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ASSOCIATION OF EDUCATION WITH COGNITIVE FUNCTION IN NEWLY DIAGNOSED PARKINSON'S DISEASE

OH-DAE KWON[1], MIN-JAE LEE[1], HYE-GUK RYU[2]

[1]School of Medicine, Catholic University of Daegu, Daegu, Korea
[2]Pohang University of Science and Technology, Pohang, Korea

Oh-Dae Kwon – https://orcid.org/0000-0002-7465-2904
Min-Jae Lee – https://orcid.org/0000-0001-7884-2927
Hye-Guk Ryu – https://orcid.org/0000-0002-5901-1316

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Association of Education with Cognitive function in newly diagnosed Parkinson's disease

Oh-Dae Kwon[1], Min-Jae Lee[1], Hye-Guk Ryu[2]
[1]School of Medicine, Catholic University of Daegu, Daegu, Korea
[2]Pohang University of Science and Technology, Pohang, Korea

Parkinson's disease (PD) is the second most common neurodegenerative disorder. Low education is known to be a risk factor for Alzheimer's disease (AD). Since many patients with PD show pathological findings similar to AD in addition to Lewy body, we reasoned that low education might also be associated with decreased cognition of PD

Methods. We studied 154 unrelated PD patients recruited consecutively from May 2003 until March 2008 in the outpatient Movement Disorder Clinic of the Daegu Catholic University Medical Center. The diagnosis was made through manifestations of two or more cardinal features of PD: initially unilateral resting tremor, bradykinesia or rigidity, levodopa-responsiveness, and absence of clinical features of atypical PD. The 150 controls were without a diagnosis of a neurodegenerative disorder, who were the spouses or other caregivers of the patients. Cognitive function was assessed using a standardized cognitive function test, Seoul Neuropsychological Screening battery.

Results. The number of women was higher in PD patients, contrasting with Controls (p=0.000). The mean score of the Korean-mini mental state examination (K-MMSE) of PD was lower than that of controls (p=0.008). Patients with lower education related with higher age (p=0.030), higher women proportion (p=0.000), lower alcohol drinking (p=0.028), older age at onset (p=0.024), higher Unified Parkinson Disease Rating Scale part III score (p=0.050), lower K-MMSE (p=0.000), higher Geriatric Depression Scale (GDS) score (p=0.020). K-MMSE score of PD patients is strongly related to education level after adjusting age, sex, and GDS (p=0.000). Lower education (p=0.000) and higher GDS (p=0.007) has an association with lower K-MMSE in PD by univariate regression analysis.

Conclusion. As we hypothesized, newly diagnosed PD with low education showed lower cognitive performance. PD itself was seemed to be a risk factor for lower cognition as well as depression.

Keywords: *Parkinson disease, Cognition, Education, Mini-mental state examination*

Паркинсон ауруының алғашқы кезеңдеріндегі Білім және таным

О-Дэ Квон[1], Мин-Джэ Ли[1], Хе-Гук Рю[2]
[1]Тэгу католик университеті, Тэгу, Корея
[2]Пхохан ғылым және технологиялар университеті, Пхохан, Корея

Паркинсон ауруы (ПА) - ең көп таралған екінші нейродегенеративті ауру. Білімнің төмен деңгейі Альцгеймер (АА) ауруының қауіп факторы екені белгілі. Көптеген ПА пациенттерінде Леви тауықтарынан басқа, АА-ға ұқсас патологиялық белгілер анықталғандықтан, біз төмен білім деңгейі ПА-да танымдық қабілеттің төмендеуімен де байланысты болуы мүмкін деп болжадық.

Әдістері. Біз 2003 жылдың мамырынан 2008 жылдың наурызына дейін Тэгу Католик университетінің медициналық орталығының моторлық бұзылулардың

Oh Dae Kwon
e-mail: dolbaeke@cu.ac.kr

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амбулаториялық клиникасында жүйелі түрде қабылданған ПА бар 154 пациентті зерттедік. Диагноз екі немесе одан да көп ПА негізгі белгілерінің көрінісі негізінде жасалды, олар: бастапқыда бір жақты тыныштық треморы, брадикинезия немесе қаттылық, леводопаға реакция және атипті ПА клиникалық белгілерінің болмауы. Бақылау тобының 150 адамында нейродегенеративті бұзылыс диагнозы қойылмаған, олар ерлі-зайыптылар немесе пациенттерге күтім жасайтын басқа адамдар болған. Когнитивті функция стандартталған когнитивті тест, нейропсихологиялық скринингтің Сеул батареясы арқылы бағаланды.

