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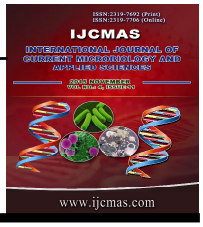

Original Research Article

Role of Genetic Risk Factor APOEε4 and Peripheral Inflammation Marker in Amnestic Mild Cognitive Impairment and Alzheimer's disease

R.F. Situmeang[1,2,3], E.J. Wahjoepramono[2,3], C. Kaelan[4,5], J.S. Purba[6], Suhadi FXBe,[3] As'ad S,[7] A. Aliah[4,7], I. Patellongi[7] and S. Wahid[5,7]

[1]Memory clinic Siloam Hospitals Lippo Village, Tangerang, Indonesia
[2]Neuroscience Department, Siloam Hospitals Lippo Village, Tangerang, Indonesia
[3]Doctoral Program, Faculty of Medicine, Pelita Harapan University, Tangerang, Indonesia
[4]Neurology Department, Hasanuddin University, Makassar, Indonesia
[5]Pathology Anatomy Department, Hasanuddin University, Makassar, Indonesia
[6]Neurology Department, University of Indonesia, Jakarta, Indonesia
[7]Doctoral Program, Hasanuddin University, Makassar, Indonesia
**Corresponding author*

Keywords

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A B S T R A C T

Alzheimer's Disease (AD) is the leading cause of dementia. APOEε4 is a strong genetic risk factor for AD. Inflammation has been shown to play a role in cognitive decline and AD. Correlations between peripheral inflammation markers and cognitive decline are still inconclusive. Moreover, pathogenic link between APOEε4 and inflammation leading to AD is challenging. Objectives of the study are to find correlations between APOEε4 and peripheral inflammation markers in amnestic mild cognitive impairment (aMCI) and AD Cross-sectional, comparative analysis. Sixty subjects (AD: 20, aMCI: 17, normal cognition: 23) were included. Subjects carrying ε4 allele were more likely to have AD by 3.9-fold, increased to 13-fold in subjects ≤70 years. There is a significant correlation between IL-10 HS level and cognitive function which showed the role of anti inflammation in aMCI and AD. Subjects with APOEε4 have higher mean Hs-CRP level compare to non-carriers. Correlations between APOEε4(+) and other inflammatory markers are not significant. Different with mainstream hypothesis which state the role of proinflammatory cytokines that elaborate progressive synaptic and neuritic injury in AD, our study found the significant correlation between anti-inflammatory marker (IL-10 HS) and cognitive decline instead of proinflammatory markers such as Hs-CRP and IL-6 HS. This result needs further investigation to understand the potential pathogenic link between APOEε4, inflammation, and cognitive function.

Introduction

Dementia is a syndrome due to disease of the brain – usually of a chronic or progressive nature – in which there is disturbance of multiple higher cortical functions, including

memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgment. Alzheimer's disease is the most common form of dementia and possibly contributes to 60–70% of cases. It is approximately occurred in 13% of people over the age of 65 to 45% people over the age of 85 (Alzheimer's Association. 2012). The strongest risk factor for AD is the ε4 allele of the apolipoprotein E (APOE) (Corder *et al.*, 1993; Bu, 2009; Huang and Mucke, 2012). There are three polymorphic alleles of APOE gene—ε2, ε3 and ε4—which APOE ε3 allele is the most frequent in worldwide population (77.9%), followed by ε4 (13.7%) and ε2 (8.4%) (Farrer La, 1997). Risk of AD was increased in individual with one copy of ε4 allele (heterozygote) and even higher in two copies (homozygote) (Farrer La, 1997).

ApoE isoforms have distinct functions in regulating brain lipid transport, glucose metabolism, neuronal signalling, neuroinflammation, and mitochondrial function (Liu *et al.*, 2013; Reiman *et al.*, 2009). Neuroinflammation contributes to neuronal damage in the brain and is implicated in AD pathogenesis. ApoE colocalizes with plaque-associated amyloid and microglia, suggesting a role for ApoE innate immune response in AD. Immunohistological evidence demonstrates that ApoE is co-deposited in senile plaques in the brains of AD patients (Namba *et al.*, 1991). ApoE4 seems to have proinflammatory and/or reduced anti-inflammatory function, which could further exacerbate AD pathology. In addition, young APOE ε4 carriers show an increased inflammatory response that may relate in AD risk later in life. Consistent with this notion, non-steroidal anti inflammatory drugs were shown to reduce AD risk only in APOE ε4 carrier, suggesting that APOE genotype might determine the effect of anti-inflammatory medication for AD.

