Long Term Memory Outcome in Transient Global Amnesia Patients with Abnormal MRI

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Introduction

Transient global amnesia (TGA) is a syndrome which patients encounter an episode of memory impairment. Typical presentation is sudden onset of anterograde and retrograde amnesia with preserve consciousness and personal identity.[1,2] Although both types of amnesia usually resolve within 24 hours after onset, any events occurred during the attack would not be recalled permanently. This symptom demonstrates disease manifestation that involves not only memory retrieval but also memory registration process. MRI brain which done within 48-72 hours after onset with high b-value (b = 2000-3000 s/mm^3) may detect the abnormality of 1-5mm of punctate or dot-like foci of restricted diffusion in DWI at CA1 region of hippocampus.[3,4]

Although TGA is a benign and spontaneous recoverable condition, general concerns of patients and their family are long-term memory outcomes. The result of long-term sequelae effect of TGA on memory is inconclusive. Early studies, mostly before 2005, showed that there was a persistent memory deficit in TGA patients especially about verbal memory, and visual memory.[5-12] Moreover, in a recent study of TGA in Taiwan by Sung-Wung Hsieh et al[13], they concluded that TGA increases the long-term risk of dementia. However, meta-analysis of 25 studies in 2009[14] show no long-term performance differences detected in TGA patients and healthy control. Inconclusive outcome could be from the uncertain diagnosis as there were some syndromes such as transient epileptic amnesia and transient ischemic stroke that could mimic the clinical syndrome of TGA.[1,2]

Therefore, this study aims to explore long-term memory outcome of the TGA patients with abnormal MRI in hippocampal area compared to healthy control of the same age. We are also interested in

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the influence of characteristics of lesions on MRI on memory outcome in TGA patients.

Materials and Methods

Subjects

Electronic medical records of patients who were diagnosed with TGA (Hodge and Warlow criteria[15]) between 2006 to 2020 at King Chulalongkorn Memorial Hospital (KCMH) were reviewed. Only the patients whose MRI brain showed restricted diffusion in the hippocampal area were included in this study. Controls are healthy people with age and sex match. Any subjects who previously had neurological or psychiatric impairment such as stroke, epilepsy or dementia were excluded from this study.

Neuropsychological test

The Thai version of Montreal cognitive assessment (MOCA) and comprehensive neuropsychological battery tests were done on both TGA and control group. In the TGA group, the tests were performed at least 6 months after onset of episode.

Aim of the comprehensive neuropsychological battery test was to assess 2 dimensions of memory quality and quantity. The first aspect was the memory domain which could be divided into verbal and visual memory. The second aspect was the memory type which could be divided into immediate memory and delayed memory. Immediate verbal memory was assessed by digit span (DS) test according to Wechsler Adult Intelligence Scale IV Edition (WAIS-IV). Symbol span (SSP) test, as a part of Wechsler Memory Scale IV Edition (WSM-IV), represented immediate visual memory. To assess delayed verbal and visual memory, we used logical memory (LM), verbal paired association (VPA) and visual reproduction (VR) test from WSM-IV respectively. Recognition tests of logical memory (LM), verbal paired association (VPA) and visual reproduction (VR) were done at the end of each test. Each subtest result was calculated to scale score compared to normal population in same age and turned into composite memory scale score for each main assessed function. Details of each subtest are summarized in Table 1.

Data Analysis

Quantitative data between groups such as age, composite memory scale score of neuropsychological tests, were compared by mean using Independent T-Test for normal distribution data and Mann-Whitney U test for skewed distribution data. Qualitative data such as gender and educational status were compared between group by Chi-square and Fisher's exact test. Comparison within groups was done by One-way ANOVA. Interaction between each factor such as side of lesion, memory domain and memory type were studied by Three-ways mixed ANOVA.

