Hyperhomocysteinemia in Alzheimer Dementia Patients and Cognitive Decline after 6 Months Follow-up Period

Min-Chien Tu[1], Chi-Wei Huang[1], Nai-Ching Chen[1], Wen-Neng Chang[1], Chun-Chung Lui[2], Chih-Feng Chen[2], Ching Chen[3], Ya-Ling Wang[3], Yu-Ting Lin[1], Chiung-Chih Chang[1]

Abstract-

Purpose: White matter hyperintensities (WMHs) on magnetic resonance imaging (MRI) are commonly found in Alzheimer's disease (AD) and may contribute to cognitive impairment. Plasma total homocysteine (tHcy) had also been linked with cognitive decline in AD. We examined the relationship among change of cognition, tHcy level, and WMHs on MRI in AD patients with a follow-up periods of 6 months.

Methods: AD patients with normal creatinine level and initial clinical dementia rating (CDR) of 1 to 2 were enrolled. tHcy and biochemistry tests related to cerebral vascular risk factors were collected. WMHs were measured on MRI fluid attenuated inverse recovery sequence and classified into deep white matter hyperintensities (DWMHs) and periventricular white matter hyperintensities (PWMHs) by visual rating scale. Neuropsychological tests including cognitive ability screening instrument (CASI), mini-mental state examination (MMSE) converted from CASI scores and CDR were collected twice during the follow-up period of 6 months.

Results: Ninety-two AD patients, 30 men and 62 women completed the study while the tHcy level was not significantly different between AD and age matched controls. tHcy level showed no correlation with CASI or MMSE score, at either the first or second examination. tHcy showed positive correlation with decline of CASI total score and abstract thinking (both $p < 0.01$) but not in MMSE decline. There was no significant correlation between neuropsychiatric assessment and WMHs, but the decline of abstract thinking score was related to frontal PWMHs (R square = 0.237, $p = 0.007$).

Conclusion: tHcy might be associated with rapid cognitive decline in AD after a 6-month follow-up period and the effect might not be directly through WMHs. tHcy level correlated with greater WMHs in the trigone area although greater lesion load by MRI was in the occipital lobe.

Key Words: Alzheimer's disease, cognitive ability screening instrument, cognitive decline, homocysteine, white matter hyperintensities.

Acta Neurol Taiwan 2010;19:168-177

From the Departments of [1]Neurology, [2]Radiology, [3]Psychiatry, Chang Gung Memorial Hospital-Kaohsiung Medical Center and Chang Gung University College of Medicine, Kaohsiung, Taiwan.
Received December 24, 2009. Revised January 18, 2010.
Accepted May 26, 2010.

Correspondence to: Chiung-Chih Chang, MD. Department of Neurology, Kaohsiung Chang Gung Memorial Hospital, #123, Ta-Pei Road, Niaosung, Kaohsiung County 833, Taiwan.
E-mail: neur099@adm.cgmh.org.tw

INTRODUCTION

Elevated plasma total homocysteine (tHcy) has been considered as a modifiable risk factor in both normal and demented elderly[1] and hyperhomocysteinemia is associated with poor cognitive function in non-demented elderly[2]. The Personality and Total Health through life study revealed that tHcy level is correlated with poor immediate and delayed recall of verbal memory in randomly selected community-dwelling individuals[3]. A large cohort from the Framingham study also suggested that increased tHcy is a strong, independent risk factor for developing AD[4].

White matter hyperintensities (WMHs) are often found in vascular dementia, and are traditionally considered as a consequence of hypoperfusion associated with cerebral vascular disease[5]. The presence of WMHs is not exclusively linked to vascular dementia, but is also associated with aging process[6], in AD[7] and in dementia with Lewy bodies[8]. Although most reports considered the adverse effect of WMHs on dementia severity[7,9], others considered it to be a frequent incidental finding[10].

In randomly selected community-dwelling individuals, higher tHcy was significantly related to greater WMHs volume[3]. For the sake of unanimity on the interaction between tHcy, WMHs, and cognition in AD patients, linkage among it, if any, deserves to be further elucidated. Based on the details of the aforementioned literature search, we hypothesized that the elevation of tHcy may correlate with cognitive deficit in AD through the effect of WMHs.

