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한국인 알츠하이머병 환자에서 한국형 간이정신상태검사 점수의 진행양상에 관한 연구

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ABSTRACT

Progression of Alzheimer' s Disease (AD) is well known from studies regarding the natural courses, while only few studies have shown in patients on medications. Previous clinical trials addressed that cholinesterase inhibitors (ChEIs) and N-methyl-D-aspartate (NMDA) receptor blockers in Alzheimer' s disease(AD) alter the rate of cognitive decline, but their long-term effects need further investigation. In this study, we aimed to demonstrate the long-term cognitive changes on Korean AD patients in clinical settings receiving pharmacological treatments and identify the associated variables affecting the rate of cognitive decline.

This was a retrospective cohort study from patients whom visited Seoul National University Bundang Hospital, between 2003 to 2013. From medical records of AD patients using ChEIs and/or NMDA receptor blockers, we determined the progression of Korean Mini-Mental Status Exam (K-MMSE) by calculating the rate of change in years from each pairs of consecutive K-MMSE assessments. The mixed random/fixed coefficient method was used for modeling predictions of K-MMSE progressions and verifying the rate modifying risk factors.

Total number of 366 patients and their 1337 assessments were included in analysis. Mean rate of K-MMSE change calculated from 971 pairs of K-MMSE per year was 1.31 points (95% CI

−1.47 to −1.14) in all score ranges. From the mixed model analyses, earlier−onset disease, presence of APOE ε4 allele, higher level of education, and lower initial K−MMSE scores were associated with faster cognitive decline rates.

Compared to previous studies, rate of K−MMSE changes has decelerated. The effects of rate modifying factors from analyses lined with our current knowledge. This was the first study in Korean AD patients on pharmacological treatments demonstrating the long−term progression course in clinical settings. We were able to predict the rate of decline and verify the risk variable effects. The model acquired from our study may be of use to clinicians who encounter AD patients in long−term follow−up, by giving information on progression rate and aiding clinical decisions.

Keywords: Cognitive function, MMSE, Mixed model, Alzheimer' disease, Cholinesterase inhibitor, NMDA receptor blocker

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Introduction

Alzheimer's disease (AD) is a devastating condition with increasing prevalence worldwide. The diagnosis of AD is based on the National Institute of Neurological and Communication Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NIA-AA) criteria, which emphasizes incorporating biomarkers in clinical diagnosis1. Current hypotheses suggest pathologic changes in the very early stage of the disease 2, thus the need for early diagnosis for treatment. However in clinical situations, the diagnoses rely on the clinical symptoms of cognitive decline as measured by neuropsychiatric evaluations. The treatment options concentrates on modifying symptoms, as novel disease modifying treatment modalities are still in on-going trials. Drugs such as cholinesterase inhibitors (ChEIs) and NMDA receptor blockers (memantine) are most commonly used after clinical diagnosis3.

Many studies have proven the efficacy of standard treatment drugs, and for the past years, the disease progression course of majority of patients has been ameliorated bytreatment. Previous longitudinal studies on the natural course of AD progression, showed persistent decline of cognition but with alteration in progression rates among disease stages4-9. This finding was consistent over multiple test modalities and modeling procedures, but also may be due to floor and ceiling effects of the

measurement tools. Relevant factors identified from past studies, regarding the rate of cognitive decline were gender, age of onset, APOE phenotype, severity of dementia, and education 5,9-11. The models predictdisease progression by assessing the characteristics and cognitive functions of individual patients, which results in providing clinician information on the patients' prognoses and treatment effectiveness12,13. It also enables the patients and their families to plan ahead for long-term patient management.

A few studies regarding prediction of the course of AD with treatments demonstrated that while the current treatments did slow the progression, they did not change the overall course of the disease14,15. However most of these studies were conducted within clinical trials of limited time, thus the information on more advanced staged patients and patients with longer follow-upin actual clinical setting is scarce.

On Korean patients, the natural course of AD progression have been reported in one other study6 but no long-term longitudinal studies with patients receiving treatment have been done. In this study, we sought to gain insight with long-term cognitive changes in Korean AD patients receiving standard treatments with ChEIs or memantine or both, and identify the relevant factors affecting cognitive decline rate.

Materials and methods

Study design and subjects

This was a retrospective cohort study on a single center of tertiary referral clinic, with homogeneous ethnicity but with various backgrounds. We retrospectively collected clinical information and neuropsychiatric test data of Seoul National University Bundang Hospital's electronic medical record database, from patients whose cognitive function was evaluated during May 2003 to December 2013. Patients were eligible for inclusion if they met the NIA-AA criteria for probable Alzheimer's disease; had a CDR score of 0.5 to 2.0; taken ChEIs (donepezil, rivastigmine, galantamine) and/or NMDA receptor blocker (memantine) at the time or taken the above medication within one month of assessment; at least two assessments taken; and at least 6 months of follow-up period.

Administration of standard treatments (choosing between the medications and its dosage) were considered optimal on the clinicians' decision. As this was a retrospective naturalistic study, patients' medication may change due to many reasons, we regarded the whole group as optimally treated. Patients with other concomitant conditions that may have caused cognitive decline such as events of poor general medical condition, surgical condition, and psychiatric condition including severe

depression were excluded in the study. Only patients with all information on relevant variables were included for analyses.

