分類学上は区別されることもある。そこで、ALS-D と ALS に主眼を置いて、FTLD の後向き臨床病理学的疫学検討を行った。

B. 研究方法

当教室（鳥取大学医学部脳病態医科学分野：旧脳神経病理学部門）で過去 49 年間に病理学的確定診断をされた 2212 症例について、後ろ向き研究を行った。当教室のファイルより ALS および FLTD の症例を全て抽出した。特に ALS と ALS-D については、病理データに加え、臨床情報も検討を行った。

ユビキチン免疫染色については、パラフィン材料を使用して、再検討を行った。パラフィン切片は、各症例ごとに 6μm 厚切片を作成した。これら切片は免疫染色に供すると共に、routine 染色として HE、Klüver-Barrera、Holzer、Bodian、Gallyas-Braak、Bielschowsky-平野変法の各染色法を施した。免疫染色に関しては、脱パラフィン後、0.3%H_2O_2（室温、30 分）、5%の homologous normal serum で blocking（室温、30 分）を行い、一次抗体（4℃、overnight）を施した。一次抗体としては抗ユビキチン抗体を用いた。これ以後の反応は、avidin-biotin-immunoperoxidase complex method との組み合わせで行った。一次抗体の代わりに PBS を用いて同様に染色し対照実験とした。

本研究は、主に病理標本を用いた後ろ向き研究であったが、倫理面についても十分に配慮し、患者情報の匿名化に最大限努力したうえで研究を遂行した。

C. 研究結果

2212 症例中、FTLD に該当したものが 17 症例（ALS-D 5 症例、進行性核上性麻痺 6 症例、前頭側頭認知症 6 症例）であった。

一方、ALS について解析したところ、2212 症例中 56 症例の ALS が確認された。この 56 症例の ALS のうちユビキチン染色陽性封入体を同定でき、認知機能障害を認めた症例は 5 症例で、この 5 症例の ALS-D は上述の FTLD に該当していた症例群であった。同時に、ALS-D 症例の臨床症状の後ろ向き研究を実施したところ、前頭側頭型認知症に類似した性格変化、異常行動、認知機能低下、失語症状などの高知機能障害の合併が確認された。

D. 考察

これまで、FTLD の約 55%がユビキチン陽性封入体をもつ FTLD-U であることが知られており、その FTLD-U の中の約 5～10%で運動ニューロン疾患を合併していると報告されている。ALS に着目した場合、ALS の約 12%が ALS-D であると報告されている。我々の研究結果では、病理学的に ALS と診断された症例の約 9%が ALS-D とであり、既報の報告に大きな隔たりのない結果であった。また、後ろ向き臨床情報の解析結果からは、異常行動・言語障害といった特徴的な症状を呈していたという結果を得られたが、それぞれの症例によって高次機能障害の内容や程度には多様性がみられた。

E. 結論

FTLD は病理学的確定診断が必須な疾患であり、病理学的確定診断のついている症例が利用可能なことは、今後の FTLD の研究には極めて有益であることが判明した。

F. 健康危険情報

特記なし

G. 研究発表

1. 論文発表

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H. 知的財産権の出願・登録状況

1. 特許取得　なし
2. 実用新案登録　なし
3. その他　なし

厚生労働科学研究費補助金（難治性疾患克服研究事業）
分担研究報告書

前頭側頭葉変性症の疫学的検討ならびに診断基準に関する研究

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研究要旨

高齢者うつ病患者は認知症のハイリスク群であり認知症との鑑別を要するが，その認知機能，脳機能，精神症状，社会機能の相互の関連は不明な点も多い．認知機能，脳機能と社会機能，精神症状の関連を明らかとすることを目的とし，65歳以上の高齢者うつ病36名と性別，年齢を一致させた健常対象群35名に作業記憶課題（2-back課題）を施行した．同時に作業記憶課題遂行中の脳機能画像を52チャンネル近赤外線スペクトロスコピーを用いて評価した．社会機能評価尺度としてSASS（social adaptation self-evaluation scale)を，うつ病症状評価尺としてBDI（Beck depression inventory)，HAMD（Hamilton rating scale for depression）を用いて評価し，脳機能と社会機能および精神症状との関連を検討した．患者群では対照群と比較し作業記憶課題成績の有意な低下を示した（P<0.01）．また同様に作業記憶課題遂行中の前頭前部および側頭部の血液量増加の有意な減少を認めた（29/52チャンネル，FDR補正，課題成績補正 P:0.001～0.042）．患者群で作業記憶課題遂行中の前頭前部および側頭部の血液量増加の減少とSASSのスコアは有意に正の相関を示した（12/52チャンネル，R:0.41～0.52；多重補正 P: 0.001～0.013）．一方，患者群での作業記憶課題遂行中の前頭前部および側頭部の血液量増加の減少とBDI，HAMDスコアとの有意な相関は認められなかった．高齢者うつ病では認知機能，脳機能が低下しているが，それらと社会機能との関連が示された一方でうつ病の症状との関連は示されなかった．

A．研究目的

制止を認める高齢者うつ病は仮性認知症と呼ばれ高齢者うつ病と認知症の鑑別が困難な場合がある．その違いはうつ病患者の認知機能障害は精神症状に影響を受けるため可逆的であるとされてきたが，近年はうつ病は認知症のリスク因子とされ，うつ病の症状改善後も認知機能障害・脳機能低下が持続することが指摘されるに至り，仮性認知症の概念も揺らぎつつある．

また近年，疾患の治療評価項目として症状の改善のみならず社会機能の改善が重要視されるようになったが，神経・精神疾患において社会機能は認知機能と関連することも示唆されている．

高齢者うつ病患者は認知症のハイリスク群であり認知症との鑑別を要するが，その認知機能，脳機能，精神症状，社会機能の相互の関連は不明な点も多い．そこで本研究では高齢者うつ病において認知機能，脳機能と社会機能，精神症状の関連を明らかとすることを目的とする．

B．研究方法

対象：鳥取大学医学部付属病院精神科を受診した65歳以上にて発症したうつ病患者36名と，年齢，性別を一致させた健常対象群35名である．患者は診断基準であるDiagnostic and Statistical manual of Mental disorders-four（アメリカ精神医学会）にて大うつ病と診断され，かつ65歳以降に初めて大うつ病を発病した者のうち，検査時に抗うつ薬を未服薬であることを組み入れ基準とした．除外基準はMini-Mental State Examination<24点，頭部外傷の既往，

脳血管障害の既往,その他の中枢神経疾患の臨床徴候，物質依存の既往を含めた罹患とした.健常対象群は患者群と同様の除外基準の他に精神疾患の既往も含めた罹患を除外基準とした.

方法:52チャンネル近赤外線スペクトロスコピー（ETG-400, Hitachi Medical Co.）を用いて各被験者の作業記憶課題（2-back課題）遂行中の脳血液量の変化を測定する.その他，社会機能評価尺度であるSASS（social adaptation self-evaluation scale）およびうつ病評価尺であるBDI(Beck depression inventory), HAMD（Hamilton rating scale for depression）にて社会機能および精神症状を評価し脳血液量の変化との関連を検討する.

倫理的配慮:全ての参加者に研究プロトコールを説明した上で書面にて同意を得た.なお本研究は鳥取大学医学部倫理委員会にて承認されている.

C．研究結果

患者群では対照群と比較し，作業記憶課題成績の有意な低下を示した（$P<0.01$）．また同様に作業記憶課題遂行中の前頭前部および側頭部の血液量増加の有意な減少を認めた(ch6,7,8,9,10,11,12,14,15,18,20,21,23,24,25,28,29,31,34,36,39,41,42,43,44,45,47,51,52 多重補正，課題成績補正，P:0.001～0.042).

患者群では作業記憶課題遂行中の前頭前部および側頭部の血液量増加の減少とSASSのスコアは有意に正の相関を示した（ch1,2,5,15,17,25,26,27,30,36,39,47，R:0.41to 0.52; FDR補正 P: 0.001～0.013)．一方，患者群での作業記憶課題遂行中の前頭前部および側頭部の血液量増加の減少とうつ病の症状評価尺度であるBDI，HAMDスコアとの有意な相関は認めなかった.

D．考察

高齢者うつ病患者では健常対象群と比較し作業記憶課題成績が低く，また同課題中の脳機能の低下も認めた.またその脳機能の低下と社会機能は正の相関を示したが,その一方で脳機能の低下と精神症状の関連は認めなかった.これらの結果を認知症のリスクという観点から考えると高齢者うつ病患者ではうつ病の症状のみならず，認知機能，脳機能，社会機能など多面的に評価する必要性があると考えられる.

