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Association of Apolipoprotein E Polymorphism with Cognitive Functions in Elderly

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ABSTRACT

Objective: This study aims to examine the association between apolipoprotein E polymorphism (APOE) and cognitive functions test using Montreal Cognitive Assesment- Indonesian version 2012 (MoCA-Ina) in elderly.

Method: A cross-sectional study of 112 elderly participants from two nursing homes in Jakarta. APOE gene polymorphism was analyzed using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP).

Results: There are four genotypes: E2/E2 10(8.9%), E3/E3 38(33.9%), E3/E4 46(41.1%) and E4/E4 18(16.1%). The percentage of E2 allele 20(8.9%), E3 122(54.5%), E4 82(36.6%). The cognitive function test, MoCA-Ina ≥ 26: 34(40%) participants with genotype E2/E2 3(8.8%), E3/E3 7(20.6%), E3/E4 16(47.1%) and E4/E4 8(23.5%). MoCA-Ina < 26: 51(60%) 51 participants with genotype E2/E2 7(13.7%), E3/E3 14(27.5%), E3/E4 22(43.1%) and E4/E4 8(15.7%). A significant relationship between APOE gene polymorphism with MoCA-Ina-abstraction: E3/E4 vs. E3/E3 p 0.019, E4/E4 vs. E3/E3 p = 0.028, a significant relationship between APOE gene polymorphism with MoCA-Ina-language: E3/E4 vs. E2/E2 p = 0.03, E4/E4 vs. E2/E2 p 0.029, and a significant relationship between APOE gene polymorphism with naming: E3/E4 vs. E2/E2 p = 0.048.

Conclusion: High percentage of APOE allele E4 may be one of the causes of high cognitive function decline. APOE gene polymorphisms associated with the decreased cognitive function; abstraction, language, and naming. Allele E4 may be a potential factor for cognitive function decline.

Keywords: *MoCA-Ina, Elderly, polymorphism, APOE, gene.*

INTRODUCTION

Dementia is a complex neurodegenerative disease in the elderly with multifactorial causes and characterized by various cognitive abnormalities, which could interfere with daily activities. [1, 2] Alzheimer's Disease (AD) is one of the most common types of dementia and associated with the aging process. AD results in a gradual decline in cognitive functions and daily activity due to degeneration processes that damage the brain structures and neurotransmitters. [1,3] In the AD, the patient's ability to remember, understand, communicate and comprehend causality decreases gradually, which ultimately lead to death. [1, 3-5] Many factors can clinically affect the progress of the damage, including brain atrophy[1, 6-8], vascular factor[1, 9] and immunological factor.[1, 10] Currently 35 million people have dementia worldwide, expected to reach 65 million by 2030 and 113 million by 2050. [5] The prevalence of dementia in Indonesian older adults aged 65 years is 5% and increases to 20% at aged above 85. [11]

A genetic factor that is known to play a role in the development of AD is the APOE gene polymorphism, lies on chromosome 19 and has three alleles: E2, E3, E4 and six genotype variations: E2/E2, E2/3, E2/4, E3/

E3, E3/E4 and E4/E4.[12, 13] The allele E4 is associated with an increased risk of the AD (14-16), whereas the allele E2 appears to be a protective factor.[5, 17] Having APOE genotype E4/E4 not only increases the risk of AD but also affects the cognitive symptoms and neuroanatomical forms of the disease. E4 carriers tend to have worse memory decline compared to non-carriers, while the APOE E4 non-carrier tend to have more difficulty maintaining attention, working memory, executive functions, and lexical access.[14]

This genetic factor is stronger in the European population[18] and weaker in the African, American and Hispanic community.[5, 19] Recent studies show that the effects of APOE E4 allele on cognitive functions depend on the age and level of education of the individuals.[20] It is still debatable whether APOE E4 is related to cognitive functions or cognitive impairment.[20] With polymerase chain reaction-restriction fragment length polymorphism, the association between APOE E4 polymorphism and cognitive function was analyzed.

