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Short Communication

Cardiovascular Risk Factors and Phenoconversion to Neurodegenerative Synucleinopathies in Idiopathic REM Sleep Behavior Disorder

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Abstract. Several studies have suggested that atherosclerotic diseases and diabetes may be risk factors for α-synucleinopathies. This prospective cohort study evaluated whether cardiovascular diseases and metabolic risk factors alter the rate or type of phenoconversion from idiopathic/isolated REM sleep behavior disorder (iRBD) to parkinsonism or dementia. Polysomnography-confirmed iRBD patients recruited between 2004 and 2020 were followed annually. Baseline history of cardiovascular disorders, hypertension, hypercholesterolemia, and diabetes were compared among patients who developed outcomes versus those who remained outcome-free. No atherosclerotic risk factors were associated with development of α-synucleinopathies. Patients with hypercholesterolemia were somewhat more likely to develop dementia with Lewy bodies rather than Parkinson's disease.

Keywords: REM sleep behavior disorder, cardiovascular disease, hypertension, diabetes, hypercholesterolemia, α-synucleinopathies, Parkinson's disease, dementia with Lewy bodies, cohort

INTRODUCTION

Accumulation and alteration of α-synuclein in the brain (α-synucleinopathies) underlies neurodegenerative disorders such as Parkinson's disease (PD), multiple system atrophy (MSA), and dementia

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with Lewy bodies (DLB) [1, 2]. Idiopathic/isolated rapid eye movement sleep behavior disorder (iRBD) is a parasomnia and a well-established predictive marker for development of these α-synucleinopathies [3, 4].

Several studies have investigated whether cardiovascular disorders (CVD) and metabolic risk factors (i.e., hypertension, diabetes, hypercholesterolemia) predict α-synucleinopathies, and have found contrasting findings [5, 6]. Some studies found no association between these variables and α-synucleinopathies [7], while some reported them either as a risk factor [8–10], or protective factor for α-synucleinopathies [11–14].

Since iRBD is a window into the early stages of synucleinopathies, we aimed to evaluate whether CVD and metabolic risk factors could predict phenoconversion to α-synucleinopathies in this population. Moreover, since cardiovascular conditions and risk factors could potentially modulate the vulnerability of different neuronal tissues to neurodegeneration (e.g., cortex vs. brainstem) [15], we assessed if they alter the type of neurodegenerative syndrome (i.e., parkinsonism-first vs. DLB-first).

MATERIALS AND METHODS

The Montreal-iRBD cohort is an ongoing cohort of iRBD patients referred to the Centre for Advanced Research in Sleep Medicine, Hôpital du Sacré-Cœur de Montréal, Montreal, Canada. Patients were recruited between 2004 and 2020 and were followed up annually until development of neurodegenerative disease or death. Diagnosis and recruitment details are explained elsewhere [4, 16]. Briefly, diagnosis of iRBD was confirmed with history and polysomnography according to the International Classification of Sleep Disorders (ICSD-II) criteria [17, 18]. All patients had neurological exams and complete neuropsychological assessments and were free of parkinsonism or dementia at baseline.

Complete self-reported medical history including CVD (any self-reported history of myocardial infarction, coronary artery disease, angioplasty, coronary artery bypass graft, arrhythmias, valvulopathies, and congestive heart failure), hypertension, diabetes, hypercholesterolemia, and medications were obtained from all patients.

The research protocol was approved by the local research ethics board (REB), and written informed consent was obtained from all participants.

Outcome assessment

Follow-up visits were performed annually to assess the development of parkinsonism or dementia. Home evaluation was conducted for patients who could not attend clinic visits. Parkinsonism was defined according to Movement Disorders Society (MDS) diagnostic criteria [19] as bradykinesia along with either rigidity, rest tremor, or both. Patients who developed outcome before 2015 were diagnosed according to UK Brain Bank criteria [20]. Dementia was diagnosed based on MDS Dementia criteria [21] by consensus between the neuropsychologist and neurologist. According to the 2017 DLB criteria, all dementia phenoconverters are considered as probable DLB [22, 23].

Statistical analysis

The primary analysis was to measure the risk of developing any defined neurodegenerative outcome (PD, MSA, or DLB). A secondary analysis investigated the risk of developing each individual outcome separately. We calculated the hazard ratio (HR) using Cox regression model. Both crude HR and age/sex-adjusted HR (aHR) are presented.

