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Apolipoprotein E Genotypes and Behavioural and Psychological Symptoms of Dementia (BPSD) in Malaysian Patients with Dementia

(Genotip Apolipoprotein E dan Gejala Tingkah Laku dan Psikologi Demensia (BPSD) dalam Kalangan Pesakit Demensia di Malaysia)

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ABSTRACT

*The aim of this study was to determine the relationships between ApoE genotypes and 'behavioural and psychological symptoms of dementia' (BPSD). A cross-sectional study was conducted on 46 outpatients with dementia (aged 60 and above) and their caregivers attending the psychogeriatric clinics at Universiti Kebangsaan Malaysia Medical Centre (UKMMC) and Hospital Kuala Lumpur. Neuropsychiatric Inventory (NPI) was used for the assessment of BPSD. The patients' blood samples were taken for Apolipoprotein genotyping after consented by the caregivers. There were more female (69.6%) and Chinese (50%) patients with a mean age of 73.7 years. ApoE ε3/ε3 was the most common ApoE allele (60.7%) and mostly found in Chinese patients. ApoE genotype was significantly associated with ethnicity (*p*=0.03) and marital status (*p*=0.01). Alzheimer disease was the most common subtype of dementia (41.3%) and the highest carrier of ApoE ε3/ε3 (30.4%). The ApoE ε4/ ε4 scored highest in BPSD median score 44 (17.5 to 90) but the relationships between ApoE genotypes and subtypes of dementia or BPSD scores were not significant (*p*=0.20; *p*=0.64). Agitation was the most common symptom, with delusions showing the highest scores on the NPI with no significant association to ApoE 4 allele. In conclusion, there was no significant relationship between ApoE genotypes and severity or types of BPSD in dementia patients.*

Keywords: Apolipoprotein E; dementia

ABSTRAK

*Tujuan kajian ini adalah untuk menentukan kaitan antara jenis gen Apolipoprotein (Apo) E dan gejala tingkah laku dan psikologi demensia (BPSD). Satu kajian menggunakan kaedah hirisan lintang telah dikendalikan dalam kalangan sekumpulan 46 pesakit luar yang berumur 60 tahun ke atas bersama dengan penjaga masing-masing di klinik psikogeriatrik di Pusat Perubatan Universiti Kebangsaan Malaysia (PPUKM) dan Hospital Kuala Lumpur. 'BPSD' pesakit telah dinilai dengan menggunakan inventori neuropsikiatri (NPI). Sampel darah pesakit diambil untuk menentukan genotip Apolipoprotein E setelah kebenaran diberi oleh penjaga pesakit. Terdapat lebih ramai pesakit perempuan (69.6%) dan berketurunan Cina (50%) dengan min umur 73.7 tahun. ApoE ε3/ε3 merupakan alel ApoE yang terbanyak (60.7%) dan banyak terdapat dalam kalangan pesakit berketurunan Cina. Genotip ApoE berkait rapat secara signifikan dengan bangsa (*p*=0.03) dan status perkahwinan (*p*=0.01). Penyakit Alzheimer merupakan jenis demensia yang terbanyak (41.3%) dan pembawa ApoE ε3/ε3 (30.4%) yang tertinggi. ApoE ε4/ ε4 menunjukkan skor median BPSD yang tertinggi iaitu 44 (17.5-90) tetapi tiada kaitan rapat secara signifikan antara genotip ApoE dan jenis-jenis demensia atau skor BPSD (*p*=0.20; *p*=0.64). Agitasi merupakan gejala yang paling kerap berlaku dan delusi menunjukkan skor NPI yang tertinggi, tetapi keduanya tiada kaitan rapat yang signifikan dengan alel ApoE. Kesimpulannya, tiada hubungan yang signifikan antara genotip ApoE dengan keterukan atau jenis BPSD dalam kalangan pesakit demensia di Malaysia.*

Kata kunci: Apolipoprotein E; demensia

INTRODUCTION

Apolipoprotein E (ApoE) was initially known to be involved in the transport of cholesterol and development of cardiovascular disease but more recently, its role has extended to other biological processes not directly related to lipoprotein transport, including, immunoregulation, nerve regeneration, tissue repair, cognitive functioning and Alzheimer disease (AD). ApoE is now identified as a non-modifiable factor of dementia and the only valid determinant of AD of the sporadic type (Seripa et al. 2009).

