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Short communication

Predictors for mild parkinsonian signs: A prospective population-based study

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ABSTRACT

Objective: Mild parkinsonian signs (MPS) are common in the elderly population and are associated with a wide range of adverse health outcomes, including incident Parkinson's disease (PD). We aimed to prospectively evaluate potential risk factors for incident MPS.
Methods: Participants of the population-based Bruneck Study representative for the general elderly community underwent a baseline assessment of substantia nigra (SN)-echogenicity with transcranial sonography, olfactory function with the Sniffin' Sticks identification test and vascular risk according to the Framingham risk score as well as a baseline and 5-year follow-up neurological examination. MPS were defined according to established criteria based on the entire motor section of the Unified PD Rating Scale. Participants with PD at baseline or follow-up and subjects with MPS at baseline were excluded. A logistic regression analysis adjusted for age and sex was used to detect risk factors for incident MPS in the remaining 393 participants.
Results: SN-hyperechogenicity and hyposmia were related to the development of MPS with odds ratios of 2.0 (95%CI, 1.1–3.7) and 1.6 (95%CI, 1.0–2.7), respectively, while increased vascular risk was not. Having both, SN-hyperechogenicity and hyposmia, was associated with an odds ratio of 3.0 (95%CI, 1.2–7.7) for incident MPS. Among the various motor domains, increased SN-echogenicity predicted the development of bradykinesia and rigidity, whereas diminished olfactory function predicted the development of impaired axial motor function.
Conclusions: In addition to their established roles as risk factors for PD, SN-hyperechogenicity and hyposmia are associated with an increased risk for MPS in the general elderly community.

1. Introduction

Mild parkinsonian signs (MPS) are defined as features of bradykinesia, rigidity, tremor as well as gait and postural changes occurring in isolation or combinations that do not meet clinical criteria for a diagnosis of parkinsonism and have been reported in up to 40% of community-dwelling elderly without known neurological disease [1]. These signs are related to a wide range of adverse health outcomes including an increased risk of Parkinson's disease (PD), cognitive impairment and dementia, as well as development of functional disability and increased mortality [1–3]. Only a few studies have aimed at evaluating potential risk factors for MPS and it is not clear if MPS share the same risk factors as PD or if their occurrence might also be associated with vascular risk. A recent study has highlighted the role of incidental Lewy bodies and neuronal loss in the substantia nigra (SN) in decreased motor function in old age [4]. SN-hyperechogenicity on transcranial sonography (TCS) represents a time-independent trait marker for an increased vulnerability of the dopaminergic nigrostriatal system in the elderly and thus for PD [2,5]. Furthermore, olfactory dysfunction is an established risk marker for PD [2,6] and one study showed that impaired olfaction is associated with a more rapid progression of parkinsonian signs present in older persons [7]. However,

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prospective studies of such markers and the risk to develop MPS are lacking.

Therefore, the present study was designed to prospectively assess the associations of increased SN-echogenicity, olfactory dysfunction and increased vascular risk with the development of MPS in the general elderly population.

2. Methods

The Bruneck Study Cohort of 2005 (n = 574 subjects representative for the general elderly community, age 55–94 years) [8] was used for the present study. The study protocol was approved by the local ethics committee and all subjects gave written informed consent according to the declaration of Helsinki. The interviews and examinations were carried out by two neurologists with special expertise in movement disorders blinded to TCS results. Participants underwent a standard interview including drug history and a standardized neurological examination including the Unified PD Rating Scale motor section (UPDRS-III) at baseline and were followed up using the same protocol 5.0 ± 0.1 (mean, standard deviation) years later during the Bruneck Study 2010. Subjects diagnosed with PD or secondary parkinsonism and those with residual motor deficits due to cerebral infarction during the study (i.e. at baseline or at follow-up) as well as subjects presenting with MPS at baseline were excluded (n = 120). Of the 454 remaining subjects at baseline, 393 (86.6%) returned for the follow-up examination and formed the target population of this study. At baseline all subjects additionally underwent assessment of SN-echogenic areas with TCS, performed by the same experienced ultrasound examiner (HS) blinded to clinical results with a 2.5-MHz transducer (Logiq 7; General Electric, Milwaukee, WI) as described elsewhere [8] and olfactory testing with the Sniffin' Sticks 12-item odor identification test (SS-12; Burghart Medizintechnik, Germany) [2]. Thirty-seven subjects had no sufficient bone window to perform TCS. SN-hyperechogenicity was defined at ≥ 0.18 cm^2 of the side with the larger echogenicity according to a receiver-operating characteristic curve analysis between PD patients and healthy controls in the Bruneck Study cohort [8]. As reported previously, there was a high inter- and intrarater reliability of TCS measurements with intraclass correlation coefficients of >0.91 in our sample [8,9]. Hyposmia was defined at ≤ 8 correctly identified odors according to the manufacturer criteria. Vascular risk was calculated for each participant from the information obtained in the general part of the Bruneck Study 2005 using the Framingham risk score (FRS) [10]. Subjects with a >20% risk of a cardiovascular disease event at 10 years were categorized as having a high vascular risk.

There are several different definitions of MPS in the literature [1]. In order to have a sensitive and concise tool in detecting MPS, we decided to use an established definition based on the entire UPDRS-III as follows: ≥ 2 UPDRS-III items with a score of 1, 1 item with a score of ≥2, or UPDRS-III rest tremor item ≥1 (1) [11]. MPS were assigned to one or more out of 5 domains (bradykinesia based on UPDRS-III items 23, 24, 25, 26, and 31; rigidity based on UPDRS-III item 22; axial function based on UPDRS-III items 18, 19, 27, 28, 29, 30; rest tremor based on UPDRS-III item 20; and postural tremor based on UPDRS-III item 21) when ≥ 1 UPDRS-III item with a score of ≥1 in the respective domain was present.