Нәтижелері. ПА бар әйелдердің саны бақылау тобымен салыстырғанда жоғары болды (p = 0,000). Корей психикалық жағдайының мини-тестінің орташа балы (K-MMSE) бақылау тобына қарағанда төмен болды (p = 0,008). Төменгі білім деңгейлі пациенттер жасы үлкен (p = 0,030), әйелдердің үлесі жоғары (p = 0,000), алкогольді аз тұтыну (p = 0,028), аурудың басталуындағы жасы үлкен (p = 0,024), Паркинсон ауруының бірыңғай рейтинг шкаласы бойынша жоғары балл, III бөлім (p = 0,050), k-MMSE (p = 0,000), депрессияның гериатриялық шкаласы (GDS) бойынша жоғары балл (p = 0.020). ПА пациенттерінің k-MMSE бағалауы жасына, жынысына және GDS (p = 0,000) түзетілгеннен кейін білім деңгейіне байланысты. Төмен білім деңгейі (p = 0,000) және GDS шкаласы бойынша жоғары балл (p = 0,007) бір өлшемді регрессиялық талдау нәтижелері бойынша ПА-да төменгі K-MMSE-мен байланысты.

Қорытынды. Біз болжағанымыздай, алғаш анықталған ПБ-мен төмен білім деңгейі бар науқастарда танымдық қабілеттердің төмен деңгейі байқалады. ПМУ өзі танымдық қабілеттің төмендеуі, сондай-ақ депрессия үшін қауіпті фактор екені белгілі болды.

Негізгі сөздер: *Паркинсон ауруы, таным, білім, психикалық жағдайды қысқаша зерттеу*

Связь образованности и когнитивных функций на ранних стадиях болезни Паркинсона

О-Дэ Квон[1], Мин-Джэ Ли[1], Хе-Гук Рю[2]
[1]Католический университет Тэгу, Тэгу, Корея
[2]Пхоханский университет науки и технологий, Пхохан, Корея

Болезнь Паркинсона (БП) - второе по распространенности нейродегенеративное заболевание. Известно, что низкий уровень образованности является фактором риска болезни Альцгеймера (БА). Поскольку у многих пациентов с БП, помимо телец Леви, обнаруживаются патологические признаки, похожие на БА, мы предположили, что низкий уровень образованности также может быть связан со снижением познавательной способности при БП.

Методы. Мы изучили 154 неродственных пациентов с БП, поступивших последовательно с мая 2003 года по март 2008 гг, в амбулаторной клинике двигательных расстройств Медицинского центра католического университета Тэгу. Диагноз был поставлен на основании проявления двух или более основных признаков БП: изначально одностороннего тремора в покое, брадикинезии или ригидности, реакции на леводопа и отсутствия клинических признаков атипичной БП. У 150 человек контрольной группы диагноз нейродегенеративное расстройство не был поставлен, они были супругами или другими лицами, ухаживающими за пациентами. Когнитивная функция оценивалась с помощью стандартизированного теста когнитивной функции, сеульской батареи нейропсихологического скрининга.

Результаты. Число женщин с БП было выше по сравнению с контрольной группой (p = 0,000). Средний балл корейского мини-теста психического состояния (K-MMSE) БП был ниже чем у контрольной группы (p = 0,008). Пациенты с более низким уровнем образованности связаны с более старшим возрастом (p = 0,030), более высокой долей женщин (p = 0,000), меньшим употреблением алкоголя (p = 0,028), более старшим возрастом в начале заболевания (p = 0,024), более высоким уровнем баллов по унифицированной рейтинговой шкале болезни Паркинсона, часть III (p = 0,050), более низким K-MMSE (p = 0,000), более высокими баллами по Гериатрической шкале депрессии (GDS) (p = 0,020). Оценка K-MMSE пациентов с БП сильно зависит от уровня образованности после корректировки возраста, пола и GDS (p = 0,000). Низкий уровень образования (p = 0,000) и более высокие баллы по шкале GDS (p = 0,007) имеют связь с более низким K-MMSE при БП по результатам одномерного регрессионного анализа.

Заключение. Как мы и предполагали, у больных с низким уровнем образованности впервые выявленной БП отмечается более низкий уровень когнитивных способностей. Оказалось, что сама по себе БП является фактором риска снижения

познавательной способности, а также депрессии.