Measurements

The main outcome measurement used to assess cognitive function used in this study was the Korean Mini-Mental Status Examination (K-MMSE), the Korean version of MMSE, with scores ranging from 0 to 30 points. The MMSE is the most widely used tool due to its easily applicable nature[16,17],despite its weaknesses such as decreased sensitivity in mild cognitive deficits and lack of diagnostic specificity. The capability of assessing multiple cognitive domains in a relatively short time and high test-retest reliability makes it a practical tool - numerous longitudinal natural course studies and clinical trials in assessing the effectiveness of drugs have used MMSE as their outcome measures. The K-MMSE has been widely used in Korea, and its validity and reliability has been previously reported[18].

For potential risk factors, gender, age of disease onset (under 65 or 65 years and over), the presence of APOE $\varepsilon 4$ alleles, degree of severity of white matter lesions (WMLs), were defined. On WML degrees, we used the classification system which the Clinical Research Center for Dementia of South Korea (CREDOS) group[19] developed, using a combination of deep and periventricular white matter hyperintensities (WMHs). The brain

magnetic resonance imaging (MRI) of each patient was evaluated according to the classification and was graded as mild, moderate, or severe. We only included mild and moderate cases in our analysis, for those considered severe were more likely to have mixed dementia due to AD and vascular dementia, As K-MMSE score relies not only on the cognitive level, but is very much influenced by test age and educational level, we also collected those data.

Statistical Analysis

A T-test was used to analyze the differences among the means for two independent variables, a χ^2 test for categorical variables, and Analysis of variance (ANOVA) with Bonferroni correction was used for three independent groups. Normality of all variables were evaluated, and correlation was assessed by Pearson's correlation.

We planned two stepped analyses. First, we tried to determine the overall rate of progression using the whole K-MMSE score data, second, and more importantly, performed the modeling procedure to predict the disease progression and relevant variables. For the overall rate of progression, we calculated the differences between each pair of consecutive K-MMSE scores.

Differences between consecutive K-MMSE scores (ΔM_k) : $\Delta M_k = M_k - M_{(k+1)}$,(M=MMSE score, M=1,2,…,30; k=number of

assessments done, k=1,2,..,n) — (a)

We divided (a) with time intervals (T_k, in years) between assessments to calculate the rate of change(D_k), in points per year.

Rate of Change (D_k): $D_k = \Delta M_k / T_k$ — (b)

Then we calculated the average D_k for each K-MMSE scores to determine the average decline in points per MMSE scores.

To predict the course of AD, we used the mixed random/fixed coefficient model using subject as a hierarchical variable, which has the advantage of incorporating between-subject, within-subject differences and disease course modifying factors by specifying generalized functions for each individual[20,21]. In this way, it is flexible for missing, unbalanced data and at different time points, and duration[21]. Collinearity was checked among variables using collinearity analyses, and model assumptions were also checked with residual analyses.

For each patient (i=1,2,3,… ,m) and their assessments (k=1,2,3,… n), fixed and random variables were accounted for. Fixed variables investigated as the variables of interest, included time in years, age of onset (< 65yrs and ≥65 accounting for early-onset AD and late-onset AD), education (in years), gender (male, female), APOE $\varepsilon 4$ carrier, WML degrees (mild,

moderate) and test age (in years) and their interactions with each other. As shown by previous studies, cognitive decline follows non-linear time course, so we incorporated a quadratic term on time for better fitting of the model. On random terms were the intercept and time in years, with unstructured covariance matrix. We then performed a mixed random/fixed coefficient procedure by every single variable and interaction, and chose the most relevant factors by the forward selection method. Non-significant variables (P-value >0.05) were excluded from the model, but if they could explain higher order interaction, or were consistent with clinical settings, those variables were remained in the model.

All statistical analyses were performed by R (version 3.2.0)[22-28].

Results

Demographic and Clinical characteristics

Of 611 patients who underwent at least two neuropsychiatric evaluations in our institution during the period, 498 patients were diagnosed as probable AD. Among those patients, 477 patients were prescribed standard treatment, and 418 of them had more than two assessments taken while they were on medication. Then we screened for patients with rapid progression (Dk $\geq$8) or unusually high improvement (Dk $\leq$−5), to make sure the patients' cognitive decline were primarily due to course of AD and not by other factors. We also excluded the patients with missing values in relevant variables, as a result, the total of 366 patients met our final inclusion criteria. The demographics of the patients are presented in Table1.

The number of K−MMSE assessments in the included dataset was 1337 (K−MMSE score range from 0 to 30). Female (252/366, 68.9%) to male(114/366, 31.1%) gender ratio was more than 1:2, which correlates to the fact that in AD is more prevalent in female than in males 29,30. Late−onset patients were dominant (313/366, 85.5%), and the presence of APOE ε4 allele was seen in 178 cases out of 366 subjects (48.6 %). Test interval range was 0.22 to 6.23years (median: 0.99 , interquartile range : 0.96−1.10), number of assessments ranged

from 2 to 10 (median : 3, interquartile range : 2-5) and the total follow-up period from 0.57 to 9.07 years (median : 2.57, interquartile range : 1.25 - 4.11).

From the baseline characteristics of our subjects, female patients (mean : 17.48 , SD 5.23) scored lower average MMSE than male patients (mean : 20.67, SD 4.89) of 3.18 points (95% CI 2.07-4.29, $t(232)=5.64$, $p<0.01$). The MMSE positively correlated with education level (Pearson's R = 0.45, $p<0.01$) and longer education years among male (mean : 11.96, SD : 5.72) than female patients(mean : 6.85, SD : 5.17) of average 5.1 years (95% CI 3.87-6.35, $t(200)=8.14$, $p<0.01$) was seen. In addition, early-onset patients showed higher education level than late-onset patients (mean : 10.68, SD : 5.12 vs mean : 8.06 , SD : 5.88, mean difference : 2.62, 95% CI 1.07-4.17, $t(77)=3.37$, $p<0.01$).