E．結論

高齢者うつ病では認知機能,脳機能が低下しているが,それらと社会機能との関連が示された一方でうつ病の症状との関連は示されなかった.

F．健康危険情報

特記事項なし.

G．研究発表

1.論文発表

Pu S, Yamada T, Yokoyama K, Matsumura H, Mitani H, Adachi A, Kaneko K, Nakagome K. Reduced prefrontal cortex activation during the working memory task associated with poor social functioning in late-onset depression: Multi-channel near-infrared spectroscopy study. Psychiatry Research: Neuroimaging 2012 (in press)

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H．知的財産権の出願・登録状況

特記事項なし.

III. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Nomura T, Inoue Y, Kagimura T, Uemura Y, Nakashima K.	Utility of the REM sleep behavior disorder screening questionnaire (RBDSQ) in Parkinson's disease patients.	Sleep Med	12(7)	711-713	2011
Uemura Y, Wada-Isoe K, Nakashita S, Nakashima K.	Mild parkinsonian signs in a community-dwelling elderly population sample in Japan.	J Neurol Sci	304 (1-2)	61-66	2011
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Beck G, Sugiura Y, Shinzawa Y, Kato S, Setou M, Tsujimoto Y, Sakoda S, Sumi-Akamaru H.	Neuroaxonal dystrophy in calcium-independent phospholipase A2β deficiency results from insufficient remodeling and degeneration of mitochondrial presynaptic membranes.	J Neurosci	31	11411-11420	2011
Okamoto Y, Shirakashi Y, Ihara M, Urushitani M, Oono M, Kawamoto Y, Yamashita H, Shimohara S, Kato S, .Hirano A, Tomimoto H, Ito H, Takahashi R	Colocalization of 14-3-3 proteins with SOD1 in Lewy body-like hyaline inclusions in familial amyotrophic lateral sclerosis cases and the animal model.	PLoS ONE	6	e20427 (1-6)	2011
青木正志, 加藤信介	ALS-SOD1の臨床と病理.	Clinical Neuroscience	29	1040-1043	2011
Wada-Isoe K, Uemura Y, Nakashita S, Yamawaki M, Tanaka K, Yamamoto M, Shimokata H, Nakashima K.	Prevalence of dementia and mild cognitive impairment in the Rural Island town of Ama-cho, Japan.	Dement Geriatr Cogn Disord Extra	2(1)	190-199	2012
Pu S, Yamada T, Yokoyama K, Matsumura H, Mitani H, Adachi A, Kaneko K, Nakagome K.	Reduced prefrontal cortex activation during the working memory task associated with poor social functioning in late-onset depression: Multi-channel near-infrared spectroscopy study.	Psychiat Res: Neuroimag		in press	2012

IV. 研究成果の刊行物・別冊

Sleep Medicine 12 (2011) 711–713

Contents lists available at ScienceDirect

Sleep Medicine

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

Brief Communication

Utility of the REM sleep behavior disorder screening questionnaire (RBDSQ) in Parkinson's disease patients

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ARTICLE INFO

Article history:
Received 30 November 2010
Received in revised form 18 January 2011
Accepted 21 January 2011
Available online 22 June 2011

Keywords:
RBD
RBDSQ-J
Parkinson's disease
Screening
Cut-off value
ROC

ABSTRACT

Objective: We evaluated the usefulness of the REM sleep behavior disorder (RBD) screening questionnaire (RBDSQ) among patients with Parkinson's disease (PD).
Methods: Forty-five patients with PD were evaluated (22 male and 23 female, 72.9 ± 9.1 years old). After patients completed the RBDSQ, we conducted interviews regarding RBD symptoms and performed polysomnographic examinations on the subjects. We then compared RBDSQ scores among the following groups: PD with RBD (n = 19), PD without RBD (n = 26), and idiopathic RBD (n = 31, 22 male and 9 female, 67.8 ± 6.5 years old), and estimated the cut-off score for an RBD diagnosis.
Results: RBDSQ scores in PD with RBD and idiopathic RBD groups were similar and higher than those in the PD without RBD group (PD with RBD: 7.2 ± 1.9, idiopathic RBD: 7.9 ± 2.8, PD without RBD: 2.9 ± 1.6). Cronbach's α for RBDSQ sub-scores was 0.73, suggesting a fair internal consistency. A receiver-operator characteristics curve revealed that a total score of 6 points on the RBDSQ represented the best cut-off value for detecting RBD (sensitivity = 0.842, specificity = 0.962).
Conclusion: RBDSQ could be a useful tool for the screening of RBD in PD patients.

1. Introduction

REM sleep behavior disorder (RBD) is characterized by vigorous and injurious behaviors related to vivid, action-filled, and violent dreams during nocturnal REM sleep [1]. Many patients with neurological disorders are reported to have RBD symptoms (secondary RBD). In particular, RBD has been widely accepted as one of the preclinical symptoms of Parkinson's disease (PD) [2]. In the second edition of the International Classification of Sleep Disorders (ICSD second), the existence of REM sleep without atonia (RWA) on polysomnogram (PSG) is essential for the diagnosis of RBD [3]. However, it is impossible to perform PSG on all the patients with suspicion of RBD because the examination is time- and labor-consuming. Hence, an appropriate questionnaire for RBD screening in clinical settings is warranted.

Stiasny-Kolster et al. created the RBD screening questionnaire (RBDSQ) as a diagnostic instrument and have already validated its diagnostic accuracy [4]. The Japanese version of RBDSQ was also validated (RBDSQ-J), targeting idiopathic RBD [5]. These two studies agreed that a total score of 5 points on the RBDSQ represented a cut-off value for the screening of idiopathic RBD with the highest sensitivity and specificity. However, the usefulness of the RBDSQ for screening secondary RBD in PD patients, in whom non-violent dream enactment behaviors based on the existence of RWA (non-violent RBD symptoms) are relatively common [6], has not been evaluated. Therefore, in this study we explored the effectiveness of RBDSQ as a screening tool for secondary RBD among PD patients.

2. Subjects and methods

The ethics committees of Tottori University approved this study. Forty-five consecutive PD patients hospitalized at the University Hospital of Tottori University, Division of Neurology gave informed consent to participate in the study (mean age: 72.9 ± 9.1 years old, 22 male and 23 female, length of PD morbidity: 8.6 ± 7.2 years, Hohen and Yahr grade: 2.8 ± 0.9). For comparison, 31 age- and gender-matched idiopathic RBD patients who had received the diagnosis based on both PSG findings and the results of clinical interviews at the Japan Somnology Center were included in the study (mean age: 67.8 ± 6.5 years old, 22 male and 9 female). Overnight PSG recordings were performed by standardized methods [7], and RWA was defined according to the scoring manual of the American Sleep Disorders Association [8].

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doi:10.1016/j.sleep.2011.01.015

All the patients and their bed partners were asked to complete the RBDSQ-J and were then systematically interviewed regarding sleep problems (with an emphasis on dream enactment behavior or vocalization while dreaming) by sleep disorder expert physicians who were blind to the RBDSQ-J results. The diagnosis of RBD was made according to criteria from the ICSD second [3]. Next, we categorized the PD patients into PD groups with RBD and those without RBD (including the patients with normal REM sleep and those with RWA but clearly not having RBD symptoms). We compared the scores of RBDSQ-J sub-items between PD patients with violent RBD versus those with non-violent RBD. In addition, we compared the positivity rate of RBDSQ-J sub-item scores between all PD patients having RBD symptoms and iRBD patients to determine differences in the distribution of positive scores on each sub-item between these two groups.

Internal consistency of the RBDSQ-J was estimated using Cronbach's α coefficient. The criterion value was $\geqslant 0.70$ for item homogeneity. Moreover, sensitivity and specificity for different cut-off points for total RBDSQ-J score for the screening of RBD among the PD patients were both calculated and presented by means of a receiver-operator characteristics curve (ROC) function. The diagnostic value of the RBDSQ-J was calculated by using the area under the curve (AUC), which was independent of an arbitrary choice of a cut-off point, and statistical significance was tested using the Mann–Whitney U test.

