Figure 4. Effect of chronic propranolol treatment on spatial memory and neuropathology in Tg2576 mice. (A-D) The influence of chronic propranolol treatment on Aβ related spatial memory in Tg2576 mice by Morris water maze test (A) Visible trial (B) Swimming speed (C) Hidden platform learning acquisition, latency score represents time taken to escape to the platform from the water. (D) Probe trial. Percent of time in quadrant is calculated as the ratio of time spent in the target quadrant area relative to the time spent in the rest of the pool. (E-F) The influence of chronic propranolol treatment wild type mice by Morris water maze test: (E) Hidden platform learning acquisition (F) Probe trial. (G-H) Brain and plasma levels of total Aβ1-40 and Aβ1-42 peptides following chronic propranolol treatment. Values represent group mean ± SEM, n = 7–8 per group.
doi:10.1371/journal.pone.0065232.g004

studies, we tested whether it will interfere with spatial memory in wild type (WT) mice. WT mice were treated with the same treatment regime for 6 months and subjected to MWM test. We found propranolol at 15 mg/kg/day dose did not affect spatial memory in WT mice, as reflected by their normal learning progress during the 7 day training (Figure 4E). The probe trial also confirms that both propranolol-treated and non-treated control WT mice spent significantly more time in the target quadrant (~40% of time, much more than the 25% chance level, Figure 4F), indicating that propranolol at the treatment dose did not affect spatial memory function.

We next measured the brain neuropathology and found that, similar to the short-term treatment, 6 months of chronic propranolol treatment significantly reduced the level of both Aβ1-40 and Aβ1-42 in the brains compared to the control non-treated mice (Figure 4G). However, measurements of plasma levels of Aβ showed that there was no change in Aβ1-40 and Aβ1-42 (Figure 4H) which is different from the short-term treatment results (Figure 2M).

Chronic nicardipine treatment in Tg2576 showed similar behavior results. No benefits of cognitive improvement were observed following 6 months treatment by MWM test (Figures 5A–5C). Surprisingly, contrary to the short-term results that nicardipine treatment significantly lowered the brain levels of Aβ1-40 and Aβ1-42 (Figure 2H), chronic nicardipine treatment did not affect the levels of Aβ in the brain (Figure 5D). There was no difference in plasma levels of Aβ1-40 and Aβ1-42 following chronic treatment, which is also different from the short-term result that there was a significant reduction in plasma Aβ following 1 month treatment (Figure 2N).

Discussion

AD is rapidly becoming one of the leading causes of disability and mortality, and it is expected that the prevalence of AD in the US will quadruple over the next 50 years [30;31]. With baby boomers reaching retirement age and life expectancy continuing to increase, an increasing number of elderly people will be taking one or more medications. Whether current commonly prescribed medications can worsen or improve AD dementia, and to what extent they might influence dementia from normal aging or from other neurodegenerative conditions, are issues with enormous public health implications.

In this study, we surveyed 1600 FDA approved drugs for their ability to modulate aberrant generation of AD-type Aβ peptides from the amyloid precursor protein (APP) process in primary cortico-hippocampal cell cultures generated from the Tg2576 mouse AD model. We found a subset of medication that

