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ORIGINAL ARTICLE

Yamaguchi fox–pigeon imitation test (YFPIT) for dementia in clinical practice

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Abstract

Background: In out-patient clinics, having simple procedures to check for signs of dementia is invaluable. In the present study, we evaluated the imitation of hand gestures to detect visuomotor deficits in dementia in clinical practice.

Methods: In all, 1219 subjects were enrolled in the present study, including 497 with Alzheimer's disease (AD), 98 with dementia with Lewy bodies (DLB), 71 with other types of dementia diseases, 175 with a Clinical Dementia Rating (CDR) of 0.5, and 378 normal controls. All subjects were aged 65 years or older. Subjects were recruited from 10 clinics and two communities. Visuomotor function was evaluated by the Yamaguchi fox–pigeon imitation test (YFPIT), which consists of a simple one-handed sign for 'fox' and a complex two-handed sign for 'pigeon', a rapid, game-like test with low psychological burden.

Results: The success rate (successful/total) for imitating the 'pigeon' hand gesture was reduced as the severity of the dementia increased: 85.7% in normal controls, 60.6% in CDR 0.5 (mild cognitive impairment), 39.2% in CDR 1 (mild dementia), 21.2% in CDR 2 (moderate dementia), and 5.7% in CDR 3 (severe dementia). The success rate for imitating the 'pigeon' hand gesture was higher in patients with DLB than AD within the CDR 1 group (51.2% *vs* 35.4%, respectively), but lower for patients with DLB than AD within the CDR 2 group (12.5% *vs* 24.4%, respectively). The success of imitating the hand gesture for 'fox' was similar for patients with AD and DLB. Of those subjects who failed to imitate the hand gesture for 'pigeon', 49.5% of those with AD showed the palm–palm pattern (both palms facing outward), suggesting deficits of perspective conversion from the first-person to the third-person. Conversely, 52.8% of patients with DLB showed a dorsum–dorsum pattern (both dorsa facing outwards), suggesting deterioration of visual attention and recognition.

Conclusion: In conclusion, the YFPIT is a useful test to detect visuomotor deficits in dementia that can differentiate between AD and DLB.

Key words: *Alzheimer's disease, dementia, dementia with Lewy bodies, hand gesture imitation, perspective taking, visuomotor deficit.*

INTRODUCTION

We have proposed a hand gesture imitation test, the Yamaguchi fox–pigeon imitation test (YFPIT), which consists of a simple one-handed sign for 'fox' and a complex two-handed sign for 'pigeon', as a rapid, game-like test for dementia/Alzheimer's disease (AD) that has a low psychological burden.[1] The aim of the YFPIT is to examine the representation of the body state and visuomotor function, which deteriorate from the early stages of AD. Before the onset of clinical symptoms, the bilateral parietal lobes are affected with AD-related pathology, showing hypoperfusion as

a characteristic finding on single photon emission computed tomography (SPECT).[2] Therefore, clarification of deficits in gesture imitation, which requires parietal function, is useful for understanding disease presentation. Gestures can be categorized into meaningless non-symbolic and semantic/symbolic gestures. It has been reported that the recognition and execution of meaningless gestures, such as body posture, are affected by parietal lobe deficits, whereas semantic recognition and execution are related to temporal function.[3] Thus, to eliminate semantic components, we adopted meaningless non-symbolic gestures in the YFPIT; it is important that the examiner should conduct the YFPIT without saying anything that would stimulate semantic ideas regarding the gestures. The YFPIT is very easy, requiring only 1 min to perform, and is an enjoyable game-like test with a low psychological burden on patients.[1] Moreover, the outcomes of the YFPIT provide information as to the difficulties patients may face in everyday life, because the visuomotor function concerning representation of the body state is important in daily living.

Because our previous report involved only one clinical site,[1] we conducted the YFPIT in a larger-scale study involving 1219 patients at 10 clinical sites to confirm its validity and found that it could differentiate between AD and dementia with Lewy bodies (DLB).

METHODS

As part of the present study, the YFPIT was applied to 1219 subjects. In all, 1041 subjects were recruited from nine clinics in the Kanto area (Gunma, Tokyo, and Kanagawa Prefectures) and from one clinic in the Tohoku area (Iwate Prefecture). In addition, 178 normal controls (NC) were recruited from community dwellers in two cities in Gunma Prefecture. The Ethics Board of each of the participating sites approved all study procedures (e.g. Gunma University, no. 21–26), and written informed consent was obtained from the participants or their proxies. Subjects were diagnosed by specialists of dementia medicine based on current criteria for dementia diseases, such as the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) diagnostic criteria for AD[4] and the third report of the DLB Consortium.[5] Normal controls were confirmed to be free of dementia by interviews conducted by doctors specializing in dementia. The inclusion criterion was age ≥65 years. Exclusion criteria included the presence of psychiatric diseases, delirium, verbal incomprehension including aphasia, an inability to walk, and motor deficits, such as paralysis. We recruited 378 NC, 175 patients with mild cognitive impairments (MCI), and 666 subjects with dementia (497 AD, 98 DLB, 30 with frontotemporal dementia, 22 with vascular dementia, and 19 with other types of dementia) to the present study.

In the present study, subjects were classified according to the Clinical Dementia Rating (CDR). Patients with a CDR of 0.5 were defined as having MCI, although different classifications have been proposed whereby CDR 0.5 encompasses both mild and earlier dementia[6] or it corresponds to very mild dementia.[7]

The mean (± SD) age of subjects in the present study was 77.7 ± 7.4 years, and there were no significant differences in age or gender among the patient groups. The level of education (11.1 ± 3.6 years in education) did not differ significantly between patient groups.

The YFPIT requires subjects to imitate the hand gesture for 'fox' (Fig. 1a) contiguous with the hand gesture for 'pigeon' (Fig. 1b). The precise protocol for the YFPIT is as follows:[1]

1. The examiner sits face-to-face with the subject.
2. The examiner gives the simple instruction. 'Watch my hand gesture carefully and imitate it'. The instruction can be repeated if necessary.
3. Then, the examiner makes the sign for 'fox' using his/her left hand: fingers III and IV touching the thumb on flexion of the metacarpophalangeal joints with fingers II and V held up (Fig. 1a).
4. The examiner maintains the gesture for 10 s. The subject imitates the gesture concurrently with the examiner. The examiner says nothing during the 10 s of the test. The examiner must be careful not to say the word 'fox' or to give any further instructions.
5. The examiner judges whether the subject has produced the same sign within 10 s of demonstration; the subject may use either hand.
6. The examiner then gives the same instruction, 'Watch my hand gesture carefully and imitate it', but this time makes the sign for 'pigeon' using both hands: crossing the hands, palms facing the body, with fingers II–IV extended upward and the two thumbs crossing each other (Fig. 1b).
7. The examiner maintains the gesture without saying anything, especially the word 'pigeon' and/or

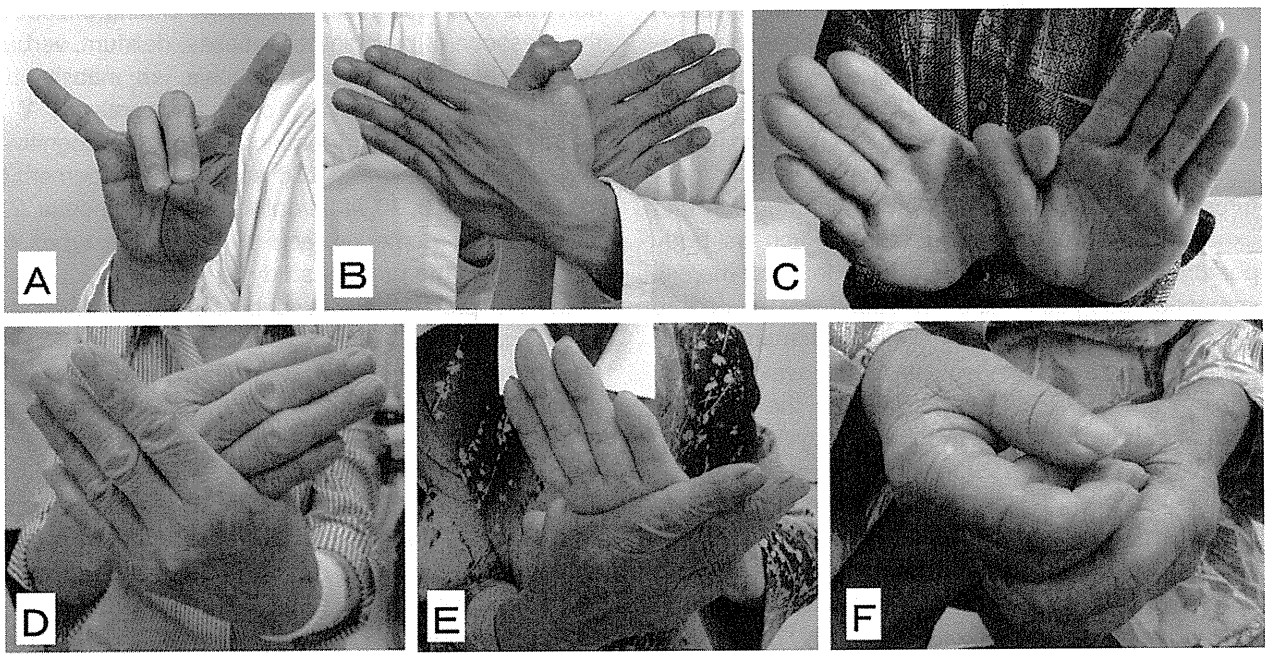

Figure 1 Demonstration by the examiner of the (a) 'fox' and (b) 'pigeon hand gestures. (c–f) Typical error patterns: palm–palm (c), dorsum–dorsum (d), palm–dorsum (e) and 'others' (f).

repeating the instructions, during the 10 s of the test.