3. Results

According to the above-indicated criteria, the PD patients were divided into 19 patients with RBD (42%, violent RBD: $n = 13$, non-violent RBD: $n = 6$) and 26 patients without RBD (58%). But all the iRBD patients had clear violent RBD symptoms. The mean total RBDSQ-J scores were 7.2 ± 1.9 in the PD group with RBD (range: 3–11), 2.9 ± 1.6 in the group without RBD (range: 1–7), and 7.9 ± 2.8 in the iRBD group (range: 2–12). There was a significant difference in the total RBDSQ-J scores among the three groups as revealed by an analysis of variance [$F_2 = 37.28$, $p < 0.001$], and a *post hoc* Bonferroni correction determined that the PD group with RBD and the iRBD group had significantly higher values compared to the PD group without RBD. However, there were no significant differences in the total RBDSQ-J scores between the former two groups (Fig. 1).

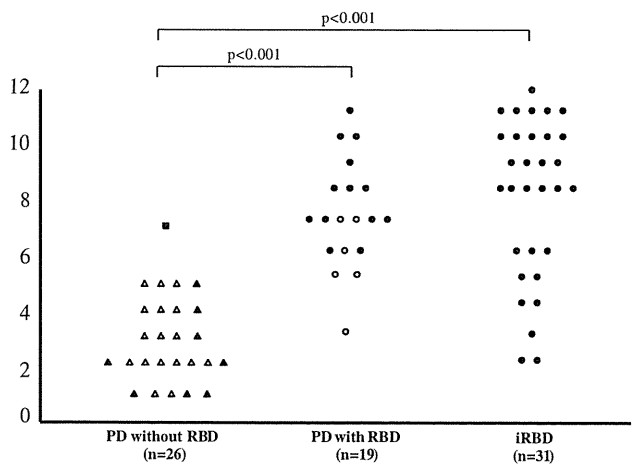

Fig. 1. Comparison of RBDSQ-J scores among the three groups. symbols indicate individual RBDSQ-J scores for each patient among the subject groups (PD without RBD, PD with RBD, iRBD). ●, Violent RBD symptoms; ○, non-violent RBD symptoms; ■, non-violent symptoms without RWA; ▲, RWA with no RBD symptoms; △, neither RWA nor RBD symptoms.

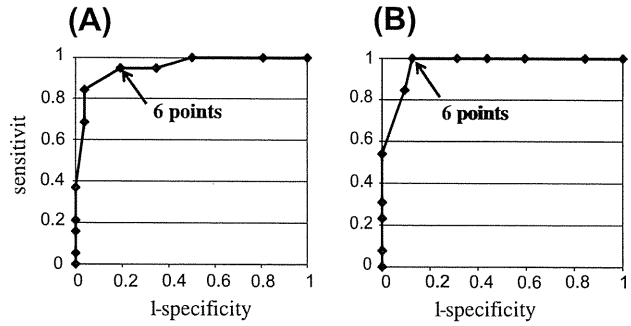

Fig. 2. Receiver-operator characteristics (ROC) curves of PD patients. Curves show distributions of sensitivity and specificity for the existence of any RBD symptom (A) and violent RBD symptoms only (B). The cut-off value of RBDSQ-J scores for the existence of any RBD symptoms in PD patients was 6 points, with a sensitivity of 0.842 and a specificity of 0.962. The AUC was 0.953. The likelihood ratios of positive and negative results were 21.872 and 0.164, respectively (A). When the target was restricted to cases with violent RBD symptoms, the cut-off value was again 6 points with a sensitivity of 1.000 and a specificity of 0.875. The AUC was 0.969 in this case, and the likelihood ratios of positive and negative results were 8.000 and 0.875, respectively (B).

The thirteen items of the RBDSQ-J had an overall reliability coefficient (Cronbach's α) of 0.73, indicating a high degree of internal consistency. Each of the thirteen items of RBDSQ-J was judged to measure a particular aspect of the same overall construct.

We compared the positivity rate of each RBDSQ-J item score between PD patients with RBD and iRBD patients using a χ^2-test. iRBD patients had significantly higher positivity rates for item 5 (they hurt their bed partner or themselves; PD with RBD: 1/19, iRBD: 15/31, $p = 0.006$) and lower positivity rates for item 10 (they have/had a disease of the nervous system; PD with RBD: 19/19, iRBD: 5/31, $p < 0.001$) versus PD patients with RBD. However, there were no significant differences in the rates of positivity for the other items between the two groups. After item 10 was removed, there was also a significant difference in the total RBDSQ-J score between the two groups (PD with RBD: 6.2 ± 1.9, iRBD: 7.7 ± 2.7, $p = 0.025$).

The mean total RBDSQ-J scores in 13 PD patients with violent RBD were significantly higher than that in 6 PD patients with non-violent RBD symptoms (8.0 ± 1.6 vs. 5.5 ± 1.5, Mann–Whitney U test $p = 0.007$). Moreover, there were significant differences in the positivity rates between these two groups for items 6.2 (they have/had sudden limb movements, "fights" during their dreams; violent RBD: 9/13, non-violent RBD: 0/6, $p = 0.005$), 6.3 (they have/had displayed gestures and complex movements during their dreams; violent RBD: 9/13, non-violent RBD: 1/6, $p = 0.033$), 6.4 (they fell down somewhere around the bed during their dreams; violent RBD: 6/13, non-violent RBD: 0/6, $p = 0.044$), and 7 (their movements awaken themselves; violent RBD: 10/13, non-violent RBD: 0/6, $p = 0.002$).

ROC curve analyses revealed that a total score of 6 points on the RBDSQ represented the best cut-off value for detecting any RBD symptoms (sensitivity of 0.842 and specificity of 0.962) and for detecting violent RBD symptoms (sensitivity of 1.000 and specificity of 0.875) (Fig. 2). Three PD cases with non-violent RBD symptoms showed a false negativity as judged from this cut-off value. However, all of them had a positive score on item 6.1 (they have or had symptoms of speaking, shouting, swearing, or laughing loudly during dreams).

4. Discussion

From our results, the mean total RBDSQ score in the iRBD group was 7.9 ± 2.8 points, which is similar to the values reported by

Miyamoto et al. (7.5 ± 2.8 points) [5], indicating a good score reproducibility between two different cohorts of Japanese iRBD patients.

The present study also showed that RBDSQ had a fair internal consistency even in PD patients, suggesting a proper validity for the screening of RBD in this population. Of note, 6 points was revealed to be the best cut-off value for the screening of RBD in this population. This cut-off value for RBD secondary to PD was approximately 1 point higher than that reported for iRBD in previous studies [4,5]. However, the cut-off value of RBDSQ in this patient population would become equal to the above-indicated value of iRBD patients if item 10 were removed.

Our results demonstrated that PD patients with violent RBD symptoms had higher total RBDSQ scores compared to those with non-violent RBD symptoms. The difference in the positivity rate in some items between total PD patients having RBD and iRBD patients could reflect the phenomenon that approximately 30% of the former group had only non-violent RBD symptoms. In addition, patients with iRBD had higher RBDSQ scores compared to PD patients with RBD after item 10 was removed. These findings suggest that PD patients had milder RBD symptoms compared with iRBD patients. However, the cut-off value for RBD positivity was the same between the analyses after including or not including the patients with non-violent symptoms. Considering that the sensitivity and specificity of RBDSQ-J for the screening of RBD in our PD patients was similar to the results obtained by Miyamoto et al., RBDSQ may be useful for detecting RBD among PD populations regardless of the RBD symptom content. In addition, positivity on item 6.1 might represent a key criterion for analyzing populations with non-violent RBD.

In our study, the main limitation was that we could not investigate the test–retest reliability of RBDSQ-J among the study population.

In conclusion, the RBDSQ could be useful for the screening of RBD among PD populations. Reportedly, the existence of RBD in PD patients is associated with the development of dementia and/or autonomic failure [9,10]. We want to emphasize that the use of RBDSQ should be promoted in PD clinics for detecting RBD symptoms and could thereby facilitate the prediction of clinical courses of PD patients.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: doi:10.1016/j.sleep.2011.01.015.

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Journal of the Neurological Sciences 304 (2011) 61–66

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

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

Mild parkinsonian signs in a community-dwelling elderly population sample in Japan

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ARTICLE INFO

Article history:
Received 8 September 2010
Received in revised form 24 December 2010
Accepted 11 February 2011
Available online 5 March 2011

Keywords:
MPS
Parkinson's disease
Screening
Prevalence
Depression

ABSTRACT

Mild parkinsonian signs (MPS) may represent the mild end of a disease spectrum that spans from normal aging to neurodegenerative diseases. We conducted a population-based study in a rural island town in western Japan, Ama-cho. Participants included 1129 subjects, aged 60 years and older, residing in the town. Participants were classified according to a modified Unified Parkinson's Disease Rating Scale (mUPDRS) score. MPS was determined to be present if any of the following conditions were met: (1) two or more mUPDRS ratings = 1 [MPS-mild]; (2) one mUPDRS rating ≥ 2; or (3) mUPDRS rest tremor rating ≥ 1; [(2) and (3): MPS-severe]. Subjects wore a uniaxial accelerometer (Actiwatch), resulting in the measurement of actigraphic activity counts (AC).

