Parkinsonism and Related Disorders xxx (2017) 1–6

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Subclinical vascular disease and the risk of parkinsonism: The Rotterdam Study

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ARTICLE INFO

Article history:
Received 10 February 2017
Received in revised form
3 June 2017
Accepted 27 June 2017

Keywords:
Parkinsonism
Vascular pathology
Risk factors
Etiology

ABSTRACT

Background: Parkinsonism is a common neurodegenerative syndrome in middle-aged and elderly persons. The etiology is multifactorial with a possible vascular contribution, but this has not been comprehensively studied.
Objective: To determine whether selected markers of subclinical vascular pathology are associated with the risk of all-cause parkinsonism in the general population.
Methods: We assessed a range of markers of subclinical vascular pathology (ankle-brachial index, carotid plaques and intima media thickness, retinal arteriolar and venular calibers) in 6199 persons from the population-based Rotterdam Study, who were free of parkinsonism and dementia at baseline. We followed these persons up till onset of parkinsonism, dementia, and death for 89,387 person-years until January 1, 2013. Hazard ratios (HRs) for all-cause parkinsonism and separately for Parkinson disease (PD) versus non-PD were estimated from competing risk regression models adjusting for potential confounders.
Results: During follow-up, we identified 211 cases of parkinsonism (110 had PD). None of the five markers of subclinical pathology was associated with all-cause parkinsonism. Only low ankle-brachial index was associated with a higher risk of non-PD parkinsonism (HR = 0.79, 95%CI: 0.68–0.92), but not with the risk of PD.
Conclusion: We did not find a consistent pattern of associations between systemic vascular pathology markers with parkinsonism, suggesting that the potential involvement of vascular pathology is not prominent or needs further evaluation in studies with an even larger sample size.

1. Introduction

Parkinsonism, with its most frequent subtype Parkinson disease (PD), is a common chronic neurodegenerative syndrome in the elderly [1,2]. Although many genetic and environmental factors have been implicated in the multi-factorial etiology of parkinsonism [1], there is still much uncertainty about the exact mechanisms underlying neuronal cell loss in patients with Parkinson disease and non-PD parkinsonism. There is a scarcity of knowledge on early markers and potential neuroprotective therapies in early stages of parkinsonism, and patients are typically already in an advanced pathological disease stage when the diagnosis is made [1]. Therefore, there is a need for novel insight into factors associated with all-cause parkinsonism.

Markers of subclinical vascular pathology are strongly implicated in the etiology of the two common neurological syndromes, stroke and dementia [3]. Furthermore, a high prevalence of lacunar infarcts have been reported in the cerebral white matter and basal

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http://dx.doi.org/10.1016/j.parkreldis.2017.06.022
1353-8020/

ganglia of patients with parkinsonism [4], which indicates a potential vascular etiology. During the course of Alzheimer's disease 25% of patients develop parkinsonism [5], whereas approximately 30% of patients with PD are eventually diagnosed with dementia [6]. However, in spite of an overlap in clinical and pathological findings between primary parkinsonism (such as PD) and dementia or stroke, the role of vascular pathology in the etiology of parkinsonism syndromes remains unclear.

Vascular pathology can be non-invasively measured both in large systemic vessels as well as in microvasculature locally [7]. Commonly used, non-invasive measurements of vascular pathology of the large vessels include ultrasound measures of carotid arteries (intima media thickness and plaques) and ankle-brachial index (ABI) [8,9]. Furthermore, structural changes in the retinal vasculature have long been recognized as an important marker of microvascular pathology [10]. These non-invasive measures provide an insight into the condition of the large and small blood vessels.

We hypothesized that subclinical vascular pathology is associated with an increased risk of parkinsonism in the general population. We used noninvasive measurements of subclinical vascular disease to test our hypothesis in a large, population-based cohort study.

2. Methods

2.1. Setting and study population

This study was conducted as part of the Rotterdam Study, a community-based prospective cohort study in elderly adults [11]. There were only two selection criteria: persons had to live in the well-defined Ommoord district of Rotterdam in 1990, and they had to be aged 55 years or older. Out of 10,215 eligible individuals, 7983 agreed to participate and provided informed consent.

All participants were interviewed and underwent extensive physical examination at the research center, including screening for parkinsonian signs and markers of vascular pathology at baseline (1990–1993) and at four follow-up rounds (1993–1995, 1997–1999, 2002–2004, and 2009–2011).