ApoE exists in people in three different forms or alleles (ApoE 2,3,4) which differ from each other by one to two base pairs. Each person has two copies of the ApoE gene. Thus an individual could have any of the following combinations: ApoE 2/2, 3/3, 4/4, 2/3, 3/4 and 2/4. The ApoE locus on chromosome 19 is a gene that contributes to the susceptibility of a person for AD. The progression of

illness and age of onset of AD is influenced by the ApoE polymorphism, defined by these three alleles of the gene: ε2 (normal); ε3 and ε4 (dysfunctional).

The risks of getting Alzheimer disease increases by a factor of 4 if an individual has one copy of the ApoE ε4 gene and a factor of 10 if having two copies of the ApoE ε4 gene (Bales et al. 2002), more likely for the late-onset AD (Wijsman et al. 2011). However, there is also evidence that the ApoE2 allele may serve as a protective role in AD (Corder et al. 1994). The genotype most at risk for AD at earlier age is the homozygous ApoE 4/4, at higher risk than the ApoE 3/4 genotype. The genotypes ApoE 3/3 is considered to be at normal risk for AD and ApoE 2/3 at a lesser risk for the disease. Interestingly, people with both a copy of the 2 allele and the 4 allele, ApoE 2/4, are at normal risk similar to the ApoE 3/3 genotype. Slooter et al. (1997) reported that the ApoE ε4 allele has been known to be a genetic risk factor for dementia with stroke, including vascular dementia (VaD), AD with cardiovascular diseases (CVD) and other dementias, like dementia of Lewy Body (DLB).

The distribution of ApoE alleles vary in different ethnic groups throughout the world (Corbo & Scacchi 1999). It was noted that the most common in all human societies is the ApoE allele 3, especially in populations with long-established agricultural economy (Takeda et al. 2010). Frequencies of the ApoE4 allele are reported to be relatively increased in healthy Africans and some non-Africans, including indigenous people in Malaysia by about 14–41% (Kalaria et al. 2008). A study by Wan et al. (2004) which had determined ApoE genotyping in Malaysia, found that the most common ApoE genotype among the Malays, Chinese and Indians was E3/E3, thus making E3/E3 as the most common ApoE allele among Malaysians. This study also reported that the ApoE ε2 allele was totally absent among the Indians.

Behavioural and psychological symptoms of dementia (BPSD) are non-cognitive symptoms commonly experienced by dementia patients. The most common are depressive symptoms followed by anxiety and paranoid or schizophreniform psychosis. It is important to recognize the coexistence of BPSD as they are responsible for the increased number of hospitalizations or emergency room visits, premature institutionalizations, increased burden of care, disability in patients with dementia and diminished quality of life for patients and caregivers. A Brazilian study on BPSD reported that almost 80% of patients with AD had one or more symptoms whereby apathy was present in more than half (53%), followed by depression (38%), sleep alterations (38%) and anxiety (25%) (Tatsch et al. 2006).

There have been equivocal opinions as whether ApoE causes BPSD (Pritchard et al. 2007). Studies have shown that ApoE 4 carriers are significantly more likely to demonstrate agitation and aggression in AD (Craig et al. 2004) and have a 19.0-fold risk of developing hallucinations and 3.4 – fold risk for delusions (Chang et al. 2004). A study in Taiwan by Chen et al. (2011) found that ApoE ε 4 had higher risk for subsyndromal agitation /aggression and delusion in AD. Unfortunately, there is a lack of local data on the ApoE genotyping in dementia. This study aimed to identify ApoE genotypes of patients with dementia and investigate for their associations with disturbing behavioural and psychiatric symptoms.