8. The examiner then judges whether the subject has made the same sign within 10 s of demonstration

The following aspects of the 'pigeon' hand gesture need to be evaluated: (i) the direction of the arm and fingers II–V should be upward: hand positions in horizontal or downward directions are judged as failures; (ii) gestures made with the right hand in the inward position and the left hand in the outward position or vice versa are both correct; (iii) both palms should be facing the body; and (iv) the thumbs should be crossing each other.

For qualitative analysis, we categorized four error patterns of the 'pigeon' hand gesture based on the direction of the hands: (i) a palm–palm pattern, with both palms facing outward (Fig. 1c); (ii) a dorsum–dorsum pattern, in which both dorsa face outward (Fig. 1d); (iii) a palm–dorsum pattern, in which one palm and one dorsum face outward (Fig. 1e); and (iv) other patterns (Fig. 1f). Error pattern analysis of the 'pigeon' hand gesture was conducted on patients classified as CDR 1 and CDR 2, because most of patients classified as CDR 3 completely failed to imitate the gestures (e.g. Fig. 1f). The rate of each error pattern (no. each error/total errors) was compared between AD and DLB patients.

RESULTS

The success rate (no. subjects who successfully imitated the hand gestures/total no. subjects) of the YFPIT for all participants is given in Table 1 and Fig. 2. Imitating the 'pigeon' hand gesture was much more difficult than imitating the hand gesture for 'fox', and the success rate for imitating the 'pigeon' hand gesture decreased according with increasing CDR stage from 85.7% in NC, 60.6% in CDR 0.5, 39.2% in CDR 1, and 21.2% in CDR 2 to 5.7% in CDR 3. Participants from one site in the Tohoku area classified as CDR 1 and CDR 2 exhibited greater success in imitating the hand gestures; thus, the success rate for participants from the Tohoku area is shown separately from that in other sites in the Kanto area in Fig. S1, available as an accessory publication to this paper.

Comparing results for AD and DLB patients, the success rate for imitating the sign for 'pigeon' was higher for patients with DLB than AD rated as CDR 1 (51.2% *vs* 35.4%, respectively), but lower for patients

Table 1 Success rate of hand gesture imitation

	CDR	*n*	'Fox' (all)	'Pigeon'			
				All	AD	DLB	Other type of dementia
NC	0	378	99.2 (375)	85.7 (324)			
MCI	0.5	175	93.7 (164)	60.6 (106)			
Mild dementia	1	334	86.2 (288)	39.2 (131)	35.4 (90/254)	51.2 (22/43)	51.4 (19/37)
Moderate dementia	2	227	76.7 (174)	21.2 (48)	24.4 (40/167)	12.5 (5/40)	13.0 (3/23)
Severe dementia	3	105	55.2 (58)	5.7 (6)	7.6 (6/79)	0.0 (0/15)	0.0 (011)

Data show the percentage in each group, with the actual number of subjects given in parentheses.
NC, normal controls; MCI, mild cognitive impairment; CDR, Clinical Dementia Rating; AD, Alzheimer's disease; DLB, Dementia with Lewy bodies.

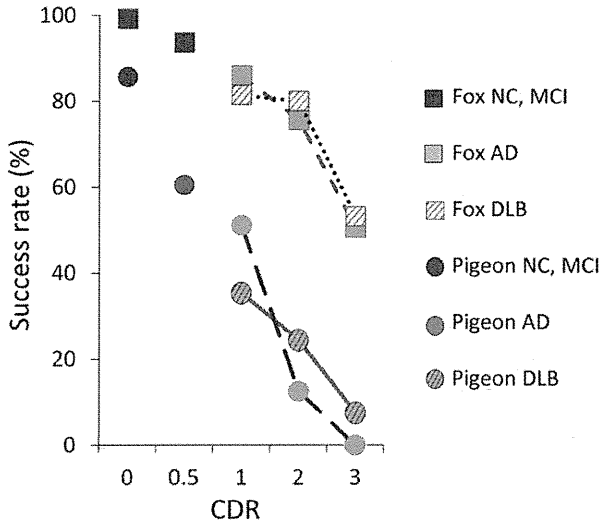

Figure 2 Success rate for the imitation of the 'fox' and 'pigeon' hand gestures in different patient groups and with different Clinical Dementia Rating (CDR) scores. NC, normal control; AD, Alzheimer's disease; DLB, dementia with Lewy bodies; MCI, mild cognitive impairment.

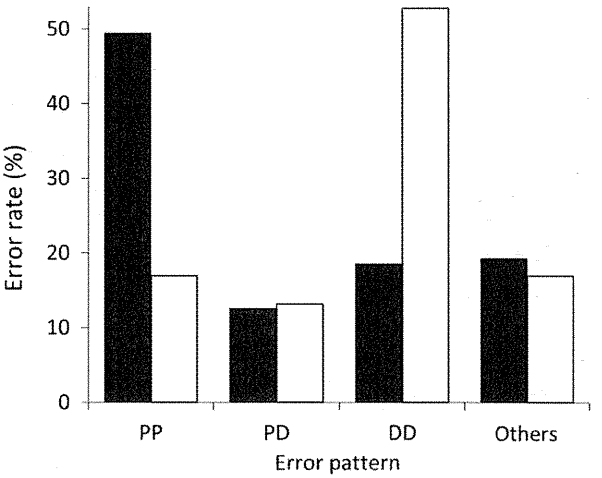

Figure 3 Comparison of the rate of different error patterns for the imitation of the 'pigeon' hand gesture among 285 errors made by patients with Alzheimer's disease (■) and 53 errors made by patients with dementia with Lewy bodies (□). PP, palm–palm pattern; PD, palm–dorsum pattern; DD, dorsum–dorsum pattern. The figure shows the ratio of each error pattern (errors/total errors) for patients with AD or DLB rated as Clinical Dementia Rating (CDR) 1 and 2.

with DLB than AD rated as CDR 2 (12.5% *vs* 24.4%, respectively). However, the success rate for imitating the sign for 'fox' was almost the same between the AD and DLB patient groups.

In patients who failed to imitate the sign for 'pigeon', the rate of each type of error pattern was compared between 285 AD and 53 DLB patients (from a total of 418 AD and 83 DLB patients in the CDR 1 and CDR 2 groups; Fig. 3). Approximately half the errors (141/285; 49.5%) made by AD patients were of the palm–palm pattern (both palms outward), suggesting deficits of perspective conversion from the first-person to the third-person. In contrast, only 17.0% of errors (9/53) made by DLB were of this pattern. Approximately half the errors (28/53; 52.8%) made by DLB patients were of the dorsum–dorsum pattern (both dorsa outward), compared with only 18.6% (53/285) of this type of error in the AD group. The palm–dorsum pattern accounted for 12.6% (36/285) of errors made by the AD patients and for 13.2% (7/53) of errors made by DLB patients.

DISCUSSION

The rate of successfully imitating the 'pigeon' hand gesture decreased with increasing CDR stage. This shows that the YFPIT is useful for the detection of deficits in hand gesture imitation in patients with dementia, confirming previous findings.[1] Furthermore, we were able to identify differences between AD and DLB on the basis of YFPIT results.

Gesture imitation starts with a recognition of another's actions and then requires perspective conversion to match one's own actions with those of the other. We perceive a visual scene from our own perspective (first-person perspective), but successful imitation of the 'pigeon' hand gesture requires viewing the same scene from another person's perspective (the third-person perspective).[8] Patients with AD may have difficulties in converting perspective, which is a function related to the parietal lobes.[9] Previous imaging studies have reported that the third-person perspective recruits the bilateral parietal area more intensely than the first-person perspective;[10] a significant reduction in regional cerebral blood flow has been reported in the bilateral parietal area in the early stages of AD.[2] In the present study, almost half the errors made by AD patients consisted of the palm–palm pattern, whereas this pattern accounted for <20% of the errors made by patients with DLB. As mentioned above, the palm–palm pattern may be related to deficits in conversion of perspective, because the subjects see the dorsum of both the examiner and themselves. Most patients showing a palm–palm pattern did not notice their errors because they may have lost the concept of conversion of perspective.

