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Temporal lobe epilepsy with or without hippocampal sclerosis: Different neuropsychological profiles and associated clinical factors

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Abstract

Objective: To elucidate the neurocognitive profiles in temporal lobe epilepsy with or without hippocampal sclerosis (TLE-HS vs TLE-noHS) and ascertain clinical factors associated with the different scores of neurocognitive tests. *Methods:* TLE patients who underwent neuropsychological tests (NPTs) in our center were recruited. The NPTs included the Wisconsin Card Sorting Test, Stroop Color-Word Test, Trail Making Test, the Wechsler Adult Intelligence Scale - fourth edition and the Wechsler Memory Scale - fourth edition. Student t-test or Mann–Whitney U test was used to assess the difference in scores between groups. Univariate and multivariate linear regression analyses were also used to assess clinical factors associated with statistically significant NPT scores. *Results:* Among 109 recruited patients, 81 were TLE-HS, and 28 were TLE-noHS. NPT score results showed that verbal comprehension index (VCI) and auditory memory index (AMI) were significantly lower in TLE-HS. A lower VCI score was associated with earlier onset, longer duration of epilepsy, presence of generalized tonic-clonic seizure, history of febrile seizure, and some antiseizure medication uses. HS was an independent factor associated with lower VCI, whereas, in addition to HS, some clinical factors, i.e., history of status epilepticus, lower highest years of education or psychiatric comorbidities, were also independently associated with lower AMI.
Conclusions: Our findings suggest that TLE-HS had unique clinical characteristics and different NPT scores from TLE-noHS. In clinical practice, we should be aware that NPT scores might be affected by some clinical factors, and only VCI is a promising test that can help differentiate these two conditions.

Keywords: Neuropsychological profiles, temporal lobe epilepsy, hippocampal sclerosis

INTRODUCTION

Epilepsy is estimated to affect up to 50 million people worldwide.[1] Temporal lobe epilepsy (TLE) is the most common type of adult epilepsy.[2,3] TLE with hippocampal sclerosis (HS) (TLE–HS) accounted for 60–70% of the TLE patients, whereas the remaining 30–40% were TLE with other pathology or no lesion identified (TLE-noHS). Hippocampus plays a crucial role in memory, and hippocampal pathology, particularly HS, is a significant predictor of memory dysfunction.[4] Memory impairment was reported in both TLE-HS and TLE-noHS, although it tended to be more severe in TLE–HS.[4,5] Assessment of the differences in neurocognitive profiles between these two groups has rarely been studied. Few studies with a limited number of patients suggested that TLE–HS showed more verbal memory impairments.[6-8] Since epilepsy is a network disease, epileptic lesions/foci in one region may affect functions of the distant brain areas.[9-12] Detailed differences may broaden our understanding of both the neuropsychological functions of the hippocampus (HC) and the effects of HS pathology. In terms of functional disturbance in TLE, neuropsychological tests (NPTs) may be a valuable tool to help disclose an area of dysfunction, whether it is in the area of HC or other areas of the temporal lobe, particularly in patients with no lesion identified on the MRI.

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A neuropsychological assessment (NPA) provides an objective measure of the extent of the deficits and determines whether they are global or more specific to particular areas of the brain. NPT indicates an area of brain dysfunction, but it requires careful interpretation since it could be affected by many factors other than the brain pathology. The International League Against Epilepsy (ILAE) and the International Neuropsychological Society (INS) defined factors that could influence NPA performance. These include 1) fixed factors including nature of underlying pathology, laterality of pathology, location of pathology, age of onset of seizure, age of onset of treatment, impact on education, gender, and intellectual capacity; 2) course of disease including history of status epilepticus (SE), history of generalized seizure, history of head injuries, and history of comorbidities; and 3) remedial factors including medication, electroencephalographic (EEG) abnormalities, seizure control, mood, motivation, quality of sleep, and proximity of last seizure to assessment.[13]

This study aimed to systematically evaluate the difference in the NPT scores between TLE-HS and TLE-noHS patients. Second, we assessed clinical factors that might be associated with these differences. After adjustment of the effects of the significant associated clinical factors, we also assessed which NPT score could be an independent predictor to be used to help differentiate these two conditions.

METHODS

Participants

This retrospective study was performed in the Chulalongkorn Comprehensive Epilepsy Center of Excellence (CCEC), King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand. The study was reviewed and approved by the Research Ethics Review Committee, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand. Informed consent was waived due to the retrospective nature of the study, and anonymous clinical data were used for analysis. All consecutive TLE patients who underwent NPTs between 2014 and 2021 in our center were recruited. All included patients were diagnosed according to the ILAE classification of epilepsy by certified epileptologists.[14] The diagnosis was mainly based on seizure semiology and interictal and ictal EEG findings suggestive of TLE. Epilepsy patients without TLE were excluded. TLE with definite MRI findings of HS was defined as TLE–HS, whereas the others without HS were defined as TLE-noHS. Lateralization was based on lateralized EEG discharges and MRI lesions.

All participants underwent a battery of standardized NPTs. All tests and questionnaires were administered by one neuropsychologist who was blinded to clinical information. Reviewed clinical factors that influence NPA performance[13], according to the ILAE neuropsychology committee, were also collected by an independent neuropsychologist.

Neuropsychological test batteries

The Wisconsin Card Sorting Test-Computer Version 4 (WCST-Com Ver.4) was used to assess executive functions, including decision-making, planning, conceptual shifting, new rule learning, and the ability to change cognitive strategies depending on changes in environmental conditions.[15,16] The WCST consists of a total of 16 measures. In this study, we used 2 measures: average total score and perseverative errors (concentration score). An average score is 92-106. A low score showed impairment of executive function.

