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Fatigue is associated with the onset of hallucinations in patients with Parkinson's disease: A 3-year prospective study

Masanori Ikeda, Hiroshi Kataoka *, Satoshi Ueno

Department of Neurology, Nara Medical University, Kashihara, Nara, Japan,

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ABSTRACT

Hallucinations remain problematic in Parkinson's disease (PD). Various factors have been studied, and many previous studies identified risk factors for hallucinations, such as sleep disorders. At the same time, fatigue is a common symptom in Parkinson's disease, and any factors associated with fatigue in PD have been reported. Factors associated with fatigue in PD are likely to be similar to risk factors for hallucinations. However, fatigue has been not been reported to be a risk factor for hallucinations in previous studies. We prospectively studied non-hallucinators with PD during 3 years to identify factors associated with the onset of hallucinations, including fatigue. We initially screened 100 consecutive patients and registered 78 patients with PD. During 3 years of follow-up, 31 patients newly presented with visual hallucinations. A total of 18 variables were evaluated by logistic regression analysis. Brief Fatigue Inventory (BFI) (OR = 1.027, p = 0.045, 95% CI = 1.001–1.053) was related to first-onset hallucinations on multivariate logistic regression analysis. The present study is the first to demonstrate an association of fatigue with the onset of hallucinations. Fatigue, especially mental fatigue, can be a risk factor for future hallucinations.

1. Introduction

Hallucinations remain problematic in Parkinson's disease (PD) because they negatively affect the quality of life of not only the patients, but also the caregivers. We often encounter patients with new-onset hallucinations that progress to uncontrolled delirium. Knowledge about predictable risk factors for first-onset hallucinations is thus very important. Various factors have been studied, and many previous studies identified risk factors for hallucinations, such as older age, female gender, prolonged disease duration, depression, daytime somnolence, insomnia, excessive daytime sleepiness, cognitive impairment, severity of motor symptoms, motor complications, autonomic dysfunction, and medication dosage [4,11,14,17,42]. In particular, sleep disorders, including rapid eye movement (REM)-sleep behavioral disorder, dream-enacting behavior, and nightmares, are known to an important risk factor for hallucinations [4,11,14,17]. At the same time, fatigue is a common symptom in Parkinson's disease (PD), ranging in prevalence from 37% to 56% [6]. Many factors associated with fatigue in PD have been reported, such as PD duration, female gender, depression, sleep disturbance, excessive daytime sleepiness, REM behavioral disorder, motor symptoms, autonomic dysfunction, apathy, and dopaminergic treatment [2,5,6,32,38,40]. Now, the presence or severity of fatigue is recognized to be significantly associated with both motor and non-motor symptoms in PD [37]. Factors associated with fatigue in PD are likely to be similar to risk factors for hallucinations. To our knowledge, however, fatigue has been not been reported to be a risk factor for hallucinations in previous studies [4,11,14,17,42]. We prospectively studied non-hallucinators with PD during 3 years to identify factors associated with the onset of hallucinations, including fatigue and sleep disorders.

2. Material and methods

2.1. Participants and initial assessments

We initially screened 100 consecutive patients who fulfilled the UK Parkinson's Disease Society Brain Bank criteria [22]. In accordance with our recently reported methods [26,27], we first had the patients complete diary questionnaires for 4 weeks (Supplemental material 1) to exclude patients who had hallucinations or who had dementia or higher brain dysfunction that would preclude following our instructions. The clinical diary included a total of 10 questions and inquired about hallucinations (item 9), vivid nightmares (items 1 and 2), dream-enactment behavior (items 3, 4, 5, and 7), and sleep fragments associated with vivid dreams (item 8). Items 3, 5, 7, and 9 were asked to both the patients and their bed partners. The patients wrote their responses to the questions after awakening in the morning. If a patient had drunk alcohol the previous night (item 10), we did not use their

* Correspondence to: Department of Neurology, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 634-8522, Japan.
E-mail address: hk55@naramed-u.ac.jp (H. Kataoka).