Table 1 Neuropsychological tests

Assessed Function	Test	Task
Immediate verbal memory	Digit span (DS)	- repeat number of digits forward, backward and sequencing the given digits in order
Immediate visual memory	Symbol span (SSP)	- repeat the given set of 2-5 geometric pictures in order
Delayed verbal memory	Logical memory (LM)	- free recall of 2 short stories about 60-100 words 20 minutes after the first story was told
	Verbal paired association (VPA)	- pairing groups of given coherent and incoherent words 20 minutes after first set of words
Delayed visual memory	Visual reproduction (VR)	- draw given geometric pictures 20 minutes after a glance
Recognition	Recognition	- answer yes-no question at the end of task (LM, VPA, VR)

Results

From 2006 - 2020, there were 55 TGA patients whose MRI showed abnormal restricted diffusion in hippocampus and were admitted at KCMH. There are 26 patients whose contact records are confirmed and participated in this study. 26 healthy volunteers were included in a control group. There was no significant difference between baseline characteristics of 2 groups including gender (female 69.2% in TGA vs 61.5% in control), age (63.1 ± 5.7 in TGA vs 61.8 ± 4.6 in control). Education status tends to be higher in TGA group but not statistically significant. MOCA score in TGA group was not significant different from control group (26.12 ± 2.86 in TGA vs 26.92 ± 2.19 in control).

In TGA group, 13 patients (50%) had lesions in left hippocampus while 7 patients (26.9%) had lesions in right hippocampus. There were 6 patients who had lesions on both sides (23.1%). 19 of 26 patients (73.1%) had a single lesion while the rest had multiple lesions (26.9%). The mean size of lesions was 3.19 ± 1.13 mm and the median follow up time after TGA onset was 44 months (IQR 23 - 68). Baseline characteristics of subjects were summarized in Table 2.

Table 2 Baseline characteristic of subjects

	TGA (%)	Controls (%)	p-Value
Subjects (N)	26	26	
Gender			0.56 $^{\chi}$
- Male	8 (30.8)	10 (38.5)	
- Female	18 (69.2)	16 (61.5)	
Age	62.8 ± 5.7	61.4 ± 4.8	0.338 $^{\beta}$
Education			0.110 $^{\gamma}$
- Below Gr 6	2 (7.7)	1 (3.8)	
- Gr 7 - Gr 12	6 (23.0)	1 (3.8)	
- Bachelor	11 (42.3)	14 (53.8)	
- Master and doctor	7 (26.9)	10 (38.5)	
MRI Brain characteristic			
Side of lesions on MRI			
- Left	13 (50)		
- Right	7 (26.9)		
- Both	6 (23.1)		
Amount of lesions			
- single	19 (73.1)		
- multiple	7 (26.9)		
Size of lesions on MRI (cm)	3.19 ± 1.13		
Follow-up periods (months)	45 (IQR 23, 68)		
MOCA	26.12 ± 2.86	26.92 ± 2.19	0.258 $^{\beta}$

$^{\chi}$ Pearson Chi-square

$^{\beta}$ Independent T-test

$^{\gamma}$ Fisher's Exact

MOCA: Montreal cognitive assessment

MRI: Magnetic resonance imaging

In comprehensive neuropsychological battery test, control group had better performance than TGA in immediate visual memory test (8.88 ± 2.16 vs 10.12 ± 1.7, t = 2.281, p = 0.027). While in other domains, control group also tended to perform better but not statistically significant. In recognition tests, visual reproduction recognition score was significantly lower in TGA when compared to the controls (p = 0.037) (Table 3).

