Metabolic syndrome and dementia associated with Parkinson's disease: impact of age and hypertension

Síndrome metabólica e demência associada à doença de Parkinson: impacto da idade e da hipertensão arterial

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ABSTRACT

Objective: To determine correlations between age and metabolic disorders in Parkinson's disease (PD) patients. **Methods:** This observational cross-sectional study included brief tests for dementia and the Mattis test. Signals of metabolic syndrome were evaluated. **Results:** There was no significant effect from the presence of hypertension (OR=2.36 for patients under 65 years old and OR=0.64 for patients over 65), diabetes or hypercholesterolemia regarding occurrences of dementia associated with PD (24% of the patients). The study demonstrated that each year of age increased the estimated risk of dementia in PD patients by 9% (OR=1.09; 95%CI: 1.01–1.17). **Conclusion:** There was no evidence to correlate the presence of metabolic syndrome with the risk of dementia that was associated with PD. The study confirmed that dementia in PD is age dependent and not related to disease duration.

Key words: dementia, Parkinson's disease, dyslipidemia, hypertension.

RESUMO

Objetivo: Determinar correlações entre idade e acometimento metabólico em doentes com Parkinson. **Métodos:** Estudo observacional, transversal, incluindo testes breves para demência e teste de Mattis. Foi avaliada presença de síndrome metabólica. **Resultados:** Não houve efeito significativo da presença de hipertensão arterial (OR=2,36 em pacientes com menos de 65 anos e OR=0,64 em maiores de 65 anos), diabetes e hipercolesterolemia sobre ocorrência de demência associada com a doença de Parkinson (24% dos pacientes). O estudo demonstrou que, a cada ano de idade, o risco estimado para presença de demência em parkinsonianos aumentou em 9% (OR=1,09; IC95%: 1.01–1.17). **Conclusão:** Não houve evidências para associar presença de síndrome metabólica com o risco de demência associada à doença de Parkinson. O estudo confirmou que a demência na doença de Parkinson é idade-dependente e não está relacionada ao tempo de duração da doença.

Palavras-Chave: demência, doença de Parkinson, dislipidemia, hipertensão.

Identification of risk factors for cognitive impairment in patients with Parkinson's disease (PD) has been the subject of many studies. Many of these have listed factors that were affirmed as predictive of situations associated with the natural history of dementia and PD, including postural instability and gait difficulty, advanced age, male sex and poor performance in baseline cognitive tests[1-3]. On the other hand, other studies have identified comorbidities associated with the risk of dementia in patients with PD, such as depression and gastroenterological disorders that are suggestive of autonomic dysfunction[4,5]. Some recent reports have shown an apparent protective effect from hypercholesterolemia; however, hypertension is considered to be a risk factor for PD[6,7]. The proposed clinical picture of Parkinson's disease dementia (PDD) is often limited to the presence of depression, visual hallucinations and greater impairment in visual reasoning tests, complemented with memory and executive impairment[1].

Few studies have focused on the correlation between cerebrovascular disease and the risk factors and cognitive symptoms of PD. In 1974, while analyzing Parkinson's cerebral arteriosclerosis

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and what was then named senile dementia, Parkes et al.[8] were unable to establish a single diagnosis for many patients, who were therefore excluded from their analysis. This shows the difficulty that existed at that time in distinguishing between these groups and, even more so, in establishing comorbidities. In 1998, based on pathological findings, Yoshimura[9] determined that 13.5% of dementia patients with PD presented histopathological findings compatible with both PD and vascular dementia (VaD). This author drew attention to the fact that clinical Parkinsonism was frequently masked by vascular symptoms and that these cases tended to be diagnosed as multi-infarct dementia.

The objective of the present study was to estimate the prevalence of dementia in patients with PD and the effect of risk factors, diabetes, hypertension and dyslipidemia, on occurrences of dementia in this population at a referral clinic within the public healthcare system.

