Association between Parkinson's disease and diabetes: data from NEDICES study

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ABSTRACT

Background: Despite growing evidence showing an association between Parkinson's disease (PD) and diabetes, epidemiological studies have shown conflicting results.

Aims of the study: To evaluate the association between PD and diabetes, and the impact of diabetes duration in this association in an elderly (≥65 years) Spanish population.

Methods: Data for this cross-sectional population-based analysis were obtained from NEDICES study. Subjects were identified from census list. Diagnosis of PD was confirmed by neurological examination. Diabetes was defined by self-report, being on anti-diabetic medication or diagnosis on medical records. Logistic regression analysis adjusted by potential confounders was performed to estimate the association between both conditions and also after dividing patients into short-duration (<10 years) and long-duration (≥10 years) diabetes.

Results: 4998 subjects were included (79 PD and 4919 controls). Univariate analysis did not show any association between prevalence of PD and diabetes (OR 1.89, 95% CI 0.90 – 3.98, $P = 0.09$) though subgroup analysis showed a positive association in those with long-duration diabetes (3.27, 95% CI 1.21 – 8.85, $P = 0.02$).

Conclusions: diabetes duration might be an important factor in the association between PD and diabetes and the risk might be limited to those with longer disease duration.

Introduction

Increasing evidence suggests that insulin dysregulation and diabetes might contribute to the development of Parkinson's disease (PD) by shared molecular pathways.[1-3] However, this potential association remains controversial from an epidemiological perspective. The aim of the present study is to evaluate the relationship between PD and diabetes in the baseline assessment of the *Neurological Disorders in Central Spain* (NEDICES) study and evaluate the potential role of diabetes duration in that association.

Methods

Study population

NEDICES study is a longitudinal population-based survey carried out between 1994-2007 assessing community-dwelling ≥65 year-old individuals in order to estimate prevalence, incidence and determinants of major age-associated neurological conditions.[4] Study protocol was approved by the local ethics institution and all subjects signed an informed consent at enrolment. Detailed of the study population and sampling methods have been published elsewhere.[4-6] Briefly, subjects were selected by means of census lists from three different populations in central Spain in 1994-1995. Data from this baseline cross-sectional evaluation were used for this study.

Diagnosis of Parkinson's disease and diabetes

All those subjects who screened positive on the initial validated screening questionnaire for parkinsonism were assessed and examined by a senior neurologist to confirm the diagnosis of PD.[5,6] PD was defined by the presence of 2 cardinal signs of bradykinesia, resting tremor, rigidity and impairment of postural reflexes (or 1 cardinal sign in those on antiparkinsonian medication) and exclusion of other causes of parkinsonism. Only subjects with idiopathic PD were included in the study (Table 1).

Diabetes was defined by self-reported diagnosis, treatment with antidiabetic medication (oral antidiabetics and/or insulin), or diagnosis present on medical records. Subjects lacking data on diabetes status were excluded from the analysis.

Statistical analysis

Variables were not normally distributed (for each Shapiro-Wilk test, $P < 0.001$). Chi-squared or Fisher's exact tests were used for categorical variables and Wilcoxon test for continuous or ordinal variables. All the tests were two-sided and a value of $P<0.05$ was considered statistically significant. Statistical analyses were performed using the statistical software Stata 12 (StataCorp, TX).

Adjusted binary logistic regression analyses were performed with PD as the dependent variable and diabetes (presence/absence) as the independent variable. To assess the association between PD and diabetes duration patients were divided into short-duration (<10 years) and long-duration diabetes (≥10 years) as per previous studies in the literature.[7,8] Potential confounding was controlled by including demographics (gender, age); cardiovascular risk factors, previous cerebrovascular disease and antidiabetic treatment.

Results

This study included 4,998 subjects from a total of 6,395 community-dwelling elders (Fig. 1). Their baseline demographic and medical characteristics are shown in Table 2. There were 2,121 men and 2,877 women with a median age of 73 years (interquartile range -IQR 68 - 79). The diagnosis of prevalent PD was confirmed in 79 subjects (1.6%). Diabetes was diagnosed in 842 subjects (16.8%) with a median duration of 5 years (IQR 2-13), though the information on disease duration was only available in 657 subjects. Main variables did not differ between both groups although PD subjects were slightly older ($P < 0.001$) and with a higher frequency of male gender ($P = 0.03$) than controls (Table 2).