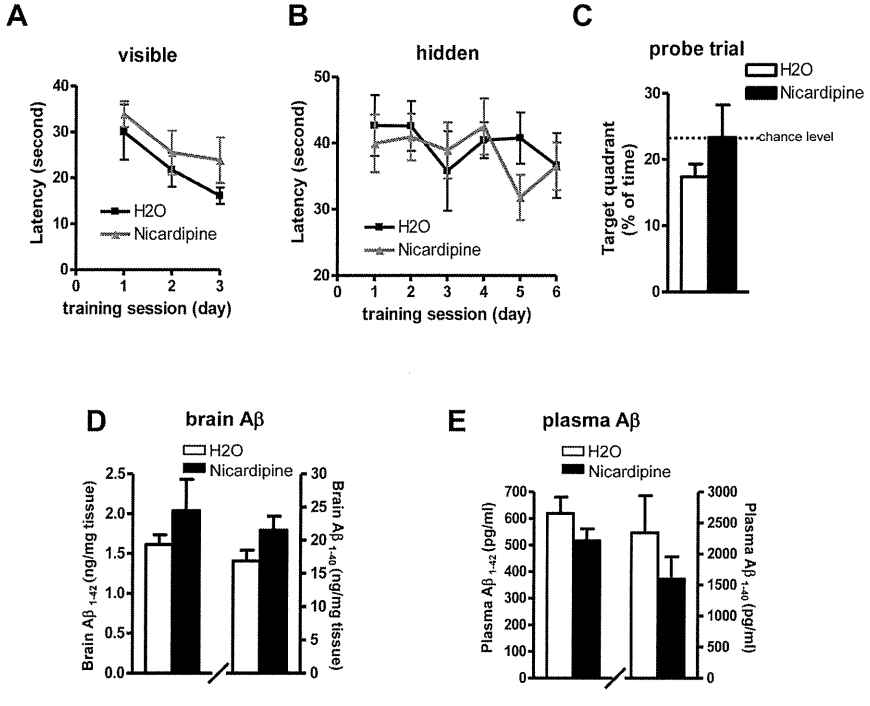

Figure 5. Effect of chronic nicardipine treatment on spatial memory and neuropathology in Tg2576 mice. (A-C) The influence of chronic nicardipine treatment on Aβ related spatial memory in Tg2576 mice by MWM test: (A) Visible trial (B) Hidden platform learning acquisition (C) Probe trial. (D-E) Brain and plasma levels of total Aβ1-40 and Aβ1-42 peptides following chronic nicardipine treatment. Values represent group mean ± SEM, n = 9–11 per group.
doi:10.1371/journal.pone.0065232.g005

significantly increased and a second subset of medications that significantly reduced generation of Aβ peptides in primary neuron cultures.

Since cardiovascular disorder is one of the most prevalent diseases among the elderly, we focused on the potential role of cardiovascular drugs in regulating Aβ generation. We found that most of the FDA-approved cardiovascular drugs have no detectable activity with regard to the generation of Aβ peptides from our *in vitro* primary cortico-hippocampal screening system. However, we identified select cardiovascular drugs, such as propranolol and nicardipine, that exert *in vitro* Aβ-lowering activity, and other cardiovascular drugs, such as furosemide, that significantly promote the generation of Aβ peptides *in vitro*.

Among the subset of cardiovascular drugs we found to promote Aβ generation *in vitro*, several (e.g., trandolapril, quinapril) are angiotensin converting enzymes (ACE) inhibitors. This observation is consistent with recent evidence suggesting ACE may be involved in the degradation of Aβ peptides [32;33]. Indeed, the ACE inhibitor, captopril, has previously been shown to increase Aβ accumulation *in vitro* [32;33]. However, in our primary screening, we found captopril barely increased Aβ levels in the conditioned medium of primary neurons following treatment. This discrepancy might have been caused by the usage of different in vitro systems. Zou et. al used COS cells for their study [33] and Hemming et. al. used CHO and HEK293 cells [32]. In both studies, ACE was over expressed in the cell lines. While in our study, we used primary neurons derived from Tg2576 mice and the inhibition was towards endogenous ACE. It is possible that ACE is not a major contributor in Aβ catabolism in primary neurons *in vitro*. Another observation is that the majority of ACE inhibiting cardiovascular drugs we screened (5 of 8 ACE inhibitors screened) did not exhibit Aβ-modification activity. Thus it is also likely that not all ACE inhibitors are equally effective in preventing Aβ degradation.

Based on evidence that trandolapril is capable of promoting Aβ generation *in vitro*, we explored the physiological impact of trandolapril on Aβ neuropathology *in vivo*. In contrast to our *in vitro* evidence, results from our short-term study in Tg2576 mice treated for 1 month with trandolapril at a dose equivalent to the clinical dosage showed that trandolapril significantly reduced Aβ contents in the brain while it significantly increased Aβ contents in the plasma. Interestingly, the other drug furosemide, which showed Aβ promoting activity *in vitro*, also reduced brain levels of Aβ accompanied by increased levels of Aβ in plasma following short-term treatment in Tg2576 mice. Based on these observations, we suggest that some of the cardiovascular drug, when administered in short-term, might promote generation of Aβ in the brain. However, the treatment might temporarily alter the dynamic balance of Aβ between brain and plasma, e.g. increase the Aβ efflux or reduce the Aβ influx which may result in the promotion of transport of Aβ from the brain to the periphery. It would be interesting to measure the levels of transport proteins such as receptor for advanced glycation end products (RAGE) and Lipoprotein receptor-related protein (LRP) following the short-term treatments.

Since most cardiovascular diseases are chronic conditions, the medications are generally prescribed for a prolonged period of time. Therefore, in our study, we also tested the effect of chronic drug application in cognitive function and brain neuropathology. Previously, we have shown that valsartan, one of the angiotensin receptor blocker medications identified in the secondary screening (Table 1), could reduce Aβ neuropathology and improve spatial memory function in Tg2576 mice following chronic treatment [20]. We also showed in another study that carvedilol, a nonselective β-adrenergic receptor blocker, can prevent cognitive deterioration and reduce brain neuropathology by interfering with Aβ oligomerization and improving basal synaptic transmission in the TgCRND8 mouse model of AD [22;34].