METHODS

This was an observational cross-sectional study conducted at a referral clinic (Botucatu University Hospital) in a medium-sized city (Botucatu; 150,000 inhabitants), between August 2009 and May 2010. The study was approved by the Research Ethics Committee of Botucatu Medical School, São Paulo State University. All participants, or their legal guardians, provided written informed consent.

Selection and description of participants

This study was open to patients with a clinical diagnosis of PD[10] who were attending the Movement Diseases Outpatient Clinic.

Patients were excluded if they presented focal lesions in neuroimaging examinations or a prior history of stroke (<6 months ago), if they were under investigation for atypical Parkinsonism or if their diagnostic hypothesis was dementia with Lewy bodies.

At baseline, 81 PD patients underwent a brief battery of screening tests for the presence of cognitive impairment. Patients with B12 and folate deficiency (n=2) were not considered eligible for analysis, thus leaving a total of 79 patients for this study. Those selected were further analyzed by means of a more specific neuropsychological schedule for dementia diagnoses.

Technical information

The patients underwent a two-stage protocol. The cognitive screening (brief cognitive battery) included tests on memory and executive functions; a delayed recall test[11]; category verbal fluency; phonemic verbal fluency; and an executive clock drawing task (CLOX)[12]. The patients selected were assessed for particular cognitive traits using the Mattis Dementia Rating Scale (MDRS)[13], with five subscales analyzing distinct cognitive domains: attention, initiative/persever-

ance, construction, concept and memory. These scales have been validated for the Brazilian population[14].

The following data were collected: sociodemographic (sex, age and education level); clinical history (diagnosis and treatment time); lipid profile (total cholesterol over 200 mg/dL); arterial blood pressure, in which levels above 140/90 mmHg were designated as hypertension; and diabetes, established through findings of glycemia greater than 126 mg/dL in two samples.

The main sociodemographic and clinical characteristics of the sample are presented in Table 1.

Statistical analysis

The study population was characterized according to demographic variables, potential risk factors and dementia.

The statistical analysis was divided into three stages:

1. Identification of variables/confounding factors (Tables 2 and 3).
2. Estimation of possible effects of double and triple interaction on the percentage occurrence of dementia (Table 4), using the Fisher exact test.

Table 1. Sociodemographic and clinical variables of the sample.

Variables	n	%
Age (years)		
From 42 to 60	17	21.3
From 61 to 65	13	16.3
From 66 to 70	13	16.3
From 71 to 75	20	25.0
From 76 to 80	12	15.0
Over 80	4	5.0
Sex		
Male	54	67.5
Female	25	31.5
Risk factors		
Diabetes	12	15.2
Hypertension	42	55.3
Dyslipidemia	29	37.2
Total risk factors		
0	27	33.8
1	27	33.8
2	19	23.8
3	6	7.5
Dementia status		
No	60	76.0
Yes	19	24.0

Table 2. Adjusted logistic regression model estimating the effects of age, sex and time of diagnosis on occurrences of dementia.

Variables	β	p	OR	95%CI
Age (years)	0.08	0.027	1.09	(1.01–1.17)
Male sex	0.11	0.852	1.11	(0.37–3.36)
Time of diagnosis (years)	-0.02	0.729	0.98	(0.88–1.10)

β: estimated effect; OR: odds ratio; CI: confidence interval; p: p-value.

3. Estimation of the effects of diabetes, hypertension and dyslipidemia on dementia, adjusted for confounding factors that were identified in step 1, and considering the possible effects of double and triple interaction (Tables 5 and 6) using point and interval estimates (95%CI) of the odds ratio (OR).

All analyses were performed using SPSS software, version 15.0.

The number of patients in the study (n=79) was determined through the number of eligible patients attended by the service who were included in the study. Despite this lim-

Table 3. Adjusted logistic regression model estimating the effect of age on diabetes, hypertension and dyslipidemia in patients with Parkinson's disease.

Outcome	β	p	OR	95%CI
Diabetes	0.03	0.393	1.03	(0.96–1.11)
Hypertension	0.06	0.023	1.07	(1.01–1.13)
Dyslipidemia	-0.01	0.836	0.99	(0.94–1.05)

β: estimated effect; OR: odds ratio; CI: confidence interval; p: p-value.