As most studies on MPS have been performed using another definition based on an abbreviated 10-item version of the UPDRS-III (speech, facial expression, tremor at rest, rigidity rated separately in the neck, right arm, left arm, right leg, and left leg, posture, and body bradykinesia) [1], we additionally classified participants according to this definition [3] for the purpose of a sensitivity analysis.

For between-group comparisons of metric and categorical variables the Mann–Whitney-U-test and the chi-square-test were used, respectively. Logistic regression analyses were employed to document the associations of the potential risk factors with the development of MPS, given as odds ratios (OR) and 95% confidence intervals (95%CI). All potential risk factors were treated as continuous and categorical variables. OR of continuous variables were calculated for a one standard deviation unit change of the respective variable in order to render odds comparable. SPSS 22.0 was used for all statistical analyses.

3. Results

Table 1 shows the baseline characteristics of the 393 subjects included at baseline. At follow-up, 109 subjects presented with incident MPS (45.9% bradykinesia, 14.7% rigidity, 70.6% axial symptoms, 5.5% rest tremor, and 33.0% postural tremor; 46.8% parkinsonian signs in one domain, 53.2% parkinsonian signs in 2 or more domains).

Age, increased SN-echogenicity, decreased olfactory function and increased FRS were identified as MPS-risk factors (Table 2, Model-A), while there was no effect of sex. Correction for age, the strongest MPS-risk factor, attenuated associations of FRS, but not of SN-echogenicity and SS-12 (Model-B and Model-C). The strong association for SN-echogenicity was mainly based on bradykinesia and rigidity items whereas the weaker association for olfactory function was mainly based on axial motor function items (Supplementary Table 1). The FRS was not significantly associated with risk for MPS and it was therefore used as a correcting variable with regard to individual MPS (Supplementary Table 1). When excluding subjects with SN-hyperechogenicity from the dataset, however, there was a weak relation of higher baseline vascular risk scores with the development of MPS (OR 1.44 [95%CI, 1.01–2.06], p = 0.047).

Table 1
Baseline characteristics of subjects according to the group at follow-up.

Characteristic	All (n = 393)	MPS negative at follow-up (n = 284)	MPS positive at follow-up (n = 109)	p-Value
Age	66.5 ± 7.8	64.3 ± 6.9	71.7 ± 7.3	<0.001
Female (%)	53.2	52.5	55.0	0.65
UPDRS-III	0.1 ± 0.2	0.0 ± 0.2	0.1 ± 0.3	0.002
SN-echogenicity (cm^2)	0.12 ± 0.05	0.11 ± 0.05	0.13 ± 0.06	0.037
SS-12	9.2 ± 2.1	9.5 ± 1.9	8.5 ± 2.3	<0.001
FRS (%)	23.2 ± 14.1	20.8 ± 12.8	28.8 ± 15.5	<0.001
SN-hyperechogenic (%)	22.0	19.0	29.7	0.037
Hyposmic (%)	32.4	28.6	45.9	<0.001
High vascular risk (%)	48.6	41.4	66.1	<0.001

Linear variables age, SN echogenic areas, SS-12 values, UPDRS-III scores and FRS are given as means (±standard deviation). p-Values are given for the comparison of the baseline characteristics between MPS-negative versus MPS-positive subjects at follow-up.
FRS: Framingham risk score; MPS: mild parkinsonian signs; UPDRS-III: unified parkinson disease rating scale motor section; SN: substantia nigra; SS-12: Sniffin' Sticks 12-item odor identification test.

As a sensitivity analysis, logistic regressions were repeated using an alternative definition of MPS [3] detecting 56 incident MPS cases at follow-up. There were no changes with regard to the association of increased SN-echogenicity to MPS-risk, but associations of impaired olfaction and vascular risk were not significant when correcting for age and sex (Supplementary Table 2).

4. Discussion

In this prospective 5-years study of nearly 400 community-dwelling elderly the established PD risk markers SN-hyperechogenicity areas and hyposmia were found to also represent risk factors for MPS with odds ratios of 2.0 and 1.6, respectively. Having both, SN-hyperechogenicity and hyposmia, was associated with an odds ratio of 3.0 for incident MPS. A recent clinicopathologic study reported SN neuronal loss in one-third and incidental Lewy bodies in one-sixth of community-dwelling elderly and identified nigral pathology as major contributor to the loss of motor function in old age [4]. Accordingly, in our cohort increased SN-echogenicity was found in one-quarter of subjects [8] and we here demonstrate its close relation to the development of MPS, mainly bradykinesia and rigidity. This echosignal has been associated to an increased vulnerability of the nigrostriatal dopaminergic system and determined as a strong risk factor for the development of PD [2,5]. Our data therefore substantiate the relation between subclinical nigral pathology indicated by this easily assessable echomarker and the development of motor impairment in elderly individuals without overt PD. This is further supported by a recent genetic study linking several PD risk loci to the development of parkinsonian motor signs and nigral pathology in older persons [12].

In line with the hypothesis that PD pathology first starts in extranigral sites, many studies have highlighted the fact that non-motor symptoms such as hyposmia may antedate the clinical manifestation of cardinal motor PD features by several years [2,6].

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