Overall progression rates of cognitive decline

From the data of total K-MMSE assessments of 1337 cases, we were able to retrieve the D_k values of 971 pairs of consecutive tests. The calculated rate of K-MMSE score change was -1.31 points per year (95%CI: -1.47 to - 1.14). The average MMSE decline rate for different values of MMSE is stated in Table2, and Figure1. Range of average rates were from -3.44 to 0.26. Additional groupings were done to demonstrate the differences between the mild (K-MMSE 21-30),

moderate(11−20), and severe(0−10) groups (Figure2). The average decline rate for mild group was −1.42 (95%CI −1.68 to −1.15), −1.21(95%CI:−1.46 to −0.97) for moderate group, and −1.34(95%CI:−1.75 to −0.93) for the severe group. This rate of decline in groups did not differ against each other (F(2,377)=0.62,p=0.54).

Prediction of Cognitive Decline with models

Prediction of MMSE change along with the goal of identifying the long−term outcome modifying variables was performed using mixed random/fixed coefficient model from 1337 observation points. The significant predictors, β coefficients and standard error are shown in Table3. The variables which showed significance on alpha level of 0.10 were time, time^2(quadratic term of time), initial MMSE and the interactions between time x education, time x onset, time^2 x initial, and time^2 x APOEε4. Education, APOEε4 and interactions of time x initial, time x APOEε4 were included to account for the higher order interactions. Gender and onset were included to adjust for the baseline. Goodness of model fit measures are also depicted in Table3 and Figure3, which shows a well correlation between observed and predicted values.

To show effects of relevant variables on rate of decline, effect plots were produced (Figures4−7). From the plots, as time progresses, early−onset patients of estimated onset age younger

than age 65 showed faster cognitive decline than the late-onset patients. Presence of APOE $\varepsilon 4$ allele has minimal advantage on first 1-2 years, then declines faster afterwards. Higher educated subjects tend to have faster decline, while higher initial MMSE scores were associated with slower rate of decline.

Discussion

We set out to determine what factors minimize or accelerate cognitive decline in AD patients receiving medication as evaluated by the K-MMSE scores. We used the mixed random /fixed regression method for analysis, which is widely used in longitudinal research. This method has the strength in depicting data of repeated measures of flexible interval and durations, with accounting for individual subjects' risk factors and the random differences in people[21].

Many studies have tried to demonstrate the course of AD by longitudinal follow-up and by mathematical modeling[20]. These studies can be categorized by studies on the natural control groups[4-9] or studies on treated groups[14,15,31,32]. The former have shown that the rate of cognitive decline in AD is slow in the mild stages, faster in moderate stages and slows down again in the severe late stages[5,8], indicating a nonlinear course of cognitive decline. Assumption of non-linear decline may restrict the usage of regression analysis, but by incorporating quadratic, cubic terms or transformations to logarithmic terms can help simplify the choice of analysis instead of choosing complex models such as the growth-curve model[7] or tri-linear model[33].

The selection of measurement method is also important for the results of analyses, as this may interfere with data interpretation with variability in assessment domains, power and reliability,

While MMSE may be less sensitive in very early stages or late stages due to ceiling and floor effects, its easy-to-use nature enables it to be widely used in primary clinics. Our study used the K-MMSE to facilitate easy usage in Korean patients, since most patients undergo the test every year in clinics.

The overall rate of cognitive decline using whole data showed decreased rate of cognitive decline from prior studies of natural course[5,6], which concretes the evident treatment efficacy of current standard treatments. Previously reported decline rates ranged from average 1.3 to 6.0 points per year, whereas our study shows 0 to 2.76 points decrease per year. From this result, longer disease duration is expected among well-treated patients, thus the need for long-term care of patients should be of concern.

Prediction of MMSE scores using mixed random/fixed coefficient model demonstrated that younger onset age, higher education, presence of APOE $\varepsilon 4$ allele and lower initial scores were associated with faster cognitive decline. Young onset patients were associated with faster decline as supported from large previous studies [34-36], which may account for different disease progression mechanism between early onset AD and late onset AD. The effect of education on cognition has raised questions, but in general, higher educated people have lower incidence of AD, but if they are diagnosed, they show rapid decline rate on cognition [36,37]. This is mostly explained through higher cognitive

reserve in educated subjects, by neural reserve of efficient neural network and neural compensation with alternative system[38]. Presence of APOE ε4 allele is a well known genetic factor which increases the risk of developing AD [39,40]. Our model also could account for the faster cognitive decline of APOE ε4 carriers.

The variable effects can be interpreted as following. First, the factor itself has a rate modifying effect in the disease course; second, the effect itself maybe due to treatment and reflect the factors that has impact in treatment efficacy, or both. We cannot distinguish these effects in the current study, since this study was an observational, retrospective cohort design. This can only suggest the association between cognitive decline and relevant variables.

The strength of our study is that this is the first predictive study in the Korean population reporting the course of long-term cognitive decline with AD patients on medication. One observational study[6] of the Korean population was previously reported, but it presented only one-year follow up scores, though the study analyses extended to multiple measures such as Alzheimer's Disease Assessment Scale - Cognitive subscale (ADAS-Cog) and other functional measures. With effective drugs presently available, such observation-only studies are no longer considered ethical. Our study subjects were in settings of outpatient clinic, with longest follow-up of being up to 9 years,

with interquartile range of 1 to 4 years. This gives more information on patients with longer disease duration whom are in late stages of AD and their progression rate.