Patients with DLB may have difficulties in action recognition,[11] which is related to the visual association cortex. Previous imaging studies have shown significant reductions in glucose metabolism in the visual association cortex of patients with DLB compared with patients with AD.[12] More than half the patients with DLB made the dorsum–dorsum error pattern, whereas this type of error accounted for <20% of the errors made by AD patients. With the dorsum–dorsum pattern, the conversion of perspective is retained but visual recognition deteriorates. Disturbed attention may be at the core of the defects in visual recognition in DLB patients, to divide and shift attention among relevant factors, ignoring irrelevant distractors.[13] In the present study, the DLB patients had a tendency to focus their visual attention on certain specific parts of the gesture, failing to perceive the overall gesture (e.g. crossing the hand or only clinging to the thumb). Then, they tried to shift their attention to another part of the gesture in vain. As such, disturbed attention in DLB patients led to difficulties using visual information to coordinate hand movements.

Simple one-handed gesture imitation was preserved until the late stages of dementia. Successful imitation of the 'fox' hand gesture means that most demented patients understand verbal commands and that failure imitating the 'pigeon' hand gesture is not due to disturbed verbal comprehension. Imitation of the gesture requiring bimanual coordination deteriorated from the mild stages of dementia, especially in AD. In DLB, the visuomotor function was relatively preserved until the mild stage of CDR 1, but function was clearly deteriorated at the moderate stage of CDR 2.

Regarding the success rate of imitating the 'pigeon' gesture, regional differences were observed, which went against our hypothesis. Subjects from one site in the Tohoku area were more successful in imitating the 'pigeon' hand gesture than subjects from other sites, as well as compared with subjects evaluated in a previous study.[1] The Tohoku area is located in the northern part of Japan, where population mobility is low especially in agrarian communities. According to their doctors' observations, the patients who succeeded in imitating the 'pigeon' hand gesture were more likely to have engaged in 'shadow play' as children using hand gestures for 'fox' and 'pigeon'. Thus, these subjects may be using procedural memories, which are preserved long after the deterioration of episodic memories. Thus, we should carefully analyze patients with these sorts of childhood experiences of hand play.

On the first visit to an outpatient clinic, a brief assessment is required for the approximate examination of patients. Easy and simple visuomotor assessment using the YFPIT may assist in detecting visuomotor deficits in dementia, as well as distinguishing between AD and DLB.[14] In this respect, the YFPIT is useful as a pretest before further detailed investigation of a patient's cognitive function.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1 Comparison of success rates for imitation of the 'pigeon' hand gesture between are Kanto areas (nine sites) and the Tohoku area (one site). The success rate for imitating the 'pigeon' hand gesture in the Kanto and Tohoku areas was 59.2% *vs* 64.0%, respectively, for patients classified as Clinical Dementia Rating (CDR) 0.5; 34.4% *vs* 53.6%, respectively, for patients classified as CDR 1; 16.8% *vs* 35.2%, respectively, for patients classified as CDR; and 7.1% *vs* 0%, respectively, for patients classified as CDR 3.

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ORIGINAL ARTICLE

A figurative proverb test for dementia: rapid detection of disinhibition, excuse and confabulation, causing discommunication

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Abstract

Background: Communicative disability is regarded as a prominent symptom of demented patients, and many studies have been devoted to analyze deficits of lexical-semantic operations in demented patients. However, it is often observed that even patients with preserved lexical-semantic skills might fail in interactive social communication. Whereas social interaction requires pragmatic language skills, pragmatic language competencies in demented subjects have not been well understood. We propose here a brief stress-free test to detect pragmatic language deficits, focusing on non-literal understanding of figurative expression. We hypothesized that suppression of the literal interpretation was required for figurative language interpretation.

Methods: We examined 69 demented subjects, 13 subjects with mild cognitive impairment and 61 healthy controls aged 65 years or more. The subjects were asked the meaning of a familiar proverb categorized as a figurative expression. The answers were analyzed based on five factors, and scored from 0 to 5. To consider the influence of cognitive inhibition on proverb comprehension, the scores of the Stroop Colour–Word Test were compared concerning correct and incorrect answers for each factor, respectively. Furthermore, the characteristics of answers were considered in the light of excuse and confabulation qualitatively.

Results: The proverb comprehension scores gradually decreased significantly as dementia progressed. The literal interpretation of the proverb, which showed difficulties in figurative language comprehension, was related to disinhibition. The qualitative analysis showed that excuse and confabulation increased as the dementia stage progressed.

Conclusions: Deficits in cognitive inhibition partly explains the difficulties in interactive social communication in dementia. With qualitative analysis, asking the meaning of a proverb can be a brief test applied in a clinical setting to evaluate the stage of dementia, and to illustrate disinhibition, confabulation and excuse, which might cause discommunication and psychosocial maladjustment in demented patients.

Key words: *Alzheimer's disease, behavioural and psychological symptoms of dementia, confabulation, excuse, pragmatic language deficits, proverb comprehension.*

INTRODUCTION

As patients with dementia gradually lose their identity, the care burden placed on their family members increases with the patients' dependence and unpredictability. One of the major problems in the care of patients with dementia is discommunication; even patients with preserved verbal intelligence might fail to engage in interactive social communication. In human speech, we often make use of non-literal expressions. For example, in Japan, 'apple-cheeked' is an expression for cute children, and 'a fat-bellied man' means a generous-minded man. In these cases,

direct literal interpretation leads to misunderstanding. However, it was reported that patients with dementia have difficulties with non-literal language comprehension,[1,2] and that this might contribute to their deficits in social communication.

To our knowledge, there is no quick test available in a clinical setting to check for deficits of figurative interpretation in patients with dementia. In the present study, we assessed the interpretation of a figurative proverb as a clinical test; proverb comprehension is often used to assess the tendency of patients with schizophrenia to provide literal explanations for figurative expressions.[3–5] The aim of the present study was to show the characteristics of proverb comprehension in dementia, and test the hypothesis that suppression of the literal interpretation was required for figurative language interpretation.[2,6–8] Adding to this kind of disinhibition, we checked excuses and confabulation from the context. Clinical observation suggested that patients with dementia tended to make excuses to protect themselves, and they were prone to confabulation to compensate for their memory distortion.[9]

To obtain effective information in a busy outpatient setting, brevity and simplicity are critical components. Asking the meaning of a single proverb is simple yet informative; it takes less than 1 min and no tools are needed, but it shows the typical symptoms of disinhibition, excuse and confabulation. Furthermore, asking the meaning of a well-known proverb does not cause the patients' distress, which is often associated with ordinary cognitive tests. It is also beneficial for family members (caregivers) to obtain information on patients' deficits in figurative comprehension, which can result in communication gaps with patients.

METHODS

Among the participants, the outpatients were classified according to the Clinical Dementia Rating scale (CDR): 13 with mild cognitive impairment (MCI; CDR 0.5), 30 with mild dementia (CDR 1), 28 with moderate dementia (CDR 2) and 11 with severe dementia (CDR 3). The ages of the patients were as follows: 81.4 ± 8.8 years (mean ± SD) in CDR 0.5, 81.8 ± 7.5 years in CDR 1, 82.3 ± 6.2 years in CDR 2 and 83.6 ± 4.3 years in CDR 3. The male-to-female ratio was 3:10 in CDR 0.5, 9:21 in CDR 1, 5:23 in CDR 2 and 3:8 in CDR 3. Among patient groups, there was no significant difference in age ($P = 0.87$; one-way ANOVA) or sex ($P = 0.65$; χ^2-test). A total of 61 normal controls (NC; 28 in their late 60s, 23 in their early 70s and 10 in their late 70s) were healthy community dwellers. The exclusion criteria were: age less than 65 years, psychiatric diseases, delirium and verbal incomprehension including aphasia.

The Ethics Board of Gunma University School of Health Sciences approved all procedures (No. 21–26), and informed consent was obtained from all participants. Subjects were diagnosed based on the criteria for dementia diseases: Alzheimer's disease (AD) by NINCDS-ADRDA,[10] dementia with Lewy bodies (DLB) by the third report of the DLB Consortium[11] and MCI by the report of the International Working Group on Mild Cognitive Impairment.[12] CDR 0.5 was regarded as mild cognitive impairment (MCI), although a different classification was proposed whereby CDR 0.5 encompasses both mild and earlier dementia[13] or it corresponds to very mild dementia.[14] Normal controls (NC) were judged based on an interview and a questionnaire on the symptoms of dementia. The diagnoses were: 53 AD including AD with cerebral vascular changes, 13 DLB and three vascular dementia.

