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ApoE and Quality of Life in Nonagenarians

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Abstract

Objectives—ApoE ε4 is associated with adverse health conditions that negatively impact the quality of life (QOL). The relationship between ApoE ε4 and QOL has not been explored in the oldest old. Our study aimed to examine ApoE in the oldest old, and explore its association with QOL.

Design—Cross-sectional cohort study.

Setting—A medium sized community in Olmsted County, Minnesota, USA.

Participants—90–99 year old individuals living independently or in long term care environments.

Measurements—We collected demographic information and measured cognitive function (Short Test of Mental Status [STMS], Mini-Mental State Examination [MMSE], Mattis Dementia Rating Scale [DRS]), QOL (Linear Analogue Self Assessment [LASA]) and ApoE distribution. Subjects were classified as cognitively normal, mild cognitive impairment (MCI), dementia (DEM), or dementia with stroke and/or parkinsonism (DEMSP). Regression model was used to assess the predictors of QOL.

Results—121 subjects (45 cognitively normal, 13 MCI, 34 DEM, 29 DEMSP) aged 90–99, 106 (87.6 %) females, were included. Frequency of ApoE ε3 allele was highest [194 (80.2%): ε2/3 18, ε3/3 77, ε3/4 22] followed by ApoE ε4 [25 (10.3%): ε2/4 3, ε3/4 22] and ApoE ε2 [23 (9.5%): ε2/2 1, ε2/3 18, ε2/4 3]. None of the subjects carried ApoE ε4/4 genotype. QOL was similar between ApoE ε4 carrier and non-carriers. Physical well-being, emotional well-being, intellectual well-being, social connectedness and coping ability were positively associated with QOL, whereas male gender, DEMSP, pain frequency and pain severity were negatively associated.

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Conclusions—The most common ApoE in the oldest old was $\epsilon 3/3$ genotype and $\epsilon 3$ allele. No association was found between ApoE $\epsilon 4$ and QOL. However, those with high physical, emotional and intellectual well being, social connectedness and coping ability had the highest overall QOL.

Keywords

Well being; oldest old; apolipoprotein E

Introduction

Quality of life (QOL) has lately emerged as an important issue and outcome measure in health care, especially in the geriatric population (1, 2). QOL is influenced by various environmental, functional and health factors, while health may be affected by genetic factors. Apolipoprotein E (ApoE) is a gene on chromosome 19 with three allelic forms $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$, of which $\epsilon 4$ is associated with adverse health conditions that can affect the QOL. ApoE $\epsilon 4$ has been associated with cardiovascular and neurodegenerative conditions like Alzheimer's disease (AD), cognitive decline, coronary artery disease, vascular disease in diabetes, stroke, and unfavorable outcomes after intracerebral hemorrhage (3–9). Age alone is also an important risk factor for these co-morbidities, which negatively impact the QOL and increases mortality (10–12). In addition to associated adverse health outcomes, ApoE $\epsilon 4$ carriers may respond differently to psychological stress than non-carriers, which in turn may affect their QOL (13).

Associations between ApoE $\epsilon 4$ and overall QOL were demonstrated in a community sample of biracial older adults (mean age 77.8 year), although two-thirds of the sample was younger than 80 years (14). Another study similarly did not find any association between ApoE $\epsilon 4$ and health related QOL in an elderly group aged between 52–82 years (15). While the above mentioned studies have investigated associations between ApoE $\epsilon 4$ and QOL in the elderly, no studies have explored this relationship in the oldest old. With the worldwide population of nonagenarians growing rapidly, studying QOL in the oldest old is becoming more important. Our study examined the distribution of ApoE genotype and alleles in a community sample of the oldest old, investigated the relationship between ApoE $\epsilon 4$ and QOL and identified other factors that affect the QOL in nonagenarians.

Methods

This cross-sectional cohort study was approved by Institutional Review Board of Mayo Clinic. A sample of individuals from Olmsted County who were 90–99 years old was selected from Rochester Epidemiology Project (REP) (16). All nonagenarians from a convent and two senior communities (which consist of independent living, assisted living and 24-hour nursing care facilities), and an additional random sample living elsewhere in Rochester, were sent letters describing the study and asked permission to contact them for participation. Those who agreed to participate were interviewed and enrolled in the study with details described in our previous reports (2, 17).

