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Reasons for mild parkinsonian signs – Which constellation may indicate neurodegeneration?

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ABSTRACT

Introduction: Mild parkinsonian signs (MPS) are common in the elderly population. Several factors including physical decline and comorbidities in addition to neurodegeneration may be possible sources for MPS. The objective was to examine whether MPS are associated with a history of orthopedic disturbances, vascular diseases or prodromal markers for neurodegeneration.
Methods: The TREND study is a prospective longitudinal cohort study in individuals >50 years with biennial assessments designed to identify prodromal markers for neurodegeneration. In this substudy, 1091 elderly individuals were evaluated for a possible association of MPS with prodromal markers for neurodegeneration, orthopedic disturbances, vascular diseases, as well as cerebral abnormalities. These factors were assessed by self-administered questionnaires, with a structured health interview, a neurological examination and by transcranial sonography.
Results: 82 participants showed MPS. They were found to have more often hyposmia and RBD, had a higher autonomic dysfunction score and they more frequently showed hyperechogenicity of the substantia nigra compared to controls. Neither orthopedic disturbances nor vascular diseases were significantly associated with the prevalence of MPS.
Conclusion: MPS might be a sign of early neurodegeneration rather than caused by other motor influencing diseases.

1. Introduction

Mild parkinsonian signs (MPS) have been described first in the elderly without known neurological disease [1,2], as older age is often associated with slowness, stiffness, stooped posture and changes in gait [3]. However, the resemblance with Parkinson's disease, which is implicated in the expression MPS, is striking. Most of the individuals with MPS reveal signs in gait/balance, bradykinesia and rigidity, less have rest tremor [4,5]. However, these symptoms, known as cardinal symptoms of PD are less strongly expressed (mild signs) in MPS. It is obvious that symptoms summarized in the expression MPS can be caused by a variety of non-neurological conditions such as deconditioning, orthopedic disturbances and vascular diseases, as well as by neurological disorders different from neurodegeneration. Each of these conditions can result in motor impairment leading to symptoms of MPS. To better estimate the course of MPS and possibly progression to more severe conditions, especially in light of the fact that the neurodegenerative process in PD proceeds very slow it is necessary to evaluate the cause of these symptoms. In case non-neurodegenerative sources can be excluded, at least this subgroup of individuals with MPS might be a population in early stages of neurodegeneration and thus of high interest for further studies which aim to a better understand and possibly intervene one day at these early stages.

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To the best of our knowledge, there is no study yet available that evaluates the degree of association of different factors which may obviously contribute to the occurrence of MPS in a large cohort. To address this issue we investigated a large cohort of healthy elderly and individuals with MPS using transcranial sonography of the brainstem and ventricles, ultrasound for the measurement of the intima-media thickness of the carotids, self-administered questionnaires for prodromal markers, questionnaires evaluating orthopedic and vascular disturbances. Additionally a neurological examination was performed.

2. Subjects and methods

2.1. Study population

The TREND study (*T*übinger evaluation of *R*isk factors for *E*arly detection of *N*eurodegenerative *D*isorders) is a prospective follow-up study in individuals aged older than 50 years with biennial assessments until death/autopsy. For a detailed outline of the TREND study, inclusion and exclusion criteria and baseline assessments see Gaenslen et al. [6]. In brief, the TREND study comprises a large assessment battery with mainly quantitative, unobtrusive measurements, which may be repeated easily and objectively. All assessments are performed by a group of experienced investigators. To make sure that there is no bias in data acquisition all investigators are blinded to the results of all other examinations. In 2011/2012 the TREND study comprised 1102 participants. We excluded 11 participants which received a diagnosis of parkinsonism at their study visit because our intention was to study possible reasons for MPS and to evaluate whether they may constitute a prodromal marker of PD. Therefore this substudy investigate 1091 participants (median age 64 (50–83); 564 males and 527 females).

2.1.1. Ethics statement

The study was approved by the ethical committee of the Medical Faculty of the University of Tuebingen (Nr. 90/2009BO2), and all subjects gave written informed consent.

2.2. Neurological examination

Each participant underwent a standardized neurological examination including evaluation of reduced arm swing and the motor part of the revised Unified Parkinson's Disease Rating Scale (UPDRS) by an experienced movement disorder specialist [7]. PD was diagnosed according to the UK Brain Bank clinical diagnostic criteria [8]. According to Louis et al. [5] the diagnosis of MPS may be based on 10-items of the UPDRS part III. The selected items were speech, facial expression, rigidity (rated separately for neck, right arm, left arm, right leg and left leg), posture, body bradykinesia and rest tremor. An item score of 0 indicates no symptoms, a score of 4 the most severe stage. Based on this information, a MPS score (range, 0–40) was calculated for each participant. As recommended by Louis et al. we defined MPS as present when one of the following conditions was met: (i) two or more items of the abbreviated UPDRS rating ≥ 1 (ii) one item of the abbreviated UPDRS rating ≥ 2 or (iii) rest tremor item ≥ 1.

To check for motor asymmetry an asymmetry score was calculated by subtracting the left summed scores from right summed scores of the UPDRS III items 3 to 8 and 15 to 17 and normalizing them by dividing the difference with the aggregate sum of the left and right scores. For better visualization we multiply the value by 100. A value of 0 stands for maximum symmetry and 100 for maximum asymmetry.