Prevalence of diabetes did not show any significant differences among PD (17.7%) and non-PD patients (16.8%) and the crude (unadjusted) prevalence ratio for PD among diabetics vs non-diabetics was 1.06 (95% CI 0.60 – 1.89, $P = 0.83$). Results of the adjusted analysis did not modify the results of this association (OR 1.89, 95% CI 0.90 – 3.98, $P = 0.09$). Covariates significantly associated to prevalent PD in this model were age (OR 1.05 per year, 95% CI 1.01 – 1.09, $P = 0.014$), and male gender (OR 4.06, 95% CI 2.03 – 8.12, $P < 0.001$) whilst current smoking showed a negative association to PD (OR 0.23, 95% CI 0.06 – 0.83, $P = 0.024$).

Participants were divided according to diabetes duration. All patients with PD were included in this analysis but only 643 out of 828 diabetic controls (77.7%) had this information available. Groups did not differ in age or gender. Results showed a significant positive association between the longer diabetes duration group with prevalent PD after adjustment for potential confounders (reference: no diabetes; OR

for short-duration diabetes 1.68, 95% CI 0.70 – 4.03, P = 0.24; OR for long-duration

diabetes 3.27, 95% CI 1.21 – 8.85, P = 0.02).

A summary of the results of the statistical analysis with the associations between

different groups is shown in Table 3.

Discussion

In this large population-based cross-sectional study we found no significant

association between diabetes and PD among Spanish elderly. However our results

suggest that diabetes duration might be an important factor on this association and

the risk of PD might be limited to those patients with long-duration diabetes as there

was a significant positive association between PD and those patients with long-

duration diabetes (>10years duration).

Our study did not show a significant association between PD and diabetes in our

sample population (OR 1.89, 95% CI 0.90 – 3.98, P = 0.09). Results of observational

studies evaluating this association are conflicting [9,10] although in recent meta-

analysis of prospective studies diabetes was found to be a risk factor for future PD

(RR = 1.26 [95%CI 1.03-1.55]; p <0.0001).[11,12]

To our knowledge, the potential time-dependent effect of the association has been

assessed only in two previous studies.[7,8] Our results are in agreement with those of

the Xu *et al* [8] showing that most of the risk is attributed to patients with disease

duration of more than 10 years. The effect of diabetes duration is important in the

interest of giving a pathophysiological explanation of the association, as if diabetes is

a risk factor for PD, one will expect a higher risk among those with long history or

complicated diabetes. Driver et al [7] found that the increased risk for PD was highest among individuals with uncomplicated or short-duration diabetes (<10 years of duration) which was explained by the authors as a possible selection bias from increased medical surveillance or an underlying common biological mechanism.

The heterogeneity of the published studies, ascertainment of PD and diabetes, and the effect that environment, ethnic factors and diabetes medications might have on the association, might explain in part the inconsistency of the results. Unfortunately detailed information on diabetes control and medications were not available in our cohort and the influence that this may have on the risk of PD could not be assessed.

One of the main strengths of our study is the confirmation of PD diagnosis by a neurologist in all cases. PD cases in our study were identified from the census list in three different communities irrespective of their medical care with a more representative sample of the population with a low chance of selection bias among community-dwelling subjects. Results were adjusted by multiple potential confounders using defined and validated information obtained through face-to-face interviews including vascular risk factors and cases of vascular parkinsonism were excluded. On the other hand, our study included a relatively small number of PD patients (n=79) and therefore results should be interpreted with caution before making any firm conclusions. The cross-sectional design of the study and the lack of information about the temporal relation between the two diagnoses do not allow establishing the direction of the causal relationship between diabetes and PD.

Apart from the observational studies discussed above, there is growing evidence from various areas of research suggesting a common link between diabetes and PD. It has been hypothesised that aberrant insulin signalling triggers a step wise

sequence of disruptions of regulatory pathways (including mitochondrial dysfunction, neuroinflammation, increased endoplasmic reticulum stress, abnormal protein aggregation and metabolic abnormalities) which would lead to insulin resistance and diabetes, and might ultimately put an individual at increased risk for PD.[1-3] In addition to a potential increased risk for PD, diabetes has also been suggested as a modifying factor of the disease contributing to more severe motor symptoms requiring higher doses of levodopa for symptom control,[13] more prominent axial motor symptoms and cognitive impairment.[14] The possibility that PD and diabetes share dysregulated pathways is particularly important as further study of these mechanisms might lead to more effective treatments or disease modifying therapies for PD and diabetes. In this regard, exenatide, a synthetic agonist for the glucagon-like peptide 1 receptor recently granted for the treatment of diabetes, has been shown neuroprotective effect in an initial open label randomised controlled trial comparing 20 patients with PD treated with exenatide and 24 PD patients acting as controls. [15]

Conclusions

The results of this population-based cross-sectional study shows no significant association between PD and diabetes but suggests a possible disease-duration dependent effect in this relationship as there is an increased prevalence of PD in those with long-duration diabetes after adjustment for confounding factors. Diabetes duration appears to reflect the effect of the cumulative toxicity of the underlying shared pathological mechanisms between these two diseases. Future studies should further explore this possibility and the effect of good diabetes control in the association between PD and diabetes.