Also, the interpretation of our study result is easier to apply clinically. It could be simplified as an answer to how much points in MMSE will it decrease in a year when a patient marks a certain score. Our datasuggests we can assume that most patients will decline by 0 to 1 points by K-MMSE per year, and if the patient progresses more rapidly, the possibility of treatment failure or other comorbid condition has to be considered.

There are many limitations in our data, of which the most important is that there may have been a self-selection bias as this is a single center study, with patients with complaints of memory discomfort. Patients or care-givers are more likely to pay close attention to memory compared to the general population. Also while applying the inclusion criteria, data of patients who were newly diagnosed AD but did not meet the number of assessments required were removed, which may have resulted in aggravation.

Secondly, we tried to identify the most relevant factors, but since mild to moderate depression co-reside with AD, thus complicating the treatment effects, for depression also has impacts on cognition. Some of the patients exhibiting improvement or apparent slow decline of their cognition along

the disease courses may be related to improvement of depression, which was not included in our current analyses.

Lastly, mixed random/fixed coefficient models are under assumptions that changes are in linear correlations, but cognitive changes take more non-linear courses. To get the better fitting and predictions, we used the quadratic terms in time, but it complicated the interpretation of effects in models, albeit the model itself. Using the exponential terms or other growth curve may elaborate the model fit, but it worsens the intuitive understanding of the variable effects, therefore we chose the quadratic model.

Further studies should include external validation using a different, larger population. Incorporation of other biomarkers such as hippocampal atrophy, clinical information on depression with depression scale scores and use of antidepressants may help in building accurate predictions of cognitive decline, thus furthermore enhance our understandings in course of AD progression.

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Table1. Baseline Demographics

	AD (N=366)
Age	74.8 ± 7.3
Sex	
- Male	114 (31.1%)
- Female	252 (68.9%)
Onset	
- <65	53 (14.5%)
- ≥65	313 (85.5%)
APOE ϵ4	
- 0	188 (51.4%)
- 1 or more	178 (48.6%)
WML	
- Mild	251 (68.6%)
- Moderate	115 (31.4%)
Education	8.4 ± 5.8
Initial MMSE	18.5 ± 5.3

Table2. Mean MMSE change/year on different values of MMSE

MMSE	No. of Subjects	points/year	95 % CI	
0	3	0.26	-0.87	1.40
1	6	-0.00	-0.60	0.60
2	3	-0.91	-1.17	-0.65
3	5	-1.70	-3.30	-0.11
4	3	-1.25	-3.93	1.44
5	7	-2.47	-3.34	-1.60
6	12	-1.29	-2.24	-0.33
7	10	-1.47	-3.01	0.07
8	23	-2.11	-3.29	-0.93
9	13	-0.43	-1.88	1.02
10	47	-1.32	-2.17	-0.47
11	40	-1.17	-2.03	-0.30
12	27	-1.73	-2.89	-0.57
13	26	-1.84	-3.26	-0.43
14	42	-1.59	-2.33	-0.85
15	46	-1.34	-2.11	-0.57
16	45	-1.50	-2.33	-0.67
17	59	-1.51	-2.25	-0.77
18	86	-0.67	-1.26	-0.07
19	56	-1.02	-1.70	-0.34
20	63	-0.88	-1.57	-0.20
21	76	-0.94	-1.50	-0.38
22	68	-1.44	-2.09	-0.78
23	71	-1.50	-2.09	-0.91
24	49	-1.34	-2.08	-0.60
25	34	-1.30	-2.21	-0.38
26	31	-1.81	-2.53	-1.10
27	10	-3.04	-4.57	-1.51
28	6	-3.44	-4.98	-1.89
29	3	-0.28	-2.97	2.41
30	1	-2.15	N/A	

Table3. Fitted Model

Fixed Effects				
	Value	SE	p-value	
(Intercept)	0.0846	0.3606	0.8145	
Time	−0.8271	0.4014	0.0396	*
$Time^2$	−0.2094	0.0281	0	***
Sex	−0.1744	0.1542	0.2586	
Onset	0.0615	0.1952	0.7529	
Education	0.0146	0.0141	0.2996	
Initial	0.9955	0.0145	0	***
APOE $\epsilon 4$	0.0148	0.1410	0.9165	
Time:Onset	0.4251	0.2410	0.0781	
Time:Education	−0.0388	0.0113	0.0006	***
Time:Initial	−0.0292	0.0176	0.0974	
$Time^2$:Initial	0.0117	0.0011	0	***
Time:$\epsilon 4$	0.2892	0.1836	0.1155	
$Time^2$:$\epsilon 4$	−0.1162	0.0114	0	***
Random Effects				
	SD	Correlation		
(Intercept)	0.1708165	$(Intr)$		
Time	1.3635452	0.971		
Residual	1.5588117			
Goodness of Fit				
	AIC	BIC	Log Likelihood	
	5917.0793	6243.9017	-2895.5396	

$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Figure1. The Rate of cognitive decline on different points of MMSE. The average decline rates per year is depicted as a boxplot in groups of each MMSE points.