Neurological assessment including medical and neurological history, language testing, full neurological examination, and Short Test of Mental Status (STMS, ranging from 0–38, lower score indicating poor cognitive function) (18, 19) was performed by a behavioral neurologist. The study group was divided into four groups based on the cognitive functioning - cognitively normal, mild cognitive impairment (MCI), dementia (DEM), and dementia with stroke and/or parkinsonism (DEMSP). The rationale for this division based on cognitive functioning was to differentiate dementia associated with a presumed neurodegenerative disorder (probable AD) from those with stroke and/or parkinsonism

(those with parkinsonism may have AD plus Lewy body disease (LBD), or only LBD). Dementia was diagnosed based on the criteria described previously (20). Each subject was administered the Mini-Mental State Examination (MMSE) (21), and the Mattis Dementia Rating Scale (DRS) (22). MMSE scores range from 0–30 and DRS scores range from 0–144, with lower scores on both measures indicating poor cognitive function. The Linear Analogue Self Assessment (LASA) comprises a series of ten questions to assess the overall QOL and nine dimensions of physical, emotional, mental, and social well-being, faith and religious involvement, pain, and coping (23–26). Each item was rated from 0 to 10, with 0 being the worst and 10 being the best for each domain. Blood sample was collected from all participants and ApoE genotyping was determined by standard methods described previously (27, 28).

Analysis

The data obtained from the study participants were summarized within groups defined by cognitive status. Quantitative data were summarized with medians (Q1, Q3) and rank sum tests were used to compare the centers of the distributions among the study groups. Primary comparisons were based on global assessments of differences among all four cognitive groups. When the global comparisons reached statistical significance, pairwise comparisons were made among the four groups to evaluate which of the groups were significantly different from one another. Also, correlation between overall QOL and ApoE ϵ 4 were estimated and tested using Spearman correlation coefficients. Regression analyses were used to find the associations between QOL and other variables. All analyses were performed using SAS software (SAS Institute, Cary NC).

Results

There were 595 nonagenarians identified from the census, and a total of 292 subjects were contacted for participation, of which 66 (22.6%) refused. Out of the remaining 226 potential subjects, 30 moved out of Rochester and 36 died before scheduled appointment. There were 160 subjects examined, of which 39 were excluded due to incomplete data leaving 121 subjects for inclusion in our analysis.

The 121 patients recruited had a median age of 93.0 (IQR 92.0, 96.0) years and 88% were females (Table 1). Participants were divided into 4 groups based on cognitive functioning (cognitively normal=45, MCI=13, DEM =34 and DEMSP=29). Age and gender distribution did not differ between 4 groups. Overall QOL score was fairly high at 8.0 (IQR 7.0, 9.0). The DEMSP group showed significantly lower overall QOL compared to normal group, but was not different from MCI or DEM groups.

Genotype and allele frequency among 4 groups are described in Table 2. The most frequent allele was ApoE ϵ 3 [194 (80.2%): ϵ 2/3 18, ϵ 3/3 77, ϵ 3/4 22], and less common were ApoE ϵ 4 [25 (10.3%): ϵ 2/4 - 3, ϵ 3/4 - 22] and ApoE ϵ 2 [23 (9.5%): ϵ 2/2 - 1, ϵ 2/3 - 18, ϵ 2/4 - 3]. None of the subjects carried ApoE ϵ 4/4 genotype. There were 3 (2.5%) patients with ApoE ϵ 2/4 alleles who were excluded from the analysis for association between ApoE ϵ 4 and QOL. After exclusion there were 22 subjects in the ApoE ϵ 4 group (ϵ 3/4, ϵ 4/4), and 96 in the non-ApoE ϵ 4 group (ϵ 2/2, ϵ 2/3, ϵ 3/3). We then compared the mean overall QOL scores between ApoE ϵ 4 and non-ApoE ϵ 4 groups and found no difference ($p=0.12$). In addition, no correlation was found between ApoE ϵ 4 and overall QOL in dementia (DEM and DEMSP), non-dementia (normal and MCI) and all groups combined.

Using regression model including age, gender, education, and ApoE ϵ 34/ ϵ 44 vs. ϵ 22/ ϵ 23/ ϵ 33, only gender was found to be significantly associated with QOL (females had higher QOL than males, $p=0.005$). Using similar models (each model including age, gender,

education, ApoE $\epsilon 34/\epsilon 44$ vs. $\epsilon 22/\epsilon 23/\epsilon 33$, and risk factor one at a time), we found significant associations between QOL and the following variables: DEMSP ($p=0.05$), pain frequency ($p=0.003$), pain severity ($p=0.006$), physical well-being ($p=0.0002$), emotional well-being ($p=0.003$), intellectual well-being ($p<0.0001$), social connectedness ($p=0.002$), and coping ability ($p<0.0001$) (Table 3).

Discussion

In this population based cohort of oldest old, ApoE $\epsilon 3$ allele was the most common. None had ApoE $\epsilon 4/4$ genotype. Physical well-being, emotional well-being, intellectual well-being, social connectedness and coping were positively associated with QOL, while male gender, dementia with stroke and parkinsonism, pain frequency, and pain severity were negatively associated with QOL. There was no evidence for any association between ApoE $\epsilon 4$ and QOL.