In this study, we found that chronic treatment with propranolol could significantly reduce brain amyloid neuropathology but had no effect on cognitive function. It is possible that reducing amyloid alone might not be sufficient to improve cognition. It is also possible that propranolol is able to reduce total amyloid but is not able to influence the level of soluble oligomeric Aβ species, which are increasingly regarded as neurotoxic and largely responsible for synaptic failure in AD models [6–8;35–37]. Brain neuropathology results from nicardipine, again suggesting that short-term treatment might temporarily alter the hemodynamic between the brain and blood resulting in increased clearance while prolong treatment may not have any effects. Future studies will focus on mechanistic investigation of how certain drugs might influence APP processing or Aβ catabolism and their possible role in Aβ oligomerization which may explain the lack of behavior improvements in propranolol treated mice.

It is not surprising that *in vitro* and *in vivo* studies showed differences in biological efficacies. First of all, brain bioavailability is one of the major obstacles and some of the drugs might not be able to pass the blood brain barrier to influence brain amyloid processing and, therefore, are not able to exert their activities in the brain. Secondly, some of the drugs might have gone through extensive metabolism and the metabolites might not behave as the original drugs. Thirdly, some of the drugs might also impact other systems (such as vessel permeability, periphery protein degradation pathway, etc.) that will eventually affect the net outcome of the drug treatment. More importantly, drugs modifying amyloid may or may not have significant impacts in modulating AD-type cognitive function.

Therefore, in order to identify drugs that might have beneficial effects, such as reducing Aβ neuropathology and improving cognitive function, for the consideration of physicians over drugs that might be potentially detrimental to cognition, individual drugs must be investigated on a case by case basis and these results should be supplemented with data obtained from clinical studies with patients following long-term drug treatment. A good example is that our preclinical study demonstrated that chronic application of ARB valsartan can significantly reduce the levels of soluble Aβ as well as total amyloid plaque load in the brain in a mouse model of AD [20]. Data collected from the National Alzheimer Coordinating Center (including 29 centers across the US) confirms that patients receiving ARB medication have less amyloid deposition compared to untreated patients or patients with non-ARB antihypertensive medications [38]. Collectively, these studies may provide useful information for physicians when prescribing antihypertensive drugs.

Author Contributions

Conceived and designed the experiments: JW LH GMP MY. Performed the experiments: EL WZ XQ DF AC PV KO. Analyzed the data: JW ZZ EL. Contributed reagents/materials/analysis tools: JW ZZ GMP. Wrote the paper: JW AEB GMP.

