Combining Physical and Cognitive Functions to Discriminate Level of Gait Independence in Hospitalized Patients with Alzheimer's Disease

（入院中アルツハイマー病患者における身体機能と認知機能の組み合わせによる歩行自立度の判別）

主指導教員：岡村　仁 教授
（医系科学研究科　精神機能制御科学）
副指導教員：花岡　秀明 教授
（医系科学研究科　老年・地域作業機能制御科学）
副指導教員：岡田　剛 准教授
（医系科学研究科　精神神経医科学）

中川　敬汰

（医系科学研究科　総合健康科学専攻）

Introduction

Alzheimer's disease (AD) causes gait disturbances, which become more complex with disease progression, as well as with aging and comorbidities. Thus, accurate gait assessment is difficult to accomplish in patients with AD; however, promoting walking activities reduces the decline in their activities of daily living and functional status, leads to improved quality of life, and lowers mortality risk. Therefore, it is important to diagnose the optimal level of gait independence in a real-world setting in patients with AD while maintaining a perspective that supports their walking activities as much as possible.

Patients with AD experience a disease-specific decline in physical and cognitive functions, which are important for gait. With respect to physical function, a reduction in muscle strength and balance ability has been reported. These are important functions related to walking itself in patients with AD and are considered to be the foundation elements of gait. On the other hand, cognitive function is regarded as an applied component of gait, as it is associated with the ability of patients with AD to safely walk in a real-world setting and to adapt to their surroundings. In particular, the association between attention, executive function, and gait has been widely demonstrated. Thus, physical and cognitive functions are associated with different elements of gait. To illustrate this concretely, take the example of a patient's daily task of going to the toilet. In this case, physical function requires muscle strength and balance ability to go steadily along the path and distance to the toilet while avoiding obstacles, whereas, cognitive function requires recognizing and paying attention to external factors such as obstacles and sudden calls while retaining in memory the purpose of going to the toilet. Therefore, it is suggested that it is important to consider both physical and cognitive functions when determining the optimal level of gait independence in patients with AD in a real-world setting.

Nonetheless, current reports on discrimination accuracy pertaining to gait independence in patients with AD are limited to knee extensor strength (KES). Furthermore, previous studies had certain limitations such as the range of a patients' gait ability within groups in both the independent and dependent gait groups; additionally, some studies did not measure gait in a real-world setting, which does not correspond to the situation when assessing gait in a real environment. Given the increasing number of patients with AD and their rehabilitation needs, there is an urgent need for research to support optimal decision-making in clinical practice.

Therefore, the present study aimed to investigate the accuracy of an assessment method that combined muscle strength, balance ability, and cognitive function parameters in discriminating the level of gait independence in a real-world setting in hospitalized patients with AD.

Materials and Methods

This cross-sectional study included patients with AD who were admitted to a single hospital between October 2021 and September 2022. The inclusion criteria were as follows: (1) a diagnosis of AD made

by psychiatrists according to the International Classification of Diseases, Tenth Edition; (2) age ≥65 years; (3) Mini-Mental State Examination (MMSE) score ≥10; (4) Functional Independence Measure (FIM) mobility items with a gait score of ≥5; (5) hospital stay ≥7 days; and (6) consent obtained from the patient and/or surrogate. Eligible patients were excluded if they had: (1) an inability to understand test instructions; (2) an inability to perform the test; (3) a contraindication to ambulation; (4) coexisting severe paralysis, aphasia, or visual impairment; or (5) non-independent ambulation due to cardiac disease, respiratory disease, lower limb amputation, or pain. This study was conducted in accordance with the principles embodied in the Declaration of Helsinki and was approved by the Epidemiology Research Ethics Review Committee of Hiroshima University (approval number: E-2610). The participants and/or surrogates were fully informed in writing and orally, and informed consent was obtained from them in writing.