Ключевые слова: *болезнь Паркинсона, познание, образованность, краткое обследование психического состояния*

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder. It is primarily a motor disorder [1], but there are many non-motor symptoms, including cognitive disorders [1, 2]. The rate of mild cognitive impairment in newly diagnosed PD is two times of normal controls [2, 3]. Moreover, 20-57% of newly diagnosed PD developed mild cognitive impairment within five years of diagnosis [4-6]. Dementia prevalence of a meta-analysis showed that 40% of PD developed dementia [7]. The pathophysiology of cognitive dysfunction is not clearly understood. Dopaminergic neuronal loss and deficit of dopaminergic stimulation upon basal ganglia and the whole brain were suspected as the cause of cognitive dysfunction. However, dopaminergic therapy did not significantly improve PD's cognitive function and sometimes worsened behavioral symptoms and cognitive symptoms [8]. Therefore, another explanation for the cognitive decline is needed. Many PD patients have cholinergic deficits due to the cholinergic pathway's degeneration, including nucleus basalis of Meynert, similar to that of AD [9]. Choline acetyltransferase activity is also decreased in the cerebral cortex of PD, and reductions of Chloineacetyl transferase in the temporal neocortex are related to cognitive dysfunction [10]. Concurrent AD upon PD surely affects PD's cognitive decline [11].

Education and nurture positively affect brain development, including synaptic density and cell density of the brain. Development in an enriched environment increases total brain weight [12] and cortical thickness [13]. Low education is an important risk factor for AD [14, 15], and the prevalence of dementia is high in illiterate people [16]. There is a significant correlation between cerebral atrophy and educational level [17].

The reason we thought that lower education affects negatively the cognitive function of PD are as follows. First, there are concurrent AD pathologies in some patients with PD, and lower education is a risk factor for AD. Second, both AD and dementia in PD show cholinergic dysfunction. Third, education itself affects brain development. We hypothesized that lower education is related to lower cognitive performance in newly diagnosed PD and evaluated it by comparing neuropsychological performance between PD and normal controls and three educational groups in PD.

Methods

Subjects

This study was conducted in Daegu Catholic University Medical Center in southeast Korea. The 154 patients with PD were recruited from the patients who visited the outpatient Movement Disorders Clinic in the Department of Neurology, Daegu Catholic University Medical Center between May 2003 and March 2008. They are newly diagnosed and drug naïve. Age- and education-matched 150 controls were selected from the caregivers of the patients. Each person in the control group was examined by a neurologist and not diagnosed with any neurodegenerative disease. The protocol was approved by the ethics committee of Daegu Catholic University Medical Center.

Diagnosis

A neurologist with a specialty in neurodegenerative diseases evaluated all the patients and controls. All patients were diagnosed with PD based on previously published diagnostic criteria, including having at least two cardinal signs, rest tremor, rigidity, bradykinesia, and postural instabilities, of PD and levodopa-responsiveness [18]. Patients with other causes of parkinsonism such as progressive supranuclear palsy, primary dementia, cerebellar dysfunction, or drug-induced parkinsonism were excluded by neurological examination and thorough history followed by follow-up examination for at least one year, laboratory findings, and brain magnetic resonance imaging. Participants also were excluded if they had a family history of parkinsonism.

Neuropsychological tests

We performed a standardized neuropsychological battery, the Seoul Neuropsychological Screening Battery (SNSB) [19], in all subjects. The battery contains tests for attention, language, praxis, four elements of Gerstmann syndrome, visuoconstructive function, verbal and visual memory, and frontal/executive function. Among these tests, the components that could be scored were: digit span (forward and backward); the Korean version of the Boston Naming Test; written calculations (three items each for addition, subtraction, multiplication, and division; one point for each correct item); the Rey-Osterrieth Complex Figure Test (RCFT: copying, immediate and 20-minute delayed recall as well as recognition); the Seoul Verbal Learning Test (SVLT: three learning-free recall trials of 12 words, 20-minute delayed recall trial for these 12 items and a recognition test); the phonemic and semantic Controlled Oral Word Association Test (COWAT); the Stroop Test (word and color reading of 112 items in two minutes); and Barthel-ADL which was considered normal when perfect score was performed. Instrumental ADL was also done with a cut-off point of less than eight. Cognitive function was also assessed using the Korean version of the mini-mental state examination (K-MMSE) and clinical dementia rating (CDR) scale. The geriatric depression scale (GDS) was also performed.

Statistical analysis

For comparison of the PD group and Control group, an Independent sample T-test was done. The comparison of three educational groups in PD was made by ANOVA test.