MATERIALS AND METHOD

Collection of Samples

Participants of this a cross-sectional was 112 elderly aged between 60 - 90 years, consisting of 99 women and 13 men from two nursing homes in Jakarta. The DNA was analyzed to find out APOE genotypes. Cognitive functions examination was carried out on 85 female participants using MoCA-Ina questionnaire and its items (visuospatial, naming, attention, language, abstraction, memory delay, orientation) from the neurology department, University of Indonesia. MoCA-Ina scores divided into normal cognitive function ≥26 and cognitive impairment <26.

PCR-RFLP Analysis

Blood samples obtained from a peripheral vein using 3 ml vacutainer tubes containing EDTA. The blood samples were centrifuged for 30 minutes at 3000 rpm and separated into serum from sediment. The sediment Examinated for APOE genes. DNA is extracted from blood samples using a DNA Extraction Kit (Bioline) according to the manufacturer's instructions.

DNA extraction

200 ul of the blood sample inserted into a 1.5 ml sterile microcentrifuge tube. 20 ul Proteinase K then added into the tube. The solution is homogenized by pipetting and then incubated at 60 ° C for 5 minutes. Add 200 ul Buffer GSB (Geneid) and vortex the tube. Incubate the tube again at the same temperature for 2 minutes. Add ethanol absolute (96%) and vortex for 10 seconds. Pour the mixture into the spin column and centrifugate at 14,000 xg for 1 minute. Remove the collection tube under the spin column and replace it with a new one. Add 400 ul of buffer W1 and centrifuge for 30 seconds with the same speed. Discard the liquid that is on the collection tube. Add 600 ul of wash buffer (Geneid), centrifuge the mixture for 30 seconds, and dispose of liquid in the collection tube. Centrifuge again for 3 minutes. Remove the collection tube and place a sterile microcentrifuge below the spin column. Next, add 100 ul of Elution buffer. Let the mixture stand for 3 minutes and then centrifuge with the same speed for 30 seconds. The fluid containing the DNA stored in a microcentrifuge tube at -20 ° C and will be used as template DNA for PCR.

The genotype of the APOE gene

The extracted DNA added into PCR Mix, which consists of 5 µL 5X buffer, 2 µL MgCl2, 1 µL dNTP mix, 1 µL APOE-F Primer (5'-ACA GAA TTC GCC CCG GCC TGG TAC AC-3') , 1 µL Primary APOE-R (ApoE-R: 5'-TAA GCT TGG CAC GGC TGT CCA AGG A-3'), 0.25 µL Hotstart Taq (Qiagen) enzyme, 5 µL DNA template and free-water nuclease. The total volume is 50 µL. The amplification process started with one cycle of pre-denaturation at 95°C for 7 minutes. It was followed by 40 cycles of the following steps: denaturation at 95°C for 45 minutes, followed by annealing 65°C for 45 seconds and extension at 72°C for 1 min. The gene polymorphism determined using PCR-RFLP in 112 subjects, and the APOE gene was successfully amplified at 244 bp band, three alleles and six genotypes could be generated after excavation with HhaI endonuclease restriction (BioLabs).

Data Analysis

The statistical analysis was done to examine the relationship between APOE genotypes and alleles with MoCA-Ina questionnaire and its items (visuospatial, naming, attention, language, abstraction, memory delay, orientation).