Mild Cognitive Impairment (MCI) is a transitional stage between normal cognitive function and dementia. Amnestic MCI (aMCI) is associated with increased risk of AD (Morris *et al.*, 2001), is estimated to progress into clinically diagnosable AD in 10–15% of cases per year, compared to a rate of 1–2% per year among healthy elderly individuals (Petersen *et al.*, 1999). APOE ε4 affects memory performance in people with MCI (Smith *et al.*, 1998; Farlow *et al.*, 2004), both in middle age (40–59 years) and elderly (60–85 years) people (Ramakers *et al.*, 2008; Dik *et al.*, 2000). In addition, MCI patients with APOE ε4 experience more-rapid decline in several cognitive and functional assessments (Farlow *et al.*, 2004; Bunce *et al.*, 2004; Lin *et al.*, 2012), which leads to increased risk of progression from MCI to AD-type dementia (Caselli *et al.*, 2009; Liu *et al.*, 2013; Eriksson *et al.*, 2011). Consistent with younger age of AD onset in individuals with APOEε4, it also applies in aMCI (O'Bryant *et al.*, 2010). These findings indicate that the APOE ε4 genotype in patients with MCI can serve as a predictive factor for determination of clinical outcome and the risk of conversion to AD (O'Bryant *et al.*, 2010).

In the present report, we studied the correlations between genetic risk factor APOEε4 with peripheral inflammation marker in both aMCI and AD.

Materials and Methods

Subjects in this study were patients who visited memory clinic of Siloam Hospitals Lippo Village from September 2013 to September 2014. We included all subjects who fulfilled inclusion criteria: 1) age >60 years old, 2) able to speak Bahasa or English

(premorbid), 3) able to read and write (premorbid). We excluded subjects with impaired renal function and subjects with major vascular lesions or other structural lesions in MRI.

Subjects were categorized into three clinical diagnoses: normal aging, amnestic mild cognitive impairment, and AD. We performed physical, neurological, and neurobehavioral examinations including Mini Mental Status Examination (MMSE), Montreal Cognitive Assessment (MoCA), and Consortium to Establish a Registry of Alzheimer's Disease (CERAD). We used AD-8 questionnaire and Instrumental Activity Daily Living (IADL) to determine impairments on activities of daily living. We determined severity of AD using Clinical Dementia Rating Scale (CDRS) and Global Deterioration Scale (GDS). MRI test was executed on subjects who had stroke history or suspected to have other causes of dementia.

We performed blood test to examine ureum, creatinine, APOEε4 with restriction fragment length polymorphism, high sensitive C-reactive protein, high sensitive interleukin-6 and high sensitive interleukin-10. All data analyses were performed using IBM SPSS statistics (IBM Corp. Released 2011, version 20 Armonk, NY, US). The measures were expressed as mean ± standard deviation. We evaluated the association between two qualitative variables using Chi Square Test and the association between qualitative variable and quantitative variable using "t-test". We performed multivariate analysis using logistic regression and the correlation test. A probability value less than 5% was considered statistically significant. Research ethical board of Mochtar Riady Institute of nanotechnology approved this study. We obtained written informed consent from all patients.

Results and Discussion

A total of 80 subjects in memory clinic were evaluated in which 65 patients among them met our inclusion criteria. We excluded five subjects due to a major infarct in MRI findings (one subject) and the impairment of renal function (four subjects). Sixty subjects were eligible for further step analyzing. Diagnosis is divided into 3 groups: AD: 20, aMCI: 17, and normal cognition: 23 subjects. Forty-two subjects were women (70%) and unlike common demographic profile in Indonesia, half of the subjects had high education level (>12 years of formal education) (Table 1).

There is a significant correlation between APOE ε4 genotype with cognitive function in HC versus AD group (Table 2). Subjects carrying the ε4 allele were more likely to have AD by 3.9 times compared to non-carriers. The risk of AD is increased in subjects with age-group ≤70 years (OR 13). Mean of peripheral inflammation markers are higher in AD groups compare to HC and aMCI groups, particularly significant in IL-10 HS level (Table 3). Correlation between peripheral inflammation marker and cognitive function is significant in IL-10 HS level as an anti-inflammatory in HC compared to aMCI and AD group (Table 3). There is no correlation between two proinflammatory markers (Hs-CRP and IL-6) and cognitive function.

We investigated the mean difference of Hs-CRP, IL-6 HS, and IL-10 HS in APOEε4+ carriers compared to non-carrier and found it significant in Hs-CRP (Table 4). Subjects with APOEε4+ have higher mean Hs-CRP level than APOEε4(-). We found no significant correlation between APOE ε4 genotype and level of IL-6 HS and IL-10 HS.