ANCOVA analysis for the association between education level and K-MMSE after adjusting age, sex, GDS among the three educational groups of PD was also done. Lastly, we adjust the Univariate Regression analysis to find out any relations between educational level and covariates. SPSS for Windows (version 17.0 SPSS Inc.) was used for all statistical analyses, and p values <0.05 were regarded as statistically significant.

Results

The number of women was higher in PD patients, contrasting to that of Caucasians (Table 1). The mean score of K-MMSE of PD was lower than that of controls (Table 1) by independent sample T-test. Patients with lower education related with higher age, higher women proportion, lower alcohol drinking, older age at onset, higher Unified Parkinson Disease Rating Scale part III score, lower K-MMSE, higher GDS score (Table 2) by ANOVA test. THE mean K-MMSE score of PD patients is strongly related to education level after adjusting age, sex, and GDS(F=5.154, P=0.000) by ANCOVA test. Lower education and higher GDS have an association with lower K-MMSE in PD by univariate regression analysis (Table 3).

Discussion of results

Many patients with PD develop dementia in the late stage [7]. Moreover, many patients with PD show a cognitive decline in the early stage of PD [2, 3]. There is no conclusive evidence about the pathology of cognitive decline of this neurodegenerative disease. Some patients with PD show pathologic findings similar to those of AD [11]. Therefore, we thought the cognitive decline in PD might share the pathogenesis of AD as well as the risk factors of cognitive decline. We focused on the education level as a risk factor of cognitive decline of PD. To know the relationship between education level and cognitive decline, we compared the cognitive function between newly diagnosed PD and normal controls. We also compared cognitive functions among three educational groups in the patients.

The number of women was higher in the PD group than the control group, and it was contrasting to the previous studies, which showed male preponderance in prevalence

Table 1. General Characteristics of patients with Parkinson's disease and Controls

Characteristic	PD	Controls	*P* Value
Number	154	150	
Men/women	47/107	82/68	0.000*
Age, mean±SD (yrs)	71.38 ± 7.93	71.79 ± 4.14	0.571
Education, mean±SD (yrs)	5.76 ± 4.75	5.43 ± 2.87	0.459
K-MMSE	24.68± 4.05	25.79 ± 3.26	0.008*

*** Independent sample T-test**

Table 2. Clinical & neuropsychological characteristics among the education groups.

	Education group (Total n=154)			P	LSD
	0-5 yrs(n=66)	6-12 yrs(n=74)	>12 yrs (n=14)		
Age, mean (SD) yrs	73.03(6.62)	70.66(8.24)	67.43(10.29)	0.030*	1=2, 1>3, 2=3
Education, mean(SD) yrs	1.39(1.36)	7.78(2.28)	15.64(1.39)	0.000*	1<2<3
Men:Women (% women)	6:60(90.9%)	29:45 (60.8%)	12:2 (14.3%)	0.000*	1>2>3
Current alcohol drinking	22 (33.3%)	28 (37.8)	10 (71.4%)	0.028*	1=2, 1<3, 2<3
Current smoking	14 (21.2%)	26 (35.1%)	7 (50.0%)	0.051	1=2, 1<3, 2=3
Family History					
Dementia	4 (6.1%)	6 (8.1%)	1 (7.1%)	0.897	1=2=3
Stroke	10 (15.2%)	18 (24.3%)	3 (22.4%)	0.403	1=2=3
Current illness					
Hypertension	27 (40.9%)	37 (50.0%)	8 (57.1%)	0.406	1=2=3
Diabetes mellitus	16 (24.2%)	19 (25.7%)	4 (28.6%)	0.941	1=2=3
Age at onset of PD, mean (SD)	69.27(7.05)	65.68(10.19)	63.79(9.99)	0.024*	1>2, 1>3, 2=3
Hoehn-Yahr Stage, mean (SD)	2.29(0.65)	2.22(0.63)	2.21(0.43)	0.777	1=2=3
UPDRS III score, mean (SD)	25.85(8.20)	21.00(9.11)	20.17(6.71)	0.050*	1>2, 1>3, 2=3
Neuropsychological tests					
K-MMSE, mean (SD)	21.94(3.49)	26.53(3.28)	27.79(1.97)	0.000*	1<2, 1<3, 2=3
GDS, mean (SD)	18.18(7.59)	16.17(6.87)	11.92(6.80)	0.020*	1=2, 1>3, 2=3

n;number, SD;standard deviation, K-MMSE:Korean version of mini-mental state examinationUPDRS: Unified Parkinson Disease Rating Scale, P values are by 1-way ANOVA.

Table 3. Uni-variate associations between covariates and K-MMSE score.

