White Matter Lesions in Community Dwelling Thai Elders with MCI and Dementia

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Abstract

Objectives: To look at factors related to WML severity in brain MRI in Thai elders with dementia and MCI.

Materials & Methods: 223 community dwelling Thai elders underwent brain MRI. Fazekas and Scheltens scores were rated. Subjects were classified into dementia, MCI and non- cases. Thai ADL, Thai Mental State Examination (TMSE), timed get up and go test (TGUG), Tinetti scale, clinical dementia rating scale (CDR), vascular risk factors, neuropsychological assessments, and ApoE4 status were explored. ANOVA and Chi square test were used.

Results: Mean age was 71.46 (6.45). 78(35%) were men. 133 (62.4%) had mild, 60(26.9%) had moderate WML and 26(11.7%) had severe WML, p<0.001. 33% of elders with dementia had severe WML (p <0.001). TMSE, Thai ADL, and CDR-SB were statistically different among the 3 groups. TGUG test revealed the slowest time in severe WML group (mild: 12.95(5.82) sec, moderate: 14.37(8.51) sec, severe: 19.04(15.45) sec, p=0.004. Number of comorbidities and prevalence of memory complaint were differed among 3 groups (p<0.01). Serum homocysteine level was highest in those with severe WML (p<0.001). The action fluency, both visual and logical memory scores were lowest in the severe WML group (p<0.01). ApoE4 status was statistically different among those with different WML severities [mild: 16.2%, moderate: 32.1%, severe: 36%]. Severity of WML was related to depression, global cortical atrophy, and other small vessel pathologies.

Conclusions: Severe WML is significantly associated with vascular factors, poor motor perfor-

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mance, worse cognitive and depressive scores. Prevalence of ApoE4 carrier was high in severe WML group.

Keywords: MRI, WML, MTA, MCI, Alzheimer, Thailand

Introduction

Cerebral small vessel is related to age and functional disability, in a dose dependent manner[1]. Cerebral small vessel disease can be visualized on brain magnetic resonance imaging (MRI) as white matter hyperintensities (WMH), lacunes, cerebral microbleeds, and enlarged Virchow Robin spaces.[2] Cerebral WMH are highly prevalent in healthy elderly. They have been reported in 27%–92% in elderly populations.[3,4] The underlying pathology of WMH varies from mild demyelination to incomplete subcortical infarctions[5]. Cerebral WMH have been related to cognitive impairment, motor impairment, and functional disability[6] and are highly correlated to vascular risk factors.[7] It has been proposed that prevalence of WMH on MRI in Asian countries is as common as in Western countries, with prevalence ranging from 28.8% to 77.1%[8] . Notably, no studies have been performed to investigate the burden of cerebral WMH in community dwelling elderly, suffering from cognitive impairment, living in Thailand. This study explored the prevalence of WMH on MRI in elderly diagnosed with mild cognitive impairment (MCI) or dementia. We further investigated the relation between WMH load and measures of cognition, motor performance, cerebrovascular risk factors and APOE. This study is a part of dementia and disability project in Thai elderly (DDP). The background of the DDP has been described in a previous report.[9]

Materials & Methods: The methodology, inclusion criteria, exclusion criteria, brain MRI method, and measurement are described in the earlier report.[9] Two hundred and twenty three Thai elders had MRI brain(11.3% of 1973). Twenty four were non MCI non dementia, one hundred and seventy one were MCI, and twenty eight were dementia. There was no statistical difference in age and neuropsychiatric symptoms between dementing elders and elders with MCI who having and not having bran MRI. Though, those who came to have brain MRI tended to have lower Thai mental state examination (TMSE) score (dementia group: those with brain MRI TMSE=18.96(4.56), those without brain MRI TMSE=15.56(6.12), p=0.006; MCI group: those with brain MRI TMSE=24.02(2.75), those without brain MRI TMSE=23.21(3.67), p=0.010. Visual rating white matter lesions(WMLs), utilizing Fazakas score and Scheltens score, presence of lacunar infarction, presence of cerebral microbleeds, assessed by T2*-weighted MRI, visual rating global cortical atrophy, and medial temporal atrophy(MTA) were assessed from MRI brain imaging. Neuropsychological assessment, Thai geriatric depression scale (TGDS)-30 items, Thai mini mental state examination (TMSA), gait performance utilizing timed get up and go (TGUG) and Tinetti gait scale, functional assessment using Thai activity of daily living scale (Thai ADL) and clinical dementia rating scale-sum of the boxes (CDR-SB), were applying at baseline. Blood tests for homocysteine levels and ApoE 4 gene status were done.

