ApoE Genotype and Its Influence on Magnetic Resonance Imaging Brain Pathology

Vorapun Senanarong
Mara Ten Kate

Abstract

Background: Apolipoprotein E e4 (ApoE e4) genotype is a risk factor for sporadic Alzheimer's disease (AD). It is known that ApoE e4 is associated with increased atrophy of medial temporal in subjects with AD. Relative sparing of medial temporal lobe in non-carriers, especially early-onset AD. Furthermore, subjects with ApoE e4 often have an increased burden of small vessel disease in the brain.

Objectives: To assess effects of ApoE e4 genotype on MRI pathology in a Thai sample at the memory clinic at Siriraj Hospital.

Material and Methods: Patients with memory problems who had magnetic resonance imaging (MRI) of the brain and ApoE genotype analysis at the memory clinic, Siriraj Hospital during 2010-2015 were recruited in this study. Small vessel pathology from MRI of the brain including Fazekas (F) score, Age-Related White Matter Changes (ARWMC) on Magnetic Resonance Imaging (MRI), Medial temporal Lobe Atrophy (MTA) score, Posterior Cortical Atrophy (PCA) score, Global Cortical Atrophy (GCA) scale, number of lacunar infarction and number of large vessel infarction.

Results: One hundred and eleven individuals from the memory clinic at Siriraj Hospital were included. Thirty-one were ApoE e4 carriers. Mean age of ApoE E4 carriers was 70.4 ± 10.2 and mean age of ApoE e4 non-carriers was 68.6 ± 7.9. Only moderate to severe white matter lesions on Fazekas scale were associated with ApoE e4 carrying status.

Conclusion: We found that ApoE e4 genotype was related to small vessel brain pathology. Due to small sample size, only white matter lesions of the brain assessed by Fazekas scale was significant related to ApoE e4 status in our study.

Keywords: ApoE e4, dementia, MCI, white matter lesions, small vessel disease

Vorapun Senanarong[1], Mara Ten Kate[2]
[1]Division of Neurology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University
[2]Department of Radiology, VU Medical Center, University, Amsterdam, the Netherland

Corresponding author:
Associate Professor Dr Vorapun Senanarong
Division of Neurology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University
email vorapun.sen@mahidol.ac.th

Background

Late-onset Alzheimer Disease (LOAD) is the most common form ofAlzheimer Disease (AD) LOAD is defined by onset age older than 65 years. The established gene variant of the LOAD risk factor is the apolipoprotein E e4 (ApoE e4) allele[1]of the apolipoprotein E gene on chromosome 19q13. In subjects with AD, there is an increased hippocampal atrophy.[2] Previous studies showed that the APOE e4 allele drives atrophy to the medial-temporal lobe region in AD and mild cognitive impairment (MCI).[3] In normal ageing, there is an increased burden of small vessel diseases.[4,5] Those with ApoE e4 carriers, the vascular burdens in the brain are more prominent.

Objectives

We aimed to assess effects of ApoE e4 genotype on MRI pathology in a Thai sample at the memory clinic at Siriraj Hospital during 2010-2015.

Materials & Methods

Patients with memory problems who had magnetic resonance imaging (MRI) of the brain and ApoE genotype analysis at the memory clinic, Siriraj Hospital during 2010-2015 were recruited in this study. Small vessel pathology from MRI of the brain including Fazekas (F)[6] score, Age-Related White Matter Changes (ARWMC)[7,8] on Magnetic Resonance Imagings (MRI), Medial temporal Lobe Atrophy (MTA)[9] score, Posterior Cortical Atrophy (PCA)[10] score, Global Cortical Atrophy (GCA)[11] scale, numbers of lacunar infarction and numbers of large vessel infarction. The visual ratings were performed by MTK who was a radiologist in training and a PhD student in Neuroradiology and Neurology at VU Medical Center, VUniversity, Amsterdam, the Netherlands. Dementia was diagnosed by DSM IV TR[12] and standard dementia criteria. Mild cognitive impairment(MCI)[13] was diagnosed by P5etesen's criteria. SPSS 18 was used. Chi Square test and Fisher Exact Test were used to compare proportions of a categorical outcome according to different independent groups. The non-parametric Mann-Whitney U test was used in place of an unpaired t-test. P value of <0.05 was regarded as statistical significance. The Institute Review Board (IRB) at Faculty of Medicine Siriraj Hospital, Mahidol University had approved this study under the study of the memory clinic at Siriraj Hospital.