Table 3 Mean scores and standard deviation in memory task compared between TGA and controls done by Independent T-test

	TGA vs Control			
Memory domain	TGA mean+/-SD	Control mean+/-SD	t	p
Immediate verbal	10.31 ± 2.65	11.15 ± 2.36	1.216	0.23
Immediate visual	8.88 ± 2.16	10.12 ± 1.70	2.281	0.027*
Delayed verbal	10.79 ± 2.82	11.88 ± 2.22	1.542	0.13
Delayed visual	11.15 ± 2.44	11.83 ± 1.92	1.103	0.28
Recognition test				
LM rec	4.54 ± 1.75	4.46 ± 1.60	-0.165	0.869
VPA rec	4.73 ± 1.56	5.19 ± 1.20	1.253	0.216
VR rec	4.85 ± 1.16	5.46 ± 0.91	2.138	0.037*

Three-ways mixed ANOVA was performed on group (TGA vs control), memory domain (verbal vs visual) and memory type (immediate vs delayed test) to explore main effect and interaction between within-subject and between-subject variables (see figure 1). There were main effects on group study (performance better in control, F = 4.19, p = 0.046), memory domain (performance better in verbal test, F = 4.284, p = 0.044) and memory type (performance better in immediate memory test, F = 31.236, p < 0.001). There is significant interaction between memory domain and memory type (F = 6.831, p = 0.068). Visual memory scores in both groups were lower than verbal memory in immediate memory test but not in delayed test (Table 4).

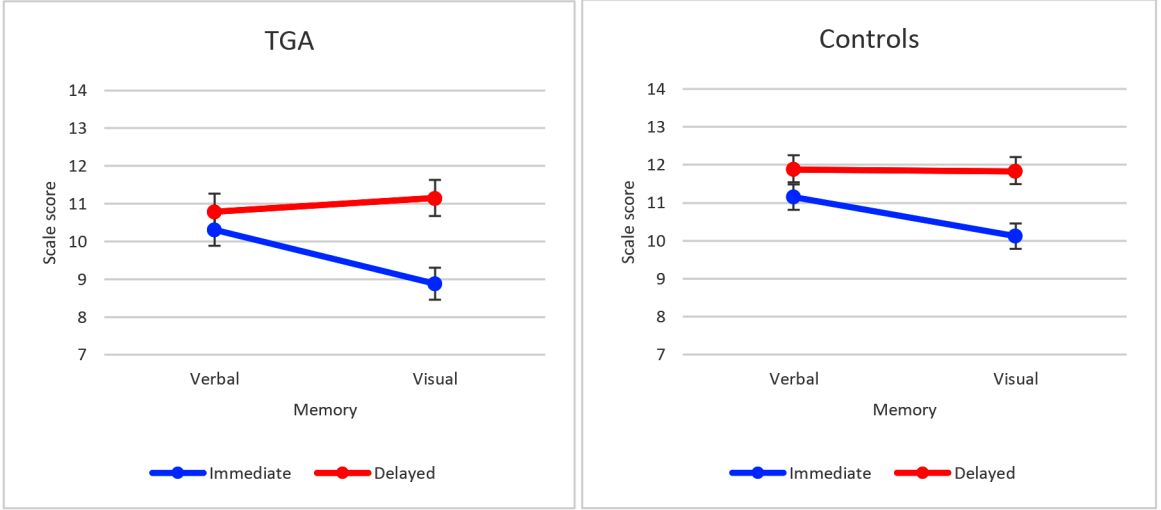

Figure 1 Interaction graph between memory domain and memory type compare between TGA and control

Table 4 Effect of group study, memory domain and memory type on composite memory scores done by three-ways mixed ANOVA

Effect	F	P
Group study (TGA or control)	4.190	0.046*
Memory domain (verbal or visual)	4.284	0.044*
Memory type (immediate or delay)	31.236	< 0.001*
Group*Memory domain	< 0.001	0.978
Group*Memory type	0.117	0.734
Memory domain*Memory type	6.831	0.068*
Group*Domain*Type	0.563	0.056

In subgroup analysis of TGA patients, comparison of comprehensive neuropsychological battery tests among side of lesions was done by One-way ANOVA. There was no significant difference in immediate verbal memory (F = 0.396, p = 0.68), immediate visual memory (F = 0.096, p = 0.91), delayed verbal memory (F = 0.623, p = 0.55), and delayed visual memory (F = 2.516, p = 0.103). In recognition tests, there was no significant difference in recognition scores among sides of lesions. (Table 5)