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TABLES

Table 1. Diagnostic criteria for parkinsonism and etiologic subgroups.[5,6]

Diagnosis	Criteria
Parkinsonism	Presence of ≥2 cardinal signs (tremor, bradykinesia, rigidity, postural disturbances) in a subject not on antiparkinsonian medication *or* Presence of ≥1 cardinal sign in a patient on antiparkinsonian medication
Drug-induced parkinsonism	Treatment with dopaminergic blocking drugs within 6 months before symptom onset *and* Previous negative history of parkinsonian symptoms or signs *and* Improvement or resolution of the symptoms within 6 months after discontinuation of the offending drug [a]
Vascular parkinsonism	Presence of ≥2 of the following features: History of cerebrovascular disease with sudden onset and stepwise progression of parkinsonian symptoms *or* Arterial hypertension *or* Emotional incontinence and pseudobulbar palsy *or* Broad-based rigid gait *or* Widespread pyramidal signs
Atypical parkinsonism	Parkinson-plus syndromes, parkinsonism secondary to central nervous system infection, repeated head trauma, brain tumors or other conditions affecting the basal ganglia [b]
Idiopathic Parkinson´s disease	Presence of parkinsonism and enough clinical information to exclude vascular, drugs or atypical causes
Unspecified parkinsonism	Presence of parkinsonism with insufficient clinical information to reach an etiological diagnosis

Footnotes. [a] whenever possible; [b] defined by routine clinical diagnosis.

Table 2. Demographic and clinical characteristics of participants.

	Total (n=4998)	Parkinson's disease (n=79)	Controls (n=4919)	P Value
Sex, female (%)	57.7	45.6	57.8	0.03
Age, years (IQR[a])	73 (68-79)	77 (72-82)	73 (68-79)	<0.001
Diabetes (%)	16.8	17.7	16.8	0.83
Anti-diabetes therapy*				0.62
None (%)	47.5	57.1	47.3	
Oral (%)	36.6	35.7	36.6	
Insuline (%)	15.9	7.1	16.1	
Diabetes duration, years (IQR)	5 (2-13)	8.5 (2-17)	5 (2-13)	0.52
<10 years (%)	65.0	50.0	65.3	
≥10 years (%)	35.0	50.0	34.7	
Hypertension (%)	50.9	59.5	50.8	0.13
Dyslipemia (%)	29.1	23.7	29.2	0.30
Alcohol consumption				0.24
Never (%)	46.2	55.9	46.0	
Former (%)	20.9	19.1	21.0	
Current (%)	32.9	25.0	33.1	
Smoking				0.31
Never (%)	61.3	64.7	61.2	
Former (%)	26.9	29.4	26.9	
Current (%)	11.8	5.9	11.9	
Body mass index				0.13
Underweight (%)	1.6	5.0	1.5	
Normal (%)	31.2	35.0	31.1	
Overweight (%)	42.6	41.7	42.6	
Obese (%)	24.6	18.3	24.7	
Stroke/TIA (%)	4.9	6.3	4.9	0.55
DRB[b] drugs (%)	4.9	4.9	6.3	0.56

Footnotes. *Only 657 diabetic patients included in the analysis; [a]inter quartile range;

[b]dopamine receptor blocking drugs.

Table 3. Association between diabetes and Parkinson's disease (OR and 95% CI) according to diabetes status and duration.

	PD (n=79)	Controls (n=4919)	Unadjusted model	Adjusted model
Diabetes				
No	65 (1.56%)	4091 (98.44%)	1.0	1.0
Yes	14 (1.66%)	828 (98.34%)	1.06 (0.60-1.89)	1.89 (0.90-3.98)
Diabetes duration				
None	65 (1.56%)	4091 (98.44%)	1.0	1.0
<10y	7 (1.64%)	420* (98.36%)	1.05 (0.49-2.26)	1.68 (0.70-4.03)
≥10y	7 (3.04%)	223* (96.96%)	1.98 (0.91-4.28)	3.27 (1.21-8.85)

Footnotes: data shown are n (%) or OR (95% CI). Adjusted model: adjusted for sex, age, hypertension, dyslipemia, antidiabetic treatment, alcohol consumption, smoking status, body mass index, presence of cerebrovascular disease and treatment with potential parkinsonism-inducing drugs in the logistic regression analysis. * only 643 controls (from a total of 828) had diabetes duration information available and were included in this analysis.

FIGURES

Fig 1. Flow-chart of the study.