The Stroop Color-Word Test-Classic Version (Stroop) was used to measure attention with an interference task in which the subject has to name the colour of the ink in which a word is printed.[17]

The Trail Making Test (TMT) consists of two parts (TMT-A and TMT-B). In TMT-A, the respondent is asked to connect randomly arranged circles containing numbers from 1 to 25, following the number sequence and doing it as quickly as possible. The task in TMT-B is similar to TMT-A, but the respondent has to alternate between numbers and letters. Different cognitive abilities underlie the execution of the two parts of the TMT. Graphomotor speed and visual scanning play an important role in completing TMT-A and TMT-B, while executive function components such as divided attention, working memory, inhibition control, or set-switching abilities are more specifically involved in TMT-B performance.[18]

The Wechsler Adult Intelligence Scale - Fourth Edition (WAIS-IV) was used to estimate global intellectual functions. 10 subtests comprised 4 indices: Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI), Working

Memory Index (WMI), and Processing Speed Index (PSI). VCI is designed to measure verbal expression, verbal reasoning and verbal concept formation abilities, whereas PRI is designed to measure nonverbal reasoning, nonverbal concept formation, visual perception and organization abilities. Attention and verbal working memory abilities are assessed by WMI whereas ability of the rapidity of mentally process simple or routine information without making errors are assessed by PSI. The Full-Scale IQ (FSIQ) was calculated from the sum of the 10 scaled subtest scores. FSIQ score was the most frequently used index to quantify an individual's underlying general intelligence. General Ability Index (GAI) was calculated from the sum of the 6 scaled subtest scores that comprised the Verbal Comprehension Index (Similarities, Vocabulary, Information) and Perceptual Reasoning Index (Block Design, Matrix Reasoning, Visual Puzzles), excluding 4 scaled subtest scores that comprised the Working Memory Index (Digit Span, Arithmetic) and Processing Speed Index (Symbol Search, and Coding) that contributed to the FSIQ. The GAI can be compared to the FSIQ to assess the effects of compromised working memory and processing speed on the expression of optimal underlying cognitive ability.[19] FSIQ, GAI, and 4 indices average scores were in the 90-109 range. Subtest average scores were in the 8-12 range. A low score showed impairment of each indices or subtest abilities.

The Wechsler Memory Scale - Fourth Edition (WMS-IV); Adult Version (ages 16-69) was used to assess memory function. There are 5 indices and 6 subtests: Logical Memory (LM), Verbal Paired Association (VPA), Visual Reproduction (VR), Design (DE), Spatial Addition (SA), and Symbol Span (SSP). LM and VPA contributed to the Auditory Memory Index. VR and DE contributed to the Visual Memory Index. SSP and SA contributed to the Visual Working Memory Index. In each subtest, LM, VPA, VR, and DE were divided into 2 parts: Immediate Memory (LM I, VPA I, VR I, and DE I) and Delayed Memory Index (LM II, VPA II, VR II, and DE II). Delayed memory is remembering information after 20-30 minutes of immediate memory.[20] Five indices average scores were in the 90-109 range. Subtest average scores were in the 8-12 range. A low score showed impairment of each indices or subtest abilities.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD), whereas categorical variables were expressed in frequencies and percentages. The normal distribution of the data was tested using the Kolmogorov–Smirnov or Shapiro normality test. Score differences between TLE-HS and TLE-noHS were tested using either two independent samples t-test or the Mann–Whitney U test, depending on data distribution. Univariate and multivariate linear regression analyses were then used to ascertain clinical factors associated with statistically significant scores of different NPT. All analyses were performed using STATA software (version 16). The statistical significance level was set at $p < 0.05$.

RESULTS

Demographic and clinical characteristics (Table 1)

A total of 109 TLE patients were included, i.e., 81 TLE-HS and 28 TLE-noHS. Compared to TLE-noHS *(see Table 1)*, TLE-HS had a longer duration of epilepsy (19.28 ± 10.54 vs 14.19 ± 9.06, $p = 0.027$), a more prevalent history of febrile seizure (54.32% vs 14.81%, $p < 0.001$), more frequently using carbamazepine (CBZ) (66.67% vs 42.86%, $p = 0.026$), and less frequent being seizure-free (7.41% vs 32.14%, $p = 0.003$). There was a trend of earlier onset of epilepsy in TLE-HS (16.35 ± 10.88 vs 20.11 ± 9.64, $p = 0.051$).

Cognitive scores (Table 2)

Compared to TLE-noHS, TLE-HS had a lower score in VCI (84 ± 12 vs 90 ± 11, $p = 0.043$). In addition, index score discrepancy analysis showed significant differences in VCI-WMI (-4 ± 10 vs 1 ± 11, $p = 0.042$) and VCI-PSI (-1 ± 13 vs 5 ± 11, $p = 0.021$). Other WAIS-IV indices or subtests scores were not significantly different. Regarding WMS-IV scores, when compared with TLE-noHS, TLE-HS had lower scores in AMI (78 ± 19 vs 88 ± 17, $p = 0.024$), LM II (6 ± 3 vs 7 ± 3, $p = 0.048$), VPA I (7 ± 3 vs 8 ± 3, $p = 0.043$), and VPA II (6 ± 4 vs 8 ± 3, $p = 0.010$). There were no significant differences in immediate memory and delayed memory scores between two groups. However, both IMI and DMI scores tended to be lower in TLE-HS. No significant differences in executive scores were assessed by WCST-Com version 4, Stroop, and TMT. Global intellectual

