorter administration time (10-15 minutes), so it is less burden for ALS patient to complete the test. However, TMSE is suitable for mild disability patients. ALS patients with severe disability are not capable of completing some specific tasks such as drawing due to physical disability. The suitable test could be adapted such as answering by writing or typing in case with severe dysarthria, and by blinking or pointing in case with severe hand weakness. In ECAS test, they use dot counting and cube counting by verbal or writing for visuospatial domain, so ALS patients are more capable to perform these tests than TMSE. Moreover, the verbal fluency test in ECAS uses the modifications to control for the speed of response by calculating a verbal fluency index, so it can allow patients with upper limb weakness to be assessed meaningfully. [4] In which TMSE test is still lacking of these modifications that allow patients to answer by either verbal or written language.

Limitations of the study

1. This study has small sample size due to ALS disease in Thailand is still very rare and underrecognized, and Covid-19 pandemic within the country limited the inclusion of the patients. Most patients also missed the appointment because of lockdown situation. Further study in larger population in multiple hospital centers could be useful to clarify a clearer trend of cognitive impairment in ALS patients in Thailand.

2. TMSE has the limit for assessment in patient with hand weakness and may not be the good neuropsychological test to evaluate ALS patients. TMSE also has limited executive function assessment. There are numbers of neuropsychological tests such as Edinburgh Cognitive and Behavioural ALS Screen (ECAS), ALS Cognitive Behavioral Screen (ALS-CBS), etc. But to our knowledge, there is still no Thai translated version of these tests.

Conclusion

The results of this study have shown that one-third of the participated ALS patients have cognitive impairment which mainly shows the significant deficit in orientation. This may lead into more understanding regarding cognitive problem in ALS patients which can be occurred from the disease itself if no other cause is found. Nevertheless, this TMSE examination may not be suitable for cognitive screening of ALS patients due to its requirement of good hand function in some parts of the tests. Thus, this study may support that there should be a new Thai-translated cognitive test that properly assess the ALS patients.

Disclosure

This study has been declared that there is no conflict of interest in place.

Acknowledgement

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References

1. Al-Chalabi A, Hardiman O, Kiernan MC, Chiò A, Rix-Brooks B, van den Berg LH. Amyotrophic lateral sclerosis: moving towards a new classification system. Lancet Neurol 2016;15:1182-94. doi: 10.1016/S1474-4422(16)30199-5. PMID: 27647646.
2. Xu L, Liu T, Liu L, Yao X, Chen L, Fan D, Zhan S, Wang S. Global variation in prevalence and incidence of amyotrophic lateral sclerosis: a systematic review and meta-analysis. J Neurol 2020;267:944-53. doi: 10.1007/s00415-019-09652-y. Epub 2019 Dec 3. PMID: 31797084.
3. Mitsumoto H, Chad D, Pioro E. Amyotrophic lateral sclerosis, Reinhardt, R., F.A. Davis Company, Philadelphia, PA, 1998, pp 19, 21, 22, 26.
4. Phukan J, Pender NP, Hardiman O. Cognitive impairment in amyotrophic lateral sclerosis. Lancet Neurol 2007;6:994-1003. doi: 10.1016/S1474-4422(07)70265-X. PMID: 17945153.
5. Neumann M, Sampathu DM, Kwong LK, Truax AC, Micsenyi MC, Chou TT, et al. Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Science 2006;314:130-3.
6. Renton AE, Majounie E, Waite A, Simón-Sánchez J, Rollinson S, Gibbs JR, et al. A hexanucleotide repeat expansion in C9orf72 is the cause of chromosome 9p21 linked ALS-FTD. Neuron 2011;72:257-68.
7. Byrne S, Elamin M, Bede P, Shatunov A, Walsh C, Corr B, et al. Cognitive and clinical characteristics of patients with amyotrophic lateral sclerosis carrying a C9orf72 repeat expansion: a population-based cohort study. Lancet Neurol 2012;11:232-40. doi: 10.1016/S1474-4422(12)70014-5. Epub 2012 Feb 3. Erratum in: Lancet Neurol. 2012 May;11(5):388. PMID: 22305801; PMCID: PMC3315021.
8. Abrahams S, Goldstein LH, Kew JJ, et al. Frontal lobe dysfunction in amyotrophic lateral sclerosis. A PET study. Brain 1996;119:2105-20.
9. Brooks BR, Miller RG, Swash M, Munsat TL; World Federation of Neurology Research Group on Motor Neuron Diseases. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord 2000;1:293-9. doi: 10.1080/146608200300079536. PMID: 11464847.
10. Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, Nakanishi A. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). J Neurol Sci 1999;31;169:13-21. doi: 10.1016/s0022-510x(99)00210-5. PMID: 10540002.
11. Clinical Review Report: Edaravone (Radicava): (Mitsubishi Tanabe Pharma Corporation): Indication: For the treatment of amyotrophic lateral sclerosis [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2019 Apr. Appendix 4, Validity of Outcome Measures.
12. Turan Z, Topaloglu M, Ozyemisci Taskiran O. Medical Research Council-sumscore: a tool for evaluating muscle weakness in patients with post-intensive care syndrome. Crit Care 2020;24:562.
13. Connolly B, Salisbury L, O'Neill B, Geneen L, Douiri A, Grocott MP, Hart N, Walsh TS, Blackwood B; ERACIP Group. Exercise rehabilitation following intensive care unit discharge for recovery from critical illness. Cochrane Database Syst Rev. 2015 Jun 22;2015(6):CD008632. doi: 10.1002/14651858.CD008632.pub2. PMID: 26098746; PMCID: PMC6517154.