Statistical analysis

All analyses were performed using PASW Statistics 11 (SPSS Inc., Chicago, IL). Severity of white matter lesion severity (WMLs) was group into

mild (Fazekas score 0 and 1), moderate (Fazekas score 2), and severe (Fazekas score 3). Severity of white matter lesions by visual rating Fazekas score and Scheltens scale and subject characteristic function were summarize using descriptive statistics. Categorical variables were presented as frequency and percentage. Continuous variables were presented as mean and standard deviation (SD) or median and range. We assessed the difference of cognition among severity of white matter lesions using One-way ANOVA with Bonferroni's post hoc test or Kruskal-Wallis test with Dunn-Bonferroni's posthoc test as appropriate. Chi square test for trend was performed to assess whether comorbidities changed among severity of white matter lesions. A p-value < 0.05 was considered statistically significant.

Results

The mean age of two hundred and twenty three elders was 71.46(6.45). The means (SD) of TMSE (0-30), Thai ADL score (0-26), weight, systolic blood pressure, and diastolic blood pressure were 23.81 (3.56), 1.28 (2.67), 57.56 (11.16) kgms, 139.64 (19.23) mmHg, and 80.91 (10.50) mmHg respectively. Sixty six per cents of those with dementia, thirty seven per cents of MCI, and twenty per cents of normal controls or non-cases had moderate to severe WMLs ($p<0.001$). (Table1.) In this cohort, Fazekas score 0(F0), F1, F2, and F3 is equivalent to median Scheltens score (SS) 2 (min=0, max=16), 8 (min=0,max=24), 19(min=6, max=37), and 28.5(min=13, max=52) according (Table2, Figure1). Those with severe WML were older, performed worse in activities of daily living and global function, took more time to complete the time-get up and go test, and had poorer gait and balance assessed by Tinetti gait and balance scale. (Table 3) Those with severe WML differed from those with mild WML in terms of visual memory, category fluency (ISSAC15 but not 1 minute animal fluency), and action fluency. Only the mild WML group performed significantly inferiorly to the moderate WML group in the Trail A and immediate logical memory but not delayed logical memory. (Table 4) Memory complaint was described as either from the elders themselves or from their relatives. Non communicable diseases (NCD), including coronary artery disease, cerebrovascular disease, chronic obstructive pulmonary disease, osteoarthritis, hypertension, dyslipidemia, diabetes mellitus, hypo or hyper thyroidism, current smoking, and current alcohol drinker, were explored in this cohort. Frequency of memory complaint, NCD related comorbidities, and ApoE4 gen carriers increased steadily across mild, moderate and severe WML groups. In Thailand, the government does not support population to take vitamin supplement. Average Thai people do not buy supplement foods or vitamins routinely. They tend to find local herbal products to help their health. We found that serum homocysteine levels were increased significantly with increasing WML burdens in our study. Depression was assessed by Thai Geriatric Depression Scale (Thai GDS) -30. The prevalence of moderate to severe depression was higher in severe WML group and mild WML group. The incidence of having at least one lacuna infarct, and incidence of having at least one cerebral microbleed increased progressively across the 3 groups. Higher frequency of severe MTA (grade 3 and 4) and moderate to severe GCA (grade 2-3) were found in those with severe WML.

Table 1. Frequencies of white matter lesions (WMLs) assessed by visual rating Fazekas score in those with dementia, mild cognitive impairment (MCI), and non- case.

Fazekas score (n=223)	Non case (n=25)	MCI (n=171)	Dementia (n=27)
Grade 0 (n=21)	6(24%)	13(7.6%)	2(7.4%)
Grade 1 (n=116)	14(56%)	95(55.6%)	7(25.9%)
Grade 2 (n=60)	4(16%)	47(27.5%)	9(33.3%)
Grade 3 (n=26)	1(4%)	16(9.4%)	9(33.3%)
P<0.001			

Table 2. Severity of white matter lesions by Scheltens scale

Fazekas score	Sum Scheltens scale mean(SD)	Sum Scheltens scale* median(min,max)	WML- Fazekas score-regroup	Sum Scheltens scale* mean(SD)
Grade 0 (n=21)	3.81(4.89)	2.0(0,16)	Mild(F 0,1) n=137 (62.4%)	7.74(5.07)
Grade 1 (n=116)	8.45(4.79)	8.0(0,24)		
Grade 2 (n=60)	18.72(6.03)	19.0(6,37)	Moderate (F 2) n=60(26.9%)	18.72(6.03)
Grade 3 (n=26)	27.85(9.09)	28.5(13,52)	Severe (F3) n=26(11.7%)	27.85(9.09)