While most of the risk factors in Alzheimer dementia (AD) are not modifiable, modifiable risk factors in AD are of clinical relevance. The purpose of this study was to assess the influence of tHcy on cognition decline in AD and also assess whether the impairment of cognitive performance was related to WMHs per se. While tHcy level is positively related to renal impairment[11] and previous studies suggested a link between chronic kidney disease and cognitive impairment[12], we only selected patients with normal creatinine level (reference level 1.5 mg/dl) for this study to reduce the interference.

METHODS

Subjects and clinical investigations

The study involved enrolling 92 consecutive AD patients who visited the Department of Neurology, Kaohsiung Chang Gung Memorial Hospital from 2006 December to 2008 April. In addition, 67 age-matched normal elderly with available tHcy level from the data base were selected for comparison of tHcy level with AD. The age-matched controls were selective from our normal database. None had a history of neuropsychological disorder, and all had normal complete blood count, electrolyte panel, renal, and liver function test. Their Cognitive Ability Screening Instrument (CASI) data were within reference limit in Taiwan[13], and clinical dementia rating (CDR)[14] was zero. All the AD patients fulfilled the dementia criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition[15] and the probable Alzheimer's Disease criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association[16]. All the AD patients had received acetylcholinesterase inhibitors for treatment with CDR 1 or 2 at enrollment. Diabetes mellitus (DM) was defined as plasma glucose >126mg/dl after an overnight fast or symptoms of diabetes with random plasma glucose >200mg/dl. Hypertension was defined according to the criteria of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure with blood pressure measurement above 140/90 mmHg at two time points[17].

The exclusion criteria were: (1) renal function impairment (reference level of normal creatinine is defined as < 1.5mg/dl); (2) clinical stroke history; (3) modified Hachinski ischemic score > 4[18]; (4) abnormal liver function test (aspartate aminotransferases (AST) and alanine aminotransferase (ALT)); (5) folic acid or vitamin B12 supplement history.

Each AD subject underwent extensive medical examination at the initial visits, including standard medical history, physical and neurologic examination, blood samples, and neuropsychological tests. Brain magnetic resonance imaging (MRI) was arranged within 3 months

from enrollment. The interval between blood check and the cognition test was below 2 months. The study received approval from the human ethnic committee of Chang Gung Memorial Hospital for writing the paper. [IRB 97-0255B; 97-0526B]

Chemistry test

After an overnight fasting of 8 hours, antecubital venous blood was collected for serum fasting glucose, glycohemoglobin, creatinine, high-density lipoprotein, low-density lipoprotein, triglyceride, cholesterol, serum folate, vitamin B12, and tHcy level. Fasting blood samples were collected in evacuated tubes containing EDTA, centrifuged within 10 minutes and stored below -20˚C until analyzed. Plasma homocysteine was measured using florescence polarization immunoassay analyzer (Abbott Laboratories, Chicago, IL).

Cognitive Assessment

CASI[19] and CDR were administered by 2 trained neuropsychologists twice. The mean follow-up duration of CASI was 6.3 months (SD= 2.9). CASI provides quantitative assessment of 9 cognitive subdomains, including attention, orientation, short term memory, long term memory, language abilities, drawing, verbal fluency, abstract thinking and mental manipulation. The scores were collected for further comparison. MMSE was rated by conversion from CASI scores for further analysis. To scrutinize changes of daily functional performance, both CDR and CDR sum of boxes were used.

Assessment of white matter changes

MRI was performed using 3.0T scanner (Excite, GE Medical System, Milwaukee, WI) equipped with echo-planar capability. Axial fluid-attenuated inversion recovery (FLAIR) image sequences were as follows: 8000/100/2000/1 [TR/TE/TI/NEX]; FOV, 240 mm; matrix, 320×256; and section thickness 5 mm.

The FLAIR sequences were rated visually for the presence of hyperintensities in the white matter by using the scale developed by Ylikoski and colleagues[20]. Hyperintensities were rated in four areas in each hemisphere: frontal horns, ventricular body, trigones, and occipital horns. Trigone region is a triangular area defined by the temporal horn inferiorly, the occipital horn posteriorly, and the body of the lateral ventricle anteriorly. WMHs were further classified into deep (DWMHs) and periventricular white matter hyperintensities (PWMHs) based on its relationship with ventricles. Lesions were considered as PWMHs when they were adjacent or within 10mm perpendicularly from the ventricle border. The extending of hyperintensity beyond 10mm was scored as DWMHs. Small FLAIR hypointense lesions with peripheral hyperintense rim were defined as lacunar infarcts, and were not included for lesion-load or severity scores. Each DWMH was rated from 0 to 3 (0, no hyperintensity; 1, mild [punctuate, small foci < 5mm]; 2, moderate [cap, pencil-thin lining]; 3, severe [nodular band, extending hyperintensity > 10mm]). Total DWMHs ranged from 0 to 24. PWMH was rated similarly from 0 to 3 (0, no hyperintensity; 1, mild [punctuate, small foci]; 2, moderate [beginning confluent]; 3, severe [large confluent areas]). Total PWMHs also ranged from 0 to 24. WMHs were the sum of total DWMHs and PWMHs and ranged from 0 to 48. All the ratings were done by the two raters (C-W Huang and M-C Tu) who were blind to the clinical data. In a sample of 40 subjects from the study population, the intra-rater coefficient for WMHs score was 0.89 and the inter-rater coefficient was 0.9.