Table 1: Baseline characteristics comparing between TLE-HS versus TLE-noHS

Characteristics	TLE-HS (N=81)	TLE-noHS (N=28)	p value
Demographic Data			
Male gender, n (%)	34 (41.98)	14 (50.00)	0.461
Age (years) (mean ± SD)	35.25 ± 10.71	34.43 ± 9.57	0.721
Right handedness, n (%)	69 (85.19)	25 (89.29)	0.895
Highest year of education (years) (mean ± SD)	14.57 ± 2.02	15.07 ± 1.92	0.170
Employed, n (%)	48 (66.67)	19 (82.61)	0.144
Clinical Factors			
A: Fixed Factor			
Lateralize, n (%)			0.166
Left	50 (61.73)	15 (53.57)	
Right	24 (26.63)	9 (32.14)	
Bilateral	7 (8.64)	2 (7.14)	
Unspecified	0	2 (7.14)	
Epilepsy onset (years) (mean ± SD)	16.35 ± 10.88	20.11 ± 9.64	0.051
Duration (years) (mean ± SD)	19.28 ± 10.54	14.19 ± 9.06	0.027*
B: Course of Disease			
Febrile seizure, n (%)	44 (54.32)	4 (14.81)	<0.001***
Status Epilepticus, n (%)	12 (14.81)	4 (14.81)	1.000
Presence of GTC, n (%)	49 (60.49)	13 (48.15)	0.261
Head injury, n (%)	20 (24.69)	4 (14.81)	0.285
CNS infection, n (%)	4 (4.94)	1 (3.70)	1.000
C: Remedial Factor			
ASMs, polytherapy, n (%)	79 (97.53)	25 (89.29)	0.106
ASMs, n (%)			
Phenobarbital	9 (11.11)	3 (10.71)	1.000
Phenytoin	25 (30.86)	11 (39.29)	0.414
Carbamazepine	54 (66.67)	12 (42.86)	0.026*
Valproic acid	24 (29.63)	5 (17.86)	0.224
Topiramate	17 (20.99)	7 (25)	0.659
Levetiracetam	52 (64.20)	17 (60.71)	0.742
Seizure freedom, n (%)	6 (7.41)	9 (32.14)	0.003**
Seizure frequency/month (mean ± SD)	5.43 ± 11.75	6.52 ± 12.08	0.170
Psychiatric comorbidities, n (%)	9 (11.11)	4 (14.29)	0.737
Psychiatric drugs, n (%)	8 (9.88)	2 (7.14)	1.000
Last seizure, ≤2 weeks, n (%)	15 (18.52)	6 (21.43)	0.736

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Abbreviations; TLE-HS = temporal lobe epilepsy with hippocampal sclerosis, TLE-noHS = temporal lobe epilepsy without hippocampal sclerosis, GTC = generalized tonic-clonic seizure, CNS = central nervous system, ASMs = antiseizure medications

functions assessed by WAIS-IV, i.e., FSIQ and GAI, showed no differences between the two groups.

Independent clinical factors associated with statistically significant cognitive scores (Table 3)

When TLE-HS vs TLE-noHS variables were input to the regression model, we wanted to identify any additional independent clinical factors associated with statistically significant cognitive scores. Even though VPA I was one of the significant scores, TLE-HS vs TLE-noHS was not associated with it upon univariate analysis. We, therefore, did not perform further multivariate analysis for this score.

Table 2: Cognitive scores of TLE-HS versus TLE-noHS

Cognitive scores	TLE-HS (N=81)	TLE-noHS (N=28)	*p value*
Wechsler Adult Intelligence Scale-Fourth Edition: WAIS-IV (mean ± SD)			
FSIQ	83 ± 11	85 ± 11	0.495
GAI	84 ± 11	87 ± 10	0.164
FSIQ-GAI	-1 ± 4	-3 ± 4	0.061
Index			
VCI	84 ± 12	90 ± 11	0.043*
PRI	87 ± 11	88 ± 11	0.693
WMI	88 ± 12	89 ± 12	0.888
PSI	85 ± 14	84 ± 13	0.662
Index discrepancy			
VCI-PRI	-3 ± 10	1 ± 12	0.052
VCI-WMI	-4 ± 10	1 ± 11	0.042*
VCI-PSI	-1 ± 13	5 ± 11	0.021*
PRI-WMI	-1 ± 10	0 ± 9	0.762
PRI-PSI	2 ± 12	4 ± 11	0.372
WMI-PSI	3 ± 13	5 ± 8	0.539
Subtest			
SI	7 ± 2	8 ± 2	0.063
VC	9 ± 3	10 ± 2	0.197
IN	6 ± 2	7 ± 3	0.116
BD	8 ± 2	8 ± 2	0.211
MR	8 ± 3	8 ± 3	0.488
VP	8 ± 2	8 ± 2	0.667
DS	8 ± 3	8 ± 3	0.695
AR	8 ± 2	8 ± 2	0.775
SS	8 ± 3	7 ± 3	0.296
CD	7 ± 3	7 ± 3	0.803
Wechsler Memory Scale-Fourth Edition: WMS-IV (mean ± SD)			
Index			
AMI	78 ± 19	88 ± 17	0.024*
VMI	89 ± 14	90 ± 11	0.693
VWMI	86 ± 12	87 ± 14	0.713
IMI	82 ± 16	88 ± 11	0.122
DMI	81 ± 17	87 ± 15	0.101
Index discrepancy			
AMI-VMI	-11 ± 16	-2 ± 16	0.017*
AMI-VWMI	-8 ± 16	0 ± 21	0.035*
VMI-VWMI	3 ± 10	3 ± 15	0.956
VWMI-IMI	4 ± 12	0 ± 16	0.157
VWMI-DMI	4 ± 14	0 ± 19	0.171
IMI-DMI	1 ± 8	1 ± 7	0.705
Subtest			
LM I	7 ± 4	8 ± 3	0.107
LM II	6 ± 3	7 ± 3	0.048*
VPA I	7 ± 3	8 ± 3	0.043*
VPA II	6 ± 4	8 ± 3	0.010*
VR I	8 ± 3	9 ± 3	0.489
VR II	9 ± 3	9 ± 3	0.606
DE I	7 ± 3	7 ± 2	0.957
DE II	8 ± 2	8 ± 2	0.789
SSP	7 ± 2	7 ± 2	0.889
SA	8 ± 3	8 ± 3	0.887
Trail Making Test (mean ± SD) (n)			
Trail A	39 ± 21 (29)	33 ± 10 (11)	0.370
Trail b	124 ± 59 (29)	116 ± 67 (11)	0.750
Stroop Test (mean ± SD) (n)			
Word	81 ± 13 (30)	84 ± 14 (11)	0.523
Color	62 ± 13 (30)	64 ± 9 (11)	0.618
Word color	31 ± 8 (30)	35 ± 9 (11)	0.153
Wisconsin Card Sorting Test: WCST (mean ± SD) (n)			
WCST sum score	93 ± 16 (35)	88 ± 15 (11)	0.429
WCST concentration	96 ± 19 (35)	91 ± 18 (11)	0.226