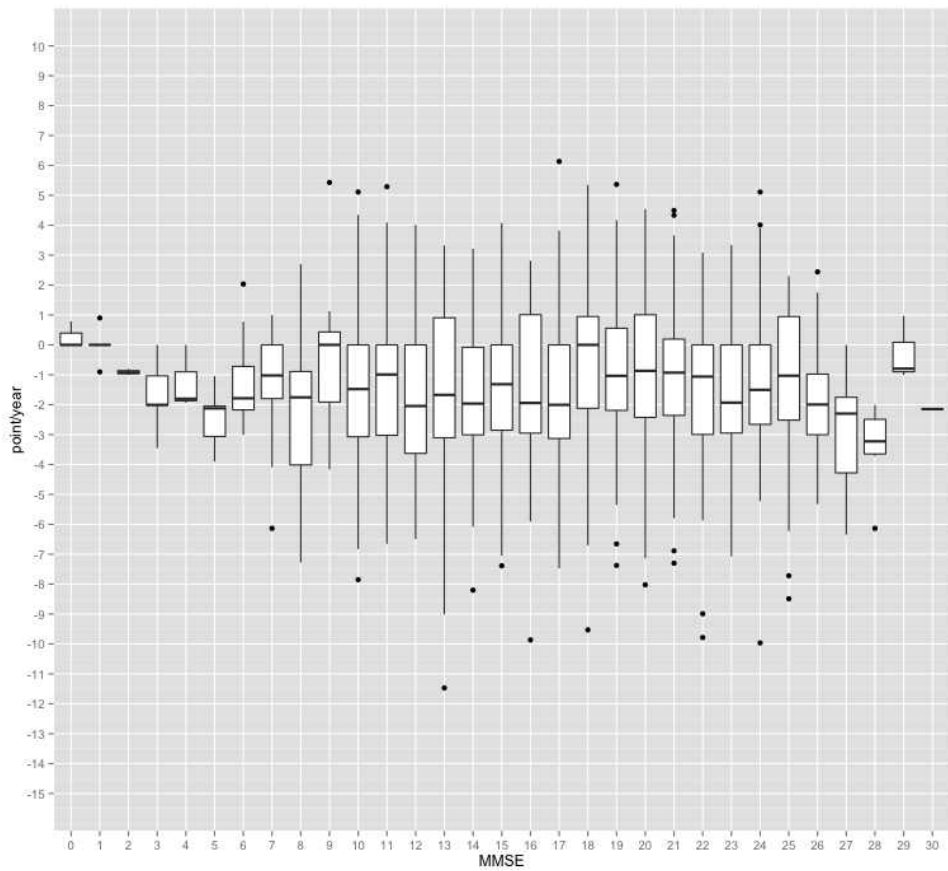


Figure 2. The rate of cognitive decline on MMSE grouped by severity. The average decline rates in groups by severity, defined by MMSE scores as mild (21-30), moderate (11-20), and severe (0-10) . The differences among groups were not significant. (F(2,377)=0.62, p=0.54)

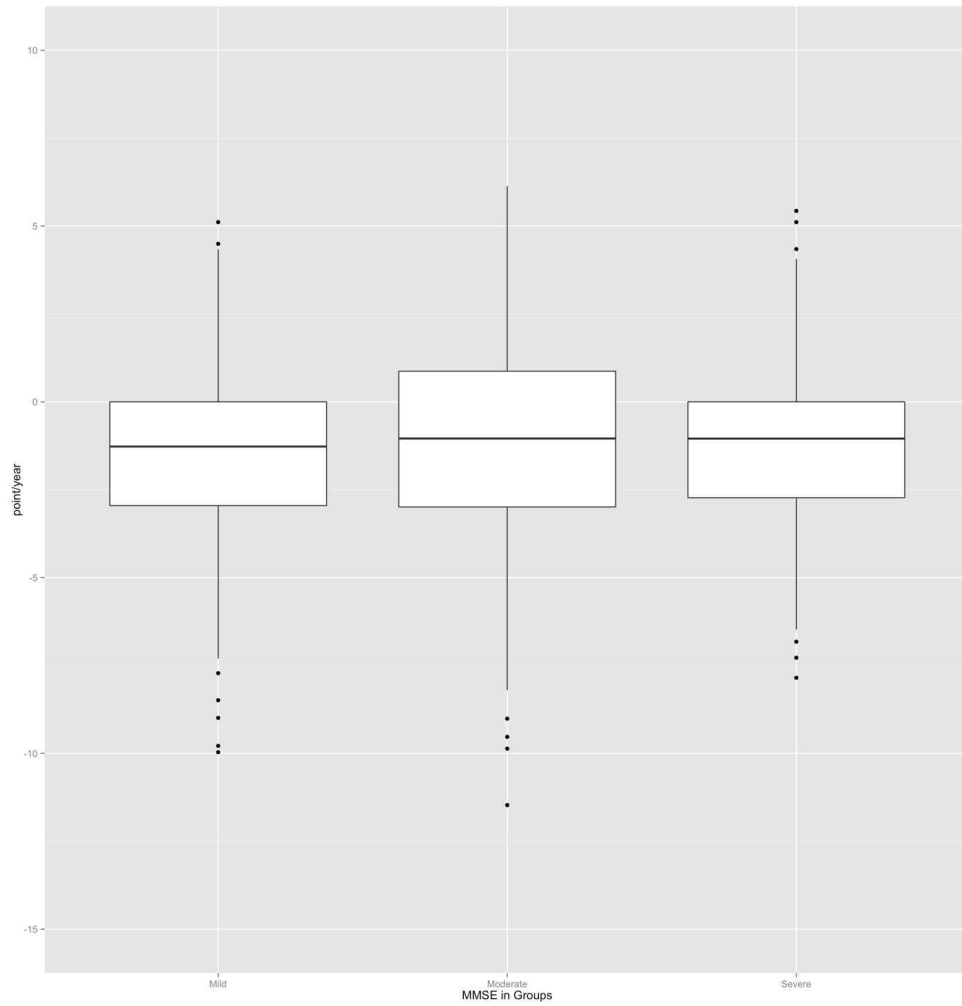


Figure 3. Correlation between observed MMSE and predicted MMSE values. A correlation plot showing prediction values with observed values. Range of prediction values tend to gather in observed values, no significant outlier is seen.