RESULTS

MoCA-Ina questionnaire were conducted to determine the number of research participants who had with impaired cognitive function. The effect of APOE gene E4 on the cognitive function is different according to age.[17]

Table 1. Relationship between MoCA-Ina score and age

MoCA-Ina	Age (years), Frequency in % (n)		
	60 – 70	71 – 80	81 – 90
≥ 26	38.24 (13)	38.24 (13)	23.52 (8)
< 26	21.57 (11)	45.1 (23)	33. 33 (17)

Fisher's Exact Test Exact: Sig. (2-sided) p 0.239

As shown in table 1; 85 participants divided into three groups: age group of 60-70, 71-80 and 81-90 years. The age group of 60 - 70 years: Percentage of participants with MoCA-Ina ≥ 26: 38.24% (13) and < 26: 21.57%(11). The age group of 71 - 80 years: Percentage of participants with MoCA-Ina ≥ 26: 38.24%(13) and < 26: 45.1%(23). For the age group of 81 - 90 years: Percentage of participants with MoCA-Ina ≥ 26: 23.52%(8) and < 26: 33.33%(17). These results show an increase in the percentage of impaired cognitive function in the age group of 71-80 years, indicating the highest number of participants with mild cognitive impairments. There was an insignificant relationship between MoCA-Ina and age groups with p = 0.239.

Table 2. Relationship between age groups and MoCA-Ina items

Age Group	MoCA-Ina Item	P-Value (Mann-Whitney)
60-70 vs 71-80	Naming	0.035
	Orientation	0.036
71-80 vs 81-90	Naming	0.018
	Orientation	0.036
60-70 vs 81-90	Naming	0.000

Table 2 shows a significant decrease in the MoCA-Ina item naming when comparing the groups 60-70 vs. 71-80 years with p = 0.035, and the groups 71-80 vs. 81-90 years with p = 0.018. A significant decrease in the MoCA-Ina item orientation is also observed when comparing the groups the 60-70 vs. 71-80 years with p = 0.036, 71-80 vs. 81-90 years with p = 0.036 as well as 60-70 vs. 81-90 with p = 0.00.

Table 3. PCR-RFLP Analysis of APOE gene polymorphism

	Genotype Frequency, % (n)				Allele Frequency, % (n)		
	E2/E2	E3/E3	E3/E4	E4/E4	E2	E3	E4
Total = 112	8.9 (10)	33.9 (38)	41.1 (46)	16.1 (18)	8.9 (20)	54.5 (122)	36.6 (82)

Table 3 shows the APOE gene polymorphism by PCR-RFLP.of all 112 participants. Results of shows the distribution of genotypes: E2/E2 8.9%(10), E3/E3 33.9%(38), E3/E4 41.1%(46), E4/E4 16.1%(18). The allele distribution were: E2 8.9% (20), E3 54.5%(122), E4 36.6%(82).

Table 4. Relationship MoCA-Ina score and APOE gene polymorphism

		Genotype frequency, % (n)				Allele frequency, % (n)		
		E2/E2	E3/E3	E3/E4	E4/E4	E2	E3	E4
MoCA-Ina Total= 85	≥26 (34)	8.8 (3)	20.6 (7)	47.1 (16)	23.5 (8)	8.8 (6)	44.1 (30)	47.1 (32)
	<26 (51)	13.7 (7)	27.5 (14)	43.1 (22)	15.7 (8)	13.7 (14)	49.0 (50)	37.3 (38)

Fisher's Exact Test Exact: Sig. (2-sided) p = 0.704

Table 4 shows the APOE gene polymorphism amongst 34 participants who obtained MoCA-Ina ≥ 26: E2/E2 8.8%(3), E3/E3 20.6%(7), E3/E4 47.1%(16), E4/E4 23.5%(8). The 51 participants who obtained MoCA-Ina < 26 consist of: E2/E2 13.7%(7), E3/E3 27.5% (14), E3/E4 43.1%(22), E4/E4 15.7%(8).