Additionally a complete neurological examination was performed including assessment of cranial nerves, the pyramidal system (paresis, spasticity, brisk reflexes and pyramidal signs), the cerebellar system (occulomotor performance including saccades, dysarthria, ataxia, intention tremor), other forms of tremor (action, postural) and peripheral neuropathy (reduced superficial sensation and vibration sense, hyporeflexia).

2.3. Assessment of demographics and medical history

Each participant underwent a structured medical interview including demographics, medical history and medication.

2.4. Family history of PD

A family history questionnaire was used to obtain information on all first- and second degree relatives of the participants. Family history of PD was recorded according to the criteria of Marder and colleagues [9]. A positive family history was stated to be present if a family member showed at least three of the following parkinsonian signs, tremor at rest, shuffling gait, stooped posture, muscular rigidity, or demonstrated one of these signs and had one of the following: general physician- or neurologist diagnosed PD or positive response to levodopa.

2.5. History of orthopedic and vascular disturbances

Orthopedic and vascular disturbances were assessed with a self-assembled medical questionnaire. The questionnaire includes orthopedic questions about the presence of joint replacements, rheumatism and arthrosis as well as vascular questions about stroke or transient ischemic attack (TIA), heart attack, heart rhythm disturbance, angina pectoris, peripheral artery occlusive disease, congestive heart failure, hypertension, hypercholesterolemia, and diabetes mellitus. The questionnaire allowed to rate existence or absence of the above-mentioned disturbances ("yes/no"). In addition the intake of medication was recorded and used to verify the negative answers.

2.5.1. Calculation of CHA_2DS_2-VASc-Score

The CHA_2DS_2-VASc-Score [10] is a risk stratification score estimating the risk of stroke in patients with non-rheumatic atrial fibrillation (AF), ranged from 0 to 9 depending on the number and weight of the score risk components and is calculated as follows: congestive heart failure (1 point), hypertension (1 point), age 65–74.9 years (1 point), age $\geq$75 years (2 points), diabetes mellitus (1 points), stroke (2 point), vascular disease (1 point), and female gender (1 point).

2.6. Assessment of prodromal markers

2.6.1. Impaired olfaction

Olfaction was tested using the 16 Sniffin' sticks battery (BurghartMedizintechnik, Germany) as described by Hummel et al. [11]. According to the suggestion of Hummel and colleagues, individuals identifying less than 75% of odors correctly were classified as having hyposmia.

2.6.2. Rapid eye movement sleep behavior disorder (RBD)

Presence of RBD was determined by a self-administered RBD screening questionnaire (RBDSQ). The RBDSQ is a recently developed questionnaire, comprising 10 items to describe the most prominent clinical features of RBD [12].

2.6.3. Depression

Depressive symptoms were measured with the Beck Depression Inventory II (BDI) [13]. The BDI is a 21-item self-report questionnaire, ranging from 0 to 63 (no depression: 0–8; minimal depression: 9–13; mild depression: 14–19; moderate depression: 20–28; severe depression: 29–63).

2.6.4. Autonomic dysfunction

The Unified Multiple System Atrophy Rating Scale (UMSARS) is a validated, disease-specific scale assessing the diverse signs and symptoms in MSA [14]. For this study we selected the autonomic questions 9 to 12 of part I assessing orthostatic symptoms, as well as asking for urinary, sexual and bowel function and built a score. Higher scores indicate more severe autonomic dysfunction.

2.7. Transcranial sonography (TCS)

TCS was performed by an experienced investigator according to a standardized protocol as described previously [15]. The specific cut-off value for SN hyperechogenicity (SN+) differs depending on the ultrasound system used. In the TREND study the ACUSON Antares ultrasound machine (Siemens, Erlangen, Germany) equipped with a 2.5-Mhz transducer was used. SN+ was stated if the planimetrical area of the SN echogenic signal exceeded 0.21 cm^2, a cut-off determined in our lab.

The ventricular system can be depicted as anechoic region surrounded by hyperechogenic borders. The diameter of the third ventricle and of the frontal horn of the contralateral lateral ventricle is determined by the maximum transverse diameter on axial scans [16]. Enlarged third ventricle was stated with a diameter exceeding >4.8 mm ± 1.9 mm (<60 years) or 7.6 mm ± 2.1 mm (≥60 years) and enlarged lateral ventricle was stated with a diameter exceeding 16.7 mm ± 2.3 mm (<60 years) or 19.0 mm ± 2.9 mm (≥60 years) [17].

Echogenicity of the lenticular nucleus is generally rated semiquantitatively. Normally, this structure is isoechogenic to the surrounding brain parenchyma (grade 1). A moderately (grade 2) or pronounced (grade 3) hyperechogenicity of the lenticular nucleus compared with the surrounding white matter is classified as abnormal [18].

2.8. Intima-media thickness (IMT)

Measurement of the right common carotid artery (CCA) was performed using a 5–10 MHz linear array transducer (VF10-5, Siemens, Erlangen, Germany). Participants were examined in a supine position with their head tilted backwards. The CCA was differentiated from the internal jugular vein in a transverse plane, displayed in a longitudinal scan while the course of the CCA was followed up to the carotid bulb. The IMT of the CCA was defined as the distance between the intima-line and the media-adventitia border at the far-wall of the CCA [19]. IMT was measured 1 cm proximal of the carotid bulb using a fourfold magnification of the ultrasound image [20].