* $p < 0.05$; (n) = number of patients being tested

Abbreviations; TLE-HS = temporal lobe epilepsy with hippocampal sclerosis, TLE-noHS = temporal lobe epilepsy without hippocampal sclerosis, WAIS-IV = Wechsler adult intelligence scale-fourth edition, FSIQ = full scale IQ, GAI = general ability index, VCI = verbal comprehension index, PRI = perceptual reasoning index, WMI = working memory index, PSI = processing speed index, SI = similarities subtest, VC = vocabulary subtest, IN = information subtest, BD = block design subtest, MR = matric reasoning subtest, VP = visual puzzle subtest, DS = digit span subtest, AR = arithmetic subtest, SS = symbol search subtest, CD = coding subtest, WMS-IV = Wechsler memory scale-fourth edition, AMI = auditory memory index, VMI = visual memory index, VWMI = visual working memory index, IMI = immediate memory index, DMI = delayed memory index, LM = logical memory subtest, VPA = verbal paired association subtest, VR = visual reproduction subtest, DE = design subtest, SSP = symbol span subtest, SA = spatial addition subtest, I = immediate, II = delay, WCST = Wisconsin card sorting Test

Table 3: Clinical factors associated with statistically significant cognitive scores

Significantly different NPT scores	Univariate analysis *p value*	Multivariate analysis *p value*	R-squared
1. WAIS-IV			
VCI			
TLE-HS vs. TLE-noHS	0.042	0.042	3.83%
Highest year of education	< 0.001		
Epilepsy onset	0.006		
Presence of GTC	0.017		
Carbamazepine	0.019		
Unemployed	0.025		
Duration of epilepsy	0.027		
Febrile seizure	0.044		
VCI-WMI			
TLE-HS vs. TLE-noHS	0.042	0.045	15.08%
Topiramate	< 0.001	< 0.001	
Febrile seizure	0.012		
VCI-PSI			
TLE-HS vs. TLE-noHS	0.021	0.024	21.71%
Febrile seizure	< 0.001		
Topiramate	0.006	0.004	
Gender	0.010	0.021	
Phenobarbital	0.014	0.010	
2. WMS-IV			
AMI			
TLE-HS vs. TLE-noHS	0.024	0.049	19.70%
Highest year of education	< 0.001	< 0.001	
Status epilepticus	0.018		
Presence of GTC	0.029		
Unemployed	0.048		
AMI-VMI			
TLE-HS vs. TLE-noHS	0.017	0.009	10.25%
Presence of GTC	0.017		
Gender	0.033	0.017	
AMI-VWMI			
TLE-HS vs. TLE-noHS	0.035	0.016	11.74%
Gender	0.007	0.003	
LM II			
TLE-HS vs. TLE-noHS	0.048	0.041	8.27%
Highest year of education	< 0.001		
Status epilepticus	0.028	0.026	
Presence of GTC	0.032		
VPA II			
TLE-HS vs. TLE-noHS	0.010	0.017	25.66%
Highest year of education	< 0.001	< 0.001	
Status epilepticus	0.023	0.029	
Psychiatric comorbidities	0.025	0.014	
Last seizure	0.035		

Abbreviations; TLE-HS = temporal lobe epilepsy with hippocampal sclerosis, TLE-noHS = temporal lobe epilepsy without hippocampal sclerosis, GTC = generalized tonic-clonic, WAIS-IV = Wechsler adult intelligence scale-fourth edition, VCI = verbal comprehension index, WMI = working memory index, PSI = processing speed index, WMS-IV = Wechsler memory scale-fourth edition, AMI = auditory memory index, VMI = visual memory index, VWMI = visual working memory index, LM = logical memory subtest, VPA = verbal paired association subtest, I = immediate, II = delay

Verbal Comprehension Index (VCI)

Upon univariate analysis, VCI score was significantly associated with TLE-HS, highest year of education, early onset of epilepsy, presence of GTC, use of CBZ, being unemployed, long duration of epilepsy, and history of febrile seizure. Multivariate analysis found that only TLE-HS pathology was an independent factor associated with low VCI scores ($p = 0.042$).

VCI-WMI and VCI-PSI

Multivariate analysis showed that TLE-HS pathology ($p = 0.045$) and TPM use ($p < 0.001$) were independently associated with low VCI-WMI scores. In contrast, in addition to TLE-HS pathology ($p = 0.024$) and TPM use ($p = 0.004$), male ($p = 0.021$) and PB ($p = 0.010$) were also independent factors associated with low VCI-PSI scores.