Of the 804 participants with complete data, 178 subjects (22.1%) were classified as demonstrating MPS. AC was significantly lower in the MPS-severe group compared with both the CTL and the MPS-mild groups. Diagnostic sensitivity for MPS-severe became 100% when we adopted a cutoff point of low physical activity, as measured by actigraphy, combined with the presence of subjective depression.

We established the prevalence of MPS in a community-dwelling elderly population sample in Japan. Actigraphy may be a useful objective tool for screening MPS-severe.

1. Introduction

Mild parkinsonian signs (MPS), including bradykinesia, rigidity, gait disturbance and resting tremor, may represent the mild end of a disease spectrum that spans from normal aging [1] to neurodegenerative diseases [2], including Parkinson's disease (PD). MPS has also been reported to be the result of nigrostriatal Alzheimer's disease (AD)-type pathology [3], associated with increased risk of dementia [4], associated with vascular lesions of basal ganglia and white matter [5,6], and a significant predictor of mortality [7]. However, the clinical significance of MPS is not yet fully understood. The prevalence of MPS in sample populations in East Boston, England [8], New York, USA [9] and Jiangsu, China [7] has been reported, but inconsistencies exist across reports because of differences in MPS definition, study methodology, age structure, and cognitive status [10]. The prevalence of MPS in Japan has hitherto not been reported.

We have conducted the first epidemiological study to suggest the prevalence of MPS in Japan. Furthermore, we examined the usefulness of actigraphy as an objective indicator for MPS through a population-based study in order to establish screening methods for MPS in association with questionnaires about motor and nonmotor symptoms of Parkinson's disease (PD).

2. Methods

2.1. Subjects

This study was conducted in the municipality of Ama-cho, a rural island town located 70 km from Yonago city, in the northwestern part of Japan [11]. To be included in the study, subjects were required to be living and to be legally residing in the town on March 31, 2008. The total population of Ama-cho on this day was 2402 (1124 men). The number of elderly people aged 60 years and older was 1129 (479 men, mean age ± SD 74.6 ± 9.1 years old). Board certified neurologists of the Japanese Society of Neurology (neurologists) belonging to our department have visited this town twice a year since 1980, and diagnosed patients having neurological disorders. Before this study, 11 patients with PD were recognized through these visits.

The study was approved by the committee for medical research ethics at Tottori University following the principles outlined in the "Declaration of Helsinki", and all participants provided written informed consent to participate in the study.

2.2. Questionnaire survey

We administered a questionnaire survey in May 2008. First, we mailed the questionnaires to residents aged 60 years or older. To assess motor symptoms, we included the Tanner questionnaire, [12], which is validated as a PD patient screening form. To evaluate depressive symptoms, we included the Japanese version of the

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doi:10.1016/j.jns.2011.02.013

Geriatric Depression Scale with 15 questions (GDS-15). [13]. It has been validated for the diagnosis of depression, and the recommended cutoff points are ≥6 as mild depression and ≥10 as severe depression [13,14]. We included the Pittsburgh Sleep Quality Index (PSQI) [15] and the REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ) [16] to assess sleep disturbances. The cutoff value of the PSQI for a poor sleeper was 5/6 points, [15], and the RBDSQ to detect REM sleep behavior disorder (RBD) was 5/6 points. [17]. Demographic data, including age, gender, duration of education, and present smoking and drinking habits, were collected using the questionnaire. In order to evaluate nonmotor symptoms, we assessed the presence of constipation, hallucinations, hyposmia, and orthostatic hypotension with the questionnaire.

2.3. Neurological examination

Each participant underwent a structured medical interview including a past history of hypertension, diabetes mellitus, and hyperlipidemia. A standardized neurological examination was conducted by one of four neurologists, including an abbreviated (10-item) version of the motor portion of the Unified PD Rating Scale (UPDRS) in 2008–2009. The 10 items screened for 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, with each item rated from 0 to 4. A rating of 1 indicated a mild abnormality and a rating of ≥2 indicated an abnormality of moderate or greater severity [9]. Subjects with a total UPDRS score of 0 were classified as being normal controls (CTL). We assigned a diagnosis of PD based on research criteria [18] and participants were considered to have PD if (1) they had previously received a diagnosis of PD by neurologists and responded to L-dopa or (2) their symptoms fulfilled the UK PD brain bank criteria, [19], or both. Those who had two or more cardinal signs (UPDRS rating≥2) on the standardized neurologic examination were classified as having parkinsonism. These cardinal signs include bradykinesia, rigidity, postural instability, and resting tremor.

MPS were defined as present when any one of the following conditions was met: (1) two or more UPDRS ratings=1; (2) one UPDRS rating≥2; or (3) a UPDRS resting tremor rating≥1 [10]. MPS was further stratified into subtypes according to symptom types and severity as shown in Table 1 [4, 20, 21].

2.4. Measurement of physical activity using actigraphy

In order to obtain participants for the actigraphy study, we gathered subjects in five districts, randomly selected from the fourteen districts in the town (participation rate: 65.0%).

Physical activity was quantified using wrist-worn uniaxial accelerometers (Actiwatch-16, Mini Mitter-Philips Respironics, Bend, OR) [22]. Physical activity was monitored in the participant's own homes, and participants were instructed to continue their normal daily routine. Participants wore Actiwatches on their nondominant wrist for 1 week collecting data in 1-minute epochs. Those subjects with unilateral PD wore monitors on their least affected side. This placement has been shown to better represent whole-body movement [25] and was intended to reduce artifacts such as low level constant activity when writing with the dominant hand or dyskinesias in the most affected arm. At the same time, all participants completed a sleep log for 7 days. All actigraphic data were validated in accordance with entries in sleep logs. Automatic activity analysis using dedicated software (Actiware, Mini Mitter-Philips Respironics) was conducted. The measures analyzed were Total AC (the sum of all valid physical activity counts for all awake epochs), Avg AC (the average of all valid physical activity counts for all awake epochs divided by the epoch length in minutes), and Max AC (the largest of any valid physical activity count for all awake epochs).

Table 1
Classification of mild parkinsonian signs.

Classification according to symptoms	
Axial dysfunction	(1) UPDRS ratings=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 in one of the four items
Abnormality in rigidity	Either (1) UPDRS ratings=1 in two or more of the five items of rigidity, or (2) one UPDRS rating≥2 in one of the five items
Tremor	A UPDRS resting tremor rating≥1
Unclassified	Could not be classified into any of the above-mentioned categories
Classification according to severity of UPDRS score	
MPS-mild	A UPDRS rating of 1
MPS-severe	A UPDRS rating of 2 or higher, or presence of resting tremor

MPS: mild parkinsonian signs, UPDRS: Unified PD Rating Scale.

2.5. Statistical analyses

The adjusted prevalence was calculated for all types of MPS and PD using the Japanese population on March 1, 2008. Paired t tests and analysis of variance (ANOVA) were used for comparison of medians for continuous variables, and categorical variables were analyzed using a chi-square test. Pearson's test was used for correlation analyses. Differences in the total physical activities between groups were evaluated with an analysis of covariance (ANCOVA), adjusting for age. Analyses of the relationship between the background of the nonmotor symptoms and MPS-severe were performed by multivariate logistic regression analysis. Significance was defined as $p<0.05$, and all analyses were conducted using the Statistical Package for the Social Sciences version 17.0 software (SPSS17.0, 2008, Tokyo, Japan).

3. Results

3.1. Questionnaire survey

Nine hundred sixty-eight (85.7%) of 1129 residents returned their questionnaire. As compared to survey nonrespondents, respondents were similar in age (mean=74.7 years vs. 75.1 years) and gender (47.1% male vs. 43.5% male).

3.2. Prevalence of PD and MPS in a community-dwelling elderly population sample

Eight hundred four of 1129 subjects received a neurological examination (71.2%). We diagnosed 69 subjects as having parkinsonism (24 men, 82.9±7.1 years). Of the parkinsonism patients, 14 were diagnosed as having PD (4 men, 79.6±7.6 years). The crude prevalence of PD and the age-adjusted prevalence when calculated using the Japanese population in 2008 were 1.5% and 1.3% for PD in those over the age of 65.