Statistical analyses

We examined the association of CASI total scores or subdomain score with tHcy and/or WMHs using Pearson correlations for continuous variables and *t* -test for comparing two independent groups. Mann-Whitney U test or Spearman correlation test were used if the continuous variables are not normally distributed. The distribution of WMH scores in each region was compared using analysis of variances with Bonferroni corrections to avoid type I error in multiple comparisons. The differences between two cognitive performance scores were compared using paired-sample *t* -test. Multiple linear regression analysis was used to examine the effects of plasma tHcy levels and WMHs on cognitive performances and partial correlation analysis was used to

Table 1. *Demographic and clinical data of Alzheimer dementia (AD) in this study*

Domain	Relation with tHcy				Relation with WMHs		
	Mean(SD)	Pearson correlations	T value	p value	Pearson correlations	T value	p value
Age	46-90 (73.77±9.4)	0.343		0.002**		0.359	0.002**
Gender (M/F)	30/62		1.095	0.277		1.303	0.197
Hypertension (+/-)	37/55		1.125	0.164		2.399	0.019
DM (+/-)	14/78		0.039	0.969		0.068	0.946
tHcy (umol/L)	12.9 (7.3)	1			0.288		0.020
AC sugar (mg/dl)	109.7 (47.0)	-0.066		0.569	-0.032		0.797
HbA1C (%)	8.3 (19.3)	-0.102		0.391	-0.091		0.476
Creatinine (mg/dl)	1.1 (0.4)	0.361		0.001**	0.274		0.020
HDL (mg/dl)	54.3 (14.8)	-0.188		0.092	-0.115		0.340
LDL (mg/dl)	108.0 (31.5)	-0.295		0.030	0.089		0.521
TC (mg/dl)	190.8 (38.2)	-0.193		0.084	0.091		0.446
Triglyceride (mg/dl)	124.8 (73.2)	0.151		0.180	-0.037		0.759
B12 (pg/dl)	698.7 (399.6)	-0.431		0.000**	0.123		0.344
Folate (ng/dl)	13.5 (5.7)	-0.378		0.001**	0.005		0.968

WMHs=white matter hyperintensities; DM= diabetes mellitus; tHcy= homocysteine level; AC sugar= fasting sugar; HbA1C= glycohemoglobin; HDL= high density lipoprotein; LDL= low density lipoprotein; TC= total cholesterol; B12 = vitamin B12; SD=standard deviation

** indicates $p < 0.01$

adjust the confounding factors. Cognitive decline was defined as ratios of scores between two time points (i.e. first CASI score/second CASI score).

All statistical analysis was conducted using the Statistical Package for Social Sciences software package (version 13 for Windows?, SPSS Inc, Chicago, IL). Statistic significance was defined as $p < 0.01$.

RESULTS

The control group included 27 men and 40 women, whose age in average was 71.7 years-old (SD = 5.8 years). The tHcy level of control group was 12.1 umol/L (SD = 4.4 umol/L). There were no significant differences between AD (mean = 12.9, SD = 7.3) and control group in tHcy level (p = 0.448). In AD patients, correlation between CASI scores or CASI decline ratio with initial biomarkers (i.e. fasting glucose, glycohemoglobin, creatinine, high-density lipoprotein, low-density lipoprotein, triglyceride, cholesterol, serum folate, and vitamin B12) was not significant.