Materials and Methods

This cross-sectional study was conducted in the outpatient psychogeriatric clinics of UKM Medical Centre (UKMMC) and Hospital Kuala Lumpur (HKL) from March to June 2011. UKMMC is a university hospital serving the population of the southern part of Kuala Lumpur, particularly, the area of Cheras and receives referrals from most hospitals and private clinics in the Klang Valley. Hospital Kuala Lumpur is Malaysia's premier and biggest Government- funded hospital, serving as a major tertiary-level hospital for referrals nationwide. UKM Medical Molecular Biology Institute (UMBI) was formed in July 2003 and is recognised as a Higher Institution Centre of Excellence (HICoE) by the Ministry of Higher Education in molecular science research. ApoE genotyping on blood samples taken from patients was done here.

The study subjects comprised of a dyad group of elderly outpatients aged 60 years and above, diagnosed as having dementia and their caregivers. All patients involved in this study had been diagnosed as Dementia according to DSM-1V TR by the psychogeriatricians. They comprised of newly referred patients as well as those already on follow-up visits at the clinics. Dementia was classified into Alzheimer's type, Vascular type and Others for statistical analysis. Exclusion criteria included patients with major psychiatric diagnoses other than dementia, those under institutional care (nursing home or old folks' home), those who were cared for by hired sitters or housemaids at home or those whose caregivers refused to allow consent for this study.

The patients and their caregivers were explained about the study before consent was taken from the latter. Confidentiality was assured by identifying subjects through a registration numbering system instead of using patients' names. After undergoing psychological assessments, the patients' blood were taken and sent for ApoE genotyping on the same day.

Information on sociodemographic data and clinical information were gathered using a questionnaire to be filled by the caregiver. The information was later confirmed through patients' medical notes if caregivers were unable to verify any information. BPSD was assessed using the neuropsychiatric inventory questionnaire (NPI) (Cummings et al. 1994).

The NPI is a relatively brief interview (10-15 min) assessing non-cognitive symptoms of dementia. It has 10 behavioural disturbance domains covering delusion, hallucination, dysphoria/depression, anxiety, agitation/aggression, euphoria, disinhibition, irritability/lability, apathy and aberrant motor behaviour. Night time behaviour and eating changes had been later included in the list. Specific follow-up questions were used to confirm the

presence of symptoms. Caregiver was asked to score the frequency of these symptoms as: 1 (occasionally), 2 (often), 3 (frequently) and 4 (very frequently). Each domain would be scored between 0-12 with a total score of all domains of 0 to 144. Caregiver was asked to score their distress level whether; not all, minimal, mild, moderate, severe and very severe. Permission to use this questionnaire had been granted by the author, Jeffry L. Cummings. This research project had been approved by the UKMMC Ethical Committee and the Ministry of Health National Medical Research Register.

Results

A total of 74 dementia patients were offered to participate in the study from HKL and UKKMC Psychogeriatric clinics. However, 28 subjects had to be excluded from the study due to patients being too agitated and uncooperative for assessment of blood-taking, clotted blood specimens, language difficulties, coming from nursing homes or were being cared for by their housemaids. So, only 46 blood samples were able to be genotyped for ApoE alleles within the stipulated research period.

APOE genotypes and socio demographic and clinical characteristics of the patients

Relationships between ApoE and all sociodemographic data are illustrated in Table 1. The most common ApoE genotype was ApoE ε3/ε3 (60.7%), followed by ApoE ε3/ε4 (13%), ApoE ε2/ε3 (10.8%), ApoE ε4/ε4 (8.7%) and ApoE ε2/ε4 (6.25%). There were no patients with ApoE ε2/ε2. ApoE ε3/ε3 was the most frequent genotype among all the three major races, more so among the Chinese and this distribution showed significant statistical difference (p=0.03). ApoE ε3/ε3 was also statistically more significant among the married subjects than those without spouse (0.01). However, ApoE genotyping did not show any significant statistical difference in its association with other sociodemographic data such as age, gender, education achievement and employment.