Results

One hundred and eleven individuals from the memory clinic at Siriraj Hospital were included. Thirty-one were ApoE e4 carriers. Fifty-three had mild cognitive impairment (MCI) and twenty-two had dementia. Mean age of ApoE e4 carriers was 70.4 ± 10.2 and mean age of ApoE e4 non-carriers was 68.6 ± 7.9. Table 1 showed subject's characteristics and table 2showed results of the study. Figure 1. demonstrated the mean MTA by ApoE e4 status of the whole samples.

Table 1 Subjects' characteristics

	Ncarriers (n=80)on	Carriers (n=31)	P value
MCI	46 (57%)	13 (42%)	p = 0.14
AD	15 (19%)	7 (23%)	p = 0.65
Mixed dementia (AD & VaD)	3 (4%)	2 (6%)	p = 0.62
VaD	5 (6%)	2 (6%)	p = 1
Subjective memory complaint, no cognitive impairment	7 (9%)	3 (10%)	p = 1
Dementia of unknown causes	4 (5%)	0	
Gender male / female	28 / 52	14 / 17	p = 0.32
Age mean ± SD	68.6 ± 7.9	70.4 ± 10.2	p = 0.29

MCI= Mild cognitive impairment, AD= Alzheimer Disease, VaD= Vascular dementia

Data were presented as count (%) or mean ± SD.

Chi square / Fisher's exact test were utilized

Table 2 Results of visual rating measures of small vessel diseases and large vessel infarction in ApoE e4 carriers and non-carriers

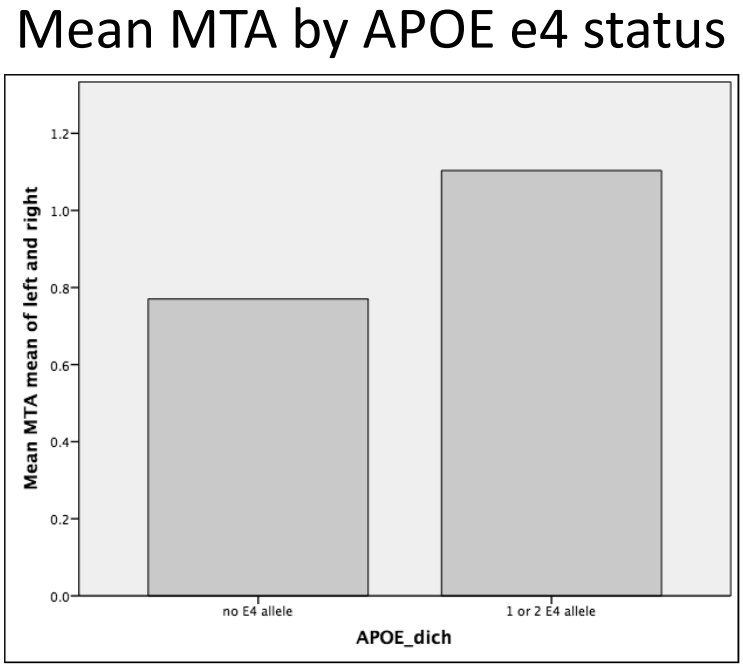
	Non carriers (n=80)	Carriers (n=31)	P value
MTA mean	0.78 ± 0.68	1.1 ± 1.1	p = 0.30
MTA max	1.00 ± 0.78	1.3 ± 1.2	p = 0.24
MTA dich ≥ 2	20 (27%)	12 (41%)	p = 0.16
MTA dich age	14 (19%)	8 (28%)	p = 0.33
GCA	0.87 ± 0.69	0.93 ± 0.78	p = 0.73
GCA dich ≥ 1	54 (69%)	20 (67%)	p = 0.80
PCA	1.2 ± 0.70	1.2 ± 0.88	p = 0.96
PCA dich ≥ 1	65 (83%)	22 (73%)	p = 0.24
Fazekas	1.1 ± 0.89	1.4 ± 0.89	p = 0.10
Fazekas dich ≥ 2	20 (27%)	14 (47%)	p < 0.05*
ARWMC	5.11 ± 4.7	6.4 ± 5.2	p = 0.28
ARWMC dich ≥ 9	16 (22%)	10 (35%)	p = 0.20
Lacunes	23 (31%)	6 (20%)	p = 0.27
Large vessel infarction	5 (7%)	2 (7%)	p = 1

