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Association of Cardiovascular Risk Factors and Parkinson's Disease – case-control study in South East Hungary

A Parkinson-kór és a kardiovaszkuláris rizikófaktorok kapcsolata – eset-kontroll vizsgálat a Dél-Alföldi régióban

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Abstract

Aims: Parkinson's disease (PD) has the second highest incidence among neurodegenerative diseases in the world population. The study aimed to investigate the presence of some cardiovascular risk factors – dyslipidemia, diabetes, and hypertension – in PD patients and to compare their risk with non-PD population in South East Hungary.

Methods: A case-control study was conducted at the Department of Neurology, University of Szeged, Hungary. The study included 1299 subjects out of which 620 patients were identified as cases of diagnosed PD and 679 as controls. Logistic regression analyses were conducted to reveal the association of vascular risk factors with PD.

Results: In the univariate analysis, diabetes mellitus was positively associated with PD, while dyslipidemia showed negative association to it in the total population, and no significant associations were found between hypertension and PD. The multivariate logistic regression models showed that the odds of diabetes mellitus was higher (OR=2.86), while the odds of dyslipidemia was lower (OR=0.58) among PD patients than in the control group. Hypertension showed a different pattern by gender: the odds of registered hypertension was significantly lower in female PD patients (OR=0.68), whereas the result was not significant in males.

Conclusions: This is the first study that provides a comprehensive view of the cardiovascular risk factors in PD patients in Hungary and shows considerable relationship between diabetes mellitus and PD.

Keywords: Parkinson's disease, cardiovascular risk factors, case-control study

Kulcsszavak: Parkinson-kór, kardiovaszkuláris rizikófaktorok, eset-kontroll vizsgálat

Absztrakt

Bevezetés és célkitűzés: A Parkinson-kór (PD) a második leggyakrabban előforduló neurodegeneratív kórkép a világon és így hazánkban is. A vizsgálat célja egyes kardiovaszkuláris rizikótényezők – lipidanyagcsere-zavarok, diabetes mellitus, magas vérnyomás betegség – előfordulásának mérése volt Parkinson-kóros és attól mentes betegek körében.

Módszer: Az eset-kontroll vizsgálat a Szegedi Tudományegyetem Neurológiai Klinikáján történt. A teljes minta 1299 főből állt, amelyből 620 fő volt a diagnosztizált PD beteg, 679 fő pedig a kontroll páciens. A vaszkuláris tényezők és a PD összefüggéseit logisztikus regresszióval modelleztük.

Eredmények: Az egyváltozós regressziós elemzés szerint a diabetesz pozitív, a lipidanyagcsere zavarai negatív kapcsolatot mutattak a PD-vel, a magas vérnyomás betegség esetében pedig nem igazolódott összefüggés. A többváltozós logisztikus regressziós modell megmutatta, hogy a diabetesz esélyhányadosa (OR=2.86; $p<0.001$) szignifikánsan nagyobb, míg a lipidanyagcsere zavaroké kisebb (OR=0.58; $p<0.001$) volt a PD betegek körében, mint a kontroll csoportban. A magasvérnyomás esélye viszont szignifikánsan kisebb (OR=0.68; $p=0.039$) volt PD esetén a nők körében, míg a férfiaknál ez nem volt megfigyelhető.

Konklúzió: Ez az első olyan hazai vizsgálat, ami a Parkinson-kórt a kardiovaszkuláris betegségek tükrében vizsgálja, és összefüggés mutatkozott a diabetesz és a PD között.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease, and it affects approximately seven million people globally, and the prevalence of the disease rises parallel with the aging of the population ¹. Approximately 20 thousand people with PD live in Hungary ². It is also well known that coronary artery diseases are among the leading causes of death in the world population as well as in Hungary ³.