Of the examined subjects, 178 were diagnosed as having MPS (62 men, 78.1±8.1 years). The crude prevalence of MPS was 22.1% (95% CI: 19.3–25.0) in participants over 60 years of age, and 23.7% (95% CI: 20.6–26.9) in participants over 65 years of age. The age-adjusted prevalence of MPS was 13.8% in the over 60 population, and 16.8% in the over 65 population. We showed the classification of MPS according to its type and severity in Table 2.

3.3. Physical activity measured by actigraphy

Using actigraphy, we evaluated 265 subjects (121 men; age: 74.2±7.9 years), including 174 control (CTL) subjects (75 men; 72.2±7.2 years), 53 subjects with MPS-mild (22 men; 78.3±7.2 years), 19 subjects with MPS-severe (5 men; 78.4±6.6 years), and 19 subjects with parkinsonism (7 men; 81.0±7.5 years) including 7 PD patients

Table 2
Age- and sex-specific prevalence of MPS.

Age (years)	Residents	Population at risk	MPS																Parkinsonism	
			Total		Type										Severity					
					Axial dysfunction		Rigidity		Mixed		Tremor		Unclassified		MPS-mild		MPS-severe			
			Cases	Prevalence	Cases	Prevalence	Cases	Prevalence	Cases	Prevalence	Cases	Prevalence	Cases	Prevalence	Cases	Prevalence	Cases	Prevalence	Cases	Prevalence
Both sexes																				
60–64	183	88	8	9.1%	1	1.1%	7	8.0%	–	–	–	–	–	–	7	8.0%	1	1.1%	–	–
65–69	180	135	18	13.3%	2	1.5%	12	8.9%	2	1.5%	2	1.5%	–	–	15	11.1%	3	2.2%	1	0.7%
70–74	198	164	28	17.1%	5	3.0%	18	11.0%	3	1.8%	2	1.2%	–	–	23	14.0%	5	3.0%	9	5.5%
75–79	227	183	49	26.8%	12	6.6%	25	13.7%	11	6.0%	1	0.5%	–	–	34	18.6%	15	8.2%	13	7.1%
80–84	158	121	43	35.5%	14	11.6%	16	13.2%	7	5.8%	2	1.7%	4	3.3%	26	21.5%	17	14.0%	11	9.1%
85–	183	113	32	28.3%	9	8.0%	18	15.9%	4	3.5%	–	–	1	0.9%	23	20.4%	9	8.0%	35	31.0%
Total	1129	804	178	22.1%	43	5.3%	96	11.9%	27	3.4%	7	0.9%	5	0.6%	128	15.9%	50	6.2%	69	8.6%
Men																			–	–
60–64	94	38	3	7.9%	1	2.6%	2	5.3%	–	–	–	–	–	–	2	5.3%	1	2.6%	–	–
65–69	84	63	8	12.7%	1	1.6%	5	7.9%	1	1.6%	1	1.6%	–	–	8	12.7%	–	–	1	1.6%
70–74	89	67	11	16.4%	1	1.5%	7	10.4%	2	3.0%	1	1.5%	–	–	9	13.4%	2	3.0%	5	7.5%
75–79	97	72	17	23.6%	4	5.6%	7	9.7%	6	8.3%	–	–	–	–	11	15.3%	6	8.3%	3	4.2%
80–84	53	38	10	26.3%	2	5.3%	3	7.9%	2	5.3%	1	2.6%	2	5.3%	6	15.8%	4	10.5%	2	5.3%
85–	62	44	13	29.5%	2	4.5%	10	22.7%	–	–	–	–	1	2.3%	11	25.0%	2	4.5%	13	29.5%
Total	479	322	62	19.3%	11	3.4%	34	10.6%	11	3.4%	3	0.9%	3	0.9%	47	14.6%	15	4.7%	24	7.5%
Women																			–	–
60–64	89	50	5	10.0%	–	–	5	10.0%	–	–	–	–	–	–	5	10.0%	–	–	–	–
65–69	96	72	10	13.9%	1	1.4%	7	9.7%	1	1.4%	1	1.4%	–	–	7	9.7%	3	4.2%	–	–
70–74	109	97	17	17.5%	4	4.1%	11	11.3%	1	1.0%	1	1.0%	–	–	14	14.4%	3	3.1%	4	4.1%
75–79	130	111	32	28.8%	8	7.2%	18	16.2%	5	4.5%	1	0.9%	–	–	23	20.7%	9	8.1%	10	9.0%
80–84	105	83	33	39.8%	12	14.5%	13	15.7%	5	6.0%	1	1.2%	2	2.4%	20	24.1%	13	15.7%	9	10.8%
85–	121	69	19	27.5%	7	10.1%	8	11.6%	4	5.8%	–	–	–	–	12	17.4%	7	10.1%	22	31.9%
Total	650	482	116	24.1%	32	6.6%	62	12.9%	16	3.3%	4	0.8%	2	0.4%	81	16.8%	35	7.3%	45	9.3%

(2 men; 77.8 ± 7.2 years). Ruling out a selection bias, there were no significant differences between activity measurement participants and non-participants with regard to age (74.3 ± 8.0 vs. 75.0 ± 9.4 years, respectively, p = 0.253), gender (43.3% male vs. 42.1% male, respectively, p = 0.390), or UPDRS score (1.4 ± 2.3 vs. 1.2 ± 2.4, respectively, p = 0.239).

While there was no significant difference in Total AC between the CTL and MPS-mild groups, Total AC in the MPS-severe group was significantly lower than that in the CTL and MPS-mild groups (Fig. 1). Our measure of Avg AC showed the same tendency as Total AC. However, our measure of Max AC was not significantly different among the groups. These three indices of physical activity were significantly associated with age (Total AC: $r = -0.358$, $p<0.001$, Avg AC: $r = -0.330$, $p<0.001$, Max AC: $r = -0.258$, $p<0.001$). ANCOVA analysis, adjusted for the age of subjects, revealed that Total AC in the MPS-severe group was significantly lower than that in the CTL group.

We divided the MPS group according to axial dysfunction scores into three subgroups: non-axial dysfunction (axial dysfunction score = 0, n = 34), mild axial dysfunction (axial dysfunction score = 1 or 2, n = 28), and moderate/severe axial dysfunction (axial dysfunction score = 3 or more, n = 10). Total AC, Avg AC and Max AC in the non-axial dysfunction group were 323,834.6 ± 21,927.8, 383.9 ± 25.0, and 2507.9 ± 151.5, those in the mild axial dysfunction group were 240,077.7 ± 22,175.5, 300.8 ± 25.9, and 2149.2 ± 124.9, and those in the moderate/severe axial dysfunction group were 193,873.6 ± 20,551.1, 245.7 ± 25.6, and 1755.9 ± 174.4, respectively. Total AC and Avg AC of the moderate/severe axial dysfunction group were significantly lower than those of the non-axial dysfunction group. In addition, Total AC, Avg AC, and Max AC of the mild axial dysfunction group were significantly lower than those of the non-axial dysfunction group. However, there were no significant differences in the three activity parameters between the mild axial dysfunction group and the moderate/severe axial dysfunction group.

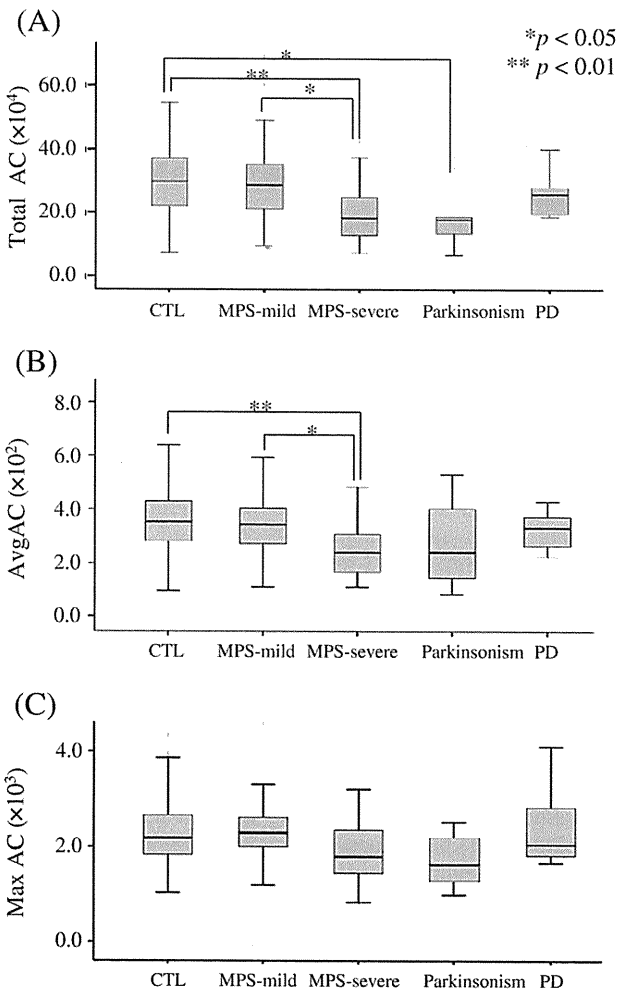

Fig. 1. Comparison of physical activity. The box plots show the median values (thick lines), 25th percentile (lower line of box), and 75th percentile (upper line of box). T bars indicate the 10th and 90th percentiles. Statistical differences were calculated using an ANOVA followed by Tukey tests. CTL: normal controls, MPS: mild parkinsonian signs. PD: Parkinson's disease. (A) Total AC: the sum of all valid physical activity counts for all epochs from the start time to the end time of the given awake interval, (B) Avg AC: the average of all valid physical activity counts for all awake epochs divided by the epoch length in minutes, (C) Max AC: the largest of any valid physical activity count for all awake epochs. *$p<0.05$, **$p<0.01$.