Similarly, ApoE was not significantly related to the types of dementia, age of onset of dementia or family history of dementia. Similar negative finding was also found in the poor relationship between ApoE genotype and medical comorbidities such as diabetes mellitus, hypertension or heart disease.

APOE genotype and BPSD

The most common BPSD was agitation (73.9%), followed by apathy (67.4%), delusions (67%), irritability (67%) and sleeping problems (65.2%) (Figure 1). However, delusions rated the highest BPSD total score (115) followed by hallucinations (104) and apathy (92) (Table 2). x^2 Kruskal Wallis test showed that among the ApoE genotypes, ApoE ε4/ ε4 scored the highest with a BPSD median score of 44 (17.5 to 90) (Table 3). However, the relationship between ApoE genotypes and BPSD score was not significant (p=0.64).

TABLE 1. Relationship between ApoE genotype and socio demographic data

ApoE genotype	ε2/ε3 *n*=5	ε3/ ε3 *n*=28	ε2 /ε4 *n*=3	ε3/ ε4 *n*=6	ε4 /ε4 *n*=4	test	*p*
Age							
60-69 (*n*=10)	3(6.5)	8(17.4)	1 (2.2)	1(2.2)	0	x^2	0.25
70-79 (*n*=21)	1(2.2)	13(28.3)	1 (2.2)	5(10.9)	4(8.7)		
≥80 (*n*=5)	1(2.2)	7(15.2)	1 (2.2)	0	0		
Gender							
Female (*n*=32)	1(2.2)	10(21.7)	0	2(4.3)	1(2.2)	x^2	0.73
Male (*n*=14)	4(8.7)	18 (39.1)	3(6.5)	4(8.7)	3(6.5)		
Race							
Malay (*n*=14)	0	11(23.9)	1(2.2)	1(2.2)	1(2.2)	x^2	0.03
Chinese(*n*=23)	4(8.7)	12(26.1)	2(4.3)	5(10.9)	0		
Indian (*n*=8)	1(2.2)	5(10.9)	0	0	2(4.3)		
Others (*n*=1)	0	0	0	0	1(2.2)		
Employment							
Never had(*n*=13)	2(4.3)	6(13)	1(2.2)	2(4.3)	2(4.3)	x^2	0.73
Ever had (*n*=33)	3(6.5)	22(47.8)	2(4.3)	4(8.7)	2(4.3)		
Marital status							
Married (*n*=29)	4(8.7)	18(39.1)	0	6(13)	1(2.2)	x^2	0.01
No spouse(*n*=17)	1(2.2)	10(21.7)	3(6.5)	0	3(6.5)		
Education							
Low(*n*=33)	5(10.9)	19(14.3)	3(6.5)	5(10.9)	1(2.2)	x^2	0.89
High(*n*=13)	0	9(19.6)	0	1(2.2)	3(6.5)		