Table 1 lists the demographic and clinical data of recruited AD patients and the association of tHcy and WMHs with these parameters. Among the serum biomarkers on initial visit, tHcy had positive correlation with age and creatinine (r = 0.343, p = 0.002 in age; r = 0.361, p = 0.001 in creatinine). Inverse correlation between tHcy and estimated glomerular filtration rate were also documented in AD patients (r = -0.4, p = 0.001). Inverse correlation between tHcy and vitamin B12/ folate were also identified (r = -0.431, p = 0.0001 in vitamin B12; r = -0.378, p = 0.001 in folate). For WMHs, age was positively correlated with WMHs (r = 0.359, p = 0.002) while the presence of hypertension and DM were not. Analysis of association between serum biomarkers and WMHs showed that only tHcy and creatinine level had positive trends with WMHs (r = 0.288, p = 0.02 in tHcy; r = 0.274, p = 0.02 in creatinine).

Table 2 shows the association of tHcy with the first, second cognitive scores and the cognitive decline ratio. Comparison of two cognitive examinations using paired t - test showed that CASI total scores deteriorated during

Table 2. *Association of homocysteine (tHcy) with first and second cognitive tests and cognitive decline ratio*

Cognitive performances	tHcy with first cognitive tests			tHcy with second cognitive tests			tHcy with cognitive decline ratio		
	Mean(SD)	Correlations	*p* value	Mean(SD)	Correlations	*p* value	Mean(SD)	Correlations	*p* value
Clinical Dementia Rating (CDR)	0.99 (0.6)			1.12 (0.6)			0.90 (0.3)		
CDR sum of boxes	5.74(3.87)	0.185	0.098	6.25(3.92)	0.178	0.114	0.97(0.47)	-0.024	0.837
Mini-mental State Examination	17.00(6.6)	0.006	0.962	16.2(6.9)	-0.032	0.772	1.11(0.39)	0.022	0.851
CASI total score	57.47 (23.7)	0.003	0.981	53.68 (24.5)	0.007	0.956	1.14 (0.5)	0.359	0.006**
Mental manipulation	4.31 (3.5)	0.001	0.993	3.83 (3.4)	0.072	0.551	1.09 (0.9)	-0.122	0.426
Attention	5.72 (1.5)	0.173	0.167	5.63 (1.8)	-0.049	0.689	1.01 (0.3)	0.144	0.295
Orientation	10.13 (5.1)	-0.126	0.317	9.18 (5.5)	-0.020	0.870	1.31 (1.0)	0.018	0.899
Long term memory	7.33 (3.0)	0.031	0.804	7.29 (3.2)	0.023	0.849	1.03 (0.4)	-0.020	0.885
Short term memory	3.83 (3.7)	-0.149	0.235	4.82 (13.0)	-0.043	0.724	1.25 (1.5)	0.036	0.805
Abstract thinking	7.55 (3.1)	-0.011	0.930	6.65 (3.5)	-0.089	0.462	1.24 (0.6)	0.350	0.009**
Drawing	5.17 (3.2)	0.137	0.277	5.06 (3.4)	0.047	0.698	1.00 (0.6)	0.298	0.036
Verbal fluency	6.47 (2.7)	-0.028	0.827	5.89 (3.1)	0.003	0.977	1.21 (0.7)	0.329	0.015
Language	6.99 (3.7)	0.012	0.925	6.58 (3.7)	-0.027	0.823	1.21 (1.7)	0.000	0.999

** = $p<0.01$, CASI= cognitive assessment screening instrument

Cognitive decline ratio is defined as score at first time divided by score at second time

Correlation study between tHcy with cognitive tests by Spearman correlation

Correlation study between tHcy with cognitive decline ratio by Pearson correlation

Table 3. *Association of white matter hyperintensities (WMHs) with first and second cognitive tests and cognitive decline ratio*

Cognitive performances	WMHs with first cognitive tests		WMHs with second cognitive tests		WMHs with cognitive decline ratio	
	Correlations	*p* value	Correlations	*p* value	Correlations	*p* value
CDR sum of boxes	0.163	0.173	0.083	0.493	0.091	0.455
Mini-mental State Examination	-0.091	0.440	-0.008	0.946	-0.138	0.256
CASI total score	0.067	0.609	-0.019	0.885	0.042	0.752
Mental manipulation	0.029	0.825	0.008	0.950	0.004	0.980
Attention	0.178	0.173	0.003	0.981	0.065	0.636
Orientation	0.055	0.677	-0.015	0.909	-0.077	0.595
Long term memory	0.072	0.587	0.121	0.346	0.015	0.919
Short term memory	0.088	0.503	-0.066	0.606	-0.015	0.920
Abstract thinking	0.116	0.376	-0.065	0.611	0.282	0.048
Drawing	0.006	0.961	0.041	0.747	0.092	0.548
Verbal fluency	-0.056	0.668	0.123	0.336	-0.014	0.922
Language	0.090	0.493	-0.080	0.532	-0.063	0.687

