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Longitudinal course of mild parkinsonian signs in elderly people: A population-based study in Japan

Kenji Wada-Isoe *, Kenichiro Tanaka, Yusuke Uemura, Satoko Nakashita, Yuki Tajiri, Shugo Tagashira, Mikie Yamamoto, Mika Yamawaki, Masafumi Kishi, Kenji Nakashima

Division of Neurology, Department of Brain and Neurosciences, Faculty of Medicine, Tottori University, Japan

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ABSTRACT

We aimed to clarify the longitudinal course of mild parkinsonian signs (MPS) and their association with dementia and functional disability by conducting a comprehensive epidemiological study, including brain MRI, and assessments of cognition, depression, and sleep, in people aged ≥65 years living in Ama-cho. We diagnosed MPS and parkinsonism (PS) using a modified Unified Parkinson's Disease Rating Scale. The phase I study was conducted between 2008 and 2010 (n = 729) and the phase II between 2011 and 2013 (n = 436). By phase II, 8.5% of the phase I participants without PS had developed PS. In addition to older age, a lower Mini-Mental State Examination (MMSE) score, and lower body mass index, the MPS rigidity subtype was a significant independent predictor of PS onset. By phase II, 10.1% of the participants without dementia or PS at phase I had developed dementia. Older age, lower MMSE score, and the axial dysfunction and tremor MPS subtypes were significant independent predictors of dementia development. By phase II, 38.8% of participants with MPS at phase I showed no motor symptoms. Younger age and adequate sleep were significant predictors for this reversion. Periventricular and deep white matter hyperintensity Fazekas scores increased with the evolution of parkinsonian signs. MPS is therefore critically, although sometimes reversibly, associated with PS and dementia development in elderly people.

1. Introduction

Mild parkinsonian signs (MPS) are defined as features of bradykinesia, rigidity, and tremor as well as gait and postural instability occurring in isolation or combinations that do not meet clinical criteria for a diagnosis of parkinsonism (PS). MPS are thought to represent the border between normal aging and neurodegenerative diseases or cerebrovascular lesions [1–3]. MPS are common in elderly people with their prevalence ranging from 15% to 52% [4–6].

MPS are thought to be a prodromal state for Parkinson's disease (PD) [7] and recent studies indicate that MPS share the same risk factors as PD such as depression, hyposmia, and substantia nigra hyperechogenicity, [6,8,9]. MPS are also associated with increased incidence of dementia [10,11] as well as functional disability [12,13] and mortality [14]. Cerebrovascular lesions have been reported to be associated with MPS [2,3]. Although neuropathological changes that underlie MPS are not clearly understood, declines in nigrostriatal dopaminergic activity, degenerative pathological changes of Lewy body or Alzheimer's disease, and vascular pathological changes in the cerebral subcortical white matter or other brain regions are possible candidates.

While clinically relevant interpretations of MPS have been described, only a few studies have sought to evaluate the longitudinal course of MPS or predict their prognosis. We conducted a prospective community-based cohort study to investigate the course of MPS and variables associated with MPS in elderly people.

2. Methods

2.1. Study samples

We conducted this study in the municipality of Ama-cho, a rural island town with a large elderly population located 70 km from Yonago city, in the northwestern part of Japan [6]. To be eligible for the study, participants were required to be physically and legally resident in the town on October 1st, 2009. Inclusion criteria were as follows: (1) 65 years of age or older, (2) agreement to participate in the study (3) completion of questionnaire and examination survey in both phase I and II studies. Exclusion criteria were as follows: (1) participants who had died or moved out of town, (2) participants who had a medical history of the head injuries, the brain tumor, the cerebrovascular diseases, or psychiatric disorders, (3) neuroleptic users and (4) participants with severe organ dysfunction. Participants who did not undergo this survey despite our eager and repeated appeals prompting their participation were classified as non-responders.

* Corresponding author at: Division of Neurology, Department of Brain and Neurosciences, Faculty of Medicine, Tottori University, 36-1 Nishi-cho, Yonago 683-8504, Japan.
E-mail address: kewada@med.tottori-u.ac.jp (K. Wada-Isoe).

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The study was approved by the Tottori University committee for medical research ethics and followed the principles outlined in the Declaration of Helsinki. All participants provided their written informed consent to participate.

2.2. Survey procedure and data collection

The phase I study was conducted from 2008 to 2010 and the phase II study was from 2011 to 2013. We first administered a questionnaire survey by mailing the questionnaires to the residents legally living in Ama-cho at the start of phase I and II studies, then, an examination survey was followed (Fig. 1).

2.2.1. Questionnaire survey

The questionnaire was constructed to collect personal information and demographic information such as age, gender, formal education level, medical history including hypertension (HT), hyperlipidemia (HL), diabetes mellitus (DM), and current habits of smoking and alcohol consumption. Medical history data were also obtained via review of electronic healthcare system databases as well as patient-administered questionnaires. The questionnaire survey was also used for assessments of subjective motor and non-motor symptoms of the subjects. We included the Tanner questionnaire, which is validated for PD screening [15]. The Japanese version of the Geriatric Depression Scale (GDS) with 15 questions was administered to evaluate symptoms of depression. The GDS has been validated for the diagnosis of depression and the recommended cutoff point for depressive symptoms is ≥6 [16,17]. We included the REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ) [18] to assess sleep disturbance, and its cutoff point to detect REM sleep behavior disorder (RBD) is ≥5 points [19]. We also included the Pittsburgh Sleep Quality Index (PSQI), which has a cutoff for a poor sleeper at ≥6 points [20]. The presence of constipation, hyposmia and orthostatic hypotension was obtained by a self-administered questionnaire in which participants were asked if they experienced these symptoms or not.