There were more females than males in all subgroups, which is expected due to higher life expectancy among females (29). DEM and DEMSP did not differ from each other in overall and different domains of QOL without adjusting for the ApoE $\epsilon 4$ distribution. Non dementia groups (MCI and normal) were also similar in over all QOL.

ApoE $\epsilon 3$ allele had the greatest frequency, while ApoE $\epsilon 3/3$ was the most frequent genotype. ApoE $\epsilon 2$ and ApoE $\epsilon 4$ alleles had low frequencies in this group of nonagenarians. None carried ApoE $\epsilon 4/4$, which was most likely due to adverse effects of ApoE $\epsilon 4/4$ genotype occurring at a younger age including cardiovascular and cerebrovascular disease (4, 5, 30, 31) and mortality (31, 32), but the mortality has not always been confirmed (33). Decreasing frequency of ApoE $\epsilon 4$ allele with increasing age has been reported previously (34). However, the distribution of ApoE alleles among nonagenarians has not been reported in the literature.

Mean QOL was good among all patients. Functional impairment due to stroke or parkinsonism appears to have significant impact on QOL irrespective of cognitive status, which is consistent with previous reports (35, 36). While looking at the association between QOL and ApoE $\epsilon 4$, patients with ApoE $\epsilon 2/4$ alleles were excluded from the analysis because of dual effect of ApoE $\epsilon 2$ (37, 38), and adverse effect of ApoE $\epsilon 4$ alleles on different health co-morbidities. No association was found between overall QOL and ApoE $\epsilon 4$ allele, which is similar to a prior report that examined the association between ApoE $\epsilon 4$ alleles and five parameters of QOL (social, economic, mental and physical health, functional status) in patients younger than nonagenarians (14). Similarly, another study found no association between health-related quality of life and ApoE $\epsilon 4$ allele in a cohort of patients aged between 52–85 years (15). Therefore, ApoE $\epsilon 4$ allele does not appears to affect QOL in geriatric patients, despite its association with risk for different co-morbidities.

QOL was lower among males, and reason for this is unclear. Pain frequency and severity had negative association with QOL when controlled for age, education and ApoE $\epsilon 4$. Nonagenarians who were physically, emotionally and intellectually well had better QOL irrespective of gender. Also, those who had more social connections and better coping ability endorsed better QOL.

Conclusions

In this community sample of oldest old, the most common genotype was ApoE $\epsilon 3/3$, while none carried ApoE $\epsilon 4/4$. ApoE $\epsilon 4$ had no association with overall QOL.

Acknowledgments

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Table 1

Demographic characteristics for subjects divided into cognitive groups

Demographics	All N = 121	Normal N = 45	MCI N = 13	DEM N = 34	DEMSP N = 29
Median age (Q1, Q3)	93.0 (92.0, 96.0)	92.0 (92.0, 95.0)	93.0 (93.0, 96.0)	93.5 (92.0, 96.0)	94.0 (92.0, 96.0)
Female Gender	106 (87.6)	40 (88.9)	12 (92.3)	31 (91.2)	23 (79.3)
Neuropsychometric measures					
STMS [†]	27.0 (21.0, 33.0)	33.0 (28.0, 34.0)	30.0 (28.0, 31.0)	19.0 (14.0, 23.0)	20.0 (12.0, 23.0)
MMSE [‡]	26.0 (21.0, 28.0)	29.0 (27.0, 30.0)	27.0 (25.0, 28.0)	20.0 (15.0, 21.0)	20.0 (16.0, 22.0)
DRS [§]	122.0 (109.0, 134.0)	136.0 (129.0, 138.5)	125.5 (119.0, 129.0)	106.0 (91.0, 113.0)	106.0 (93.0, 113.0)
Quality of life					
QOL 1 ^a / (physical well-being)	8.0 (5.0, 9.0)	7.0 (5.0, 8.0)	8.0 (8.0, 9.0)	8.0 (5.0, 10.0)	8.0 (5.5, 9.0)
QOL 2 ^a (emotional well-being)	8.0 (7.0, 9.5)	8.0 (8.0, 9.0)	8.0 (8.0, 10.0)	8.0 (7.0, 10.0)	8.0 (6.5, 9.0)
QOL 3 ^a (faith)	10.0 (8.0, 10.0)	10.0 (8.0, 10.0)	10.0 (10.0, 10.0)	9.5 (8.0, 10.0)	9.0 (6.0, 10.0)
QOL 4 ^a (religious involvement)	5.0 (2.0, 8.0)	6.0 (2.0, 9.0)	7.0 (4.0, 8.0)	3.0 (2.0, 5.0)	5.0 (1.0, 6.0)
QOL 5 ^a 2 (intellectual well-being)	8.0 (6.0, 9.0)	8.0 (7.0, 10.0)	9.0 (8.0, 10.0)	7.0 (5.0, 9.0)	6.0 (5.0, 8.0)
QOL 6 ^a (social connectedness)	6.0 (5.0, 8.0)	8.0 (5.0, 9.0)	6.0 (5.0, 8.0)	5.0 (5.0, 8.0)	6.0 (4.5, 7.5)
QOL 7 ^a 3 (pain frequency)	1.0 (1.0, 6.0)	4.0 (1.0, 8.0)	1.0 (1.0, 1.0)	1.0 (1.0, 3.0)	1.0 (1.0, 5.0)
QOL 8 ^a 4 (pain intensity)	1.0 (1.0, 5.0)	3.0 (1.0, 5.0)	1.0 (1.0, 1.0)	1.0 (1.0, 2.0)	1.0 (1.0, 4.0)
QOL 9 ^a 5 (coping)	8.0 (6.0, 8.0)	8.0 (7.0, 9.0)	9.0 (7.0, 9.0)	6.5 (5.0, 8.0)	7.0 (6.0, 8.0)
Overall QOL ^a 6	8.0 (7.0, 9.0)	9.0 (7.0, 9.0)	8.0 (8.0, 9.0)	8.0 (7.0, 10.0)	7.0 (5.0, 8.5)