Table 4. Estimated percentage of patients with dementia according to presence or absence of diabetes, hypertension and dyslipidemia.

Diabetes	Hypertension	Dementia (%)	p[1]
Absence	Absence (n=29)	24.1	1.000
	Presence (n=34)	23.5	
Presence	Absence (n=3)	33.3	1.000
	Presence (n=10)	30.0	
Diabetes	Dyslipidemia	Dementia (%)	p[1]
Absence	Absence (n=41)	17.1	0.228
	Presence (n=23)	30.4	
Presence	Absence (n=5)	40.0	1.000
	Presence (n=8)	25.0	
Hypertension	Dyslipidemia	Dementia (%)	p[1]
Absence	Absence (n=25)	20.0	0.327
	Presence (n=7)	42.9	
Presence	Absence (n=20)	20.0	0.728
	Presence (n=23)	26.1	

[1]Fisher's exact test; p: p-value.

Table 5. Adjusted logistic regression model estimating the effect of hypertension on dementia, corrected for age.

Age (years)		β	p	OR	95%CI
Less than 65	Hypertension	0.86	0.505	2.36	(0.18–29.70)
65 or over	Hypertension	-0.44	0.479	0.64	(0.18–2.18)

β: estimated effect; p: p-value; OR: odds ratio; CI: confidence interval.

Table 6. Logistic regression models adjusted to estimate the effect of diabetes and dyslipidemia on dementia.

Variables	β	p	OR	95%CI
Diabetes	0.393	0.556	1.48	(0.39–5.49)
Dyslipidemia	0.519	0.338	1.68	(0.58–4.87)

β: estimated effect; p: p-value; OR: odds ratio; CI: confidence interval.

itation, it is hoped that the tests applied have a statistical power of around 80%.

RESULTS

The majority of the patients were men (67.5%). The patients' ages ranged from 42 to 82 years. Most patients presented more than one risk factor for vascular disease, and hypertension was the most prevalent condition (55.3%), followed by dyslipidemia (37.3%).

The mean length of time for which the patients had a diagnosis of Parkinson's disease was 6.7 years. The minimum and maximum lengths of time with the diagnosis were one and 20 years, respectively, and 50% of the patients had the diagnosis for fewer than five years. Among the patients evaluated, 24% were considered to be cases of dementia, according to the scale used (Table 1).

Among the potential complication factors evaluated, there were indications that patient age had a significant effect on dementia. The logistic regression model determined that each additional year of patient age resulted in a mean increase in the estimated risk of dementia of 9% [odds ratio (OR)=1.09; 95% confidence interval (CI): 1.01–1.17] (Table 2).

Indications that age had a significant effect on hypertension were observed, showing that the mean increase in the risk of hypertension per year was 7% (OR=1.07; 95%CI: 1.01–1.13). No statistically significant effect from age was found in relation to diabetes and dyslipidemia (Table 3).

Regarding the possible effects of paired interactions between diabetes, hypertension and dyslipidemia, on dementia, the Fisher exact test showed no evidence of a statistically significant effect in relation to the percentage of occurrence of dementia (Table 4).

The effects of age on hypertension and dementia were estimated for subgroups of less than and greater than or equal to 65 years of age (Table 5). There were no indications of a statistically significant effect from hypertension, diabetes and dyslipidemia on dementia associated with PD. Among the patients under 65 years of age, the effect of hypertension on dementia resulted in an OR=2.36 (95%CI: 0.18–29.70), while for patients aged 65 years or over the values were OR=0.64 (95%CI: 0.18–2.18) (Table 5). The difference between the confidence intervals was mainly due to the difference in subgroup size (n=27 for less than 65 years of age and n=49 for 65 years or older).

The effects of diabetes and dyslipidemia were estimated independent of age (Table 6). The results provided no indications of any statistically significant effect on dementia from diabetes (95%CI: 0.39–5.49) or dyslipidemia (95%CI: 0.58–4.87) on dementia independently of patient age (Table 6).