We assessed the participants' non-literal language comprehension using a figurative proverb. The examiner asked only the meaning of a Japanese proverb, '*Saru mo ki kara ochiru*'. The proverb is one of the most familiar ones, which is taught in the early elementary school years in Japan. Literally, the sentence means that even a monkey falls from trees, and the corresponding proverb in English is, 'Even Homer sometimes nods', or 'Even a good swimmer can drown'. The figurative meaning is that even a skilled person sometimes makes a mistake in what he/she is good at. Proverbs often contain lessons regarding the context-appropriate proverb meaning;[15] in this case, the lesson is that one has to stay alert. The answers were scored from 0 to 5: one score for each component of 'skilled', 'person', 'sometimes' and 'making a mistake', and one score for extraction of the lesson of 'to stay alert.' The components of 'person' and 'making a mistake' are hypothesized as the ability to suppress the literal interpretation of 'monkey' and 'falling from trees'; thus, participants were not given a score unless they answered explicitly. Concerning the other two components of 'skilled' and 'sometimes', scores were given regardless of explicit or implicit explanations.

The answers were also considered qualitatively. We reviewed the responses and counted the number of answers including each feature: not knowing, answer out of context, literal interpretation, making excuses, and confabulation. A 'literal answer' was defined as that including the explicit expression of 'a monkey falls from a tree' instead of 'a person makes mistakes'. Multiple selections were allowed in the qualitative analysis.

To avoid scoring bias, the evaluation was carried out by two authors and a co-medical staff member who was not involved in the study. Analysis was carried out by another author who took no part in scoring.

To verify the hypothesis that suppression of the literal interpretation was required for figurative language interpretation, we used the Stroop Colour–Word Test (Stroop) with patients in stages from CDR 0.5 to CDR 2; patients in CDR 3 were excluded because the requirement of Stroop is above the level of CDR 3. The test comprises words describing a colour, but written in a different colour; for example, the word 'red' is written in green, and the test requires the subject to state the colour (green) not the word (red). The number of correct answers was regarded as the Stroop score; to answer correctly, it is necessary to inhibit the literal interpretation, which can be more automatic.[16] Individuals with AD show a stronger tendency to respond with the word rather than the colour compared with the normal aged subjects,[17] which can be regarded as one of the manifestations of disinhibition. The patients were also tested using Hasegawa's Dementia Scale-revised (HDS-R), which is similar to and well-correlated with the Mini-Mental State Examination, and common in Japan; to assess the contribution of inhibition and general cognitive function to the five components of the proverb, the scores of Stroop and HDS-R were compared between correct and incorrect answer groups, respectively. Analysis of data was carried out using the Japanese version of SPSS 18.0 (SPSS Japan, Tokyo, Japan).

RESULTS

Demographic data are shown in Table 1. The figurative proverb test scores according to CDR were 4.03 ± 1.09 in CDR 0 (NC), 2.62 ± 1.04 in CDR 0.5 (MCI), 2.53 ± 1.46 in CDR 1, 1.39 ± 1.31 in CDR 2 and 0.73 ± 0.90 in CDR 3 (Fig. 1). There was a significant difference among the groups regarding the gradual decrease ($P < 0.001$; one-way ANOVA). According to post-hoc analysis with Bonferonni correction, the scores of CDR 0.5 and CDR 1 were significantly lower than those of NC ($P = 0.002$, $P < 0.001$, respectively), and those of CDR 2 were significantly lower than those of CDR 1 ($P = 0.005$; Fig. 1). Stroop and HDS-R scores according to CDR are shown in Table 1.

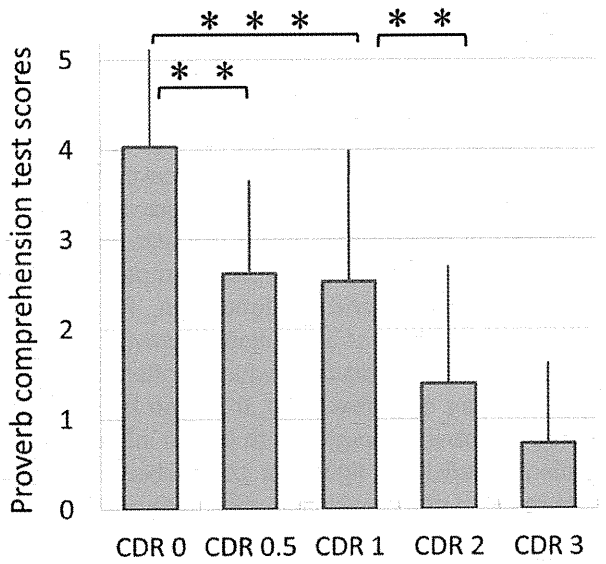

Figure 1 The figurative proverb test scores, showing a gradual decrease according to the clinical dementia rating scale (CDR). Level of statistical significance: $^{**}P < 0.01$; $^{***}P < 0.001$.

Table 1 The Stroop and Hasegawa's Dementia Scale-revised scores according to clinical dementia rating

	n	Age (mean ± SD)	Sex (male/female)	Stroop (mean ± SD)	HDS-R (mean ± SD)
CDR 0.5 (MCI)	13	81.4 ± 8.8	3/10	21.38 ± 2.40	26.77 ± 2.17
CDR 1	30	81.8 ± 7.5	9/21	17.07 ± 6.57	20.10 ± 4.85
CDR 2	28	82.3 ± 6.2	5/23	10.00 ± 8.43	14.89 ± 5.36
CDR 3	11	83.6 ± 4.3	3/8	ND	7.00 ± 7.46

Among patients' group, there was not a significant difference of ages ($P = 0.87$; 1 way ANOVA) or sex ($P = 0.65$; χ^2-test). The normal control group consisted of 28 late 60s, 23 early 70s and 10 late 70s, and all woman. CDR, clinical dementia rating; MCI, mild cognitive impairment; ND, not done.

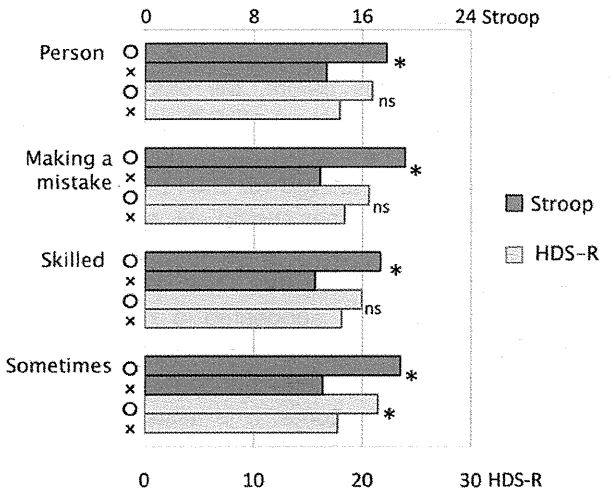

Figure 2 Comparison of the Stroop Colour–Word test and Hasegawa's Dementia Scale-revised (HDS-R) scores between the correct (○) and incorrect (×) answer groups for each component of the proverb: *$P < 0.05$.

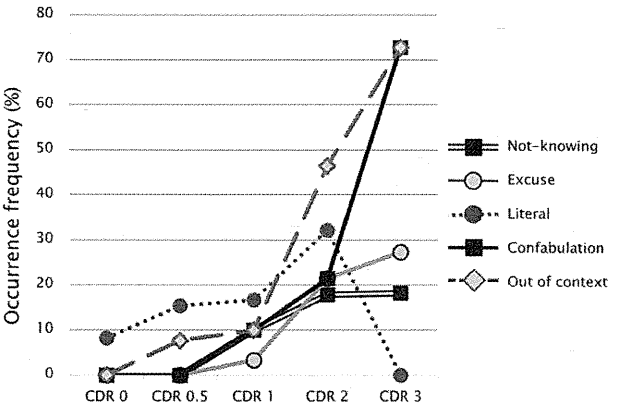

Figure 3 Occurrence frequency of five features according to the clinical dementia rating scale (CDR).

The percentage of correct answers of CDR 0 (NC) was as follows: the component of 'skilled', 95.1%; 'person', 88.5%; 'making a mistake', 86.9%; 'sometimes', 85.3%; and 'to stay alert', 47.5%.