Table 5 Mean and SD scores in memory compared between side of lesion done by One-way ANOVA

	Side of lesions				
Memory Domain	Left	Right	Both	F	p
	mean+/-SD	mean+/-SD	mean+/-SD		
Immediate verbal	10.69 ± 0.76	10.29 ± 1.11	9.50 ± 0.96	0.396	0.68
Immediate visual	9.08 ± 0.62	8.71 ± 0.84	8.67 ± 0.96	0.096	0.91
Delayed verbal	11.35 ± 0.68	10.61 ± 1.10	9.79 ± 1.48	0.623	0.55
Delayed visual	10.54 ± 0.70	10.71 ± 0.66	13.00 ± 0.96	2.516	0.103
Recognition test					
LM rec	5.15 ± 0.90	3.57 ± 2.57	4.33 ± 1.75	4.151	0.057
VPA rec	4.77 ± 1.59	4.71 ± 1.80	4.67 ± 1.51	0.005	0.945
VR rec	5.00 ± 1.16	4.71 ± 0.76	4.67 ± 1.63	0.344	0.565

comparison between three factors, which were side of lesions (left vs right vs both sides), memory domain (verbal vs visual) and memory type (immediate vs delayed test), was done by Three-ways mixed ANOVA (see Figure 2). There was a main effect only on a memory type (better in delayed memory F = 22.69, p < 0.001). There was no main effect on side of lesions and memory domain (F = 0.063, p = 0.939 for side of lesions and F= 0.415, p = 0.562 for memory domain). There was significant interaction between memory domain and memory type (F = 1.474, p = 0.011) (Table 6). Visual memory scores were all lower than verbal memory scores in immediate memory in every side of lesions. Visual memory scores were higher than verbal memory scores in delayed memory of both-sided lesions and right-sided lesions (much higher in both-sided lesions). However, in left-sided lesions, visual memory score was lower than verbal memory score in delayed memory.

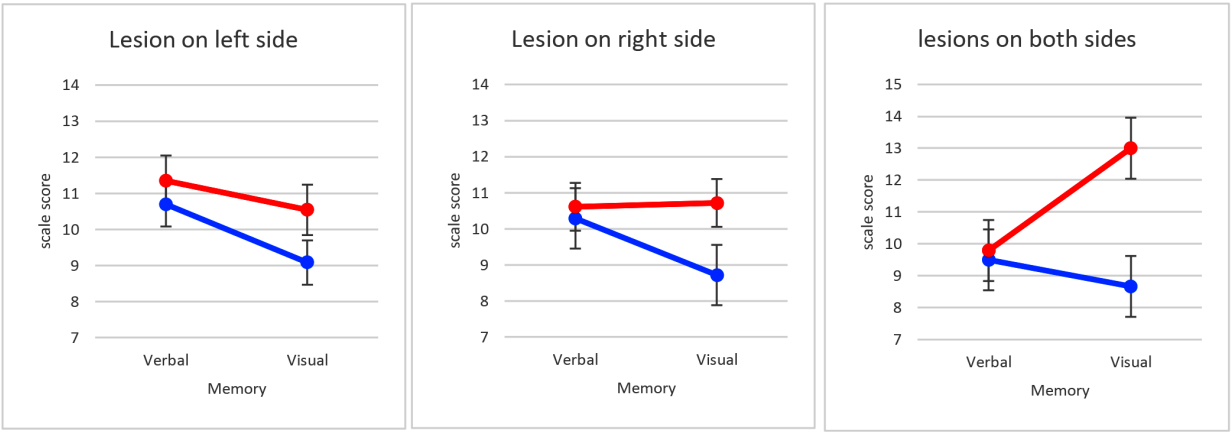

Figure 2 Interaction graph between memory domain and memory type compare between side of lesions in MRI