Auditory Memory Index (AMI)

Multivariate analysis found that TLE-HS pathology ($p = 0.049$) and lower highest years of education ($p < 0.001$) were independently associated with low AMI scores.

LM II and VPA II

Multivariate analysis showed that a low LM II score was independently associated with TLE-HS pathology ($p = 0.041$) and history of SE ($p = 0.026$). In contrast, a low VPA II score was associated with TLE-HS pathology ($p = 0.017$), lower highest year of education ($p < 0.001$), history of SE ($p = 0.029$), and history of psychiatric comorbidities ($p = 0.014$).

AMI-VMI and AMI-VWMI

Multivariate analysis showed that low AMI-VMI and AMI-VWMI scores were associated with TLE-HS pathology ($p = 0.009$ and $p = 0.016$) and male ($p = 0.017$ and $p = 0.003$).

Lateralization of TLE-HS and TLE-noHS on cognitive scores (Table 4)

Compared to lateralization of TLE-HS and TLE-noHS, patients with left TLE-HS were found to have lower VCI, AMI, VPA I and VPA II, but only VPA I and VPA II were statistically significant ($p = 0.017$ and $p = 0.025$).

DISCUSSION

This study demonstrated different neuropsychological profiles between TLE-HS and TLE-noHS, with consistently lower scores in TLE-HS. This reflects that the HS pathology or lesion location on the hippocampus or both had greater negative effects on cognitive functions. Detailed NPA revealed significantly different scores, including VCI, VCI-WMI, VCI-PSI, AMI, LM II, VPA I and II. Executive functions were not different between groups. In clinical practice, in some circumstances, when there is uncertainty about the patient having HS due to unclear MRI findings, neuropsychological tests may be another tool to help provide clues for HS. Our findings support that NPT findings should be cautiously interpreted, as several clinical factors could also affect the NPT scores. Our study demonstrated that apart from TLE-HS pathology, some clinical factors, i.e., some ASM use, level of education, history of SE or psychiatric comorbidities, might also affect the scores. Based on our findings, only a lower VCI score was associated with TLE-HS, even after adjustment for significant clinical factors. This score may be reliably used in practice to help differentiate TLE-HS from TLE-noHS.

Neuropsychological profiles in TLE-HS and TLE-noHS

Our results indicated that compared with TLE-noHS, patients with TLE-HS were more cognitively impaired. Likewise, Thanh et al. also found that TLE patients with HS had poorer cognitive performance than TLE patients without HS.[21]

Significant of lateralizaton of TLE-HS and TLE-noHS on NPT

Our findings showed the lowest VCI and AMI in left TLE-HS, but the lowest VPA I and VPA II were statistically significant when compared to others *(see Table 4)*. One study reported that TLE-HS, particularly left HS, was associated with worse performance due to impairment of functional connectivity within the default mode network (DMN).[22] Specifically, some studies described worse VCI and AMI scores in TLE-HS, and reported poor language functions and verbal memory in association with left hippocampal abnormalities.[21,23-25] Similarly, Karl-Heinz et al. described that the left hippocampus was more integrated into language networks, particularly the inferior-frontal cortex, emphasizing the

Table 4: Cognitive scores of lateralization comparing between TLE-HS versus TLE-noHS

Cognitive scores	TLE-HS (N=81)		TLE-noHS (N=28)		*p value*
	Left (N=50)	Right (N=24)	Left (N=16)	Right (N=9)	
Wechsler Adult Intelligence Scale-Fourth Edition: WAIS-IV (mean ± SD)					
FSIQ	83 ± 13	85 ± 8	85 ± 13	85 ± 6	0.901
GAI	84 ± 12	87 ± 7	86 ± 11	88 ± 6	0.433
Index					
VCI	84 ± 13	88 ± 7	89 ± 12	90 ± 9	0.226
PRI	87 ± 11	90 ± 8	87 ± 10	87 ± 8	0.659
WMI	88 ± 12	89 ± 12	89 ± 13	90 ± 9	0.985
PSI	87 ± 16	85 ± 11	85 ± 14	83 ± 10	0.889
Subtest					
SI	7 ± 2	7 ± 2	8 ± 2	8 ± 2	0.301
VC	9 ± 3	10 ± 2	9 ± 3	10 ± 1	0.440
IN	6 ± 3	6 ± 2	7 ± 3	7 ± 3	0.388
BD	8 ± 2	8 ± 1	7 ± 2	8 ± 2	0.385
MR	8 ± 3	9 ± 2	9 ± 3	7 ± 2	0.529
VP	8 ± 3	8 ± 2	7 ± 2	8 ± 1	0.776
DS	8 ± 3	8 ± 3	8 ± 3	9 ± 2	0.791
AR	8 ± 2	8 ± 2	8 ± 2	7 ± 2	0.940
SS	8 ± 3	8 ± 2	7 ± 3	7 ± 2	0.694
CD	7 ± 3	7 ± 2	7 ± 3	6 ± 2	0.902
Wechsler Memory Scale-Fourth Edition: WMS-IV (mean ± SD)					
Index					
AMI	78 ± 19	84 ± 18	86 ± 17	94 ± 15	0.075
VMI	92 ± 13	87 ± 12	90 ± 12	92 ± 7	0.340
VWMI	88 ± 12	86 ± 13	90 ± 13	84 ± 11	0.626
IMI	84 ± 15	84 ± 16	86 ± 12	92 ± 9	0.425
DMI	84 ± 16	84 ± 16	87 ± 16	92 ± 14	0.462
Subtest					
LM I	7 ± 3	7 ± 4	8 ± 3	9 ± 3	0.523
LM II	6 ± 3	7 ± 3	7 ± 3	8 ± 3	0.266
VPA I	6 ± 3	8 ± 3	8 ± 3	10 ± 3	0.017*
VPA II	6 ± 4	7 ± 3	8 ± 3	9 ± 3	0.025*
VR I	9 ± 3	8 ± 3	9 ± 3	10 ± 2	0.350
VR II	10 ± 3	8 ± 3	9 ± 3	9 ± 2	0.497
DE I	8 ± 3	7 ± 2	8 ± 2	7 ± 2	0.195
DE II	9 ± 2	8 ± 2	8 ± 2	9 ± 2	0.412
SSP	7 ± 2	7 ± 2	8 ± 3	6 ± 1	0.378
SA	8 ± 3	8 ± 3	9 ± 3	8 ± 3	0.960