Tabel 5 : Relationship APOE gene polymorphism and MoCA-Ina items

Genotype Comparison	MoCA-Ina Item	P-Value (Mann-Whitney)
E3/E4 vs E3/E3	Abstraction	0.019
E3/E4 vs E2/E2	Language	0.03
	Naming	0.048
E4/E4 vs E3/E3	Abstraction	0.028
E4/E4 vs E2/E2	Language	0.029

Table 5 shows a comparison between the APOE genotypes regarding items from MoCA-Ina in 85 participants. Analysis shows a significant relationship between APOE gene polymorphism and Abstraction: E3/E4 vs E3/E3 with p 0.019, E4/E4 vs E3/E3 with p = 0.028, language: E3/E4 vs E2/E2 with p 0.03, E4/E4 vs E2/E2 with p 0.029, as well as the item naming: E3/E4 vs E2/E2 with p 0.048. The allele E4 may be a contributing factor to the impairment of abstraction, language and naming abilities.

DISCUSSION

Memory seems to be of paramount importance as far as the cognitive decline is concerned, and other symptoms tend to receive less attention. This study shows that the age group 71-80 years is the most susceptible towards dementia with the highest percentage of individuals with impaired cognitive functions and the percentage decreases in the 81-90 year age group. This situation is not common as the risk of dementia increases with age. A significant drop in the item naming when comparing the age groups 60-70 vs. 71-80 with p = 0. 035, and 71-80 vs. 81-90 with p = 0.018. A significant decrease is also observed for the item orientation when comparing the age groups 60-70 vs71-80 with p = 0.036, 71-80 vs. 81-90 with p = 0.036 as well as 60-70 vs. 81-90 with p = 0.00.

The DNA analyzed using PCR RFLP of the 112 study participants found distribution of APOE gene polymorphism: E2/E2 8.9%(10), E3/E3 33.9%(38), E3/E4 41.1%(46) and E4/E4 16.1%(18). The alleles distribution were: E2 8.9% (20), E3 54.5%(122), E4 36.6%(82). A study in Dong-gu Korea, found distribution of APOE gene polymorphism in the population: E2/E2 0.4%, E2/E3 10.7%, E2/E4 1.3%, E3/E3 71%, E3/E4 15.6% and E4/E4 1%. The alleles distribution were: E2 11.2%, E3 71%, E4 16.6%. Another Korean study in Namwon demonstrated the following genotype distribution: E2/E2 0.4%, E2/E3 10.2%, E2/E4 1.1%, E3/E3 72.6%, E3/E4 14.9% and E4/E4 0.9%. The alleles distribution as follows: E2 10.6%, E3 72.6%, E4 15.7%. The occurrence of the allele E4 in this study (Jakarta) is thus more-than-twice higher than that of the two above mentioned Korean studies. [13]

The relationship between APOE gene polymorphism and the MoCA-Ina- item abstraction is as follow: E3/E4 vs. E3/E3 p 0.019, E4/E4 vs. E3/E3 p 0.028. Between APOE gene polymorphism and the item language: E3/E4 vs. E2/E2 p 0.03, E4/E4 vs. E2/E2 p 0.029. Between APOE gene polymorphism and the item naming: E3/E4 vs. E2/E2 p 0.048. The E4 may be a potential factor contributing to the impairment of abstraction, language and naming abilities. Naming should receive attention as the dominant symptom of cognitive function decline. In a study by Coleman et al in Frontotemporal Dementia and Related Disorders patients with MoCA-Ina questionnaires, the sub-item naming and delay memory were most frequently detected in MCI / mild cognitive impairment patients. [21] This corresponds to the conclusion drawn by David A. Wolk et al. that APOE gene polymorphism has a significant effect on cognitive functions and brain anatomical abnormalities. [14]

CONCLUSION

This study found that Decade seventh is the vulnerable group with the highest percentage with impaired cognitive functions. A high percentage of APOE allele E4 may be one of the causes of steep cognitive function decline and a higher risk for dementia. In determining the symptoms of dementia/ decline in cognitive function should not be fixated on memory loss but may be preceded by other symptoms, e.g., abstraction, language, orientation and especially naming.

Ethical Clearance - Taken from Hasanuddin University Ethics Committee, approval number: 130 /

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