*ANOVA test p<0.001

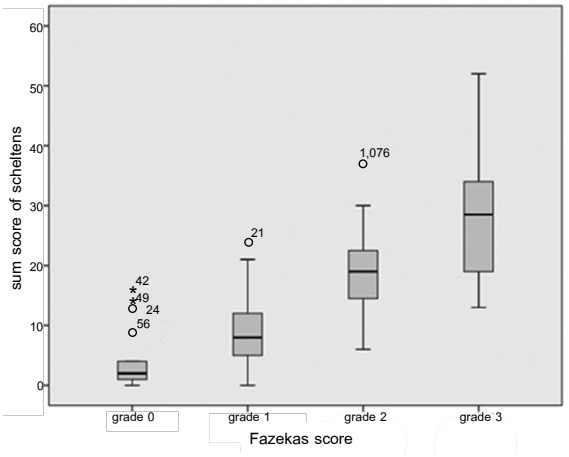

Figure 1. Box plot of sum of Scheltens white matter lesion score and Fazekas score

Table 3. White matter lesion severity and subject characteristic function

WML severity	Mild (n = 137, F=0,1)	Moderate (n =60, F=2)	Severe (n =26, F=3)	P value
Age	69.96(6.21)	73.73(5.58)	74.15(6.45)	<0.001 mild vs mod p<0.001 mild vs severe p=0.005
Gender: Male (n=78)	42 (30.7%)	24(40%)	12(46.2%)	0.074
Female (n=145)	95 (69.3%)	36(60%)	14(53.8%)	
Education (Years)				0.272
0-5 (n=195)	117 (85.4%)	56 (93.3%)	22 (84.6%)	
6-9 (n=10)	6 (4.4%)	2 (3.3%)	2 (7.7%)	
10+ (n=18)	14 (10.2%)	2 (3.3%)	2 (7.7%)	
Thai ADL scale score (0-26) mean(SD) median(min.max)	0.72(1.69) 0(0,12)	1.47(2.56) 0(0,13)	3.88(4.94) 2(0,21)	<0.001 mild vs mod p<0.001 mod vs severe p=0.001
Get up and go (Sec) mean(SD)	n=126 12.95(5.82)	n=56 14.37(8.51)	n=25 19.04(15.45)	0.004 mild vs severe p=0.003
Tinetti gait scale (1-9) mean(SD)	n=65 15.77(0.72)	n=24 15.13(1.83)	n=17 13.71(2.91)	<0.001 mild vs severe p<0.001 mod vs severe p=0.014
Tinetti balance scale (10-16) mean(SD)	8.53(0.99)	8.04(1.49)	7.53(2.03)	0.017 mild vs severe p=0.020
Sum Tinetti scale mean(SD)	24.33(1.50)	23.13(3.06)	21.24(4.89)	<0.001 mild vs severe p<0.001
CDR –SB mean(SD)	n=94 0.85(0.67)	n=41 1.16(1.13)	n=23 1.57(1.31)	0.003 mild vs severe p=0.003

WML = white matter lesion, F = Fazekas score, CDR-SB = clinical dementia rating scale sum of the boxes

Table 4. White matter lesion severity and cognition [mean(SD)]

WML severity	Mild (n = 137, F=0,1)	Moderate (n = 60, F=2)	Severe (n = 26, F=3)	P-value (ANOVA Test)
TMSE (0-30)	24.30(3.07)	23.30(4.02)	22.32(4.38)	0.016 mild vs severe p=0.030
Verbal fluency (animal)	N=97 15.18(4.42)	N=42 12.19(3.87)	N=19 10.32(5.13)	0.999
Action fluency	8.65(3.87)	7.67(3.97)	5.84(4.29)	0.015 mild vs severe p=0.016
ISSAC 15 (animal, fruit, color, province)	23.60(7.56)	19.86(6.77)	16.16(8.62)	<0.001 mild vs mod p=0.008 mild vs severe p<0.001
Visual memory (sum family picture score)	N=96 19.84(6.56)	N=40 16.98(5.94)	N=18 12.22(7.67)	<0.001 mild vs severe p<0.001 mod vs severe p=0.034
Wechsler: LM I LM II	9.16(6.58) 5(5.97)	6.02(5.04) 3.39(3.20)	5.95(5.23) 2.18(3.69)	0.006 0.034 mild vs mod p=0.017
Trail A (Sec)	N=92 129.92(96.09)	N=39 193.23(143.27)	N=17 179.82(101.68)	0.008 mild vs mod p=0.010
Trail B (Sec)	N=74 254.42(146.24)	N=26 296.42(241.54)	N=9 384.89(278.44)	0.114

TMSE = Thai mental state examination, WML = white matter lesion, F= Fazekas score, LM = logical memory