* $p < 0.05$

Abbreviations; TLE-HS = temporal lobe epilepsy with hippocampal sclerosis, TLE-noHS = temporal lobe epilepsy without hippocampal sclerosis, WAIS-IV = Wechsler adult intelligence scale-fourth edition, FSIQ = full scale IQ, GAI = general ability index, VCI = verbal comprehension index, PRI = perceptual reasoning index, WMI = working memory index, PSI = processing speed index, SI = similarities subtest, VC = vocabulary subtest, IN = information subtest, BD = block design subtest, MR = matric reasoning subtest, VP = visual puzzle subtest, DS = digit span subtest, AR = arithmetic subtest, SS = symbol search subtest, CD = coding subtest, WMS-IV = Wechsler memory scale-fourth edition, AMI = auditory memory index, VMI = visual memory index, VWMI = visual working memory index, IMI = immediate memory index, DMI = delayed memory index, LM = logical memory subtest, VPA = verbal paired association subtest, VR = visual reproduction subtest, DE = design subtest, SSP = symbol span subtest, SA = spatial addition subtest, I = immediate, II = delay

direct role of the left hippocampus in language processing during the verb-generation task, and failure of which may indirectly add to language impairment in left TLE-HS.[26] Besides, Lisa et al. studied the relation of the hippocampal formation to the language comprehension network in patients with unilateral mesial TLE. They performed an fMRI study based on a language comprehension paradigm in unilateral mesial TLE and healthy controls. These findings suggested that effective language comprehension with TLE depends on the involvement of the hippocampal formation, particularly the left hippocampal formation, which suggest left TLE-HS tends to be worse on language comprehension than right TLE-HS and TLE-noHS.[27] Whereas verbal memory deficits are highly specific for left TLE-HS. This was also supported by imaging findings of reduced connectivity of the left anterior hippocampus to the DMN hubs in left TLE and relatively reduced left hippocampal volume in patients with verbal memory deficits.[28,29] Sandra et al. found that lower LM II scores in left HS were related to neuronal losses in the CA1 hippocampal subfield.[30] Some studies suggested low VPA II scores in left TLE-HS.[31,32] As a result, patients with TLE-HS had impaired language and verbal memory more than those with TLE-noHS. Also, left TLE-HS was associated with the worst performance on language and verbal memory when compared to the right TLE-HS and TLE-noHS (left and right), respectively. According to our findings, there was a significant proportion of left lateralization in TLE-HS (61.73%) and TLE-noHS (57.14%). Low verbal scores, i.e., VCI, might be confounded by the lateralization factor rather than the HS pathology. However, upon multivariate analysis, by adding lateralization to the model after the interested factor (i.e., TLE-HS vs TLE-noHS), the interested factor remained significant, suggesting that TLE-HS vs TLE-noHS was an independent predictor for VCI and was not confounded by pathology lateralization. This can be concluded that HS pathology was more impacted on lower verbal scores than pathology lateralization.

Executive function

Cettina *et al*. and Yanping *et al*. found significant executive impairment in the TLE group. TLE was a neurological disorder affecting the integrity of networks supporting complex cognitive domains, not only memory function.[23,33] No statistical differences in executive functions between TLE-HS and TLE-noHS were observed in our study. Both groups performed WSCT and Stroop tests and showed an average score. In our study, very few TLE patients with extratemporal lesions, i.e. frontal lobe lesions, were involved, and not every patient participated in the executive function assessment. Chul-Ho et al supported our finding, where they described that executive function was mainly controlled by the prefrontal cortex of the frontal lobe.[34]

Clinical factors affecting the NPT scores

Several clinical factors could affect cognitive profiles. We found that the lower educated group had lower scores of VCI, AMI, LM II and VPA II. Lei et al. found that high educational levels were protective factors for better cognitive scores, including language and delayed verbal memory, in adult epileptic patients, describing that a high educational level had more intellectual reserves.[35] Moreover, patients with a high level of education are usually more informed of the disease and better self-disciplined, so they follow the treatment scheme more strictly, which enhances the treatment effect and reduces the risk of cognitive impairment consequently.[35] When comparing verbal versus nonverbal abilities, our findings showed females were associated with higher scores on verbal ability and verbal memory (VCI-PSI, AMI-VMI and AMI-VWMI) when compared to males in TLE-HS, as females had a higher level of functional integration and greater values of small-worldness during language processing than males.[36] Some studies of diffusion tensor imaging (DTI) showed females were more likely to have a symmetrical pattern of connections in perisylvian language pathways, a pattern of connections associated with better performance of remembering words using semantic association.[37-38] Similarly, Max *et al.* found that males tend to have poorer verbal memory outcomes compared to females.[39] Helge *et al*. found a greater vulnerability of verbal memory to left anterior temporal lobectomy (ATL) surgery in males than in females.[40] We found that the early age of onset of epilepsy, long duration of epilepsy, presence of GTC, history of febrile seizure, CBZ, TPM, and PB were associated with a low VCI score in TLE-HS. Sallie *et al*. found an association between the early onset of seizures and cognitive impairments.[41] Mei-chun *et al*. indicated that the duration of epilepsy was found to be significantly and negatively correlated with verbal functioning in TLE. Some studies reported the effects of ASMs on cognition.[42] Jerzy *et al*.