Table 6 Effect of lesion side, memory domain and memory type on composite memory scores done by Three-ways mixed ANOVA

Effect	F	P
Side of lesions (left or right or both)	0.063	0.939
Memory domain (verbal or visual)	0.415	0.526
Memory type (immediate or delay)	22.691	< 0.001*
Side*Memory domain	3.37	0.052
Side*Memory type	1.474	0.25
Memory domain*Memory type	7.596	0.011*
Side*Domain*Type	1.483	0.248

According to the amounts of lesions in TGA group, means and SD of comprehensive neuropsychological tests were compared by independent T-test. There was no significant difference in each test between single lesion group and multiple lesion group. In recognition test, there was no significant different between single and multiple lesions (Table 7).

Table 7 Mean and SD scores in memory task compared between amounts of lesions by independent T-test

	Amounts of lesions			
Memory Domain	single	multiple	t	p
	mean+/-SD	mean+/-SD		
Immediate verbal	10.68 ± 0.63	9.29 ± 0.84	1.204	0.24
Immediate visual	9.05 ± 0.50	8.43 ± 0.84	0.646	0.53
Delayed verbal	11.12 ± 0.61	9.89 ± 1.25	0.981	0.34
Delayed visual	10.66 ± 0.53	12.50 ± 0.95	1.78	0.09
Recognition test				
LM rec	4.53 ± 1.81	4.57 ± 1.72	-0.057	0.955
VPA rec	4.68 ± 1.64	4.86 ± 1.46	-0.041	0.968
VR rec	4.95 ± 1.03	4.57 ± 1.51	0.729	0.473

Three variables including amounts of lesions (single vs multiple lesions), memory domain (verbal vs visual) and memory type (immediate vs delayed) were compared using Three-way mixed ANOVA (see figure 3). There was main effect only on memory type (better in delayed memory $F = 26.72$, $p < 0.001$) but there were no main effects on amounts of lesions and memory domain ($F = 0.161$, $p = 0.841$ in amounts of lesions and $F = 0.041$, $p = 0.692$ in memory domain). There was significant interaction between amounts of lesions and memory domain ($F = 5.20$, $p = 0.032$). In single lesion, visual memory scores were lower than verbal memory scores. In multiple lesions, visual memory score was higher than verbal memory score. There was also interaction between memory domain and memory type ($F = 7.535$, $p = 0.011$). Visual memory scores were lower than verbal memory scores in immediate memory. On the other hand, visual memory score was higher than verbal memory score in delayed memory (Table 8).

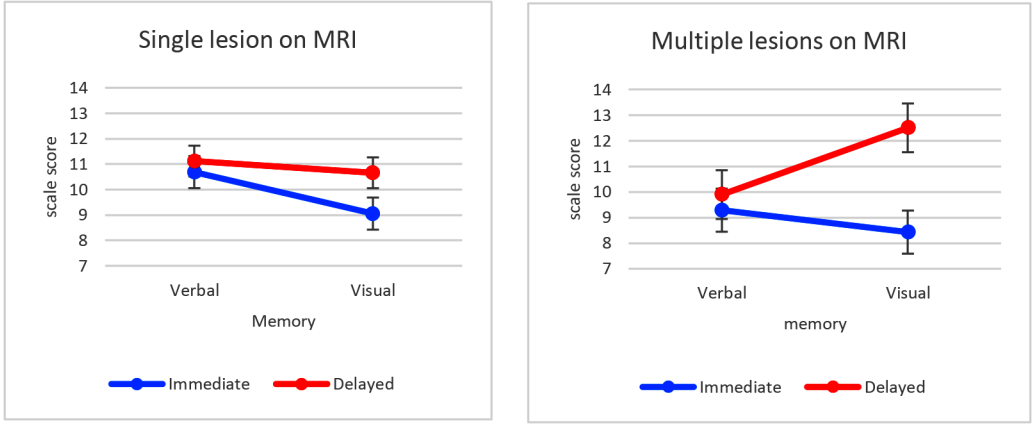

Figure 3 Interaction graph between memory domain and memory type compare between amounts of lesion