Total scores of the proverb test were significantly correlated with Stroop ($r = 0.45$, $P < 0.001$) and HDS-R ($r = 0.33$, $P = 0.005$) in CDR 0.5 to 2 subjects ($n = 71$). We, however, examined the relationship between each component of the proverb and the Stroop/HDS-R scores by dividing subjects into the correct and incorrect answer groups. The results are shown in Figure 2 and Table S1. Regarding the components of 'person', 'making a mistake' and 'skilled', the scores of Stroop in the correct answer group were significant higher than those in the incorrect answer group ($P = 0.023$, $P = 0.001$, $P = 0.011$, respectively), but not HDS-R scores ($P = 0.056$, $P = 0.146$, $P = 0.230$, respectively). Concerning the component of 'sometimes', the scores of both Stroop and HDS-R were significantly higher in the correct answer group than those in the incorrect answer group ($P = 0.004$, $P = 0.019$, respectively).

The characteristics according to stages are shown in Figure 3 and Table S2 (multiple selections allowed). There were three patterns: (i) responses characterized as 'not knowing' and 'excuse' comprised 0% in NC and then gradually increased, but remained at less than 20 and 30%, respectively, in CDR 3; (ii) The 'literal answers' increased gradually from NC to CDR 2, approximately 30%, but remained at 0% in CDR 3; and (iii) answers 'out of context' and confabulation increased more than 70% in CDR 3. The results of qualitative analyses are described in the Discussion with examples of responses.

There was a significant difference in years of education among the groups of CDR 0.5 to CDR 3 ($P = 0.010$, one-way ANOVA), and post-hoc analysis showed that participants with CDR 0.5 had received a longer education than the CDR 2 group.

The same analysis of patients with AD alone showed similar results (Tables S3, S4).

DISCUSSION

The present study showed the deficits of figurative language comprehension in dementia according to disease progression. As shown in Figure 1, the figurative proverb test scores in the CDR 0.5 (MCI) and CDR 1 (mild dementia) groups were significantly lower than those in CDR 0 (NC). It has been controversial whether the capacity for figurative language comprehension deteriorates from the early stages, or is preserved until advanced stages;[7,18] our data showed that the capacity declines from CDR 0.5 (MCI).

In the present study, we proposed a new way to analyze the answer. We divided the proverb into four components and evaluated appropriateness of the answer for each component (1 point for each). The ability to extract a lesson from the proverb was also evaluated (1 point). Extraction of the lesson is difficult, even for the individual in CDR 0, but more than 80%

of them could explain the meaning of the four components appropriately. Thus, an inappropriate answer of any component, but not extraction of the lesson, can be taken as an indication of decline of non-literal proverb comprehension in MCI and dementia.

Relationship between answers and cognitive test of Stroop and HDS-R

Regarding the components of 'person', 'making a mistake' and 'sometimes', significantly low scores were shown in Stroop, but not shown significantly in HDS-R in incorrect answer groups. The results concerning the components of 'person' and 'making a mistake' suggested that a subject might answer incorrectly when they failed to inhibit the literal interpretation, consistent with previous studies; it was reported that individuals with AD had difficulties in suppressing the literal interpretation, which is concurrently activated, even if they still retained knowledge of the figurative meaning.[2,7] No literal answers were observed in CDR 3, although they were expected to be the most frequent in this group where disinhibition was the most prominent. Literal answers could be replaced by confabulation and out of context in CDR 3.

'Skilled' is the connotation of 'a monkey' from the context. Once the semantic network is constructed, presentation of a word automatically activates related words through the semantic network of association, but patients with AD undergo deterioration of the associations,[19] which can be related to the reduced inhibitory control over concurrently activated words.[20]

The component of 'sometimes' checked the 'attention to detail'; the particle '*mo*' means 'even or sometimes'. The Stroop task is concerned with divided attention directed toward literal meaning and colour;[21] thus, the ability checked by the test could be related to such attention to the components (or syllables) of the proverb, and such attention can be related to HDS-R scores.

As aforementioned, all four components were associated with difficulties in suppressing concurrently active words, tending to comprehend figurative expressions literally in daily conversation, too.

Answers of excuse and 'not knowing'

There were qualitative differences in excuse according to the stages. Examples of CDR 1 were, 'I've heard the proverb but I don't know the meaning, because I'm foolish and I haven't studied well'. They used excuses defensively. An example of CDR 2 was, 'I haven't heard this before, the elderly say such things', and an example of CDR 3 was, 'What are you telling me for? I don't know because I don't keep monkeys'. The answer for CDR 2 contained the nuance that the examiner should ask someone else, and the answer in CDR 3 was with an accusatory nuance toward the examiner. The aforementioned qualitative differences suggested a declining tendency of self-monitoring. Such deterioration of self-monitoring can lead to anosognosia;[22] that is, unawareness of symptoms. It is assumed to result from deficits in metamemory to distinguish what they know from what they don't.[23,24] In dementia, self-awareness ranges from being somewhat aware to completely unaware of their deficits, reflecting the stage of the disease.[25] In CDR 3, approximately 20% of participants answered that they did not know the meaning. However, those who answered that they did not know were not necessarily aware of their deficits. They replied immediately before taking time to think; thus, they seemed to reply without accessing their own knowledge. The immediate answer of 'not knowing' would suppress accusation; we assumed that the patients took the intuitive precautions against accusation, after a number of experiences with failure.[26]

Confabulation and out of context

The confabulation in CDR 1 and 2 was just to add some information to the answers. Examples are: 'falling down because monkeys were not paying attention', 'falling down because it dropped food' or 'falling down because of being overweight'. In CDR 3, confabulation reached over 70% and it tended to be out of context. For example, 'I know the meaning. Monkeys fell from a mountain, I saw the scene and I felt sorry for the monkeys. I saw baby monkeys and they were cute . . .'. For clinical suggestion, the confabulation began with pretention to know the proverb; pretention is one of the characteristics of AD. Failing to explain the meaning, the story immediately shifted to their own stories; confabulation might be a manifestation of episodic memory distortion[9] and deterioration of self-monitoring.[22] They continued to fluently tell the illogical stories until being interrupted. Telling such stories showed the patients' lack of self-monitoring of the answer. However, some patients

sought the examiner's approval, which is a typical characteristic of AD to rely on others, probably because of uncertainty. This suggested that even those who lacked explicit consciousness of their deficits might have a vague perception of their illness.

Implication for family education

Social language impairment, such as deficits in the interpretation of figurative language, markedly hinders communication with those around the patient. Communication gaps, especially with families, might arouse feelings of anxiety, and trigger behavioural and psychological symptoms of dementia (BPSD) in patients.[27] Bridging such communication gaps is left to the family, and so family education to enhance communication skills can be effective to reduce BPSD.[27] It is useful for this purpose to understand the characteristics of the patient's deficits of figurative language comprehension.

As aforementioned, the difficulties in interactive social communication in dementia can be partly attributed to deficits in cognitive inhibition. With qualitative analysis, asking the meaning of a proverb is a brief test that can be applied in a clinical setting to detect disinhibition, confabulation and excuse, which are characteristics of dementia and somewhat useful for evaluating its stages. We gave an example of a Japanese proverb; even if customs and language are different, this study might be applicable in other linguistic areas using proverbs with figurative expressions, such as animal analogies.

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Effects of Intervention Using a Community-Based Walking Program for Prevention of Mental Decline: A Randomized Controlled Trial

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OBJECTIVES: To evaluate the efficacy of a municipality-led walking program under the Japanese public Long-Term Care Insurance Act to prevent mental decline.

DESIGN: Randomized controlled trial.

SETTING: The city of Takasaki.

PARTICIPANTS: One hundred fifty community members aged 72.0 ± 4.0 were randomly divided into intervention (n = 75) and control (n = 75) groups.

INTERVENTION: A walking program was conducted once a week for 90 minutes for 3 months. The program encouraged participants to walk on a regular basis and to increase their steps per day gradually. The intervention was conducted in small groups of approximately six, so combined benefits of exercise and social interaction were expected.

MEASUREMENTS: Cognitive function was evaluated focusing on nine tests in five domains: memory, executive function, word fluency, visuospatial abilities, and sustained attention. Quality of life (QOL), depressive state, functional capacity, range of activities, and social network were assessed using questionnaires, and motor function was evaluated.

RESULTS: Significant differences between the intervention and control groups were shown in word fluency related to frontal lobe function ($F(1, 128) = 6.833$, $P = .01$), QOL ($F(1,128) = 9.751$, $P = .002$), functional capacity including social interaction ($F(1,128) = 13.055$, $P < .001$), and motor function (Timed Up and Go Test: $F(1,127) = 10.117$, $P = .002$). No significant differences were observed in other cognitive tests.