2.2.2. Examination survey

Neurologists conducted a standardized neurological examination including an abbreviated (10-item) version of the motor portion of the Unified Parkinson's Disease Rating Scale (modified UPDRS). The 10 item (each rated from 0 to 4) assessed speech, facial expression, tremor at rest, rigidity (rated separately in the neck, right arm, left arm, right leg, and left leg), posture, and body (axial) bradykinesia. The mUPDRS was reported to be able to diagnose parkinsonian signs in community-dwelling elderly people [6,10,21]. The Mini-Mental State Examination (MMSE) was administered to assess global cognitive function [22]. We performed routine examinations in community centers and visited individual houses and nursing homes in order to raise participant rates in those who would otherwise have difficulty participating.

2.2.3. Assessment of cerebral white matter hyperintensities

Brain magnetic resonance (MR) imaging was performed between March 2010 and May 2010, with a 1.5 T system (Philips Gyroscan Intera 1.5 T, Philips, Tokyo, Japan) in the phase I study [24]. The Fazekas scale was used to assess periventricular hyperintensity (PVH) and deep white-matter hyperintensity (DWMH) [23]. Two investigators (M.Y and M.Y), who were blinded to the clinical information of participants, independently evaluated all brain images.

2.3. Diagnostic criteria

Those participants who had two or more cardinal signs (mUPDRS rating ≥ 2) on the standardized neurological examination were classified as having parkinsonism. Participants were classified as having MPS when they had two or more mUPDRS ratings = 1, one mUPDRS rating ≥2, or an mUPDRS resting tremor rating ≥1 [6,8,21]. Subtypes of MPS were classified as follows. Axial dysfunction; (1) UPDRS rating = 1 in two or more of the four items of axial function (changes in speech, facial expression, posture, and axial bradykinesia), or (2) one UPDRS rating ≥2 on one of the four items. Rigidity; (1) UPDRS ratings = 1 in two or more of the five items of rigidity, or (2) one UPDRS rating ≥2 on one of the five items. Tremor; UPDRS resting tremor rating ≥1. Unclassified; could not be classified into any of the abovementioned categories. Interrater reliability across two clinicians (K.T and Y.T) and intra-rater (K.T) reliability of the diagnosis of MPS or PS were good (kappa = 0.885, Cronbach alpha = 0.939 and kappa = 0.868, Cronbach alpha = 0.930, respectively). Dementia was diagnosed according to the criteria from the Diagnostic and Statistical Manual of Mental Disorders (4th edition revised) [25].

2.4. Statistical analysis

Descriptive statistics are given as the mean and standard deviation for noncategorical data and percentages for categorical data. Noncategorical variables were analyzed using Student's t test and categorical variables with a chi squared test. The risk associated with the presence of an MPS independent variable in PS or dementia newly occurring at phase II was assessed with logistic regression using participants without PS or participants without dementia at phase II as controls. Binary logistic regressions with stepwise selection and a likelihood ratio test were conducted to determine predictors for MPS reversion. The goodness-of-fit of the final model was tested using the Hosmer–Lemeshow method. Fazekas scores were compared using a Kruskal–Wallis test with a *post hoc* Mann–Whitney U test; a Jonckheere–Terpstra test was used for trend analysis. The risk of white matter hyperintensity (independent variable) in the MPS reversion (dependent variable) was assessed by binary logistic regression adjusting for age, sex, and vascular risk factors including hypertension, hyperlipidemia, diabetes mellitus, and smoking. We used $P < 0.05$ as the criterion for significance. All analyses were conducted using IBM SPSS Statistics for Windows, version 19.0 (IBM Corp, Armonk, NY).

3. Results

3.1. Participants

Fig. 2 presents a flow chart for this study. At Phase I, the number of elderly people aged 65 years or older who were legally residents in the town was 924 (374 men; mean age ± SD, 77.3 ± 7.8 years), which represented 38.0% of the population. Twenty-four subjects were deceased or had moved outside of the town at the time of the phase I survey. Of 900 eligible individuals, 729 (81.0%) underwent questionnaire and neurological examination surveys, and 689 (76.6%) underwent an MRI scan during the phase I study. Seventy-one

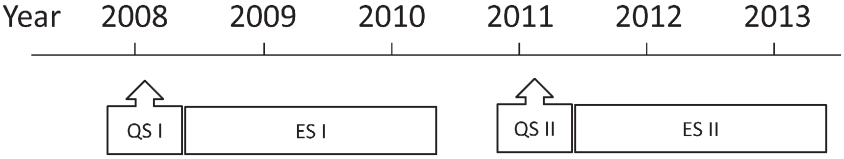

Fig. 1. Flow diagram of the surveys. QQ I = questionnaire survey phase I, ES I = examination survey phase I, QS II = questionnaire survey phase II, ES II = examination survey pause II.