	Exp(B)	Confidence Interval		P
		Lower	Upper	
Age, mean (SD) yrs	2.421	0.651	9.008	0.187
Education, mean(SD) yrs	5.161	3.638	6.684	0.000*
Men:Women	-1.009	-3.284	1.266	0.378
Current alcohol drinking	0.623	-1.102	2.349	0.472
Current smoking	-0.922	-3.287	1.443	0.438
Family History				
Dementia	0.031	-2.387	2.448	0.980
Stroke	-0.348	-1.889	1.194	0.653
Current illness				
Hypertension	-0.854	-2.187	0.48	0.205
Diabetes mellitus	-0.68	-2.168	0.808	0.363
Age at onset of PD, mean (SD)	-0.047	-0.135	0.041	0.288
Hoehn-Yahr Stage, mean (SD)	0.265	-1.568	2.097	0.773
UPDRS III score, mean (SD)	-0.029	-0.148	0.09	0.627
Neuropsychological tests				
GDS, mean (SD)	-0.134	-0.231	-0.038	0.007*

P value by univariate logistic regression anlaysis.

[20] and incidence [21]. Contrary to the early report only mentioning PD as a motor illness [1], we found significant cognitive impairment in the drug naïve PD patients. As we expected, the K-MMSE of PD was lower than that of controls. The newly diagnosed PD group's K-MMSE scores are strongly related to educational level after adjusting age, sex, and GDS. PD with lower education showed higher age, women proportion, lower alcohol drinking, higher age at onset, higher UPDRS III score, lower K-MMSE, higher GDS score. Lower education has an association with lower K-MMSE in PD and higher GDS also.

Because low education is a risk factor of AD, there were many patients with low education, even to the illiterate level, in our patient group that we focused on the relationship between educational level and cognition in the PD. For the effect of education on cognitive function, it is well known that early life education has a positive effect on late-life cognitive function [12, 22]. Furthermore, good education may protect late-life brain volume from atrophy [23]. The brain's mechanism of education is explained by increased synaptic density and the brain's cell density [12]. An early study suggested that relatively many patients with PD will develop cognitive decline early in the disease [24]. Our study is done with patients without previous PD medication, and the cognitive result was similar to it. We also thought PD's cognitive function is poor than normal controls, and the results of our study verified it.

This study has several advantages. We gathered consecutive patients with newly diagnosed PD, and none of them were on medication for the illness. Therefore, we can assess the pure disease effect on cognition. Moreover, we divided the education group into three, and it could give more information than the coefficient analysis itself.

This study also has several limitations. It is a cross-sectional study, and it is needed to follow up with the groups to know which educational group develops more AD or other types of dementia. Larger numbers of patients should be studied for more reliable results. There would be a selection bias because we gathered patients from only one university hospital in southeast Korea. Furthermore, the control group was mostly from the spouse or their children. Therefore, the control group could have shared genetic susceptibility or environmental risk factors of PD with the patients.

For the pathology of cognitive dysfunction in PD, there are several theories of pathogenesis. Firstly, AD pathology was mentioned because some PD patients showed abnormal proteins such as senile plaque and neurofibrillary tangle similar to those of AD [11,25]. However, the AD pathology is not explaining the entire aspect of cognitive decline in PD. One of our previous studies showed a very characteristic pattern of cognitive decline of PD by neuropsychological tests. Typically, memory decline is the most characteristic cognitive feature in AD. However, the PD patients showed a decline in memory and frontal executive function. The frontal executive function was more impaired between the two cognitive domains, and memory was relatively less impaired [26]. A study done in northern Europe showed that the PD group was more impaired in all neuropsychological tests than controls. The largest difference was for verbal memory, and one-fifth of the patients with PD were diagnosed with mild cognitive impairment [3]. Secondly, they think alpha-synucleinopathy, which develops the Lewy body, may result in PD's cognitive decline [27]. Moreover, many studies using levodopa to improve PD's cognitive decline were failed or with little effect [8]. Recently, a report

mentioned that striatal dopamine depletion might be related to mild cognitive impairment in de novo PD [28]. However, there is a controversy about the exact pathology of cognitive decline of PD until now.

The present study also showed the impaired cognitive function of the patients with PD compared to controls. We focused on the possible relationship between education level and cognitive function even though we did not administer all cognitive domain tests to the patients. However, the PD group had complete SNSB tests, and the result showed typical cognitive patterns.

In conclusion, we found that newly diagnosed PD with low education showed impaired cognitive performance and depressive mood. Therefore PD itself was seemed to be a risk factor of lower cognition as well as depression.

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