CONCLUSION: Walking programs may provide benefits in some aspects of cognition, QOL, and functional capacity including social interaction in elderly community members. This study could serve as the basis for implementation of a community-based intervention to prevent mental decline. **J Am Geriatr Soc 60:505–510, 2012.**

Key words: prevention of mental decline; social interaction; dementia; Alzheimer's disease; mild cognitive impairment

The Japanese public Long-Term Care Insurance Act was launched in April 2000 to respond to the growing elderly population. The revision of the act in 2008 led to a greater emphasis on preventive long-term care, and municipalities are expected to play leading roles in building the platform and network for preventive activities.[1]

The Preventive Long-Term Care program was initiated under the leadership of the Ministry of Health, Labor, and Welfare in Japan, where municipality-led preventive interventions have been encouraged in agreement with the concept of community-based rehabilitation,[2] but prevention against mental decline remains a concern, so three areas in Japan (Tokyo, Ohbu, and Takasaki) were selected as model areas to evaluate the efficacy of a community-based program for prevention of mental decline. An intervention program was conducted in Takasaki: the Takasaki Project.

In the Takasaki Project, a walking program was chosen for intervention. Previous studies have reported that regular exercise is beneficial for lowering the risk of mental decline in elderly individuals,[3–5] and the efficacy of

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walking for preventing mental decline has been reported.[6,7] Another merit of walking is its low cost; effective prevention strategies would also have public health implications by reducing economic and social burdens.

The program adopted in this intervention encouraged participants to acquire a walking habit by gradually increasing their walking steps in a group setting. Thus, combined benefits of exercise and social interaction could be expected. Social isolation is associated with greater risk of mental decline,[8,9] whereas a rich social network and interaction may protect against mental decline.[10,11]

Based on the intervention described above, the present randomized controlled trial was designed to test whether a walking program was effective in preventing mental decline in elderly individuals without dementia.

METHODS

Participants

The Takasaki Project was conducted between September and November 2010. The flow of participants is shown in Figure 1. As the first step, participants were screened using a questionnaire. The questionnaire consisted of 25 self-completed items, including three items concerning mental decline: "Have others indicated that you may have memory problems, such as 'you often ask the same things repeatedly'?" "Do you need to look up commonly used telephone numbers?" and "Do you sometimes fail to remember the date?" The questionnaire was mailed to inhabitants aged 65 and older; 2,387 residents younger than 80 answered yes to at least one of the three items, and these respondents were regarded to be at high risk of mental decline. Leaflets describing the Takasaki Project were mailed to them, and 153 agreed to participate. An additional 13 participants were also recruited at a municipal center for elderly adults. One hundred sixty-six individuals attended information meetings, and written informed consent was obtained from 162. At the initial baseline assessment, each volunteer completed the Mini-Mental State Examination (MMSE) and a medical interview with a specialist in dementia medicine. During the interview, 12 volunteers were excluded: five meeting *International Classification of Diseases, Tenth Revision*, criteria for the diagnosis of dementia, five aged 80 and older (those who reached 80 after the 25-item self-check questionnaire was mailed), and two with chronic illness. Therefore, 150 volunteers were eligible for randomization as participants. The ethics board of Gunma University School of Health Sciences approved all procedures (No. 21–47).

Assessment

Cognitive Tests

The major outcome variable was change in cognitive function. Cognitive function comprises various components; the Cognitive and Emotional Health Project in the United States focuses on five domains: learning and memory, executive function abilities (e.g., concept formation and abstract thought), language, visuospatial abilities, and sustained attention (ability to focus and perform a simple task).[12] The 5-Cog test[13] consists of five tests covering the following domains: learning and memory (category cued delayed recall test consisting of 32 words in eight

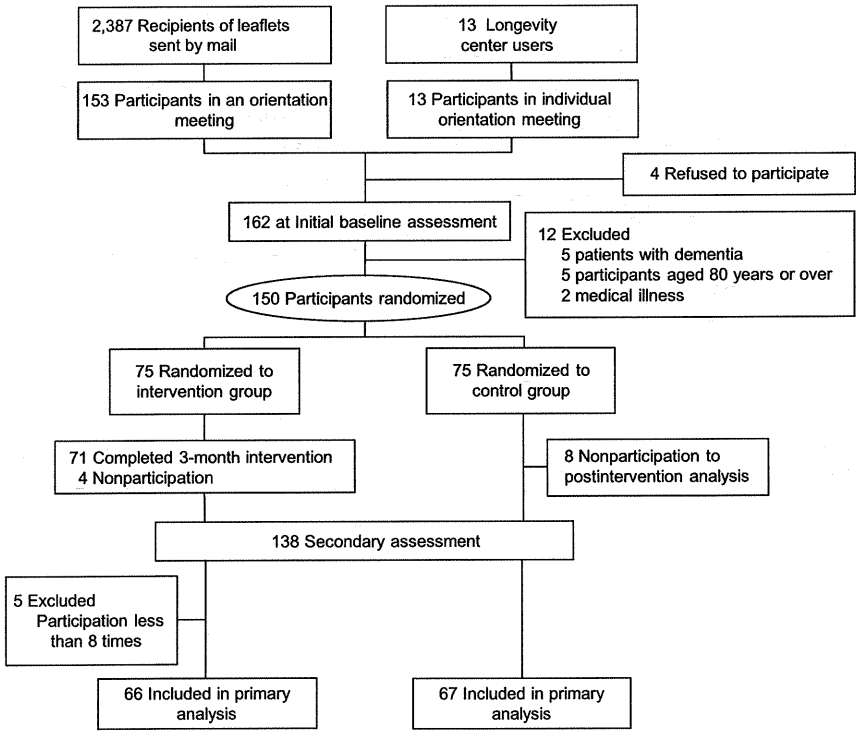

Figure 1. Flow of participants from the time of recruitment through study completion at 3 months.

categories), executive function abilities (dual-task test that requires alternating attention, abstract reasoning test similar to the Wechsler Adult Intelligence Scale-III (WAIS-III)), language (a categorical word fluency test of "animals" completed in two minutes), and visuospatial abilities (a Clock Drawing test to draw clock hands showing the time at "ten after eleven"). Mean scores ± standard deviations (SDs) in participants aged 65 to 80 (n = 800) were as follows: delayed recall test, 12.0 ± 5.8; dual-task test, 20.1 ± 9.1; abstract reasoning test, 10.8 ± 4.3; word fluency test, 13.9 ± 6.0; and Clock Drawing test, 6.7 ± 1.4. The 5-Cog is intended to be conducted in a group setting with a maximum of 50 individuals. The test set is distributed with a 35-minute-long instruction DVD so that the instructions are identical every time. Sustained attention was measured using the Digit-Symbol Substitution Test (DSST), a subset of WAIS-III, and the Yamaguchi Kanji-Symbol Substitution Test (YKSST).[14] The YKSST was developed for Japanese elderly individuals as an adaptation of the DSST; Japanese characters, kanji, were used instead of numbers, as in DSST, because elderly adults in Japan are more familiar with kanji. Mean YKSST scores were 46.9 ± 10.9 in individuals aged 65 to 79 (n = 170). The Trail-Making Test (TMT) was also administered to evaluate executive function abilities. Higher 5-Cog, DSST, and YKSST scores and lower TMT scores indicate better performance.

Questionnaires on Quality of Life, Mood, Functional Capacity, Range of Activity, and Social Network

Participants were required to complete the self-assessment questionnaires. Quality of life (QOL) was measured using a questionnaire on satisfaction in daily life (SDL).[15] Depressive state was evaluated using the Geriatric Depression Scale (GDS).[16] Functional capacity for independent living was assessed using the Tokyo Metropolitan Institute of Gerontology Index of Competence (TMIG-IC).[17] The TMIG-IC was designed to measure higher-level functional capacities in community-dwelling elderly individuals and consists of 13 items divided into three subscales: instrumental self-maintenance, intellectual activity, and social role.

The range of activity was measured using the Life-Space Assessment (LSA), which assesses how far and how often a person moves, ranging from moving around the bedroom only to traveling out of the person's town.[18] Social network size was assessed using the Japanese version of the abbreviated Lubben Social Network Scale (Lubben).[19] Higher QOL, TMIG-IC, LSA, and Lubben scores and lower GDS scores indicate better performance.

Assessment of Motor Function

Four tests were conducted: grip force to assess muscle strength, balance time on one foot (60 seconds as cutoff time), Timed Up and Go Test (TUG), and maximum walking speed for 5 meters. Improvement is reflected by an increase in grip force and balance, and by a decrease in TUG and walking speed for 5 meters. In addition to the outcome measures above, average steps per day for 7 days were measured to evaluate the direct effect of the intervention program. All participants wore a pedometer (EX-500; Yamasa Tokei Co. Ltd., Tokyo, Japan) to record the total number of steps walked in a day. Pedometers were sealed so that participants could not see the counters. The effect was assessed by comparing the average steps for 7 days just before and after the intervention.