It was not possible to establish any statistical difference between the distinct cognitive domains evaluated by the MDRS and the presence of risk factors for cerebrovascular disease (data not shown).

DISCUSSION

The study showed that 24% of the patients fulfilled the criteria for PDD. The data available showed that the mean prevalence of dementia associated with PD was 30%, with a range from 4% to 93%[1,15]. This large variability can be explained by the different methodologies used in different studies.

In 1999, Winikates et al.[16] proposed criteria for clinically distinguishing vascular dementia from idiopathic Parkinsonism, including analysis of plasma cholesterol levels and the presence of diabetes and hypertension. Among the 96 patients examined, 32 did not meet the criteria for a diagnosis of vascular dementia or for idiopathic Parkinsonism.

Analysis of risk factors did not demonstrate that hypertension exerted any statistically significant effect on dementia in patients over or under 65 years of age, similar to the findings in relation to diabetes and dyslipidemia. However, the effect of age on hypertension in PD patients was significant when faced with evidence from the literature that hypercholesterolemia, arterial hypertension and diabetes do not show correlations with the risk of PD[6,7]. It should be noted that arterial hypertension, dyslipidemia and diabetes do not seem to be associated with occurrences of either PD or dementia throughout their evolution.

Population-based studies in Brazil have shown that the prevalence of systemic arterial hypertension is 30.1%, with a significant association between arterial hypertension and age greater than 60 years, according to the hypertension criterion of ≥140/90 mmHg[17]. In a study on the relationship between hypertension alone in the elderly (over 65 years of age) and Alzheimer disease, vascular dementia and cognitive function, hypertension appears not to adversely affect memory, language or general cognitive function, but could be an antecedent of vascular dementia in the presence of heart disease or diabetes[18]. Even so, the present study did not demonstrate any significant association between arterial hypertension and age-corrected dementia (Table 5) or any correlation with the presence of diabetes or dyslipidemia (Table 6).

The effect of age on patients with Parkinson and dementia was much higher than on those without significant cognitive deficits (Table 2). Population studies have shown a direct relationship between patient age and the prevalence of dementia in patients with PD, which is higher than 60% in individuals over the age of 80 years[2,19,20].

It was not possible to demonstrate any correlation with disease duration (Table 2), which is in agreement with other reports[21,22]. The question of disease duration versus patient age reappears as a central point, thereby corroborating the affirmation that PD is a chronic progressive disorder and that the most important determinant of clinical progression is advancing age (including the risk of dementia), rather than disease duration[7]. Models focusing on separating dopaminergic effects (linked to the disease) from non-dopaminergic (acetylcholinergic) effects and other systems that have been proposed, in order to elucidate this question[23], have been reinforced by findings demonstrating that the presence of hypertension or dyslipidemia did not have any effect on dementia in PD.

Evaluation of data obtained from applying the MDRS revealed similarities between the two groups, i.e. with and without risk factors associated with dementia. No significant abnormalities were observed with regard to attention and memory disorders.

Cognitive evaluation with brief tests has demonstrated limitations in discriminating between vascular dementia and Alzheimer-type dementia[24]. Similarly, it has not been possible to demonstrate differences in cognitive evaluations when comparing patients with Parkinson's dementia and metabolic risk factors with patients who did not present dyslipidemia, arterial hypertension or diabetes.

It has been well demonstrated that comorbidities, such as hypercholesterolemia, arterial hypertension and diabetes, add to the financial cost of caring for elderly individuals with PD[25]. On the other hand, the data have raised numerous questions, including evidence that dyslipidemia, arterial hypertension and diabetes are not associated with the risk of PD development. However, after the disease has evolved for some years, an association between cerebrovascular disease and PD with dementia could still occur.

Even considering the small sample size, this study reinforces the impression that age and hypertension are important in the pathophysiology of dementia associated with PD. Further studies are required to understand these findings.

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