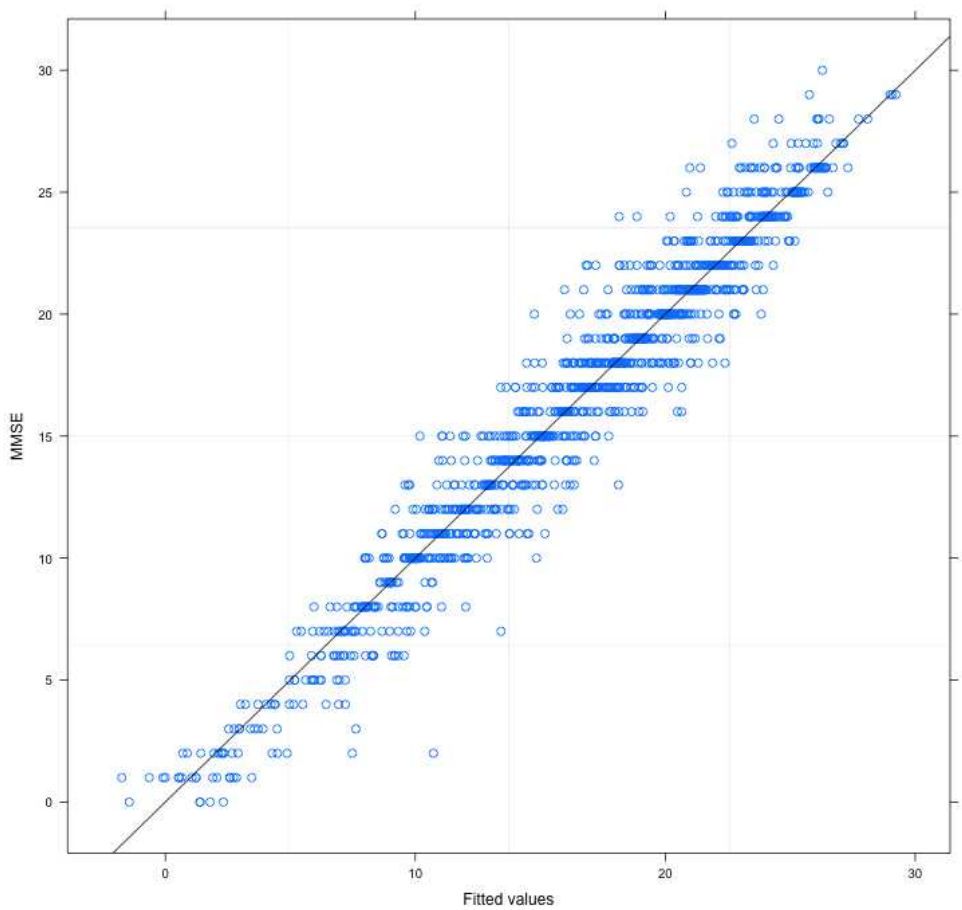


Figure 4. Effect of onset age on MMSE. Interactions between time and onset age are shown. Earlier onset patients show faster cognitive decline along the disease course.

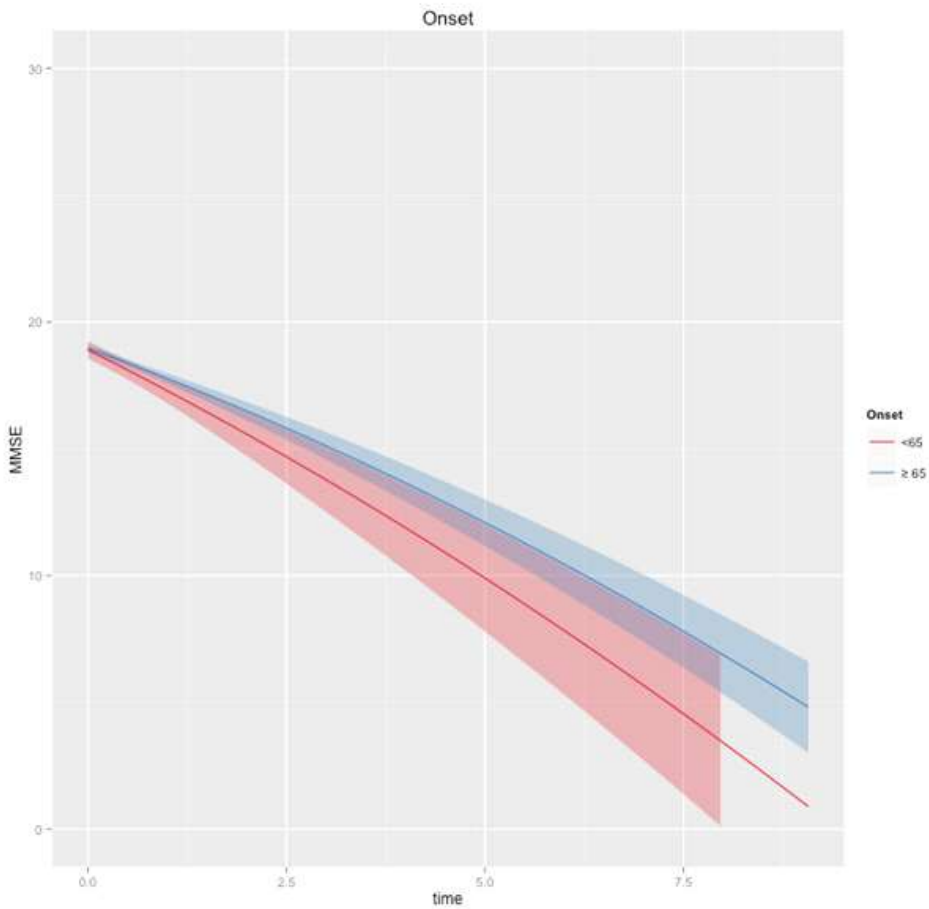


Figure 5. Effect of education on MMSE. Interactions between time and education years are shown. Patients with higher level of education (longer education years) tend to progress more rapidly than patients with lower level of education (shorter education years).