To compare the predictive role of CVD and metabolic risk factors for development of PD or DLB, we performed logistic regression analysis. Crude and age/sex-adjusted odds ratio (aOR) are reported.

RESULTS

A total of 183 participants who provided at least one follow-up data were analyzed in this study (Table 1). The mean age of included participants was 66.4 years (SD = 8.3), and 138 cases (75.4%) were male. The average time between RBD polysomnographic diagnosis and the last evaluation was 4.40 years (SD = 3.2). Among the 183 included participants, 73 (39.9%) developed outcomes (30 PD, 38 DLB, and 5 MSA) at an average interval of 3.7 years (range = 1–14 years). Those who developed outcome were significantly older than outcome-free patients (68.53 ± 8.5 vs. 64.98 ± 7.8 years, $p = 0.004$) and were older at reported RBD symptom onset (60.06 ± 10.2 years vs. 54.43 ± 14.8 years, $p = 0.013$).

Comparing 73 patients who developed outcome with 110 outcome-free patients (Table 2), we found no difference in their baseline CVD (12.3% vs. 10.0%, aHR = 0.89 [0.44,1.80]), hypertension

Table 1
Demographics and baseline characteristics

Baseline characteristics	Developed any outcome N = 73	Still outcome-free N = 110	*p*
Follow-up duration – Mean ± SD (min = 0.5, max = 15.5)	3.66 ± 3.0*	4.90 ± 3.2	**0.010**
Age at baseline- Mean ± SD (min = 39, max = 93)	68.53 ± 8.5	64.98 ± 7.8	**0.004**
Male – % (n)	71.2 (52)	78.2 (86)	0.3
RBD symptom duration – Mean ± SD (min = 0, max = 50)	7.36 ± 7.9	8.97 ± 9.1	0.2
Age of RBD onset – Mean ± SD (min = 14, max = 78)	60.06 ± 10.2	54.43 ± 14.8	**0.013**
B-SIT olfaction raw score- Mean ± SD (min = 2, max = 12)	6.57 ± 2.5	7.94 ± 2.6	**0.001**
MDS-UPDRS3 – Mean ± SD (min = 0, max = 20)	6.19 ± 5.2	3.23 ± 2.7	**<0.001**
MDS-UPDRS2 – Mean ± SD (min = 0, max = 8)	2.13 ± 2.2	1.21 ± 1.6	**0.003**
MoCA – Mean ± SD (min = 14, max = 30)	24.96 ± 3.1	25.74 ± 2.9	0.1
Systolic blood pressure drop – Mean ± SD (min = –14, max = 50)	16.03 ± 15.5	10.58 ± 15.3	**0.021**
Orthostatic symptoms – Mean ± SD (min = 0, max = 2)	0.34 ± 0.6	0.33 ± 0.6	0.8
Urinary dysfunction – Mean ± SD (min = 0, max = 2)	0.44 ± 0.6	0.38 ± 0.6	0.050
Erectile dysfunction – Mean ± SD (min = 0, max = 4)	1.60 ± 1.4	1.56 ± 1.6	0.9
Constipation – Mean ± SD (min = 0, max = 3)	0.90 ± 0.9	0.64 ± 0.9	0.1
Tonic REM percent – Mean ± SD (min = 2.7, max = 100)	56.83 ± 26.4	46.37 ± 30.8	**0.031**
Phasic REM percent – Mean ± SD (min = 6.18, max = 89)	36.59 ± 17.9	36.80 ± 18.2	0.9
Beck Depression Inventory – Mean ± SD (min = 0, max = 31)	9.63 ± 6.6	10.04 ± 7.1	0.8
Beck Anxiety Inventory – Mean ± SD (min = 0, max = 35)	8.51 ± 8.6	8.35 ± 7.0	0.9
History of antidepressant use – % (n)	20.8 (15)	32.7 (36)	0.1

*Follow-up is terminated at the time of phenoconversion in those who developed an outcome REM, Rapid Eye Movement; iRBD. idiopathic REM sleep behavior disorder; B-SIT, Brief Smell Identification Test; MDS-UPDRS, Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; MoCA, Montreal Cognitive Assessment.

(30.1% vs. 29.1%, aHR = 0.97 [0.58,1.63]), hypercholesterolemia (31.5% vs. 40.0%, aHR = 0.84 [0.50,1.41]), or diabetes (12.3% vs. 17.3%, aHR = 0.80 [0.39,1.63]). Stratification by sex, and median age did not change the results.