found that TPM had a negative impact on cognition and language performance, where TPM may affect the results of language fMRI lateralization and localization.[43] Robert *et al*. found that TPM was associated with worse language performance.[44] PB and PHT had more pronounced negative cognitive side effects than CBZ or valproic acid (VPA).[45-47] At the same time, we found a history of SE was associated with low AMI, LM II, and VPA II scores in TLE-HS. Power *et al*. studied memory in patients one year after SE. They revealed that patients with SE had poorer performance than controls on tests of memory.[48] Some studies found that history of episodes of SE, especially convulsive status epilepticus (CSE), is related to progressive hippocampal damage. Repeated SE leads to hippocampal volume loss and progresses to clinical TLE-HS.[49-50] Amy *et al*. studied the pathway following SE called "mammalian target of the rapamycin complex 1 (mTORC1)" that modulates learning and memory. Their findings indicated that mTORC1 hyperactivity contributed to early hippocampal-dependent memory deficits associated with SE.[51]

Neuropsychological clues for HS

As mentioned earlier, cognitive scores could be affected by several clinical factors. Reliable cognitive tests which are not or are minimally influenced by these factors are essentially required to help define focal cerebral dysfunction. Based on our findings, VCI is a promising test to help differentiate TLE-HS and TLE-noHS. This was supported by studies showing hippocampal dysfunction in TLE affecting language skills. Ulrike *et al*. reported a pattern of fewer words generated in fluency tasks in TLE-HS compared to healthy controls, suggesting the hippocampus plays a crucial role in verbal fluency performance.[52] Karl-Heinz *et al*. indicated that hippocampal dysfunction resulting in language impairment more in TLE-HS than TLE-noHS by using language functional magnetic resonance (fMRI). [26]

Limitations

Some limitations exist in our study. First, the patients in both groups, i.e., TLE-HS and TLE-noHS, were inhomogeneous, i.e., some TLE-HS patients also had an associated extratemporal lobe lesion and cerebral dysfunctions, and these patients were not thus uniquely confined to the hippocampus *(Supplemental Tables 1 and 2*). It was a retrospective study in a single center with a small sample size. That might affect the statistical power, limited exploration of heterogeneity, and limited generalizability.

In conclusion, TLE-HS and TLE-noHS had different neurocognitive score profiles. TLE-HS had a lower score in VCI, AMI, LM II, VPA I and VPA II when compared with TLE-noHS. Several clinical factors, such as early-onset and long-duration of epilepsy, presence of GTC, history of febrile seizure, some ASMs use (CBZ, TPM and PB), history of SE and lower highest years of education, impacted these scores, corresponding to the factors reported by the ILAE Neuropsychology Task Force. Among the lower scores of NPTs, only VCI was not affected by any clinical factors. As a result, it is a promising test to help differentiate TLE-HS from TLE-noHS.

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DISCLOSURE

Ethics: Approval from the Research Ethics Review Committee, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, IRB No. 300/64

Data availability: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supplemental Table 1
MRI findings in TLE-HS

	MRI characteristics				
	HS		Other Lesion		
TLE-HS	Lesion	Lateralization	Lateralization	Localization	Types
Case 1	Pure HS	Left HS			
Case 2	Pure HS	Right HS			
Case 3	Pure HS	Left HS			
Case 4	HS Plus	Right HS	Left	Mesial temporal lobe	Small arachnoid cyst
Case 5	Pure HS	Left HS			
Case 6	HS Plus	Left HS	Left	Mesial temporal lobe	Small size of left temporal lobe
Case 7	Pure HS	Right HS			
Case 8	Pure HS	Left HS			
Case 9	Pure HS	Left HS			
Case 10	Pure HS	Left HS			
Case 11	Pure HS	Left HS			
Case 12	HS Plus	Left HS	Left	Inferior temporal lobe	Post-traumatic encephalomalacia
Case 13	Pure HS	Left HS			
Case 14	HS Plus	Left HS	Bilateral frontal lobe and temporo-parieto-occipital areas		Increase signal intensity at bilateral frontal lobe and atrophy at temporo-parieto-occipital areas
Case 15	Pure HS	Left HS			
Case 16	Pure HS	Right HS			
Case 17	Pure HS	Left HS			
Case 18	Pure HS	Right HS			
Case 19	Pure HS	Right HS			
Case 20	Pure HS	Left HS			
Case 21	Pure HS	Left HS			
Case 22	Pure HS	Right HS			
Case 23	HS Plus	Left HS	Left	Anteromesial temporal area involving amygdala	Dysembryoplastic neuroepithelial tumor (DNET)
Case 24	HS Plus	Left HS	Left	Superior temporal lobe	Focal cortical dysplasia
Case 25	Pure HS	Left HS			
Case 26	HS Plus	Right HS	Right	Mesial temporal area involving amygdala	Ganglioglioma
Case 27	HS Plus	Bilateral HS	Left	Anteromedial temporal area	Anteromesial temporal lobe atrophy
Case 28	Pure HS	Left HS			
Case 29	Pure HS	Left HS			
Case 30	HS Plus	Left HS	Left	Amygdala	Multiloculated cystic lesion
Case 31	Pure HS	Left HS			
Case 32	HS Plus	Bilateral HS	Bilateral frontal subcortical and right superior temporal subcortical region		Several tiny foci of hypersignal intensity in bilateral frontal subcortical white matters and a small non-enhancing lesion with dark signal intensity in right superior temporal subcortical region