Currently, several epidemiological studies search for how vascular risk factors such as diabetes or hypercholesterolemia affect the occurrence of PD. Studies describing the relationship between diabetes and PD have shown controversial results. A large multicenter analysis in Germany shows that the metabolic control of PD patients is better than that of patients with type 2 diabetes ⁴, while other studies have found positive association between diabetes and the risk of developing PD ⁵⁻⁷. A large population-based case-control study in Denmark shows that those who were administered an antidiabetic drug was associated with a 35% increased risk for PD ⁵. These results have been confirmed by a biomarker analysis showing that diabetes and PD are strongly linked at the molecular level ⁸. The association between the risk of PD and hypercholesterolemia has been described by several studies, but those results are also controversial ⁹⁻¹². Some studies have found an inverse relationship between hypercholesterolemia and the risk of PD ⁹⁻¹¹, while a systematic review has stated that the results are inconsistent, and further studies are needed ¹². Other studies have investigated the associations between hypertension and antihypertensive drugs, and the risk of PD ¹³⁻¹⁵. Louis et al. have not found evidence of a protective effect of antihypertensive drugs in PD ¹³, while Ritz et al. have suggested that there is a potential neuroprotective role of centrally acting L-type calcium channel blockers of the dihydropyridine class in PD ¹⁴. Qui et al. have found

that high-normal blood pressure and hypertension are associated with an increased risk of PD in women, but there was no significant association identified in men ¹⁵.

Considering that the results of previous epidemiological studies are conflicting, the aim of our study was to investigate the prevalence of cardiovascular risk factors (diabetes mellitus, dyslipidemia, and hypertension) in PD patients and to compare their risk with non-PD population in South East Hungary.

Patients and Methods

Study Design and Participants

A classical case-control study was conducted at the Department of Neurology, Albert Szent-Györgyi Health Center, University of Szeged, Hungary. We gained our data from the computerized MedSolution integrated hospital information system between January 1, 2000 and January 1, 2013. The total sample consisted of 1299 subjects who were hospitalized during the study period at the Department of Neurology, out of which 620 patients were identified as cases and 679 as controls. Cases included all hospitalizations in the study period if they had a diagnosis of PD (ICD-10 code: G20H0). Controls were matched to cases by age and sex, and they were selected from the patients with the diagnosis of epilepsy (ICD-10 code: G40) or back pain (ICD-10 code: M54) of the same department. The exclusion criteria for the control group was previous diagnosis of Parkinson's or Alzheimer's disease, multiple sclerosis, myasthenia gravis or secondary Parkinsonism.

Study Variables

Sex, age, comorbidity of dyslipidemia (ICD-10 code: E78), diabetes (ICD-10 codes: E1–E14), and hypertension (ICD-10 codes: I10–I15) of the subjects were collected from the MedSolution system. All data were registered anonymously.

Statistical Analyses

Simple descriptive statistics were used to characterize the participants. Chi-square tests were applied to compare the basic characteristics of case and control groups. Univariate and multivariate logistic regression analyses were conducted to assess the odds of vascular risk factors (diabetes, dyslipidemia, and hypertension) in PD. All logistic models were developed for the total population, and for males and females, separately. In the regression models, we calculated the odds ratio (OR) and the 95% confidence interval (95% CI) for each predictor. Statistical significance was set up at p values lower than 0.05. Data analyses were performed using IBM SPSS software version 20.

Ethics Statement

The study protocol was approved by the Human Institutional and Regional Biomedical Research Ethics Committee, University of Szeged (Registration number: 164/2012).

Results

The mean age and gender distribution of cases (PD-patients) and controls (non-PD patients) were similar (Table 1). Diabetes mellitus was significantly more frequent, whereas dyslipidemia was less frequent in the case group than in the control group, but no difference was found related to hypertension (Table 1).

In the univariate logistic regression analyses (Table 2), diabetes mellitus was positively associated with PD, i.e., the odds of diabetes mellitus was significantly higher in the PD group than in the control group (OR_{total}=2.65, 95% CI: 2.05–3.43; OR_{male}=2.45, 95% CI: 1.74–3.45; OR_{female}=2.97, 95% CI: 2.01–4.40). Dyslipidemia showed negative association; the odds were 0.62 (95% CI: 0.49–0.79) in the total population, 0.54 (95% CI: 0.38–0.75) in males and 0.71 (95% CI: 0.51–0.99) in

females. In the univariate analyses, no significant associations were found between hypertension and PD in the total population, and among males and females, respectively.