Cognitive decline ratio is defined as score at first time divided by score at second time; CDR=clinical dementia rating; CASI= cognitive assessment screening instrument

Correlation study between WMHs with cognitive tests by Spearman correlation

Correlation study between WMHs with cognitive decline ratio by Pearson correlation

Table 4. *Levels of homocysteine (tHcy) effect on white matter hyperintensities (WMHs) score on selected area*

	Association with tHcy			After partial adjusting with age and creatinine	
	Mean (SD)	Pearson correlations	*p* value	Correlation coefficient	*p* value
Total PWMHs	10.88 (5.5)	0.288	0.020	0.113	0.380
Frontal horn	3.23 (1.4)	0.225	0.072 [a]	0.110	0.396
Ventricular body	3.19 (1.9)	0.222	0.076	0.161	0.210
Occipital horn	2.53 (2.1)	0.196	0.118	0.013	0.923
Trigone area	1.93 (1.2)	0.353	0.004**	0.252	0.048
Total DWMHs	5.86 (4.9)	0.210	0.094	0.114	0.377
Frontal horn	1.57 (1.6)	0.168	0.182	0.093	0.474
Ventricular body	2.51 (1.9)	0.275	0.027	0.161	0.210
Occipital horn	3.82 (3.1)	0.168	0.181 [b]	0.013	0.923
Trigone area	2.42 (1.9)	0.311	0.012	0.252	0.048
Total WMHs	16.74 (9.1)	0.288	0.020	0.131	0.309

SD= standard deviation; PWMHs= periventricular white matter hyperintensities; DWMHs= deep white matter hyperintensities; WMHs= white matter hyperintensities **indicate $p<0.01$; a indicate $p=0.0001$ comparing with trigone in PWMH; b indicate $p=0.0001$ comparing with frontal horn in DWMH

the follow-up period while 23 AD patients declined (25%) in CDR scores. tHcy had no correlation with first and second total or subdomain score in CASI or MMSE. In the meanwhile, tHcy was not correlated with MMSE decline over 6 months. tHcy was associated with decline of CASI total score and the subscore of abstract thinking. Significant correlation was found between CASI decline and tHcy level ($r = 0.357$, $p = 0.006$) or between abstract thinking decline and tHcy level ($r = 0.347$, $p = 0.01$) after adjustment for educational level. No significant correlation between tHcy and decline of the CDR sum of boxes was identified.

Table 3 lists the association of WMHs with first, second cognitive scores and the cognitive decline ratio. There was no correlation between WMHs and cognition tests, at either the first or second cognitive examination. There was positive a trend of corelation between WMHs with decline in abstract thinking ($r = 0.282$, $p = 0.048$). Analysis between PWMHs/DWMHs with decline in abstract thinking score showed that scores of frontal horn PWMHs ($r = 0.486$, $p < 0.001$) but not DWMHs ($r = 0.179$, $p = 0.213$) were related with abstract thinking score declining. After multiple linear regression model analysis, only the frontal horn in PWMHs was significantly related with abstract thinking score declining (R square = 0.237, beta = 0.456, $p = 0.007$). No significant correlation among tHcy and decline of the CDR sum of boxes was identified.

Table 4 lists tHcy effect and/or adjusting for confounding factors of WMHs on selected area. tHcy showed significant correlation with WMHs. On assessing area of interest, there was greater load on frontal PWMHs and occipital DWMHs. In PWMHs, the score of frontal horn was significantly higher than trigone ($p = 0.0001$) after Bonferronni correction. In DWMHs, scores of occipital horn were significantly higher than frontal horn ($p = 0.0001$) after Bonferronni correction. Correlation study showed that tHcy level was positively correlated with PWMHs in the area of triagone but not areas of DWMHs. After adjusting for the effect of age and creatinine level, the association between tHcy level and PWMHs triagone area attenuated ($p = 0.048$).