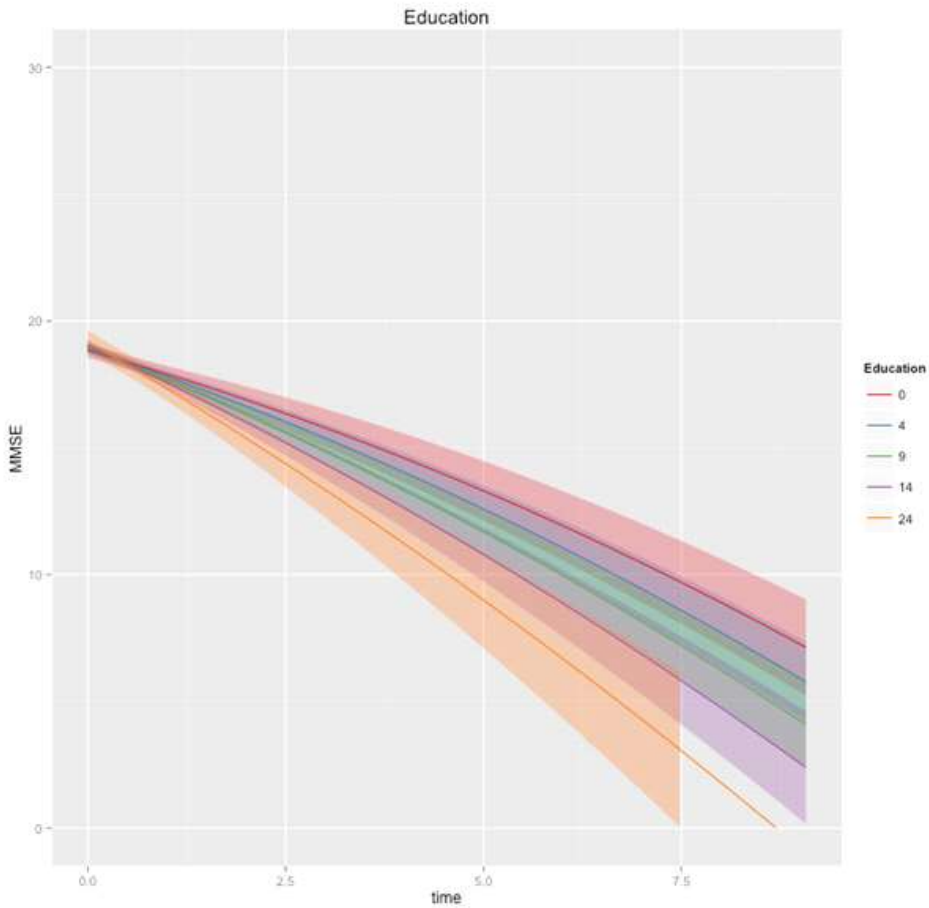


Figure 6. Effect of initial MMSE on the disease progression. Higher initial scores are correlated with slower progression of disease.