x^2 Pearson chi square

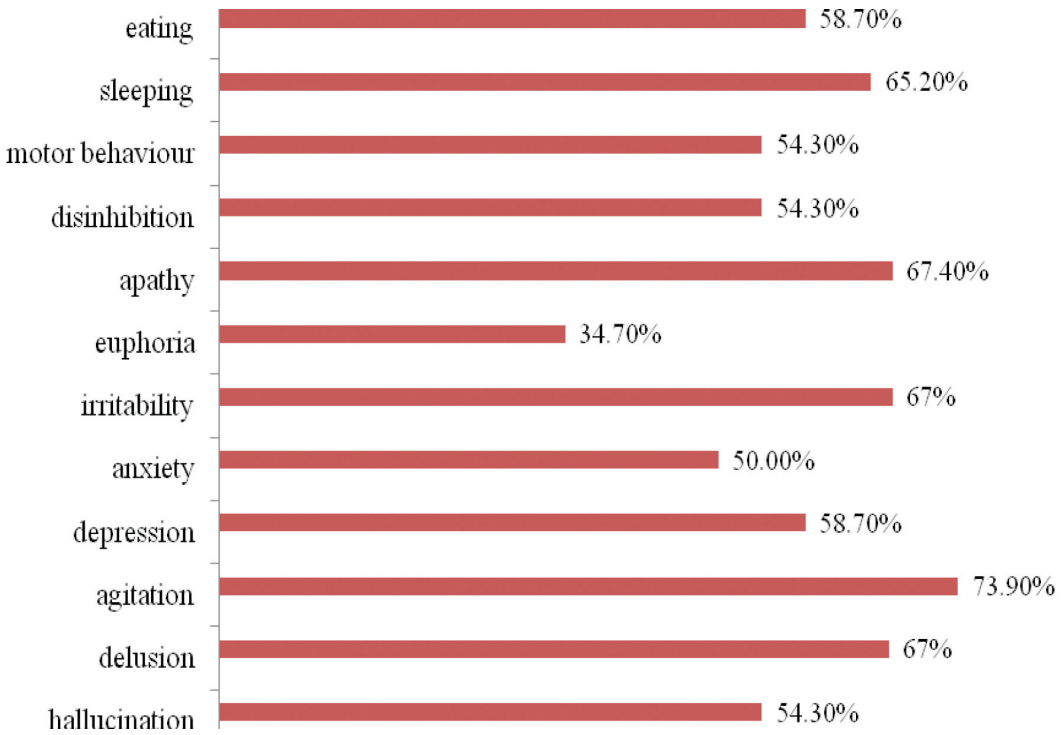

FIGURE 1. Frequency distribution of BPSD domains

TABLE 2. Total scores of BPSD symptoms

BPSD symptoms	Total score
Hallucination	104
Delusion	115
Agitation	78
Depression	53
Anxiety	51
Irritability	88
Euphoria	26
Apathy	92
Disinhibition	50
Motor behaviour	51
Sleeping problem	84
Eating problem	45

TABLE 3. Relationship between ApoE genotype and BPSD score

APOE genotype	BPSD SCORE	x^2	df	*p*
ε2/ε3 *n*=5	29(IQR: 14 - 31)			
ε3/ ε3 *n*=28	19 (IQR:7.5 - 38.5)	1.67	3	0.64
ε2 /ε4 *n*=3	35 (IQR:28 - 45.5)			
ε3/ ε4 *n*=6	12.5(IQR: 6 - 47)			
ε4 /ε4 *n*=4	44 (17.5 - 90)			

x^2 Kruskal wallis test

Statistical analysis using chi square test showed that most BPSD symptoms were more predominantly presented in the ApoE genotype ε3/ε3 such as eating disorder (52.2%), delusions (43.5%) and agitation (41.3%) (Table 4). However, none of the ApoE genotypes showed any significant association with the different types of BPSD. Only 28.3% of the patients had ApoE 4 alleles. Similarly, there were no significant associations between ApoE 4 and subtypes of dementia (p=0.51), between ApoE 4 and agitation (the most common BPSD) (p=0.73) or between ApoE 4 and psychosis (delusions and hallucinations) (p=0.33).

DISCUSSION

In this study, of 46 patients with dementia, the most common ApoE allele was ApoE ε3/ ε3. Such finding was also reported by Wan et al. (2004) in a local population study and by Tan et al. (2003) in a study on Singapore population. Both studies also reported relatively lower incidence of ApoE ε4 than other genotypes. This study revealed significant relationship between ApoE genotype and ethnicity, similar to that of a study cited by Kalaria et al. (2008). In this study, Chinese patients constituted 50% of the subjects and this reflected the racial distribution