We also divided the MPS group according to rigidity scores into three subgroups: non-rigidity (maximum rigidity score = 0, n = 17), mild rigidity (maximum rigidity score = 1, n = 53), and moderate/severe rigidity (maximum rigidity score = 2, n = 2). There were no significant differences in the three activity parameters among these groups.

Finally, we also divided the MPS group according to tremor scores into three subgroups: non-tremor (tremor score = 0, n = 67), mild tremor (tremor score = 1, n = 5), and moderate/severe tremor (tremor score = 2, n = 0). There were no significant differences in activity between these groups.

3.4. Association of nonmotor PD symptoms with MPS

There were no significant differences between the CTL group and both the MPS-mild and MPS-severe groups for habitual history, past history, nonmotor PD symptoms, or RBDSQ scores (Table 3). There was a significantly lower proportion of 'sleep disturbance' on the PSQI in the MPS-mild group, but not in the MPS-severe group, as compared with the CTL group.

The GDS scores of the MPS group were significantly higher than those of the CTL group (4.3 ± 3.4 vs. 3.2 ± 3.1, $p = 0.01$) and there was a significantly higher proportion of subjects with 'mild depression' on the GDS in the MPS group as compared with the CTL group (41.3% vs. 27.0%, $p<0.001$), indicating a strong association of subjective depression with MPS.

The proportion of subjects with 'mild depression' on the GDS was significantly higher in the MPS-mild group than in the CTL group. The proportion of subjects with 'severe depression' was significantly higher in the MPS-severe group than in the CTL group.

3.5. Screening for MPS

In the present study, when one point was assumed to be a cutoff in the Tanner questionnaire, the sensitivity for detecting PD was 100%. However, it was only 71.9% for detecting MPS (both MPS-mild and MPS-severe) and 73.3% for detecting MPS-severe. When predictors of MPS-severe were examined by multivariate logistic analysis, GDS and

Table 3
Demographic characteristics of participants stratified by MPS.

	CTL	MPS-mild	MPS-severe
Present smoking, n (%)	33 (7.5%)	4 (3.9%)	3 (7.1%)
Present drinking, n (%)	116 (26.6%)	19 (18.4%)	4 (9.3%)
Constipation, n (%)	97 (22.9%)	37 (37.0%)	15 (38.5%)
Hallucination, n (%)	30 (7.0%)	8 (8.3%)	7 (17.1%)
Hyposmia, n (%)	49 (11.4%)	17 (17.0%)	7 (17.1%)
Orthostatic hypertension, n (%)	79 (18.3%)	24 (24.2%)	14 (32.6%)
GDS ≥ 6, n (%)	123 (27.4%)	42 (40.4%)**	17 (39.5%)
GDS ≥ 10, n (%)	23 (5.1%)	7 (6.7%)	7 (17.1%)**
RBDSQ ≥ 5, n (%)	37 (8.2%)	17 (16.3%)	5 (11.6%)
PSQI ≥ 6, n (%)	107 (23.8%)	18 (17.3%)*	8 (18.6%)

GDS: Geriatric Depression Scale, PSQI: Pittsburgh Sleep Quality Index, RBDSQ: REM Sleep Behavior Disorder Screening Questionnaire. *$p<0.05$, **$p<0.01$ vs. CTL.

Table 4
Predictors of MPS-severe status by multivariate logistic regression analysis.

Variable	Pearson's rank correlation	Univariate logistic regression analysis	Multivariate logistic regression analysis
		Odds ratio (95% CI)	Odds ratio (95% CI)
Age	0.231**	1.129** (1.081–1.181)	–
Education	−0.114*	0.793* (0.665–0.946)	–
Tanner	0.261**	1.435** (1.274–1.616)	–
GDS	0.155**	1.172** (1.074–1.279)	1.4* (1.1–1.8)
PSQI	−0.021	–	–
RBDSQ	−0.010	–	–
Total AC	−0.267**	0.694** (0.553–0.870)	0.5** (0.3–0.8)

Education: duration of education, GDS: Geriatric Depression Scale, PSQI: Pittsburgh Sleep Quality Index, RBDSQ: REM Sleep Behavior Disorder Screening Questionnaire. *$p<0.05$, **$p<0.01$.

Total AC were shown to be independent predictive factors (Table 4). Based on this finding, diagnostic sensitivities, specificity, and positive predictive value (PPV) became 100%, 83.5%, and 62.2% (respectively) for MPS-severe when we adopted a cutoff point of more than 6 points for GDS or less than 40×10^4 for Total AC. When we used the same screening method, diagnostic sensitivities, specificity, and PPV became 85.7%, 83.5%, and 68.2% for the entire MPS group, 94.4%, 83.5%, and 37.8% for the parkinsonism group including PD, and 87.5%, 83.5%, and 73.3% for a combination of all the groups (MPS and parkinsonism including PD), respectively.

4. Discussion

Only a few reports have documented the prevalence of MPS, indicating a prevalence of 15.8% in retired military officers aged 75 years or older in Nanjing [7]; 14.9% (age 65–74), 29.5% (age 75–84), and 52.5% (age 85 and older) in East Boston [8]; and 40.1% in residents aged 65 years or older in New York [9]. Our study revealed that the crude prevalence of MPS was 22.1% in the population over 60 years of age, and 23.7% in the population over 65 years of age. These data are in agreement with earlier cohort studies reporting similar findings.

One of the difficulties in studying the prevalence of MPS is the definition of MPS. Several studies have defined MPS liberally (any one UPDRS rating of 1 or higher [9,21]), while others have defined it more rigorously (two or more such signs or one sign of moderate severity (UPDRS rating≥2) [10]). One motivation for using more rigorous criteria is to try to separate MPS from the signs of normal aging. The more rigorous criteria are also considered to avoid the influence of other chronic illnesses and the aging process, and thus more likely to reflect pathological brain changes resulting in MPS [10]. However, a clear distinction between MPS and normal aging has not been established.

In the present study, we classified MPS into two subgroups according to the severity of the UPDRS rating. In order to investigate differences in physical activity between these two subgroups, we measured physical activity using actigraphy. Previous studies have reported the usefulness of standard actigraphy to assess fluctuation of akinesia [23], tremor, motor fluctuation [24], and sleep in PD patients [25,26]. In the present study, measured activity counts in the PD group were higher compared to the MPS-severe group. We noted that the PD patients who showed higher activity counts on actigraphy measures tended to receive higher Levodopa equivalent doses, had a shorter PD duration, and/or displayed a resting tremor (data not shown). These factors might account for higher activity counts in the PD group compared to the MPS group or parkinsonism group. In particular, the PD patient who generated the highest activity counts in the PD group displayed excessive overactivity due to the side effects of anti-parkinsonian drugs when he wore the Actiwatch. When we excluded this patient from the analysis, the activity counts of the PD group were significantly lower than those of both the CTL group ($p=0.036$) and the MPS-mild group ($p=0.044$). Unfortunately, the number of PD patients present in this study might be too small to confidently analyze their activity counts.

On the other hand, our measure of Total AC in the MPS-severe group was significantly lower than that measured in both the CTL and MPS-mild groups. Levels of physical activity were significantly associated with age, as participants with MPS were significantly older than those in the CTL group. However, an ANCOVA analysis revealed that the Total AC of subjects in the MPS-severe group, even after adjusting for age, was significantly lower compared to the CTL group.