Report N (% among non-missing data) for dichotomous variables, median (interquartile range) for continuous variables

[†] p=0.04 for normal vs. MCI, p<0.0001 for normal vs. DEM, normal vs. DEMSP, and MCI vs. DEM; p=0.0001 for MCI vs. DEMSP

[‡] p=0.01 for normal vs. MCI, p<0.0001 for normal vs. DEM, normal vs. DEMSP, MCI vs. DEM, MCI vs. DEMSP

[§] p=0.0005 for normal vs. MCI, p<0.0001 for normal vs. DEM, normal vs. DEMSP, MCI vs. DEM, and MCI vs. DEMSP

^a 12 missing in DEM and 13 missing in DEMSP

[/] p=0.01 for normal vs. MCI, p=0.0290 for normal vs. DEM

- ² $p=0.04$ for normal vs. DEM, $p=0.0031$ for normal vs. DEMSP, $p=0.0436$ for MCI vs. DEM, $p=0.0097$ for MCI vs. DEMSP
- ³ $p=0.03$ for normal vs. MCI, $p=0.0270$ for normal vs. DEM
- ⁴ $p=0.03$ for normal vs. DEM, $p=0.0443$ for normal vs. DEMSP
- ⁵ $p=0.01$ for normal vs. DEM, $p=0.0044$ for MCI vs. DEM, $p=0.0473$ for MCI vs. DEMSP
- ⁶ $p=0.03$ for normal vs. DEMSP

Table 2

Genotype and allele frequencies for nonagenarians classified as normal, mild cognitive impairment (MCI), dementia (DEM), and dementia with stroke and parkinsonism

Genotype frequency	All N = 121	Normal N = 45	MCI N = 13	DEM N = 34	DEMSP N = 29
e 2/2	1 (0.8)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)
e 2/3	18 (14.9)	7 (15.6)	2 (15.4)	3 (8.8)	6 (20.7)
e 2/4	3 (2.5)	1 (2.2)	0 (0.0)	2 (5.9)	0 (0.0)
e 3/3	77 (63.6)	30 (66.7)	9 (69.2)	22 (64.7)	16 (55.2)
e 3/4	22 (18.2)	7 (15.6)	2 (15.4)	6 (17.7)	7 (24.1)
e 4/4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Allele frequency					
e2	23 (9.5)	8 (8.9)	2 (7.7)	7 (10.3)	6 (10.3)
e3	194 (80.2)	74 (82.2)	22 (84.6)	53 (77.9)	45 (77.6)
e4	25 (10.3)	8 (8.9)	2 (7.7)	8 (11.8)	7 (12.1)

Table 3

Predictor of overall QOL

Predictor*	Beta value	P value
DEMSP [†]	−1.13	0.05
GDS	−0.23	0.002
Physical well-being	0.33	0.0002
Emotional well-being	0.35	0.003
Intellectual well-being	0.44	<0.0001
Social connectedness	0.27	0.002
Pain frequency	−0.18	0.003
Pain severity	−0.22	0.006
Cope with stresses	0.46	<0.0001

* adjusted for age, male gender, education, and ApoE (ε34/44 vs. ε22/23/33)

[†] MCI, DEM also included in the model