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responses for last night. If they did not remember any dream or the experienced dreams were not judged to be nightmares, we did not use the responses associated with such dreams. Patients who responded that they had hallucinations (item 9) were excluded. Patients who were given quetiapine, clozapine, rivastigmine, donepezil, galanthamine, yokukansan, or neuroleptic medications were excluded. Patients who had received deep brain stimulation surgery or a previous diagnosis of schizophrenia, as well as patients who had a history of hallucinations were also excluded. The severity of PD was graded according to the scores on the Unified Parkinson's Disease Rating Scale (UPDRS) [13]. Cognition function was assessed with the Mini-Mental Status Examination (MMSE). The Brief Fatigue Inventory (BFI) included the evaluation of the severity of fatigue itself at the present time and during the past 24 h and of the impairment of 6 activities of daily living (general activity, mood, walking ability, normal work, relations with other people, and enjoyment of life), and the degree of each activity was rated from "no fatigue" and "does not interfere" (0 points) to "bad" and "completely interferes" (10 points), respectively [30]. The Zung Self-Rating Depression Scale (SDS) was used to evaluate depression [43]. SDS is widely used as a self-administered psychological test, and a high score indicates severer depression. Several studies have used SDS to evaluate depression in PD [25]. The Zung Self-Rating anxiety scale and Parkinson's Disease Sleep Scale (PDSS) [8] have also been used. PDSS items were grouped according to domain: sleep quality (items 1–3), nocturnal motor symptoms (items 9–13), and daytime somnolence (items 14 and 15) [34,39]. The daily dose of antiparkinsonian agents was converted into the equivalent dose of levodopa as follows: 100 mg standard levodopa = 140 mg controlled release levodopa = 10 mg, bromocriptine = 1 mg pergolide = 1.5 mg cabergoline = 5 mg ropinirole = 1 mg pramipexole = 10 mg selegiline [31,36]. No patient received rotigotine.

2.2. Follow-up assessments

From among the 100 patients, we registered 78 patients with PD (Fig. 1). In accordance with our previously described methods [26,27], the interviewer personally interviewed the patients once every 1 to 3 months to inquire about the presence or absence and the frequency of hallucinations in the visual, auditory, tactile, and olfactory domains, and we promptly obtained responses from all patients. The interviewer also inquired whether the hallucinations were with or without retained insight, threatening or not, and with or without delusions or delirium, and whether the patients or their caregivers suffered from the hallucinations. These questions were also asked to the patients' caregivers. If discordant responses were obtained, the interviewer used best judgment. During 3 years of follow-up, we excluded patients who showed evidence of epilepsy, stroke, transient ischemic attacks or who were admitted to the hospital because of physical problems such as cardiac failure or pulmonary infection or who had undergone surgical intervention. In addition, no patient who newly experienced hallucinations during the follow-up period had mental impairment, impaired consciousness, dementia, or impaired higher brain dysfunction such as

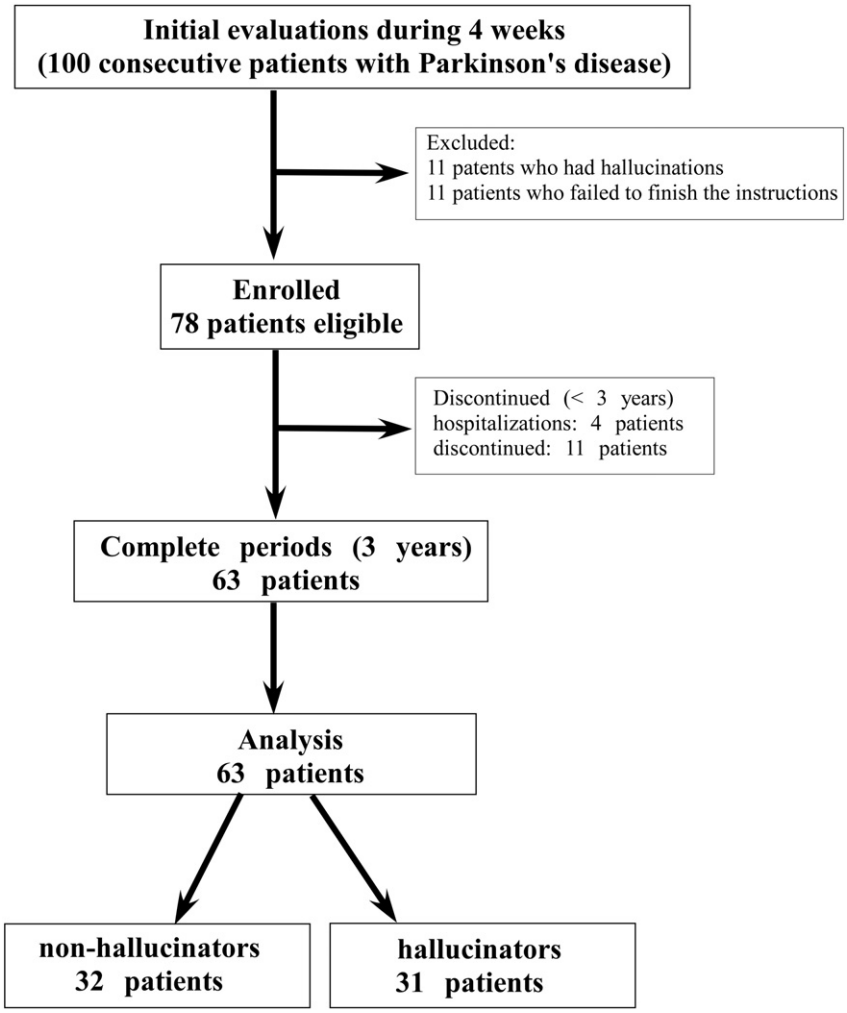

Fig. 1. Selection procedure for analyzing patients.