To further clarify the clinical meaning of our actigraphic data, we divided the MPS group according to axial dysfunction scores, rigidity scores, and tremor scores. There were no significant differences between the mild axial dysfunction group and the moderate/severe axial dysfunction group. However, there was a significant difference between the non-axial dysfunction group and the moderate/severe axial dysfunction group in both Total AC and Avg AC, and between the non-axial dysfunction group and the mild axial dysfunction group in Total AC, Avg AC, and Max AC. Among the rigidity groups, there were no significant differences, although the activity counts of the mild tremor group were higher compared to the non-tremor group.

Therefore, we believe that our actigraphic data primarily relates to axial dysfunction.

These data suggest that a UPDRS rating of 2 may be more appropriate than a rating of 1 for distinguishing between MPS and normal aging. Future longitudinal studies evaluating the condition of MPS subjects after several years should be conducted in order to assess the suitability of the distinction between MPS-mild and MPS-severe classifications.

While the sensitivity of the Tanner questionnaire for detecting PD was 100%, its sensitivity for detecting MPS-severe was only 73.3% in our sample, indicating that the Tanner questionnaire is not suitable for screening MPS. Moreover, nonmotor symptoms such as constipation, hallucination, hyposmia, and orthostatic hypotension, which have been considered to be suggestive diagnostic markers for PD, were also not suitable for screening MPS in our sample. Sleep disturbance was also inadequate as a screening marker for MPS. We had a large number of subjects with sleep disturbance in our CTL group. In contrast, GDS scores and our measure of Total AC were independent predictive factors for MPS-severe status when we entered age, duration of education, Tanner questionnaire, GDS, PSQI, and RBDSQ scores, and Total AC as predictors of MPS-severe. Interestingly, when we adopted a cutoff point of more than 6 points on the GDS or less than 40×10^4 of Total AC, diagnostic sensitivities became 100%.

Finally, although depression was associated with the presence of MPS, the presence of depression is not unique to MPS. Depression is a common and disabling disorder in later life [13,27], and while subjects with depression have been reported to have significantly lower scores for activity of daily living (ADL) and quality of life (QOL) than those without depression [28], depression in the elderly has also been reported to be associated with poor cognitive function [29], dementia [30], developing AD [31], premotor symptoms in PD [32], and cerebrovascular disease [33]. Viewing these findings together with the organic pathological changes of the brain, leads us to believe that such brain changes may influence both the mood as well as motor function of the elderly who only have mild symptoms of neurodegenerative disease.

This study has several strengths, including the assessment of a well-characterized cohort of community-dwelling elderly subjects. In addition, our findings are based on validated actigraphy. Limitations include the use of a volunteer cohort and the cross-sectional nature of our study design. An accurate evaluation of sleep disturbances and RBD was not made because we screened subjects based on subjective symptoms without polysomnography. Future longitudinal studies are necessary to clarify the prognosis of MPS and the use of UPDRS rating of 2 to distinguish between MPS and normal aging.

5. Conclusions

Here we report the prevalence of MPS in Japan for the first time. Measuring physical activity using actigraphy and evaluating depression using GDS enabled us to detect MPS, which may lead to the early intervention of neurodegenerative disorders in aging populations.

Authors' roles

Yusuke Uemura: Research project Conception, Organization, Execution, Statistical Analysis Design, Execution, Review and Critique, Manuscript Writing of the first draft, Review and Critique.

Kenji Wada-Isoe: Research project Conception, Organization, Execution, Statistical Analysis Design, Execution, Manuscript Review and Critique.

Satoko Nakashita: Research project Execution.

Kenji Nakashima: Research project Conception, Organization, Execution, Manuscript Review and Critique.

Acknowledgments

Financial disclosures: This work was supported by Grants-in-Aid from the Research Committee of CNS Degenerative Diseases, the Ministry of Health, Labour and Welfare of Japan, and the Ministry of Education, Culture, Sports, Science and Technology of Japan (No. 20590698).

We thank all the inhabitants of Ama-cho for their participation in the present study. We also thank Dr. Yamamoto, Dr. Tagashira, Dr. Imamura, Dr. Suto, Dr. Takigawa, Dr. Kitayama, Dr. Sakakibara, Dr. Kitagawa, Ms. Hamami, Ms. Nakagawa, Ms. Ikeda, Ms. Hayashi, and Ms. Yoshino for collecting and providing clinical information.

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Research Studies

OPEN LABEL TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF YOKUKANSAN, A TRADITIONAL ASIAN MEDICINE, IN DEMENTIA WITH LEWY BODIES

To the Editor: Behavioral and psychological symptoms of dementia (BPSDs), including vivid hallucinations, are commonly seen in dementia with Lewy bodies (DLB).[1] BPSDs cause distress to people with DLB and imposes a significant burden on caregivers. Antipsychotics[2] cause drug-induced extrapyramidal symptoms (EPSs) and other adverse events in DLB. The traditional Asian medicine yokukansan (YKS) has been reported to improve BPSDs in people with dementia,[3] so a multicenter case series was designed to investigate the efficacy and safety of YKS in DLB.

METHODS

Participants who were diagnosed with probable DLB according to international consensus criteria[1] and having concomitant BPSDs, with a Neuropsychiatric Inventory (NPI)[4] score of 4 or greater, were recruited from 15 hospitals in Japan. The sample size required was calculated to be 28, with an alpha error of 0.05 and power of 0.8, according to a previous report.[3] Patients who used neuroleptics, antianxiety drugs, antiepileptics, antidepressants, or herbal remedies were excluded from the study, but those who had used antiparkinsonian drugs, hypnotics, or donepezil hydrochloride continuously for more than 4 weeks were included. Participants received 7.5 g of YKS powder (Tsumura & Co., Tokyo, Japan), containing seven herbs[3] for 4 weeks. At baseline, participants' medical histories were evaluated, and they underwent physical and neurological examination and brain magnetic resonance imaging. At baseline and end point, the NPI, the Zarit burden interview—Japanese edition (J-ZBI)[5] for burden on caregivers, the Mini-Mental State Examination (MMSE)[6] for cognition, the Disability Assessment for Dementia (DAD)[7] for activities of daily living, the Hoehn-Yahr's (HY) score for Parkinsonism, the Barnes Akathisia Scale for EPSs, an insomnia subscale of behavioral pathology in Alzheimer's disease (Behave-AD)[8] for sleep disturbance, and blood examination including serum potassium concentration were administered. In some participants, the NPI and J-ZBI were conducted three times: at baseline and after 2 and 4 weeks of treatment. Results were expressed as means ± standard deviations. All changes in outcomes between baseline and end point were compared using a signed rank-sum test, except NPI and J-ZBI, for which multiple observations were adjusted for using the Bonferroni method. $P<.05$ was considered significant in statistical analyses using SAS 9.1.3 (SAS Institute, Inc., Cary, NC). The study was conducted in compliance with the ethical principles of the Declaration of Helsinki. Written informed consent from each patient or proxy consent was obtained before participation in this study. The institutional review board at each center approved the protocol, which was registered with the University Hospital Medical Information Network clinical trial registry (UMIN000001511, http://www.umin.ac.jp/ctr/index.htm).

RESULTS

Sixty-three participants were registered (30 male, 33 female; aged 78.2 ± 5.8; 2.6 ± 2.3 years duration of illness). NPI, MMSE, DAD, and J-ZBI scores were 30.3 ± 18.5, 17.7 ± 7.0, 54.4 ± 32.6, and 34.2 ± 18.9, respectively. Three potential participants who did not receive YKS were excluded from the analyses. One participant who did not come back to the clinic after the first interview and five who were found to be using neuroleptics were excluded from efficacy analysis but included in the safety analysis. Therefore, 54 participants were eligible for efficacy analysis, and 60 participants were analyzed for safety.

Participants who withdrew from the YKS treatment within the observation period were analyzed under intention to treat. Three participants withdrew because of adverse events, and one withdrew of his own volition. Significant improvements were observed in NPI total scores (Figure 1A, a mean decrease of 12.5 points, $P<.001$) and each subscale, including delusions (3.1 points, $P<.001$), hallucinations (4.0 points, $P<.001$), dysphoria (2.2 points, $P<.001$), anxiety (1.7 points, $P<.001$), and irritability or lability (2.9 points, $P<.001$). J-ZBI improved (Figure 1B, 3.6 points, $P=.02$). Participants who underwent NPI (n = 23) and J-ZBI (n = 22) showed a time-dependent improvement in these scores. MMSE (1.1 points, $P=.002$) and Behave-AD insomnia subscale ($P=.01$) scores also improved significantly. DAD showed no significant change. EPSs were not observed. Four participants had potassium levels lower than 3.5 mEq/L at the end point. Spasticity and deterioration of BPSDs were encountered in a single participant who recovered after discontinuation of YKS. Worsening hypotension was recorded in one participant. Other adverse events were gastrointestinal dysfunction and edema.