Age (years) and vascular predictors were involved in the multivariate logistic regression models of the total, the male and the female populations (Table 3). The common analysis of the factors showed that the odds of diabetes mellitus was higher ($OR_{total}=2.86$, 95%CI: 2.19–3.73; $OR_{male}=2.72$, 95%CI: 1.90–3.89; $OR_{female}=3.24$, 95%CI: 2.16–4.84), while the odds of dyslipidemia was lower ($OR_{total}=0.58$, 95%CI: 0.46–0.75; $OR_{male}=0.48$, 95%CI: 0.33–0.69; $OR_{female}=0.70$, 95%CI: 0.50–1.00) among PD patients than in the control group. Hypertension showed a different pattern by gender: the odds of registered hypertension was significantly lower in female PD patients ($OR_{female}=0.68$, 95%CI: 0.48–0.98), whereas in males the result was not significant ($OR_{male}=0.95$, 95%CI: 0.69–1.32).

Discussion

The results of our case-control study showed that diabetes mellitus was positively, while dyslipidemia was negatively associated with PD in males and females, whereas hypertension was negatively associated with PD only in females.

The association between diabetes mellitus and PD has been described in several studies^{5, 16–18}. The diagnosis or the ongoing treatment of diabetes has significantly been associated with an increased risk of PD in a Danish population-based case-control study⁵. Diabetes has been positively correlated with the severity of the disease as well ($OR=1.5$) in a Greek cross-sectional study¹⁶. Another case-control study in the USA has also found a significant relationship between PD and diabetes mellitus; the results of the study show a difference between the two genders: men with diabetes mellitus had a significantly lower risk of PD ($OR=0.52$) than men without diabetes,

whereas the association in women was not significant ¹⁷. Nonetheless, a large meta-analysis has found negative association with future PD (OR=0.75) and diabetes mellitus ¹⁸. Our findings are in accordance with the Danish, Greek and USA studies showing a considerable relationship between diabetes mellitus and PD.

The relationship between PD and cause of diabetes mellitus has been studied many times. One explanation is the inborn error of the insulin receptor expression in substantia nigra ¹⁹, but oxidative stress and mitochondrial disorders were linked to the disease process as well.

Similarly, studies about the complex problem of elevated lipid levels and PD relationship have been published, as well. A large prospective study has described that high dietary intake of cholesterol increased the risk of PD ²⁰, while high levels of cholesterol, triglycerides, total lipids and mean systolic and diastolic blood pressures have been less frequent in PD patients than in controls in a case-control study in Italy ²¹. The Honolulu–Asia Aging Study has also revealed an inverse association between LDL cholesterol and PD risk ²². In another prospective study, PD has not been significantly associated with hypertension, high cholesterol level, or diabetes, but it modestly declined with the increasing blood cholesterol level ²³. The association between blood pressure and the risk of PD has also been analyzed in other studies. High blood pressure is associated with PD only in females in the National FINRISK Study; the results indicate the importance of optimal blood pressure control to reduce the risk of PD ¹⁵. The protective effect of antihypertensive medications, such as centrally acting L-type calcium channel blockers of the dihydropyridine class in PD have been described by Ritz et al. ¹⁴.

Numerous animal experiments and human observational studies supported that a higher intake of cholesterol can reduce the risk of developing PD. The reason for this may be the increased

cholesterol turnover in the brain, which promotes central nervous system repair processes thus reducing the risk of developing PD ²⁴.

Many studies – including our study – have found inverse causal relationship of cholesterol level and risk of PD, which cannot be explained by lifestyle and dietary habits of the population, thus this may be an element of the process of PD. The possible causal relationship explored in some studies suggests that certain chronic neurodegenerative disorders – such as PD – are associated with impaired cholesterol homeostasis ²⁵.