TABLE 4. Relationship between ApoE genotype and BPSD

BPSD	ε2/ε3 *n*=5	ε3/ ε3 *n*=28	ε2 /ε4 *n*=3	ε3/ ε4 *n*=6	ε4 /ε4 *n*=4	test	*p*
Hallucination							
No (*n*=21)	3(6.5)	12 (26.1)	1(2.2)	3(6.5)	2(4.3)	x^2	0.943
Yes (*n*=25)	2(4.3)	16(34.8)	2 (4.3)	3(6.5)	2(4.3)		
Delusion							
No (*n*=17)	3(6.5)	8(17.4)	1(2.2)	3(6.5)	2(4.3)	x^2	0.604
Yes (*n*=29)	2(4.3)	20(43.5)	2(4.3)	3(6.5)	2(4.3)		
Anxiety							
No (*n*=18)	2(4.3)	11(23.9)	0	4(8.7)	1(2.2)	x^2	0.383
Yes (*n*=28)	3(6.5)	17(37)	3(6.5)	2(4.3)	3(6.5)		
Depression							
No (*n*=22)	2(4.3)	14(30.4)	1(2.2)	4(8.7)	1(2.2)	x^2	0.714
Yes (*n*=28)	3(6.5)	14(30.4)	2(4.3)	2(4.3)	3(6.5)		
Apathy							
No (*n*=19)	3(6.5)	13(28.3)	0	2(4.3)	1(2.2)	x^2	0.444
Yes (*n*=27)	2(4.3)	15(32.6)	3(6.5)	4(8.7)	3(6.5)		
Euphoria							
No (*n*=23)	1(2.2)	13(28.3)	2(4.3)	5(10.9)	2(4.3)	x^2	0.293
Yes (*n*=23)	4(8.7)	15(32.6)	1(2.2)	1(2.2)	2(4.3)		
Agitation							
No (*n*=15)	1(2.2)	9(19.6)	1(2.2)	4(8.7)	6(13)	x^2	0.243
Yes (*n*=31)	4(8.7)	16(41.3)	2(4.3)	2(4.3)	4(8.7)		
Irritability							
No (*n*=23)	3(6.5)	16(34.8)	1(2.2)	3(6.5)	0	x^2	0.277
Yes (*n*= 23)	2(4.3)	12(26.1)	2(4.3)	3(6.5)	4 (8.7)		
Disinhibition							
No (*n*=13)	3(6.5)	11(23.9)	1(2.2)	3(6.5)	1(2.2)	x^2	0.832
Yes (*n*=23)	2(4.3)	17(37)	2(4.3)	3(6.5)	3(6.5)		
Motor behaviour							
No (*n*=20)	3(6.5)	12(26.1)	1(2.2)	4(8.7)	0	x^2	0.280
Yes (*n*=26)	2(4.3)	16(34.8)	2(4.3)	2(4.3)	4(8.7)		
Sleeping							
No (*n*=18)	3(6.5)	11(23.9)	0	3(6.5)	1(2.2)	x^2	0.482
Yes (*n*=28)	2(4.3)	17(37)	3(6.5)	3(6.5)	3(6.5)		
Eating							
No (*n*=8)	0	4(8.7)	0	2(4.3)	2(4.3)	x^2	0.207
Yes (*n*=38)	5(10.9)	24(52.2)	3(6.5)	4(8.7)	2(4.3)		

x^2 Pearson chi square test

of Kuala Lumpur (DBKL 2012). Another reason for the ethnic differences could be due to the different subjective experience of burden of care among the different races, as reported in other local studies on dementia (Choo et al. 2003; Rosdinom et al. 2011a) and on Parkinson disease caregivers (Rosdinom et al. 2011b). The Chinese caregivers experienced higher level of burden compared with the Indians and Malays, thus tend to bring their relatives with dementia for treatment more readily than others. Cultural misperception towards dementia as part of normal ageing among the Malays might also be another contributing factor as to the lower percentage in Malay patients seeking treatment in hospitals.

There were no significant relationships between ApoE genotypes and the patients' clinical characteristics (duration of having dementia, family history of dementia and medical comorbidities) or the age of onset of the BPSD symptoms. On the contrary, a study by Romas et al. (2002) among Caribbean Hispanics showed that ApoE ε4 allele carriers had increased risk of developing early onset AD.