DISCUSSION

The present study demonstrates a significant improvement in BPSDs in people DLB who took YKS. Caregiver burden was also reduced. Activities of daily living did not deteriorate. Cognitive function improved slightly but significantly. These results correspond to those from a previous study.[3] YKS regulates glutamate and aspartate metabolism in the animal brain[9] and acts on 5-hydroxytryptamine-2A receptors.[10] These mechanisms may explain the clinical results. A randomized control trial that would evaluate the effects and safety of YKS for DLB is needed.

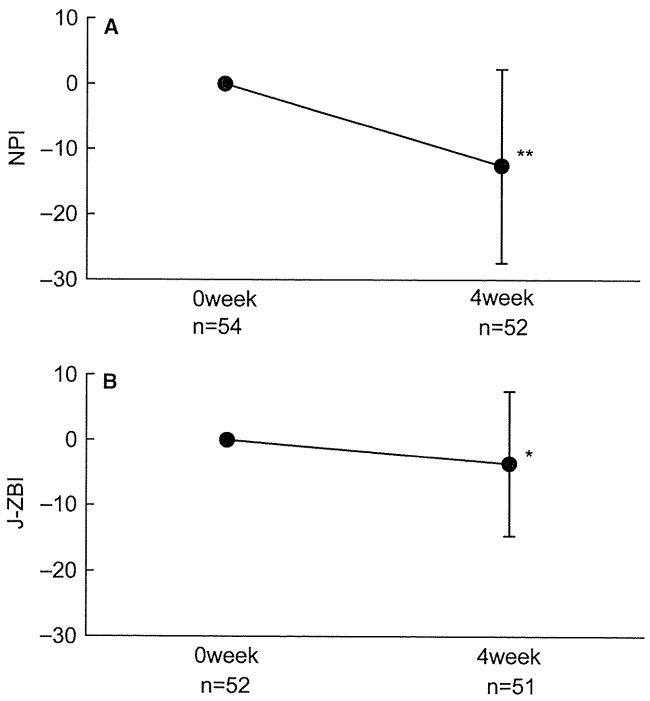

Figure 1. (A) Changes in Neuropsychiatric Inventory (NPI) total scores between baseline and end point, (B) Changes in Zarit Burden Interview—Japanese edition (J-ZBI) total scores. $^{**}P<.01$, $^{*}P<.05$, signed rank-sum test.

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ACKNOWLEDGMENTS

Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

Financial support was received from Tsumura & Co., Tokyo, Japan, which provided the YKS. The conflict of interest committee of Tohoku University carefully deliberated this conflict of interest and accepted the study design after revisions.

Author Contributions: Dr. Iwasaki drafted the manuscript, had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Furukawa and Dr. Kosaka contributed to study conception, patient recruitment, review of the data, and revision of the manuscript. Dr. Iwasaki, Dr. Okitsu, Dr. Furukawa, Dr. Kosaka, Dr. Mori, Dr. Manabe, Dr. Yoshita, Dr. Kanamori, Dr. Ito, Dr. Wada, Dr. Kitayama, Dr. Horiguchi, Dr. Yamaguchi, Dr. Fukuhara, Dr. Ouma, Dr. Nakano, Dr. Hashimoto, and Dr. Kinoshita were clinical investigators and contributed to reviewing the data.

Sponsor's Role: Tsumura & Co. had roles in data collection, data management and maintenance, and data analysis.

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Neurobiology of Disease

Neuroaxonal Dystrophy in Calcium-Independent Phospholipase $A_2\beta$ Deficiency Results from Insufficient Remodeling and Degeneration of Mitochondrial and Presynaptic Membranes

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Infantile neuroaxonal dystrophy (INAD) is a fatal neurodegenerative disease characterized by the widespread presence of axonal swellings (spheroids) in the CNS and PNS and is caused by gene abnormality in PLA2G6 [calcium-independent phospholipase $A_2\beta$ (iPLA$_2\beta$)], which is essential for remodeling of membrane phospholipids. To clarify the pathomechanism of INAD, we pathologically analyzed the spinal cords and sciatic nerves of iPLA$_2\beta$ knock-out (KO) mice, a model of INAD. At 15 weeks (preclinical stage), periodic acid-Schiff (PAS)-positive granules were frequently observed in proximal axons and the perinuclear space of large neurons, and these were strongly positive for a marker of the mitochondrial outer membrane and negative for a marker of the inner membrane. By 100 weeks (late clinical stage), PAS-positive granules and spheroids had increased significantly in the distal parts of axons, and ultrastructural examination revealed that these granules were, in fact, mitochondria with degenerative inner membranes. Collapse of mitochondria in axons was accompanied by focal disappearance of the cytoskeleton. Partial membrane loss at axon terminals was also evident, accompanied by degenerative membranes in the same areas. Imaging mass spectrometry showed a prominent increase of docosahexaenoic acid-containing phosphatidylcholine in the gray matter, suggesting insufficient membrane remodeling in the presence of iPLA$_2\beta$ deficiency. Prominent axonal degeneration in neuroaxonal dystrophy might be explained by the collapse of abnormal mitochondria after axonal transportation. Insufficient remodeling and degeneration of mitochondrial inner membranes and presynaptic membranes appear to be the cause of the neuroaxonal dystrophy in iPLA$_2\beta$-KO mice.

Introduction

Infantile neuroaxonal dystrophy (INAD) is a fatal neurodegenerative disease with various neurological symptoms (Gregory et al., 2008b). Widespread formation of axonal swellings, referred to as spheroids, and tubulovesicular structures are observed in the CNS and PNS (Cowen and Olmstead, 1963; Khateeb et al., 2006). Gene abnormality in the PLA2G6 [calcium-independent phospholipase $A_2\beta$ (iPLA$_2\beta$)] gene is associated with 80% of INAD cases (Morgan et al., 2006) and is sometimes found in patients with dystonia–parkinsonism (Paisan-Ruiz et al., 2009). The enzyme activity is impaired by the mutation associated with INAD but not in dystonia–parkinsonism (Engel et al., 2010). Recently, iPLA$_2\beta$ knock-out (KO) mice (Malik et al., 2008; Shinzawa et al., 2008) and iPLA$_2\beta$ gene-mutated mice (Wada et al., 2009) have been reported to show progressive motor deficits, and their neuropathological changes are very similar to those of INAD, although the pathomechanism remains unknown.

iPLA$_2\beta$ is a phospholipase A_2 family member that hydrolyzes the *sn-2* ester bond in phospholipids, including glycerophospholipids such as phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, and cardiolipin, to yield free fatty acids and lysophospholipids (Burke and Dennis, 2009). The functions of iPLA$_2\beta$ include remodeling of membrane phospholipids (Balsinde et al., 1997), fatty acid oxidation (Strokin et al., 2003), release of docosahexaenoic acid (DHA) and arachidonic acid (AA)

Received Jan. 21, 2011; revised May 10, 2011; accepted June 4, 2011.

Author contributions: G.B., S.S., and H.S.-A. designed research; G.B., Y.S., K.S., and H.S.-A. performed research; K.S., M.S., and Y.T. contributed unpublished reagents/analytic tools; G.B., Y.S., S.K., and H.S.-A. analyzed data; G.B., Y.S., and H.S.-A. wrote the paper.

This study was supported in part by a Grant-in-Aid for Scientific Research (C) from the Japan Society for the Promotion of Science (JSPS) (H.S.-A.), a Grant-in-Aid for Young Scientists (B) (K.S.) from JSPS, Grant S0801035 from the Ministry of Education, Science, Sports and Culture of Japan (S.K.), a Grant-in-Aid for Young Scientists (S) from JSPS (M.S.), a Grant-in-Aid for Creative Scientific Research (Y.T.), and a Health and Labor Sciences Research on Measures for Incurable Disease, Ministry on Health, Labor. and Welfare of Japan (S.S. and S.K.). We thank all members of our laboratory (particularly Chieko Tada and Rie Yoshida) for their technical assistance, discussion, and comments.

The authors declare no competing financial interests.

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DOI:10.1523/JNEUROSCI.0345-11.2011

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