The following demographic and clinical characteristics were examined: age, sex, weight, height, body mass index, Charlson Comorbidity Index, and MMSE score. The gait assessment aimed to determine the level of gait independence in a real-world setting and used the FIM gait items, which are widely used for this purpose. In order to be consistent with the actual method for determining the level of gait independence, the participants were classified into three groups—namely, the independent group (FIM, 7), which comprised patients who could independently walk in the ward without walking aids; the modified independent group (FIM, 6), which consisted of patients who could independently walk in the ward using walking aids; and the dependent group (FIM, 5), which comprised patients who did not need gait assistance in the ward but required supervision. Muscle strength was measured by a clinically useful handheld dynamometer in isometric KES assessment. The reliability of this handheld dynamometer had been confirmed in patients with AD. Knee extension torque (Nm) was determined by the muscle force value (N) and lower leg length (m), normalized by body weight. Subsequently, the body weight ratio of knee extension torque values (Nm/kg) was calculated. Balance ability was measured using the Frailty and Injuries: Cooperative Studies of Intervention Techniques – subtest 4 (FICSIT-4), which had been shown to be reliable in patients with dementia. The measurement methods were closed-leg standing, semi-tandem standing, tandem standing, and one-leg standing holding times, with a maximum total score of 5 points. The Trail Making Test part A (TMT-A) was used to measure cognitive function. Regarding cognitive function, the executive and attentional functions had been reported to be particularly related to gait in patients with AD. TMT-A is commonly used to assess the attention function and processing speed in patients with dementia. The upper limit of the implementation time was set at 300 seconds.

The sample size required for each group was calculated according to previous studies, with $\alpha = 0.05$, power = 0.80, two-tailed test, and area under the receiver operating characteristic curve (AUC) set at 0.75. As a result, the required number of participants for each group was calculated to be 19, with a total of 57 participants. Considering the possibility of dropout, 10% of the calculated number of

participants was added to the target number. Based on these considerations, the target number of participants for this study was set at 21 for each group, with a total of 63 participants. Sample size calculation was performed using R version 4.1.3.

First, descriptive statistics for each variable were computed for each group. Next, a one-way analysis of variance (ANOVA) or Kruskal–Wallis test, depending on normality and scale, was used to compare each survey item among the three groups. For items that showed significant differences, multiple comparisons were made using the Holm or Steel–Dwass method post hoc tests. Receiver operating characteristic analysis was subsequently conducted to calculate the thresholds and discrimination accuracy for the KES, FICSIT-4, and TMT-A based on the level of gait independence. Cutoff values were determined with reference to the Youden index (sensitivity + specificity − 1). Additionally, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio, negative likelihood ratio, and AUC were also calculated. Next, as the main analysis of this study, the sensitivity, specificity, PPV, NPV, positive likelihood ratio, negative likelihood ratio, and AUC were calculated for each combination of items exceeding the cutoff values. All statistical analyses were performed using R version 4.1.3, with a significance level of 5%.

Results

A total of 63 patients with AD (21 patients per group) were included as participants, thus achieving the number estimated in the sample size pre-calculation. The results of one-way ANOVA indicated significant differences only in each of the measures used to discriminate gait and in FIM ($p < 0.05$).

The KES had the highest AUC (0.793) between the independent and modified independent groups, whereas the TMT-A had the largest AUC (0.820) between the modified independent and dependent groups. The KES showed the best PPV (77.2%) between the independent and modified independent groups, whereas the FICSIT-4 had the best NPV (84.6%). Between the modified independent and dependent groups, the TMT-A had the best PPV (73.9%), whereas the FICSIT-4 had the best NPV (92.3%). The largest AUC was obtained from the combination of KES, FICSIT-4, and TMT-A, both between the independent and modified independent groups (0.853) and between the modified independent and dependent groups (0.866). Furthermore, the combination of KES, FICSIT-4, and TMT-A had the highest PPV (100%), both between the independent and modified independent groups and between the modified independent and dependent groups.

Discussion/Conclusion

Our findings indicated that the level of gait independence in a real-world setting could be discriminated with excellent accuracy when assessments for muscle strength, balance ability, and cognitive function were combined in hospitalized patients with mild-to-moderate AD. To the best of our knowledge, this is the first study to focus on an assessment method for discriminating the level of gait independence

in patients with AD using both physical and cognitive functions.