For the current study we excluded participants with prevalent parkinsonism (n = 126), incomplete neurological screening (n = 1401) at baseline, and participants with missing information regarding two or more vascular pathology markers (n = 257), leaving 6199 subjects at risk to develop any kind of parkinsonism during the follow-up period.

Similarly with other population-based studies, the Rotterdam Study overall age- and sex-adjusted incidence rate of Parkinson Disease is 1.5 per 1000 person-years [2], while age-specific incidence rates are somewhat higher than in community based studies [12].

The Rotterdam Study has been approved by the medical ethics committee according to the Population Screening Act: Rotterdam Study, executed by the Ministry of Health, Welfare and Sports of the Netherlands. All participants provided written informed consent.

2.2. Assessment of subclinical vascular disease

Recently, CT and MRI assessments were implemented in the Rotterdam Study; however, we lacked sufficient follow-up for incident parkinsonism to incorporate these measurements in our present analyses. Subclinical vascular pathology was assessed with four different measures: ankle-brachial index, carotid intima-media thickness and the presence of plaques in the carotid arteries assessed using ultrasonography and retinal vessels diameters.

2.3. Ankle-brachial index

We assessed ankle-brachial index (ABI) by measuring systolic blood pressure (SBP) in all extremities. The SBP was measured twice in both arms and at both ankles (posterior tibial artery) in each participant in the supine position with an 8-MHx continuous-wave Doppler device (Huntleigh D500, Hunteleigh Technology) which was attached to a standard random-zero sphygmomanometer [8]. To obtain the ABI we calculated the ratio of the systolic blood pressure at the ankle and the systolic blood pressure at the arm per side. ABI values higher than 1.50 were not included in the study, because that values are considered irrationally high due to calcification of the blood vessels and their inability to properly compress. We used the lowest value of the two sides for the analyses [8].

2.4. Carotid number of plaques and intima media thickness

Using B-mode ultrasonography we evaluated both carotid arteries for the presence of plaques and determined the carotid intima media thickness (cIMT) [9]. The presence of a plaque was defined as a focal widening relative to bordering segments, with protrusion into the lumen consisting of either echolucent or echogenic areas. We assessed the presence of plaques at both sides in the common carotid artery, carotid bifurcation and proximal part of the internal carotid artery. The total amount of plaques was reflected in a weighted plaque score that ranged from 0 to 6 [13]. The average of the maximum IMT was registered at both the near- and far wall of the common carotid artery for assessing the cIMT.

2.5. Retinal vessel measurements

At the baseline ophthalmic examination, simultaneous stereoscopic fundus color transparencies were taken centered on the optic disk (20° field, Topcon Optical Company, Tokyo, Japan) after pharmacologic mydriasis and were digitized with a high-resolution scanner (Nikon LS-4000, Nikon Corporation, Japan) [14]. Evaluated measures for arteriolar and venular calibers were based on improved Parr-Hubbard formulas and were corrected for magnification changes due to refractive errors of the eye [14].

Since each eye has a different magnification in case of refractive changes, summary vessel measures were additionally adjusted for the refraction and corneal curvature with Littmann's formula to estimate absolute measures [14].

2.6. Other measurements

We assessed cardiovascular risk factors by interview, physical examination and blood sampling [11]. Blood pressure was calculated as the mean of two consecutive measurements with a random-zero sphygmomanometer at the right brachial artery while the patient was in a sitting position. Serum total cholesterol was determined by an automated enzymatic procedure in a non-fasting blood sample. Serum high density lipoprotein (HDL) cholesterol was measured after precipitation of the non-HDL fraction with phosphotungstate-magnesium. Height and weight were measured and body mass index (kg/m2) was calculated. Non fasting serum glucose levels were measured using the glucose hexokinase method. Smoking habits of participants were categorized as “ever” or “never”. Uric acid was determined with a Kone Diagnostica reagent kit and a Kone auto-analyzer from blood samples of participants.

Please cite this article in press as: V. Vlasov, et al., Subclinical vascular disease and the risk of parkinsonism: The Rotterdam Study, Parkinsonism and Related Disorders (2017), http://dx.doi.org/10.1016/j.parkreldis.2017.06.022