In case of males, our results correlated with the previous findings related to the protective effect of abnormal lipid levels: we found negative association between dyslipidemia as a comorbidity and a risk of PD. The effect of hypertension was controversial, and it was also different by gender similarly to the findings of National FINRISK Study ¹⁵; according to the multivariate analyses, hypertension in females is associated with a lower risk of PD, while in males no association has been found.

The strength of the present study is that prior to this study, little research had been conducted about the association between PD and some vascular risk factors in Hungary.

Our study also has at least three limitations. First, the onset of PD and vascular risk factors/comorbidity is not clear because of the retrospective type of the study. Second, all diagnoses (PD, diabetes, hypertension, and dyslipidemia) were determined by the ICD codes gained from the MedSolution program of the hospital. Third, we lacked information regarding medications taken (e.g., antihypertensive drugs, **statins**, **antidiabetics**).

This retrospective case-control study showed considerable relationship between diabetes mellitus and PD. The association between dyslipidemia and hypertension seemed to be gender-dependent.

Further prospective studies are needed to confirm these findings and to characterize their role in the prevention or therapy of PD (e.g. assessment of hypertension, diabetes and dyslipidemia).

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Ethics Statement

The study protocol was approved by the Human Institutional and Regional Biomedical Research Ethics Committee, University of Szeged (Registration number: 164/2012).

Authors contribution: KM: study design, data collection, data evaluation, manuscript preparation; VL: study design, manuscript preparation; PE: study design, statistical analysis, manuscript preparation.

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Table 1. Baseline characteristics of participants

Characteristics	Cases	Controls	P-value*
Participants	620	679	
Age, years (mean±SD)	75.67±10.24	74.85±10.72	0.162
Female gender	294 (47.2%)	306 (45.1%)	0.390
Comorbidities			
Diabetes mellitus	222 (35.8%)	118 (17.4%)	<0.001
Dyslipidemia	160 (25.8%)	244 (35.9%)	<0.001
Hypertension	408 (65.8%)	458 (67.4%)	0.530

*Results of chi-square test

Table 2. Univariate logistic regression models of vascular factors associated with Parkinson’s disease in the case-control study

Parameters	Univariate					
	Males		Females		Total	
	OR (95 % CI)	P value	OR (95 % CI)	P value	OR (95 % CI)	P value
Diabetes mellitus		<0.001		<0.001		<0.001
Yes	2.45 (1.74–3.45)		2.97 (2.01–4.40)		2.65 (2.05–3.43)	
No	1.00		1.00		1.00	
Dyslipidemia		<0.001		0.048		<0.001
Yes	0.54 (0.38–0.75)		0.71 (0.51–0.99)		0.62 (0.49–0.79)	
No	1.00		1.00		1.00	
Hypertension		0.809		0.194		0.530
Yes	1.04 (0.76–1.42)		0.79 (0.56–1.13)		0.92 (0.74–1.17)	
No	1.00		1.00		1.00	

OR=odds ratio, CI=confidence interval

Table 3. Multivariate logistic regression models of vascular factors associated with Parkinson’s disease in the case-control study

Parameters	Multivariate*					
	Males		Females		Total	
	OR (95 % CI)	P value	OR (95 % CI)	P value	OR (95 % CI)	P value
Diabetes mellitus		<0.001		<0.001		<0.001
Yes	2.72 (1.90–3.89)		3.24 (2.16–4.84)		2.86 (2.19–3.73)	
No	1.00		1.00			
Dyslipidemia		<0.001		0.050		<0.001
Yes	0.48 (0.33–0.69)		0.70 (0.50–1.00)		0.58 (0.46–0.75)	
No	1.00		1.00			
Hypertension		0.773		0.039		0.101
Yes	0.95 (0.69–1.32)		0.68 (0.48–0.98)		0.82 (0.64–1.04)	
No	1.00		1.00		1.00	

*Adjusted for age.

OR=odds ratio, CI=confidence interval