In this study, ApoE ε3/ε3 was the most prevalent of the ApoE genotypes and patients with ApoE ε3/ε3 had significantly higher BPSD score and experienced a wider range of BPSD symptoms than other ApoE alleles. Patients with ApoE4 allele, despite their smaller number, exhibited more hallucinations, agitation, delusion and apathy. The

high percentage of agitation in ApoE 4 allele was also reported in a study by Craig et al. (2004) which showed that those with ApoE ε4 genes were significantly more likely to demonstrate agitation.

Depression was more likely to occur in patients with ApoE ε3, similar to findings of a study reported by Liu et al. (2002) which did not find any association between depression and the presence or absence of the epsilon4 or epsilon2 allele. However, other studies have shown that depressive symptomatology in AD might be related to low serum cholesterol in ApoE ε2 carriers (Holmes et al. 1996) and less likely in AD with ApoE ε4 (Ballard et al. 1997). Hallucinations and delusions were higher in ApoE ε3/ε3 genotype, which differed from findings by Zdanys et al. (2007) in which psychotic symptoms were associated with ApoE ε4 in the AD patients. Another interesting finding in this study was that there were more sleeping and eating disorders occurring in patients with the ApoE ε3/ε3 genotype, even though their relationships were not significant.

There were several limitations of this study which could have influenced the outcome of study. The small number of subjects could have affected the power of this study. Most of the study variables were not normally distributed and all the results not conclusive even though some of them had significant relationships and had similar outcomes as previous studies. One option was to recruit study subjects from other hospitals and community-based populations so that it would be more representative of the true population of Malaysia. A bigger sample size would allow classification into the different types of dementia and comparison with different types of BPSD.

Blood-taking procedure has always been unpopular and many caregivers refused to be involved as it made patients agitated during the procedure. This further reduced the number of potential suitable study subjects.

In this study, the NPI (Malay version) had not been validated in the local population. BPSD severity was assessed using the NPI, which involved subjective assessment by the caregivers. Distressed caregivers tend to score higher for the BPSD severity compared with non-distressed caregivers. There was possibility of under-reporting by the caregivers of certain symptoms due to cultural reasons or lack of awareness of these symptoms as part of the illness. In the other questionnaires, treatment history was not included in this study. This is a relevant issue as BPSD symptoms; frequency, severity and its total score might be influenced by treatment used, for example, anti- psychotics, benzodiazepines, antidepressant or hypnotics.

The role of ApoE as a biomarker in the early intervention of dementia against development of BPSD is still not proven. Other biomarkers such as neuroimaging findings when used together with ApoE may be more reliable in the study on BPSD. A comparative study between ApoE ε4 groups and non ApoE ε4 or case control study would have been a better choice.

Conclusion

In this study, dementia was more prevalent among the Chinese patients with females experiencing more severe BPSD. Other socio demographic variables did not show any significant associations with BPSD. Depression, sleeping disorder and disinhibition were significantly presented in Dementia of Alzheimer type even though the BPSD median scores were higher in other types of dementia. Agitation was the most common symptom, with delusions showing the highest scores on the NPI.

ApoE genotype was significantly associated with ethnicity and marital status. The most common genotype was ApoE ε3/ε3, more so among the Chinese patients. Alzheimer disease was the most common subtype of dementia and the highest carrier of ApoE ε3/ε3.

The ApoE allele 4 occurred more frequently in Dementia of Alzheimer type with ApoE ε4/ ε4 scoring the highest BPSD median score 44 (17.5 to 90). However, there were no associations between ApoE genotypes and subtypes of dementia or BPSD scores. Neither was there any association between ApoE 4 allele and agitation or psychosis.

Despite of the lack of significant associations between ApoE genotypes and types or severity of BPSD among our population, it is hoped that some of the findings from this study may offer insight into our patients' genetic predisposition to dementia and BPSD.

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