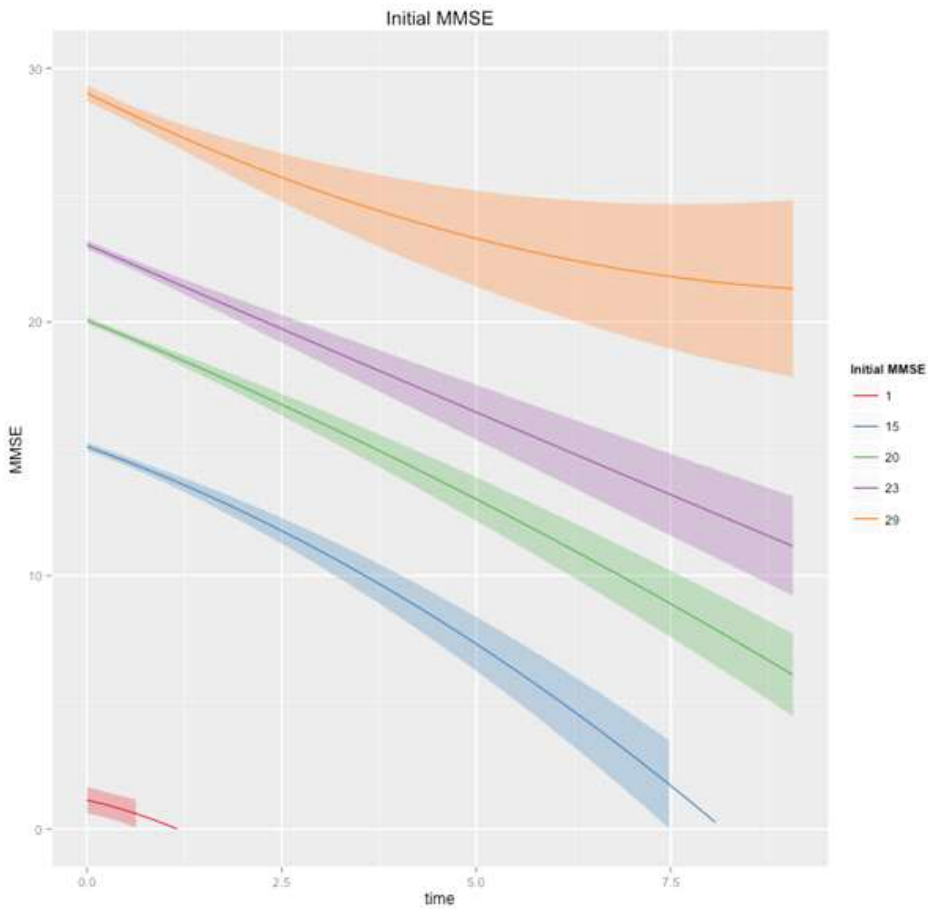
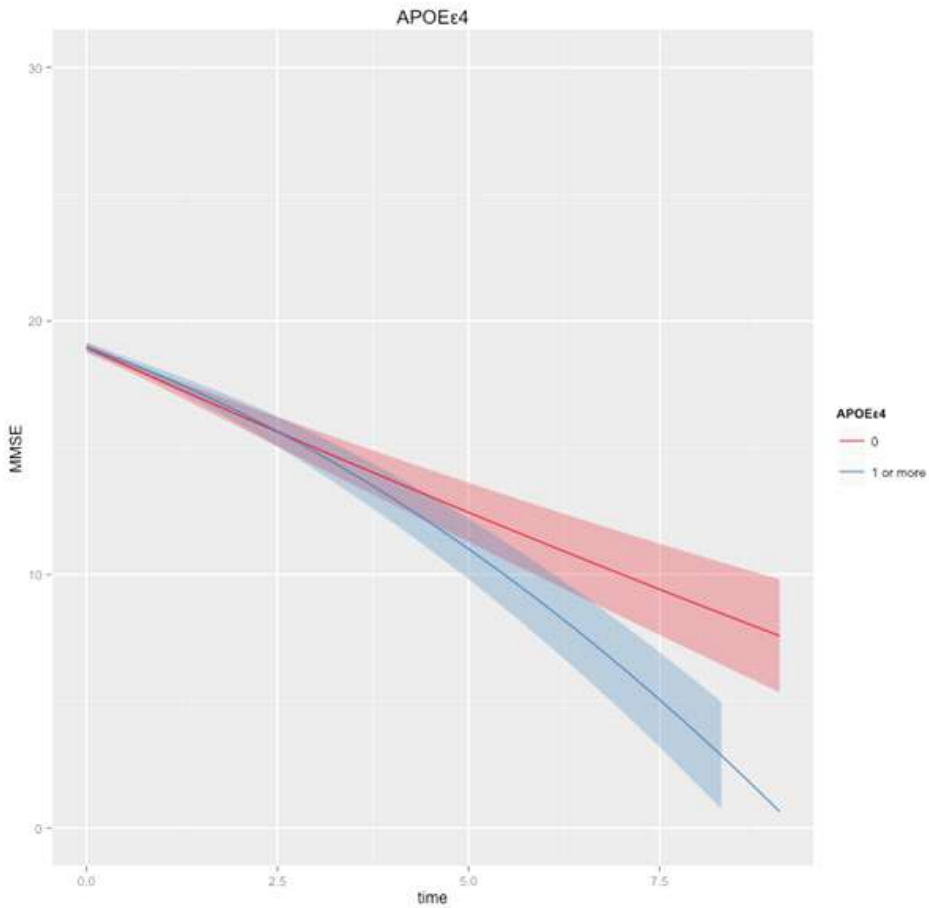


Figure 7. Effect of APOE ε4 alleles on MMSE. Presence of ε4 allele accelerates the rate of cognitive decline.



국문초록

알츠하이머병에서 널리 사용되는 표준치료 약물인 콜린분해효소억제제와 항NMDA 수용체 차단제 의 효용성은 임상시험 상에서 입증된바 있다. 현재 대부분의 환자들에서 진단 후 표준약물치료를 시행하고 있으나, 이러한 환자들의 장기적인 질병 진행양상이나 진행속도에 영향을 미치는 요인등에 대한 연구는 적으며, 한국인을 대상으로 한 연구는 전무하다. 본 연구는 표준 치료를 받고 있는 알츠하이머병 환자에서의 인지기능저하를 한국형 간이정신상태 검사로 전반적으로 측정, 선형혼합회귀법을 사용하여 모델을 도출하여 환자의 인지기능 저하 속도를 예측하고, 연관 인자를 규명하고자 하였다. 전체 환자군에서 평균 연간 점수변화는 −1.3점 (95% CI −1.47 ~ −1.14)였으며, 질병 중증도군에 따른 차이는 유의하지 않았다. 도출한 모델상에서 조기발병, 고학력, 낮은 초기 점수 및APOE $\varepsilon 4$ 유전형이 있는 경우 그렇지 않은 군에 비해 시간이 지날수록 인지기능저하가 빠르게 진행하는 양상을 보였으며, 이는 기존의 연구들과도 부합하는 결과를 보였다. 이러한 모델을 바탕으로, 장기간 치료를 받고 추적 관찰하는 환자군에서 질병의 진행을 예측하고, 이에 대해 적합한 치료계획을 도모하는 데에 기여할 것으로 기대된다.

주요단어: 알츠하이머병, 한국형 간이정신상태 검사, 선형혼합모형 , 콜린분해효소 억제제, NMDA 수용체 차단제

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