The sensitivity analysis also found no difference between exposure to CVD and metabolic risk factors between outcome-free participants and those who developed individual outcomes of PD or DLB. We did not perform sensitivity analysis on MSA patients because of the small number of cases. Comparison of PD-first vs. dementia-first patients showed lower baseline hypercholesterolemia among PD patients (16.7% vs. 44.7%, crude OR = 0.25 [0.08,0.78]).

Those who developed outcomes and outcome-free patients had similar exposure to statins at baseline (28.8% vs. 31.8, aHR = 0.92 [0.54,1.58]).

Among the nine diabetic patients who developed outcome and 19 outcome-free diabetics, 6 (66.7%) and 10 (52.6%) took biguanide-group medications (i.e., Metformin, Glucophage) at baseline, with no significant difference between medication types (aHR = 1.67 [0.35,7.97]). A similar finding was observed for sulfonylurea-group (i.e., Gliclazide, Diamicron, Glyburide, Diabeta) (22.2% vs. 21.4%, aHR = 1.50 [0.27,8.39]).

DISCUSSION

The present study suggests no clear relationship between CVD, hypertension, hypercholesterolemia, diabetes, diabetes medications, and phenoconversion to α-synucleinopathies in iRBD.

Cardiovascular disease

Our results are broadly similar to the multicenter study on iRBD in 2015 (which included some patients from this current study), in which prior atherosclerotic disease, hypertension, and diabetes did not modulate risk of phenoconversion [24]. Similarly, Vlasov et al., in their population-based Rotterdam Study, found no association between atherosclerosis as measured by carotid intima-media thickness and the risk of all-cause parkinsonism [7].

Hypertension

The 2015 multicenter study on iRBD [24], and cohort studies by Grandinetti et al. [25] and Simon et al. [26] found no association between hypertension and PD. By contrast, a cohort of Finnish population found that hypertension was associated with an

Table 2
Frequency and risk of developing different α-synucleinopathies among iRBD patients with cardiovascular disease, hypertension, hypercholesterolemia, and diabetes

		Cardiovascular disease – % (*n*)	Hypertension – % (*n*)	Hypercholesterolemia – % (*n*)	Diabetes – % (*n*)
Still outcome-free	**N = 110** Age = 64.98 ± 7.8 Male% = 78.2	10.0 (11)	29.1 (32)	40.0 (44)	17.3 (19)
Developed any outcome	**N = 73** Age = 68.53 ± 8.5 Male% = 71.2	12.3 (9)	30.1 (22)	31.5 (23)	12.3 (9)
PD-first	**N = 30** Age = 66.80 ± 8.6 Male% = 73.3	16.7 (5)	20.0 (6)	16.7 (5)	10.0 (3)
DLB-first	N = 38 Age = 71.50 ± 6.7 Male% = 73.7	7.9 (3)	34.2 (13)	44.7 (17)	15.8 (6)
MSA	**N = 5*** Age = 56.40 ± 8.3 Male% = 40.0	20.0 (1)	60.0 (3)	20.0 (1)	0 (0)
Comparison between:	95% CI's	Cardiovascular disease	Hypertension	Hypercholesterolemia	Diabetes
Any outcome vs. Outcome-free	Crude HR [95%CI]	1.00 [0.49,2.03]	1.13 [0.68,1.87]	0.99 [0.60,1.63]	0.82 [0.41,1.65]
	aHR [95%CI]	0.89 [0.44,1.80]	0.97 [0.58,1.63]	0.84 [0.50,1.41]	0.80 [0.39,1.63]
PD-first vs. Outcome-free	Crude HR [95%CI]	1.22 [0.46,3.25]	0.73 [0.30,1.79]	0.43 [0.16,1.12]	0.62 [0.19,2.03]
	aHR [95%CI]	1.12 [0.42,2.99]	0.66 [0.27,1.65]	0.38 [0.14,1.02]	0.61 [0.18,2.05]
DLB-first vs. Outcome-free	Crude HR [95%CI]	0.77 [0.23,2.56]	1.28 [0.65,2.53]	1.43 [0.75,2.73]	0.95 [0.39,2.28]
	aHR [95%CI]	0.57 [0.17,1.91]	0.96 [0.48,1.94]	0.97 [0.48,1.94]	1.07 [0.44,2.65]
PD- vs. DLB-first	Crude OR [95%CI]	2.33 [0.51,10.67]	0.48 [0.16,1.47]	**0.25 [0.08,0.78]**	0.59 [0.14,2.60]
	aOR [95%CI]	3.56 [0.65,19.60]	0.61 [0.19,1.95]	0.30 [0.09,1.04]	0.68 [0.15,3.09]