Case 33	Pure HS	Left HS			
Case 34	Pure HS	Left HS			
Case 35	Pure HS	Bilateral HS			
Case 36	Pure HS	Left HS			
Case 37	Pure HS	Right HS			
Case 38	Pure HS	Right HS			
Case 39	Pure HS	Left HS			
Case 40	Pure HS	Left HS			
Case 41	Pure HS	Right HS			
Case 42	Pure HS	Left HS			
Case 43	Pure HS	Right HS			
Case 44	Pure HS	Left HS			
Case 45	HS Plus	Left HS	Left	Anteromesial temporal area	Infarction and white matter change
Case 46	Pure HS	Right HS			
Case 47	Pure HS	Left HS			
Case 48	Pure HS	Right HS			
Case 49	Pure HS	Left HS			
Case 50	Pure HS	Left HS			
Case 51	Pure HS	Bilateral HS			
Case 52	HS Plus	Left HS	Left amygdala, bilateral frontal and right parietal lobes		Several tiny non-specific white matter changes
Case 53	Pure HS	Right HS			
Case 54	Pure HS	Left HS			
Case 55	HS Plus	Left HS	Left	Anterior temporal lobe	Increase signal intensity in white matter
Case 56	Pure HS	Right HS			
Case 57	Pure HS	Right HS			
Case 58	Pure HS	Left HS			
Case 59	Pure HS	Left HS			
Case 60	Pure HS	Right HS			
Case 61	Pure HS	Right HS			
Case 62	HS Plus	Left HS	Left	Anterior temporal lobe	Increase signal intensity in white matter
Case 63	Pure HS	Left HS			
Case 64	Pure HS	Bilateral HS			
Case 65	Pure HS	Right HS			
Case 66	Pure HS	Left HS			
Case 67	Pure HS	Bilateral HS			
Case 68	Pure HS	Left HS			
Case 69	Pure HS	Right HS			
Case 70	Pure HS	Bilateral HS			
Case 71	HS Plus	Left HS	Left	Amygdala	Low-grade tumor
Case 72	Pure HS	Right HS			
Case 73	Pure HS	Left HS			

Case 74	Pure HS	Left HS			
Case 75	Pure HS	Left HS			
Case 76	Pure HS	Left HS			
Case 77	Pure HS	Left HS			
Case 78	HS Plus	Right HS	Right	Inferior temporal area	Small old hemorrhagic lesion
Case 79	Pure HS	Left HS			
Case 80	HS Plus	Left HS	Left	Amygdala	Low-grade tumor
Case 81	HS Plus	Right HS	Right temporal lobe and left medial parieto-occipital areas		Small cystic lesion at right temporal lobe and developmental venous anomaly (DVA) at left medial parieto-occipital areas

Supplemental Table 2
MRI findings in TLE-noHS

	MRI characteristics			
TLE-noHS	**Lesion**	**Lateralization**	**Localization**	**Types**
Case 1	Lesional	Left	Temporal lobe involving amygdala	Low-grade tumor
Case 2	Nonlesional			
Case 3	Lesional	Right	Temporal and parietal lobes	Cavernoma
Case 4	Lesional	Right	Temporal lobe involving amygdala	Low-grade tumor
Case 5	Lesional	Right	Inferior temporal lobe	Low-grade tumor
Case 6	Nonlesional			
Case 7	Lesional	Right	Mesial temporal lobe involving amygdala	Cavernoma
Case 8	Lesional	Left	Posterior temporal and frontal lobes	Focal cortical dysplasia (FCD)
Case 9	Nonlesional			
Case 10	Nonlesional			
Case 11	Lesional	Left	Temporal lobe	Dysembryoplastic neuroepithelial tumor (DNET)
Case 12	Lesional	Right	Temporo-occipital areas	Polymicrogyria
Case 13	Lesional	Left	Temporal lobe involving amygdala	Dysembryoplastic neuroepithelial tumor (DNET)
Case 14	Lesional	Right	Inferior temporal lobe	Calcification and gliosis
Case 15	Lesional	Left	Temporal and frontal lobes	Suspected FCD at left temporal lobe and hypersignal intensity at bilateral frontal white matters
Case 16	Nonlesional			
Case 17	Lesional	Left temporal lobe, Bilateral frontal lobe	Temporal and frontal lobes	Small size of left temporal lobe and multiple non-specific white matter changes in bilateral frontal lobe
Case 18	Lesional	Right	Anteromesial temporal areas	Dysembryoplastic neuroepithelial tumor (DNET)
Case 19	Lesional	Left	Inferior temporal lobe	Solid-cystic mass with internal calcification with faint enchantment involving grey and white matter of inferior temporal lobe
Case 20	Lesional	Left	Temporal lobe	Small temporal lobe
Case 21	Lesional	Right	Anterior temporal lobe	Small size of anterior temporal lobe
Case 22	Nonlesional			
Case 23	Lesional	Bilateral temporal lobe, Left frontal lobe	Mesial temporal and frontal lobes	Increase signal intensity (positive Anti-Yo autoantibody)
Case 24	Lesional	Left	Mesial temporal lobe	Dysembryoplastic neuroepithelial tumor (DNET)
Case 25	Lesional	Left	Temporal lobe	Encephalocele
Case 26	Lesional	Left	Inferior temporal lobe	Gliosis
Case 27	Nonlesional			
Case 28	Lesional	Left temporal lobe, Right frontal lobe	Temporal and frontal lobes	Dysembryoplastic neuroepithelial tumor (DNET)