Randomization

Randomization was conducted at the end of the initial baseline assessment; 150 participants were randomly allocated to the intervention group or control group. Research staff undertaking cognitive assessment, physical assessment, and intervention were separated.

Intervention

The intervention was conducted using the Tokyo Metropolitan Institute of Gerontology method. The program aimed to facilitate walking habits. The 90-minute intervention program was conducted once a week for 12 weeks and consisted of a 30-minute exercise period and 60-minute group work with five to eight people. Each participant was required to set a clear short-term goal on a weekly basis in order to achieve long-term goals. They were required to record their steps every day using a pedometer (during the intervention period, the pedometer was not sealed) and to write a self-assessment of daily activities. In addition to daily walking, participants planned and executed walking events (excursion) with other group members during the intervention period.

The Facilitators

Registered physical trainers or health nurses working at hospitals or healthcare providers commissioned by the local government of Takasaki City conducted the intervention program. They received lectures before the intervention, and they were supervised so that the program was administered appropriately. They were required to behave as facilitators to motivate participants, to maintain smooth communication, and to create a comfortable atmosphere.

Control Group

Participants in this group received educational lectures on food, nutrition, and oral care that were not directly related to the prevention of mental decline.

Analysis of the Data

The data were analyzed using the Japanese version of SPSS for Windows version 19.0 (IBM Corporation, New York). For initial baseline comparison between the intervention and control groups, two-sample *t*-tests were conducted for randomization; there was no significant difference between the two groups for any outcome measure. Participants who underwent the initial baseline and postintervention assessments were included in the final analysis; participants who dropped out and those who were present at the intervention fewer than eight of 12 times were excluded from the analysis. Repeated-measures analysis of covariance, with covariates of age, sex, and years of education, was used to analyze the completed cases. The interaction was examined to assess the differential effect between the intervention

and control groups, and post hoc analysis of within-subject analysis was conducted using Bonferroni correction. Nine cognitive tests, five questionnaires, and four tests of motor function that were independent of each other were conducted. Multiple corrections were not done among these independent measures. Concerning the measures where significant interaction was shown, intention-to-treat analysis was also conducted; five participants who attended fewer than eight times were included in the intention-to-treat analysis.

RESULTS

Demographic data of the participants are shown in Table 1. The attendance rate during the intervention was 87.5%. The analysis was conducted with 66 participants in the intervention group and 67 in the control group (Figure 1).

Direct Effect of Walking Program

The intervention group had a significantly greater increase in average number of steps taken over 7 days from the pre- to the postintervention period than the control group ($F(1,123) = 7.184$, $P = .008$; intervention group, preintervention 5,621 ± 2,494 steps per day, postintervention 7,044 ± 2,891; control group, preintervention 4,639 ± 2,011, postintervention 4,940 ± 2,552).

Cognitive Tests

Word fluency scores of participants in the intervention group improved significantly more than those in the control group (interaction $F(1, 128) = 6.833$, $P = .01$). There were no significant differences in other tests of delayed recall, dual task, clock drawing, abstract reasoning, TMT, DSST, or YKSST (Table 2).

Questionnaires on QOL, Mood, Functional Capacity, Range of Activity, and Social Network

The intervention group had significantly greater improvement in QOL than the control group ($F(1,128) = 9.751$, $P = .002$). A significant difference was found for functional capacity, which resulted from a significant decrease in the control group ($F(1,128) = 13.055$, $P < .001$). There was also a significant difference in all three subscales due to a significant decrease in the control group: instrumental self-maintenance ($F(1,128) = 9.801$, $P = .002$), intellectual activity ($F(1,128) = 5.543$, $P = .02$), and social role ($F(1,128) = 24.925$, $P < .001$). There were no significant differences observed in other questionnaires on mood, range of activity, or social network (Table 2).

Table 1. Baseline Characteristics of Trial Participants

Characteristic	Intervention (n = 75)	Control (n = 75)	Total (N = 150)
Age, mean ± SD	71.9 ± 4.1	72.0 ± 3.9	72.0 ± 4.0
Sex, n			
Male	23	21	44
Female	52	54	106
Education, years, mean ± SD	11.8 ± 2.5	11.9 ± 2.3	11.9 ± 2.4
Mini-Mental State Examination score, mean ± SD	27.7 ± 1.9	27.9 ± 2.0	27.8 ± 1.9

SD = standard deviation.

Assessment of Motor Function

The intervention group had significantly greater improvement on the TUG than the control group ($F(1,127) = 10.117$, $P = .002$); one participant withdrew because of knee pain. There were no significant differences between the treatment and control groups in grip force, balance time, or walking speed tests, although the control group had a significant increase in grip force (Table 2).

All differences remained in the intention-to-treat analysis (word fluency score interaction $F(1, 133) = 7.420$, $P = .007$, post hoc analysis within subjects (intervention group $P = .001$, control group $P = .55$); QOL interaction $F(1, 133) = 6.936$, $P = .009$, post hoc analysis (intervention group $P = .03$, control group $P = .14$); TMIG-IC interaction $F(1, 133) = 12.035$, $P = .001$, post hoc analysis (intervention group $P = .21$, control group $P < .001$); TUG interaction $F(1, 131) = 9.013$, $P = .003$, post-hoc analysis (intervention group $P < .001$, control group $P < .001$)).

DISCUSSION

Significant interventional benefits were shown in word fluency, QOL, functional capacity including social interaction, and motor function. Some beneficial changes were observed in the control group, such as grip force, possibly due to effects by participation.

Optimal Cognitive Health

The benefits of a walking program in a small group setting could result from synergistic effects of enhanced motivation, positive emotion, and social interaction. The importance of motivation has been emphasized in rehabilitation,[20] and cognition and emotions interact closely, based on dynamic coordination of networks in the brain.[21]

The Cognitive and Emotional Health Project proposed that optimal cognitive health is not just the absence of cognitive deficits, but also the enhancement of cognitive and emotional health to maintain social connectedness and the ability to function independently. It has also been emphasized that cognitive and emotional health should be evaluated in the context of social functioning.[12] Concerning social interaction, an interventional effect was shown in the self-reported awareness of social role (the subscale of TMIG-IC). It was reported that elderly individuals tend to feel alienation from society without a social role, and emotional isolation could be a risk factor of mental decline.[9] We assumed that the participants would feel a sense of participation in the community through intervention.

Table 2. Results of All Participants

	Mean ± Standard Deviation							
	Intervention		Control		Interaction		Post Hoc Analysis, *P*-Value	
Classification	Before	After	Before	After	*F*-Value	*P*-Value	Intervention	Control
Cognition								
Dual task test	21.2 ± 6.4	22.9 ± 6.7	19.1 ± 8.0	21.6 ± 7.1	1.176	.28	.008	<.001
Delayed recall	14.2 ± 5.2	17.3 ± 5.9	13.3 ± 5.2	16.1 ± 5.6	0.395	.53	<.001	<.001
Clock drawing	6.8 ± 0.7	6.9 ± 0.3	6.8 ± 0.7	6.9 ± 0.6	0.236	.63	.09	.31
Categorical word fluency	16.0 ± 4.0	17.2 ± 4.8	15.8 ± 4.9	15.6 ± 4.3	6.833	.01	.003	.53
Abstract reasoning	10.1 ± 3.6	10.4 ± 3.5	10.2 ± 3.5	10.8 ± 3.0	0.433	.51	.26	.04
TMT								
Part A	41.7 ± 14.8	41.2 ± 17.5	43.4 ± 15.8	43.0 ± 17.5	0.024	.88	.70	.87
Part B	119.3 ± 46.4	109.4 ± 35.0	125.9 ± 43.6	123.6 ± 49.3	1.010	.32	.06	.67
DSST	54.8 ± 12.9	58.8 ± 15.7	53.4 ± 14.4	57.4 ± 15.4	0.002	.96	<.001	<.001
YKSST	45.0 ± 11.2	48.3 ± 12.1	43.6 ± 10.5	45.7 ± 10.1	1.735	.19	<.001	.001
Questionnaire								
QOL	44.0 ± 5.8	45.3 ± 4.4	45.1 ± 5.3	44.5 ± 5.8	9.751	.002	.005	.12
GDS	3.7 ± 3.4	3.2 ± 3.0	3.4 ± 2.9	3.4 ± 3.0	2.075	.15	.04	.97
TMIG-IC	11.7 ± 1.6	11.9 ± 1.4	12.0 ± 1.4	11.6 ± 1.6	13.055	<.001	.15	<.001
LSA	94.5 ± 16.6	101.1 ± 15.4	90.4 ± 20.0	95.9 ± 18.0	0.134	.71	.002	.009
Lubben	16.1 ± 6.3	16.3 ± 5.7	17.8 ± 5.1	16.8 ± 5.2	2.033	.16	.78	.09
Motor								
Grip force	27.5 ± 6.8	28.4 ± 7.5	25.9 ± 6.9	28.1 ± 7.0	3.397	.07	.05	<.001
Balance	47.2 ± 19.2	48.6 ± 16.1	39.7 ± 21.6	40.0 ± 21.6	0.228	.63	.43	.90
TUG	5.6 ± 0.9	4.9 ± 0.7	5.7 ± 1.0	5.4 ± 0.8	10.117	.002	<.001	<.001
Speed	2.6 ± 0.4	2.5 ± 0.3	2.7 ± 0.4	2.5 ± 0.4	0.904	.34	<.001	<.001

The interaction was examined to assess the differential effect between the intervention and control groups, and post hoc analysis was conducted within-subject with Bonferroni correction.