Table 5. White matter lesion severity and comorbidities

WML severity	Mild (n=137, F=0,1)	Moderate (n=60, F=2)	Severe (n= 26, F=3)	P-value
Memory complaint (subject or caregiver)	84(61.31%)	47(78.33%)	23(88.46%)	0.001
Number of NCD comorbidities				0.021
0	44(32.12%)	11(18.33%)	5(19.23%)	
1	58(42.34%)	18(30%)	9(34.62%)	
2	26(18.99%)	21(35%)	9(34.62%)	
3+	9 (6.57%)	10(16.67%)	3(11.54%)	
ApoE4 status: ApoE4 carrier(N=211)	N=130 21(16.2%)	N=56 18(32.1%)	N=25 9(36%)	0.004
Serum Homocysteine µmol/L mean(SD)	n=122 13.83(4.52)	n=50 15.50(4.68)	n=23 17.96(3.62)	<0.001 mild vs severe p<0.001
Thai GDS levels	N=107	N=40	N=22	0.035
Normal(0-12)	80(74.77%)	28(70%)	10(45.45%)	
Mild(13-18)	14(13.08%)	9(22.5%)	7(31.82%)	
Moderate(19-24)	13(12.15%)	2(5%)	5(22.73%)	
Severe(>24)	0(0%)	1(2.5%)	0(0%)	
MTA right	N=134	N=60	N=26	<0.001
0	21(15.67%)	4(6.67%)	0(0%)	
1	57(42.54%)	24(40%)	5(19.23%)	
2	39(29.1%)	15(25%)	10(38.46%)	
3	17(12.69%)	17(28.33%)	8(30.77%)	
4	0(0%)	0(0%)	3(11.54%)	
MTA left	N=134	N=60	N=26	0.001
0	31(23.13%)	5(8.33%)	1(3.85%)	
1	51(38.06%)	23(38.33%)	6(23.08%)	
2	40(29.85%)	20(33.33%)	10(38.46%)	
3	12(8.96%)	12(20%)	8(30.77%)	
4	0(0%)	0(0%)	1(3.85%)	
Global cortical atrophy score	N=137	N=60	N=26	0.001
0	9(6.57%)	4(6.67%)	3(11.54%)	
1	74(54.01%)	26(43.33%)	12(46.15%)	
2	52(37.96%)	30(50%)	7(26.92%)	
3	2(1.46%)	0(0%)	4(15.38%)	
Presence of lacuna infarction	20(14.6%)	27(45%)	12(46.2%)	<0.001
Presence of cerebral microbleeds	7(5.1%)	12(20%)	10(38.5%)	<0.001

WML = White matter lesion, F = Fazekas score, NCD = non –communicable disease, MTA= medial temporal atrophy score
Comorbidities include coronary artery disease, cerebrovascular disease, chronic obstructive pulmonary disease, osteoarthritis, hypertension, dyslipidemia, diabetes mellitus, hypo or hyper thyroidism, current smoking, and current alcohol drinker.

Discussion

We found that the prevalence of severe WML was higher in MCI and dementia elders than controls. Severe WML in Thai elders was associated with poor gait and balance, poor daily function, poor global cognition, worse category fluency, worse visual memory score and worse Trail A score. ApoE4 gene status and presence of depression were related to cerebral WML. The ignorance of our population regarding vitamin supplementation could possibly affect homocysteine status leading to the presence of cerebral WML. This study is the first epidemiological neuro-imaging study in Thai elderly and first WML study in elderly community cohort in Thailand. Our findings are in consistent with previous reports.[10-18] White matter lesions on MRI are seen as dots or confluent areas in bilateral cerebral hemispheric white matter. They look hyperintense on T2-weighted and fluid-attenuated inversion recovery images (FLAIR). Their location, their related vascular risk factors, and their pathology make WML a small vessel disease indicator. WMLs are known to be associated with Alzheimer disease, vascular dementia, and ageing population. Potential mechanism of cognitive decline from WMLs includes disruption of the frontal-subcortical circuits from cardiovascular risk factors, microangiopathy, lacuna infarction, cortical atrophy, and age-dependent neuronal changes. Previous studies found that subjects with severe WMLs and with small vessel ischemic vascular dementia or WML with stroke had small hippocampal volume of high MTA score.[19,20] Our findings had also observed high global cortical atrophy and more atrophy of MTA in those severe WML group. High serum homocysteine has been known to related to WML, lacunar infarction, and dementia[21]. Our population showed high levels of homocysteine in severe WML group. These data should confirm the important issue of risk management with high vitaminB6, B12 and folic acid intake in every day diet in order to help reduce stroke burden. Our data revealed that WMLs were associated with poor gait and balance, poor daily function, and increased number of comorbidities. Gait and daily function are important issues in elders. This indicates a potential intervention with modified vascular risks to prevent progression of WM burden. Regular physical exercise, vascular risk modification, and low fat low sugar diet should be encouraged to help reduce stroke burden. Non modifiable vascular factors namely age and ApoE4 carrier status are robustly found to be related to WML.

The limitation of this study is that we have only cross-sectional data and one center. Multi sites and follow up study are needed. The strong point of our data is that this report is the first time community study of brain MRI WML in elders. We utilized different measures but obtained robust results. We demonstrated the important of WML burden in Thai elderly population.

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