Table 8 Effect of amounts of lesions, memory domain and memory type on composite memory scores done by Three-ways mixed ANOVA

Effect	F	P
Amounts of lesions (single or multiple)	0.161	0.692
Memory domain (verbal or visual)	0.041	0.841
Memory type (immediate or delay)	26.72	< 0.001*
Amounts*Memory domain	5.20	0.032*
Amounts*Memory type	4.123	0.054
Memory domain*Memory type	7.535	0.011*
Amounts*Domain*Type	1.844	0.187

Discussion

As this study aimed to explore long term memory outcome in imaging confirmed TGA patients, we found that memory performance in TGA was slightly lower than the controls regardless of memory domain and memory type. The pattern of performance in memory domain and type of TGA group also resemble pattern in control group, this mean TGA episode may affect overall baseline of memory function in long term equally, not just in specific domain or type of memory. Our results

support the previous study[5,9,10] that TGA episode of patients leave some sequelae on memory outcome. However, this effect could not be observed by the general screening neuropsychological test - MOCA and did not affect patient's daily activity.

MRI brain characteristic analysis is strength of our study compared to the others. We found different pattern of memory performance between patient who had different lesion's location. Although Performance of immediate verbal and visual memory were similar in every group, but in delayed memory type, visual memory tended to be better in TGA with right-sided lesions while verbal memory performance tend to be better in left-sided lesion patients. The result of our study was contrast to the evidence of performance in neurocognitive function in patients with structural brain disease such as sequelae of stroke or epilepsy. Studies in temporal lobe resection in epilepsy patients and left-sided (dominant hemisphere) lesions ischemic stroke show a verbal memory impairment compared to visual memory and vice versa, non-dominant side lesions affect visual memory more than verbal memory.[16-19] We proposed this phenomenon may come from an unequal baseline of the subjects group. There may also be a side of the hippocampus which functions more than another one, resulting in better baseline verbal memory type if dominant hemisphere is more functional and better in baseline of visual memory type if non-dominant hemisphere is more functional. The higher functional hippocampus side is, comes the greater risk of injury from stress, which causes TGA more likely to attack on that side. Even though they had a TGA episode, in the long duration follow-up, they were still good at the memory type they had performed better in baseline. To investigate this hypothesis, we suggest exploring hippocampal volume and side of lesions in which TGA occurred may indirectly demonstrate the correlation. Baseline neuropsychological test of TGA patients right after recovery from the attack and long term follow up compared to hippocampal volume may reveal an interesting aspect of the disease.

Considering the effect of the amounts of lesions, we found that all memory domain scores in multiple lesions group tended to be lower than those with single lesion group except for delayed visual memory test which imply that multiple lesions in TGA episode had negative effect on verbal memory over visual memory. However, due to small numbers of patients in this group (N = 7), our study could not show the significant burden from amounts of lesions affecting long term memory outcome.

In this study, we found that delayed memory score was always higher than immediate memory score. This should be cautiously interpreted due to the characteristic of delayed memory tasks. In immediate recall test, the more correct answers, the more scale scores were obtained. But in the delayed memory test, the same amounts of answers could get better scores in reward for not forgetting the information. For example, corrected 15 free recall answers at the end of story would have 10 points on scale score, but corrected 15 free recall answers 20 minutes later would give them 12. This mean increase in scale score did not directly reflect better memory performance in this case. Nevertheless, we use scale score in our study because of the property of age adjusted and normalization in normal population, thus we can compare score across subjects. Another limitation of the study was lack of baseline neuropsychological test in both groups which makes the evaluation of change in cognitive function more difficult. We also did not have data on hippocampal volume to answer the hypothesis of a more functional side of the hippocampus.