The Trail-Making Test (TMT) was assessed according to time required, and other tests were assessed according to scores. Higher Dual task, Delayed recall, Clock drawing, Categorical word fluency, Abstract reasoning, Digit-Symbol Substitution Test (DSST), and Yamaguchi Kanji-Symbol Substitution Test (YKSST) scores and lower TMT scores indicate better performance.

Higher QOL, Tokyo Metropolitan Institute of Gerontology Index of Competence (TMIG-IC), Life Space Assessment (LSA), and Lubben Social Network Scale scores (Lubben) and lower Geriatric Depression Scale (GDS) scores indicate better performance.

Higher grip force and balance scores and lower Timed Up and Go (TUG) and speed scores indicate better performance.

Walking Program Emphasizing Mutual Support for Self-Management

This study showed that the acquisition of a walking habit is beneficial for the prevention of mental decline in elderly individuals, as previous observational studies suggested.[6,7] Exercise could have a larger effect in combination with social interaction. Animal studies suggest that greater benefits may be expected when exercise is conducted voluntarily in enriched environments (e.g., housing animals in groups in large cages with structures for exploration, physical activity, and sensorimotor learning).[22–24] The results could be applied to humans; exercise may have greater benefits when conducted voluntarily with social interactions in a pleasant atmosphere. Regarding voluntary involvement, the program gave priority to self-management. The participants would be encouraged toward a self-help effort to achieve the goal that they set for themselves, and the facilitators were required only to enhance participants' motivation in their self-managed activity. It has been recommended that rehabilitation for individuals with dementia should be based on five principles: keeping a pleasant atmosphere, enhancing participants' motivation and self-directed thinking, maintaining interactive communication, providing social roles to each participant, and errorless learning.[25] Although these principles focus on individuals with dementia, the concept underlying the present intervention was in accord with these principles. Motivation is essential for developing good habits. Interactive communication and sharing roles are helpful for smooth group activity. The role of facilitators is to keep the atmosphere pleasant and encourage group activities.

Feasibility of Implementation of the Community-Led Intervention Program

The intervention presented here is simple, and other municipalities can implement it easily and effectively. Regarding the time period, the 3-month period was determined in accordance with the Preventive Long-Term Care programs, which are implemented for a 3-month period. Previous randomized controlled trials of exercise intervention for prevention of mental decline set longer periods; one study used a 24-week home-based program of physical activity,[4] and another reported the effects of resistance training and balance training over periods of 6 months and 1 year.[26,27] The current study suggested that cognitive improvement could be achieved using a short-term 3-month intervention, although continuity is important to

ensure the positive effects, and thus a longer-term follow-up of the participants should be conducted.

Cost is a major concern because effective prevention strategies would have large public health implications in reducing economic and social burdens, especially in the face of progressive aging of the population. The walking program can be conducted at a low cost.

The walking program is simple enough that healthcare staff who have undergone effective training programs can conduct it. In this regard, municipality-led community-based rehabilitation could provide an effective application of the World Health Organization's task-shifting concept.[28] In recent years, the notion of task shifting has gained popularity as a potential means of providing care to greater numbers of patients in underresourced areas.[29] The Japanese policy of preventing mental decline takes advantage of the essence of task shifting to drive community-based rehabilitation and to organize and train volunteers as community rehabilitation facilitators. Those who have completed the intervention could become community rehabilitation facilitators to promote the prevention program throughout the community.

Limitations

One limitation of the study is that the participants might have been healthier people than the general population. The sample was self-selected, and fewer than 10% of those who received informational mailings were enrolled in the trial. Another bias was related to the difference of steps. The intervention group walked an average of 1,000 steps more at baseline than the control group.

This exploratory study lays the groundwork for a large intervention, and its efficacy should be examined with a larger population. This study could serve as the basis for implementation of a community-based intervention program to prevent mental decline.

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Neurobiology of Disease

Transgenic Expression of Intraneuronal $A\beta_{42}$ But Not $A\beta_{40}$ Leads to Cellular $A\beta$ Lesions, Degeneration, and Functional Impairment without Typical Alzheimer's Disease Pathology

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An early role of amyloid-β peptide ($A\beta$) aggregation in Alzheimer's disease pathogenesis is well established. However, the contribution of intracellular or extracellular forms of $A\beta$ to the neurodegenerative process is a subject of considerable debate. We here describe transgenic mice expressing $A\beta_{1-40}$ (APP47) and $A\beta_{1-42}$ (APP48) with a cleaved signal sequence to insert both peptides during synthesis into the endoplasmic reticulum. Although lower in transgene mRNA, APP48 mice reach a higher brain $A\beta$ concentration. The reduced solubility and increased aggregation of $A\beta_{1-42}$ may impair its degradation. APP48 mice develop intracellular $A\beta$ lesions in dendrites and lysosomes. The hippocampal neuron number is reduced already at young age. The brain weight decreases during aging in conjunction with severe white matter atrophy. The mice show a motor impairment. Only very few $A\beta_{1-40}$ lesions are found in APP47 mice. Neither APP47 nor APP48 nor the bigenic mice develop extracellular amyloid plaques. While intracellular membrane expression of $A\beta_{1-42}$ in APP48 mice does not lead to the AD-typical lesions, $A\beta$ aggregates develop within cells accompanied by considerable neurodegeneration.

Introduction

Various lines of evidence point to a central role of the amyloid-β peptide ($A\beta$) in the development of Alzheimer's disease (AD) (for review, see Citron, 2010). Although the disorder is etiologically heterogeneous, aggregation of $A\beta$ appears as an early pathogenic event common to all forms of AD. Aggregated $A\beta$ shows no overt acute toxicity *in vivo* in accordance with the slow progression of this chronic neurodegenerative condition (Jack et al., 2010). In human brain, $A\beta$ deposits may persist for extended periods of time until clinical symptoms become evident. Amyloid plaque-forming β-amyloid precursor protein (APP) transgenic mouse models of AD show correspondingly little neurodegeneration during their life span. $A\beta$ aggregates can affect neuronal processes at multiple levels, which may lead to a slow decompensation of functionally connected networks (Palop and Mucke, 2010). The molecular structure of the pathogenic species remains a matter of considerable debate. Both amyloid plaques, one of the pathological hallmarks of AD, as well as oligomeric forms of $A\beta$ have been implicated as pathogenic (Shankar et al., 2008; Nimmrich and Ebert, 2009). It also remains unclear to what extent intracellular and extracellular $A\beta$ aggregates contribute to pathogenesis (Gouras et al., 2010).

Recently, transgenic mice have been described expressing either of the two major $A\beta$ isoforms, $A\beta_{1-40}$ and $A\beta_{1-42}$, fused to the C terminus of the BRI protein (McGowan et al., 2005). Cleavage of the fusion proteins at a furin site leads to efficient secretion of $A\beta$ peptides. These animals demonstrated that $A\beta_{1-42}$ but not $A\beta_{1-40}$ is sufficient to promote $A\beta$ deposition *in vivo*. Overt toxicity, however, has not been found, suggesting that intracellular species might be responsible. To address this question, we have generated transgenic mice expressing intracellular $A\beta_{1-40}$ and $A\beta_{1-42}$. The peptides are preceded by a cleaved N-terminal signal sequence to cotranslationally insert them into the endoplasmic reticulum. Both transgenic lines do not develop extracellular amyloid plaques, but $A\beta_{42}$ mice (APP48) show intracellular $A\beta$ lesions. Additionally, hippocampal neurons and white matter are reduced along with a motor impairment indicating neurodegeneration in the absence of typical AD pathology.

Materials and Methods

Animal studies. A cDNA fragment encoding the rat preproenkephalin signal peptide (SPENK) was amplified from a rat brain cDNA library and ligated to cDNAs encoding human $A\beta_{1-40}$ or $A\beta_{1-42}$, followed by a TAG stop codon. The resulting SPENK-$A\beta_{40}$ or SPENK-$A\beta_{42}$ cDNA was

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