DISCUSSION

Although previous AD literatures stated the correlation between tHcy and cognition[1], tHcy with WMHs[21], and cognition with WMHs[22], the relationship among tHcy, WMHs and cognition performances were not depicted. Our study showed that tHcy level in AD was

not significantly different from the age-matched control but tHcy showed an effect on WMHs and cognitive decline in several domains. tHcy level was associated with faster cognitive decline after 6 months in this report. The decline of cognitive functions especially in CASI total score, drawing and verbal fluency subdomains were not correlated with the scores of WMHs, PWMHs, DWMHs, or vitamine B12 and folate levels. The result might suggest the linkage between neurotoxicity of tHcy and WMHs[23]. Our study results also disproved our initial hypothesis that elevation of tHcy may correlate with cognitive deficit in AD through the effect of WMHs. Although previous studies showed lower educational level may contribute to more rapid cognitive decline[24-25], the positive correlation between tHcy and decline of CASI/abstract thinking were still observed in this study after controlling for education level.

Abstract thinking decline was the only subdomain in this study to correlate with WMHs and PWMHs, especially in the frontal region. It was worth pointing out that the result represented $p < 0.05$ only, which should also be considered the possibility of a type I error. Abstract thinking had been proposed to have a relationship with left frontal inferior gyrus[26-28]. Using diffusion tensor imaging, cognitive dysfunction in early AD was also observed to correlate with frontal and parietal PWMH changes, suggesting the role of the lateral cholinergic projections and superior longitudinal fasciculus[29-30]. On the other hand, some authors had argued the relationship between WMHs and cognitive performance among AD patienes [2,10,31] and there was also study showing that white matter change had no relationship with disease progression in AD group receiving ancetylcholinerase inhibitors[32]. Whether or not white matter load correlated with cognition deficit in AD was still not uniformly agreed from a review of the literature. Our study showed that WMHs were not related with any of the cross sectional cognitive performances and that PWMHs played more important roles than DWMHs in the cognitive decline. PWMHs had stronger correlation with artherosclerosis and hypertension and were often considered as non-pathological[33-35]. Since we already excluded patients from the study with stroke history and more advanced CDR staging, the impact of PWMHs in AD was still of great clinical values.

Our study revealed MMSE scores in two time points didn't correlate with tHcy level in AD patients but the correlation was found using CASI. From the results, we still considered the impact of tHcy on cognitive decline in AD although there had been inconsistent results on the linkage between tHcy and cognition deficit in the related literature. tHcy level was linked with the impairment in visuo-constructural performance in AD patients[36]. An early Rotterdam study in healthy elderly population showed no significant correlations between tHcy and MMSE scores after a mean duration of 2.7 of years follow-up[37]. Tucker et al. used more detail neuropsychological testing and found that declines in constructional praxis and recall memory, but not in MMSE were associated with a higher tHcy in aging men[38]. Rotterdam Scan Study, however, pointed that increasing tHcy levels among nondemented elderly were associated with lower scores for psychomotor speed, memory function, and global cognitive function, and this was largely due to the association with tHcy levels in the upper quantile(>14 umol/L)[2]. Apparently, the differences in neuropsychological assessment might result in the inconsistent findings on the effect of tHcy. We had excluded the patients with renal impairment to avoid the interferences of cognition by nephropathy. Should tHcy have a threshold effect on cognitive function may not be fully explored on this study since the patients with extremely high level of tHcy related to renal impairment had been excluded from enrollment.

Although pathological studies suggest that WMHs might be ischemic in origin and caused by consistent or variable hypoperfusion, there were emerging evidences that they might also reflect vascular deposition of beta-amyloid, particularly when they were distributed in posterior areas and were present in patients with AD[39]. From our study, the highest white matter score was found in the occipital horn. Although the finding was in consistent with that by Brickman et al.[40], our study shows tHcy level correlated well with triagone in PWMHs. The attenuation of statistic significance after adjusting age and creatinine on the effect of tHcy with

WMHS suggested that tHcy may exert its influence on WMHs via the interaction of age or creatinine level. Deep white matter change related to high tHcy in AD had been reported from brain computed tomography (CT)[41] and was attributed to chronic ischemia, hypoperfusion, myelin loss, or gliosis[41-42]. Our study used FLAIR sequence, which was better suited for PWMHs than brain CT and the result also suggested that in addition to DWMH, PWMH triagone region was related with tHcy level.

In conclusion, higher tHcy level was associated with a greater decline of CASI total score and abstract thinking after 6 months although the low correlation coefficient might suggest weak associations. Correlation between tHcy with trigone region and PWMHs with abstract thinking decline suggested that the effect of tHcy on cognitive decline might not through WMHs only. Other pathological mechanisms might also have impacts on cognitive decline in AD patients.

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