Conclusion

We demonstrated the impairment in long term memory outcome in transient global amnesia patients who have abnormal MRI brain signal compared to control. There might be interesting effects of the location and amounts of lesions on memory performance. Longitudinal neurocognitive function follow-up in this group of patients should be important to observe the cognitive declination.

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References

1. Bartsch T and Butler C. Transient amnesic syndromes. Nature Review Neurology 2013;9:86-97.
2. Bartsch T, Deuschl G. Transient global amnesia: functional anatomy and clinical implications. Lancet Neurol 2010;9:205-14.
3. Bartsch T, Alfke K, Stingele R, Rohr A, Freitag-Wolf S, Jansen O et al. Selective affection of hippocampal CA-1 neurons in patients with transient global amnesia without long-term sequelae. Brain 2006;129:2874-84.
4. Arena J and Rabinstein A. Transient global amnesia. Mayo Clin Proc 2015;90:264-72.
5. Mazzucchi A, Moretti G, Caffarra P, Parma M. Neuropsychological functions in the follow-up of transient global amnesia. Brain 1980;103:161-78.
6. Caffarra, P, Moretti G, Mazzucchi A and Parma M. Neuropsychological testing during a transient global amnesia episode and its follow-up. Acta Neurol 1981; 63:44-50.
7. Cattaino G, Querin, F, Pomes A and Piazza P. Transient global amnesia. Acta Neurol Scand 1984;70:385-90.
8. Gallassi R, Stracciari A, Morreale A, Lorusso S, Rebucci G, Lugaresi E. Transient global amnesia: neuropsychological findings after single and multiple attacks. Eur Neurol 1993;33:294-8.
9. Borroni B, Agosti C, Brambilla C, Vergani V, Cottini E, Akkawi N, et al. Is transient global amnesia a risk factor for amnestic mild cognitive impairment? J Neurol 2004; 251:1125-7.
10. Le Pira F, Giuffrida S, Maci T, Reggio E, Zappala G, Perciavalle V. Cognitive findings after transient global amnesia: role of prefrontal cortex. Appl Neuropsychol 2005;12:212-7.
11. Uttner I, Weber S, Freund W, Schmitz B, Ramspott M, Huber R. Transient global amnesia - full recovery without persistent cognitive impairment. Eur Neurol 2007;58: 146-51.
12. Uttner I, Prexl S, Freund W, Unrath A, Bengel D, Huber R. Long-term outcome in transient global amnesia patients with and without focal hyperintensities in the CA1 region of the hippocampus. Eur Neurol 2012;67:155-60.
13. Hsieh SW, Chen CH, Huang P, Li CH, Yang ST, Yang YH. The long-term risk of dementia after transient global amnesia: A population-based cohort study in Taiwan. Neuroepidemiology 2019;53:201-8.
14. Jäger T, Bäzner H, Kliegel M, Szabo K, Hennerici MG. The transience and nature of cognitive impairments in transient global amnesia: a meta-analysis. J Clin Exp. Neuropsychol 2009;31:8-19.
15. Hodges JR, Warlow CP. Syndromes of transient amnesia: towards a classification: a study of 153 cases. J Neurol Neurosurg Psychiatry 1990;53:834-43.
16. Gleissner U, Sassen R, Lendt M, Clusmann H, Elger CE, Helmstaedter C. Pre and postoperative verbal memory in pediatric patients with temporal lobe epilepsy. Epilepsy Res 2002;51:287-96.
17. Tatia MC Lee, James T H Yip, Marilyn Jones-Gotman, Memory deficits after resection from left or right anterior temporal lobe in humans: a meta-analytic review. Epilepsia 2002;43:283-91.
18. Frisk V, Milner B. The role of left hippocampal region in the acquisition and retention of story content. Neuropsychologia 1990;28:349-59.
19. Doyon J, Milner B. Right temporal-lobe contribution to global visual processing. Neuropsychologia 1991; 29:343-60.