ApoE= Apolipoprotein E, MTA= Medial temporal lobe atrophy, GCA= Global cortical atrophy, PCA= Posterior cortical atrophy, ARWMC= Age related white matter change, Fazekas= Fazekas scale

Data were presented as count (%) or mean ± SD.

Mann Whitney U and Chi square tests were used.

Figure 1 The mean MTA by ApoE e4 status of the whole samples



ApoE= Apolipoprotein E, MTA= Medial temporal lobe atrophy scale

Discussion

We had demonstrated that individuals with dementia, MCI, and those with memory complaints were affected ApoE e4 genotype on white matter lesions of the brain. Small vessel cerebrovascular disease is a possible mechanism through which ApoE e4 may convene risk for AD and other dementia such as vascular dementia.

A recent meta-analysis[14] had shown that ApoE e4 is associated with white matter hyper intensities (WMHs) or white matter lesions (WMLs). Thus, ApoE e4 interacts with severity of WMHs to forecast dementia.Previous studyalso identified regional affected of ApoE e4. Brickman and coworkers[4] showed that ApoE e4was associated with increased WMHs in parietal regions and that WMHs in the parietal lobes was associated with a higher proportion of dementia. While in another study[5], they observed that ApoE e4 carriers had significantly more frontal WMH volume and increased PET-PiB SUV in frontal lobe relative to controls.Longitudinally, Longitudinally, they found progression of frontal WMH volume in ApoE e4 group was faster than non-carrier group. The ApoE e4 carriers, baseline and progression of frontal WMH volume was related with declining trend of cognition in ApoE e4 carriers.

A 5-year longitudinal study on healthy older adults[15] revealedthat over 5 years compared to non-carriers, declining ApoE e4 carriers had statistical significantly greater rates of atrophy in left and right cortical gray matter, left and right hippocampi, and greater expansion of the right inferior lateral ventricle.They concluded that ApoE e4 was related to the variability in phenotypic expression in neurodegeneration.

In the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort[16], they reported significant baseline structural differences in APOE e4 carriers

relative to non-carriers. This included the left hippocampus atrophy more than the right. A difference was more pronounced in e4 homozygotes than heterozygotes. They founded the longitudinal effects of APOE genotype on hippocampal morphometry at 6-, 12- and 24-months. There was significant morphological deformation in APOE e4 carriers relative to non-carriers in all longitudinal studies.

Our findings did not show the effect of ApoE e4 on global cortical atrophy or medial temporal atrophy assessed by visual rating scales. These were due to the limitations of the study namely it was limited number of subjects and limited number of dementia patients. We suggested a larger sample size and suggested a longitudinal follow up in the future.

Conclusion

We found that ApoE e4 genotype was related to small vessel brain pathology. Due to small sample size, only white matter lesions of the brain assessed by Fazekas scale was significant related to ApoE e4 status in our study.

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