The combination of KES, FICSIT-4, and TMT-A showed the highest accuracy both between the independent and modified independent groups and between the modified independent and dependent groups. The combination of physical and cognitive functions has superior PPV, suggesting that it is particularly suitable for definitive discrimination. On the other hand, balance ability showed a high NPV at a single cutoff value, suggesting that it is suitable for screening rather than the combined assessment. This indicates that the evaluation methods used in this study can be used for different clinical decision-making purposes. Our results suggest that this method can be used to determine the appropriate gait status of patients with AD and guide decision-making that supports patients in their walking activities.

The TMT-A had the largest AUC between the modified independent and dependent groups. Independent walking activities require the ability to pay attention to the surrounding environment and to adapt to various environments while performing other tasks. The relationship of attentional and executive functions with gait in an experimental setting has been reported in previous studies. It is noteworthy that we were able to discriminate the actual level of gait independence in a real environment. Furthermore, its use was found to be suitable for discriminating between modified independent and dependent groups. In contrast, the KES had the largest AUC between the independent and modified independent groups. The KES is reportedly a useful discriminator of the level of gait independence in patients with AD. The present study showed that the KES was particularly suitable for determining the need for the use of walking aids. Based on these findings, this study suggests the functions that patients with AD need to walk independently with a walking aid, as well as the functions that those who can walk independently should focus on to maintain their freedom of movement without the need for a walking aid.

The results of this study emphasize the importance of measuring several functional aspects of the actual gait of patients with AD. A specific example of a model that helps convey the conceptual meaning of this study is motoric cognitive risk (MCR) syndrome. MCR syndrome is determined by slow walking speed and subjective cognitive decline, each of which affects a different aspect. The conceptual framework of such simple multifactorial models is versatile and clinically useful and has been used for prognostic analysis for participants in a variety of fields. MCR syndrome can be used as a reference for further interpretation of the conceptual framework of this study as it proposes the importance of using a framework consisting of factors with different roles, such as physical and cognitive functions, to understand the actual gait of patients with AD. By taking this view, the results of this study not only provide ways to facilitate clinical decision-making for patients with AD and those involved but also suggest important insights for further research on real-world gait in patients with AD.

This study has several strengths. First, the measures used in this study to discriminate gait are simple

to perform and easy to understand. Such measurement items are considered to have high clinical utility for patients with AD. Second, the participants were classified and selected according to the method used to determine the level of gait independence in practice. Therefore, the results of this study are suitable for use in decision-making in a real-world setting.

This study had several limitations. First, the study was conducted at a single center, with a small sample size, and little patient demographic variation. This limits the generalizability of the results. However, this study applied strict inclusion and exclusion criteria, and the participants were selected to focus on those who required assessment of the level of gait independence in a clinical setting. Additionally, measures were taken to maintain the validity of the results by pre-calculating the sample size and ensuring that the number of participants in each group was uniform. Second, this study was conducted on hospitalized patients with mild-to-moderate AD. Therefore, whether the results of this study can be adapted to individuals with severe AD or in other contexts requires validation. Third, the study was designed to calculate discriminant accuracy for a combination of composite factors. Therefore, results from single-item comparisons should be interpreted as informative. Currently, the number of patients with AD and their rehabilitation needs are increasing, and it is easy to imagine that the need to support patients with AD in their ambulation will increase in the future. This fact and the predicted results indicate the importance of such studies to support decision-making for patients with AD and those who work with them in clinical practice.

Future research should consider larger sample sizes, conducting surveys at multiple facilities, and internal and external validation to obtain more reliable results. Moreover, longitudinal studies need to be designed to clarify the validity of the relationships demonstrated in this study. Furthermore, if there are assessment measures that are suitable for implementation in each clinical setting, consideration of the choice of assessment measures for physical and cognitive functions would increase their versatility for a variety of situations. The implementation of these validations may further promote walking support for patients with AD. The study has reported important results necessary to realize this.

In conclusion, we found that the combined physical and cognitive function assessment method discriminated the level of gait independence in a real-world setting with excellent accuracy in patients with AD. Therefore, this study emphasizes the importance of assessing the level of gait independence in a real-world setting in patients with AD from the perspective of both physical and cognitive functions and proposes a novel method for discriminating an optimal state.