The ε4 allele of APOE as the strongest genetic risk factor for AD has been confirmed by genome-wide association studies (Bunce *et al.*, 2004; Lin *et al.*, 2012). To our knowledge, investigation about the role of APOEε4 in AD incidence among Indonesian has not been established. In population-based studies, the APOEε4 –AD association was weaker among African Americans (ε4/ε4, OR 5.7) and Hispanics (ε4/ε4, OR 2.2) and was stronger in Japanese people (ε4/ε4, OR 33.1) compared with Caucasian cases (ε4/ε4, OR 12.5) (Caselli *et al.*, 2009). In this study, the role of APOEε4 as strong genetic risk factor had been proven; showing an increased risk of up to 4-fold for carrier APOEε4 carriers to have AD than non-carriers. This risk is increased into 13-fold for subjects with age group ≤70 years, indicating that APOEε4 confers dramatically increased risk of development of AD with an earlier age of onset.

Inflammation has been shown to play a role in cognitive decline and AD (Liu *et al.*, 2013). In this study, there is no correlation between proinflammatory markers (Hs-CRP and IL-6 level) and cognitive function. There is a tendency that means of those markers were lower in aMCI and higher in AD compare to HC subjects. Honolulu-Asia Aging Study (HAAS) found high CRP level measured in midlife was associated with a threefold increased risk of developing AD or dementia later in life (Eriksson *et al.*, 2011). It is possible that increased inflammation in midlife is either detrimental than increased level later in life or that measuring CRP in midlife better captures lifelong inflammatory exposure than measuring inflammatory markers in aged population with a high burden of morbidity. One study supporting our result found lower mean CRP levels in AD (2.9 µg/mL) versus controls (4.9 µg/mL; p= 0.003) and vascular dementia (VaD) (O'Bryant *et al.*, 2010). Other study found that lower levels of CRP were associated with more rapid cognitive and functional decline over time in patients diagnosed with AD, it was hypothesized that CRP levels would be decreased in patients with AD relative to controls (Locascio *et al.*, 2008). Histopathologically, CRP has been found in association with both neurofibrillary tangles and senile plaques in AD tissue (O'Bryant *et al.*, 2010). However, CRP levels did not predict AD development in the Conselice Study of Brain Aging over a 4-year period (Ravaglia *et al.*, 2007). Similarly, over an average of a 5.7-year follow-up period, CRP levels did not predict the development of AD among participants from the Rotterdam Study (van Oijen *et al.*, 2005). A separate analysis of a subgroup of the Rotterdam Study found a weak relationship between CRP and AD development through a strong relationship with VaD development (Engelhart *et al.*, 2004). Cross-sectionally, very little data exist regarding serum CRP levels in patients with established AD. A small study found that CRP levels were elevated in AD and VaD (Gupta *et al.*, 2004).

We found no association between IL-6 HS level and the risk of AD. This is in line with a population study from Sweden found that serum IL-6 and Hs-CRP levels were not associated with risk of AD and high serum IL-6 levels may be associated with increased risk of non-AD dementia (Sundelof *et al.*, 2009). Other studies found inconclusive results, some reported that IL-6 serum level to be decreased (Angelis *et al.*, 1998), unchanged (Hasegawa *et al.*, 2000), or increased (Bagli *et al.*, 2003) in AD.

Mean of IL-10 HS level is significantly higher in aMCI and AD compared to HC. There is also a significant correlation between IL-10 HS level and cognitive

function. It has been hypothesized that polymorphisms of interleukin IL-10 genes affect the risk of developing late onset Alzheimer's disease (AD). However, results of different studies are often inconsistent. From a meta-analysis study showed that IL-10 polymorphism (-1082G/-819C/-592C haplotype) is associated with a lower risk of AD; this effect is more evident in the oldest patients (Di Bona *et al.*, 2012). In our study, the correlation between IL-10 HS and cognitive function was observed in all age group; there was no difference in the younger age groups (<70 years) or older age groups.

Table.1 Subjects characteristics

Characteristics	n (%)	AD (n= 20)	MCI (n= 17)	HC (n= 23)	p*
Age group (years)		Mean±SD	Mean±SD	Mean±SD	0.000
60-69	26(43.3)	75.4±5.57	69.3±6.7	68.1±5	
70-79	29(48.3)				
≥80	5(8.4)				
Sex					
Female/Male	18(30)/42(70)	15/5	7/10	17/6	0.492
Education level (years)		Mean±SD	Mean±SD	Mean±SD	
< 6	7 (11.7)	11.3±4.1	13.1±3.5	13.78 ±3.2	0.08
7-12	24(40)				
> 12	29(48.3)				
Hipertension					
Yes/No	25(41.7)/35(58.3)	9/11	7/10	9/14	0.926
Diabetes Mellitus					
Yes/No	12(20)/48(80)	5/15	3/14	4/19	0.791
Family history of AD					
Yes/No	8(13.3)/52(86.7)	5/15	2/15	1/22	0.135
Genotip APOE (ε4+/ ε4-)					
a. APOEε4/4	4(6.7)				
b. APOEε3/4	13(21.7)	9/11	6/11	4/19	0.03
c. APOEε2/4	2(3.3)				
d. APOEε3/3	36(60)				
e. APOEε2/3	5(8.3)				
Inflammation Markers (Mean±SD)					
a. Hs-CRP (mg/l)	2.89±5.44	2.77±4.14	2.13±1.23	3.67±8.34	0.08
b. IL-6 HS (pg/ml)	2.60±2.53	2.12±0.97	2.24±1.42	3.46±3.98	0.17
c. IL-10 HS (pg/ml)	0.403±0.147	0.37±0.16	0.42±0.13	6.42±0.14	0.03

Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment; HC, healthy control.
* For categorical variables, Pearson chi-square was used to compute the *p* value. For continuous variables, one-way analysis of variance was used to compute the *p* value.

Table.2 Correlation between APOE ε4 genotype with cognitive function

		APOE ε4+	
Cognitive Function	***p* value**	**OR**	**95% CI**
Health control vs MCI	0.1961	2.59	0.47; 15.09
Age ≤70 y.o	0.507	1.85	0.19; 17.52

Age >70 y.o	0.2367	4.5	0.22; 274.78
Normal vs AD	0.049	3.88	0.81; 20.9
Age ≤70 y.o	0.0281	13	0.63; 732.84
Age >70 y.o	0.2656	3.6	0.28; 192.71
MCI vs AD	0.549	1.5	0.33; 7.02
Age ≤70 y.o	0.1243	7	0.32; 418.61
Age >70 y.o	0.8086	0.8	0.09; 7.51

Using chi-square test

Table.3 Correlation between peripheral inflammation markers and cognitive function group

Cognitive Function	Hs-CRP (mg/l)		IL-6 HS (pg/ml)		IL-10 HS (pg/ml)	
	Mean±SD	*p* value	Mean±SD	*p* value	Mean ± SD	p value
HC	2.77±4.14	0.205*	2.12±0.97	0.473*	0.37±0.16	0.029*
aMCI	2.13±1.23	0.054†	2.24±1.42	0.150†	0.42±0.13	0.041†
AD	3.67±8.34	0.032‡	3.46±3.98	0.201‡	0.42±0.14	0.482‡

Using Spearman 1 tail test

***** HC vs aMCI

† HC vs AD

‡ aMCI vs AD

Table.4 Correlation between APOE ε4 and peripheral inflammation markers

	APOEε4+	APOEε4-	r	*p* value
Hs-CRP (mg/l)	3.15±8.49	2.77±3.34	-0.368	0.002
IL-6 HS (pg/ml)	2.38±1.42	2.70±2.91	0.11	0.466
IL-10 HS (pg/ml)	0.38±0.13	0.41±0.15	-0.129	0.164

Using Spearman 1 tail test

Correlation between APOEε4 and inflammation has been stated by several studies. ApoE can modulate the functions of macrophages, suppress the proliferation of T cells, maintain the integrity of blood brain barrier (BBB) and blood nerve barrier (BNB), inhibit the proliferation of smooth muscle (SM cell), up regulate the production of nitric oxide (NO) of platelets, and facilitate the presentation of lipid antigen by CD-1 molecules to natural killer T (NKT cell) (Zhang *et al.*, 2011). Several studies demonstrated that exogenously applied apoE4 had robust proinflammatory activity in astrocytes and microglial cells (Guo *et al.*, 2004). Our study found that subjects with APOEε4+ have higher mean Hs-CRP level which in line with those studies mentioned above. We found no significant correlation between APOEε4 genotype and level of IL-6 HS and IL-10 HS.

Conclusions

Inflammation has been shown to play a role in cognitive decline. Activation of inflammatory processes is observed in periphery of subjects with Alzheimer's disease (AD). Whether or not inflammation represents a possible cause of AD or occurs as a consequence of the disease process, or, alternatively, whether the inflammatory response might be beneficial to slow the disease progression remains to be

elucidated. Different with mainstream hypothesis which state the role of proinflammatory cytokines that elaborate progressive synaptic and neuritic injury in AD, our study found the significant correlation between anti-inflammatory marker (IL-10 HS) and cognitive decline instead of proinflammatory markers such as Hs-CRP and IL-6 HS. This result needs further investigation to understand the potential pathogenic link between APOEε4, inflammation, and cognitive function.

Conflict of interest

The authors do not have any direct financial relation with the trademarks mentioned in the paper that might lead to a conflict of interest for any of the authors. The authors declare no potential conflict of interest. The authors would like to thanks contributors who collected samples as well as patients and their families, whose participations and help make this work possible.

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