A significance level of 0.05 was considered for all tests. PD, Parkinson's disease; DLB, dementia with Lewy bodies; MSA, multiple system atrophy; HR, hazard ratio; aHR, age/sex adjusted hazard ratio; OR, odds ratio; aOR, age/sex adjusted odds ratio. *Because of the small number of MSA patients, and sample number of exposures to cardiovascular disease, hypertension, hypercholesterolemia, or diabetes, we did not perform sensitivity analysis on MSA patients.

increased PD risk only among women [27]. Slight differences in how PD was confirmed (in particular the chance of 'vascular parkinsonism' being included), and different adjusted confounders may have influenced the results [28]. Autonomic dysfunction in prodromal stages can cause reduced blood pressure [29], thereby confounding any positive relationship; the fact that we were assessing patients from a population in which nearly all had prodromal synucleinopathy, therefore, adds non-overlapping information to that observed in population-based epidemiological studies [26, 27, 30].

Hypercholesterolemia

We found no statistically significant association between hypercholesterolemia and phenoconversion to α-synucleinopathies, but some suggestion that hypercholesterolemia may modify phenoconversion towards a 'dementia-first' subtype [31].

The literature on hypercholesterolemia and synucleinopathies is highly variable. Contrary to this study, 2015 iRBD multicenter study found a slightly lower occurrence of hypercholesterolemia in patients who converted to neurodegenerative disease [24]. Simon et al., and Sääksjärvi et al. found no association between cholesterol and PD, as in our study [26, 30]. Conversely, a Finnish study by Hu et al. reported that there might be a positive correlation between cholesterol and PD risk [10]. Other cohorts, including the Rotterdam study and two studies by Huang et al., found an inverse relationship between hypercholesterolemia and PD [11, 32, 33], suggesting a potentially protective mechanism. Another cohort by Rozani et al. also reported that hypercholesterolemia is linked to decreased PD risk [14]. A meta-analysis of three case-control and 12 cohort studies reported no association between PD and total serum cholesterol or high-density lipoprotein cholesterol but an inverse relationship between low-density lipoprotein cholesterol and PD [13].

It is unclear why we found a potential link between cholesterol and dementia-first phenoconversion. It is conceivable that hypercholesterolemia could increase cortical vulnerability to degeneration (e.g., via comorbid vascular pathology), so that the same synucleinopathy spread pattern preferentially causes degeneration in tissue critical to development of dementia [34]. Alternatively, this could simply be an additive effect, such that subtle vascular disease makes clinical cognitive impairment more likely, even with the same degree of synucleinopathy. Although, moving the prodromal state minimizes the role of reverse causation, our average follow-up period was still relatively short. Wang et al. in the Health, Aging and Body Composition study recently showed that circulating cholesterol may decrease as PD develops, likely starting in prodromal phase [35].

Diabetes

There is also ongoing debate about the association between diabetes and PD. Potashkin et al. reported that findings vary greatly depending on study type [28], with some cohort studies finding an increased risk of PD in diabetics [8, 36–38] and some case-control studies finding a decreased risk or no risk at all [39, 40]. As with CVD/hypertension, it is possible that prodromal disease could modulate diabetes risk (e.g., via weight loss); so, evaluation of diabetes effect on those already in prodromal stages provides a unique study population. Moreover, as numerous diabetes medications are suggested as potential neuroprotective treatments [41–44], it is important to study whether diabetes medications modulate the progression speed from prodromal to clinical stages. In this case, we found no clear effect of either diabetes or diabetes medications on progression speed or subtype. This might suggest that treatment of diabetes in prodromal disease may not prevent phenoconversion.

In conclusion, we found no clear evidence that either CVD or metabolic conditions accelerate phenoconversion from prodromal to clinical synucleinopathies in iRBD. Future studies using objective assessment of CVD at baseline (e.g., carotid intima-media thickness), and extending observational period and sample size (particularly to assess the effect of less-common conditions and medications) would be useful.

CONFLICT OF INTEREST

S. Zolfaghari, N. Lewandowski, A. Pelletier, S.A. Naeimi and M. Brillon-Corbeil have nothing to disclose.

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