References

1. Cummings JL (2004) Alzheimer's disease. N.Engl.J Med, 351: 56–67.
2. Selkoe DJ (2001) Alzheimer's Disease: Genes, Proteins, and Therapy. Physiol.Rev., 81: 741–766.
3. Cleary JP, Walsh DM, Hofmeister JJ, Shankar GM, Kuskowski MA, et al. (2005) Natural oligomers of the amyloid-[beta] protein specifically disrupt cognitive function. Nat Neurosci, 8: 79–84.
4. Klyubin I, Walsh DM, Lemere CA, Cullen WK, Shankar GM, et al. (2005) Amyloid beta protein immunotherapy neutralizes A beta oligomers that disrupt synaptic plasticity in vivo. Nature Medicine, 11: 556–561.
5. Kotilinek LA, Bacskai B, Westerman M, Kawarabayashi T, Younkin L, et al. (2002) Reversible memory loss in a mouse transgenic model of Alzheimer's disease. J.Neurosci., 22: 6331–6335.
6. Lesne S, Koh MT, Kotilinek L, Kayed R, Glabe CG, et al. (2006) A specific amyloid-beta protein assembly in the brain impairs memory. Nature, 440: 352–7.
7. Shankar GM, Li S, Mehta TH, Garcia-Munoz A, Shepardson NE, et al. (2008) Amyloid-[beta] protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. Nat Med, 14: 837–842.
8. Lambert MP, Barlow AK, Chromy BA, Edwards C, Freed R, et al. (1998) Diffusible, nonfibrillar ligands derived from Abeta 1–42 are potent central nervous system neurotoxins. PNAS, 95: 6448–6453.
9. Gylys KH, Fein JA, Tan AM, Cole GM (2003) Apolipoprotein E enhances uptake of soluble but not aggregated amyloid-beta protein into synaptic terminals. J Neurochem, 84: 1442–1451.
10. Braak H, Braak E (1997) Staging of Alzheimer-related cortical destruction. Int.Psychogeriatr., 9 Suppl 1: 257–261.
11. Citron M, Oltersdorf T, Haass C, McConlogue L, Hung AY,et al. (1992) Mutation of the beta-amyloid precursor protein in familial Alzheimer's disease increases beta-protein production. Nature, 360: 672–674.
12. Emilien G, Maloteaux JM, Beyreuther K, Masters CL (2000) Alzheimer disease: mouse models pave the way for therapeutic opportunities. Arch Neurol, 57: 176–181.
13. Fox C, Richardson K, Maidment ID, Savva GM, Matthews FE, et al. (2011) Anticholinergic medication use and cognitive impairment in the older population: the medical research council cognitive function and ageing study. J Am Geriatr Soc, 59: 1477–1483.
14. Forette F, Seux ML, Staessen JA, Thijs L, Babarskiene MR, et al. (2002) The Prevention of Dementia With Antihypertensive Treatment: New Evidence From the Systolic Hypertension in Europe (Syst-Eur) Study. Arch Intern Med, 162: 2046–2052.
15. Guo ZC, Fratiglioni L, Zhu L, Fastbom J, Winbald B, Viitanen M (1999) Occurrence and progression of dementia in a community population aged 75 years and older - Relationship of antihypertensive medication use. Arch Neurol, 56: 991–996.
16. Khachaturian AS, Zandi PP, Lyketsos CG, Hayden KM, Skoog I, et al. (2006) Antihypertensive Medication Use and Incident Alzheimer Disease: The Cache County Study. Arch Neurol, 63: 686–692.
17. Lopez-Arrieta JM, Birks J (2002) Nimodipine for primary degenerative, mixed and vascular dementia. Cochrane Database Syst Rev, 3: CD000147.
18. Hajjar I, Brown L, Mack WJ, Chui H (2012) Impact of Angiotensin Receptor Blockers on Alzheimer Disease Neuropathology in a Large Brain Autopsy Series 1. Arch Neurol: 1–7.
19. Anonymous.
20. Wang J, Ho L, Chen L, Zhao Z, Zhao W, et al. (2007) Valsartan lowers brain beta-amyloid protein levels and improves spatial learning in a mouse model of Alzheimer disease. J Clin.Invest, 117, 3393–3402.
21. Hsiao K, Chapman P, Nilsen S, Eckman C, Harigaya Y, et al. (1996) Correlative Memory Deficits, Abeta Elevation, and Amyloid Plaques in Transgenic Mice. Science, 274: 99–103.
22. Wang J, Ono K, Dickstein DL, rrieta-Cruz I, Zhao W, et al (2010) Carvedilol as a potential novel agent for the treatment of Alzheimer's disease. Neurobiol.Aging.
23. Diaz-Ruiz C, Wang J, Ksiezak-Reding H, Ho L, Qian X, et al. (2009) Role of Hypertension in Aggravating Abeta Neuropathology of AD Type and Tau-Mediated Motor Impairment. Cardiovasc.Psychiatry Neurol, 2009: 107286.
24. Morris R (1984) Developments of a water-maze procedure for studying spatial-learning in the rat. Journal of Neuroscience Methods, 11: 47–60.
25. Wang J, Ho L, Qin W, Rocher AB, Seror I, et al. (2005) Caloric restriction attenuates beta-amyloid neuropathology in a mouse model of Alzheimer's disease. FASEB J, 19: 659–661.
26. Reagan-Shaw S, Nihal M, Ahmad N (2008) Dose translation from animal to human studies revisited 2. FASEB J, 22: 659–661.
27. Schwabe L, Nader K, Wolf OT, Beaudry T, Pruessner JC (2012) Neural signature of reconsolidation impairments by propranolol in humans 2. Biol Psychiatry, 71: 380–386.
28. Schwabe L, Nader K, Pruessner JC (2013) beta-Adrenergic blockade during reactivation reduces the subjective feeling of remembering associated with emotional episodic memories 1. Biol Psychol., 99: 227–32.
29. Lonergan MH, Olivera-Figueroa LA, Pitman RK, Brunet A (2012) Propranolol's effects on the consolidation and reconsolidation of long-term emotional memory in healthy participants: a meta-analysis 1. J Psychiatry Neurosci, 37: 120111.
30. Sano M (2003) Current concepts in the prevention of Alzheimer's disease. Cns Spectrums, 8: 846–53.
31. Cummings JL (2004) Treatment of Alzheimer's disease: current and future therapeutic approaches. Rev Neurol Dis., 1: 60–9.
32. Hemming ML, Selkoe DJ (2005) Amyloid beta-protein is degraded by cellular angiotensin-converting enzyme (ACE) and elevated by an ACE inhibitor 5. J Biol Chem, 280: 37644–37650.
33. Zou K, Yamaguchi H, Akatsu H, Sakamoto T, Ko M, Mizoguchi K, et al. (2007) Angiotensin-converting enzyme converts amyloid beta-protein 1–42 (Abeta(1–42)) to Abeta(1–40), and its inhibition enhances brain Abeta deposition 1. J Neurosci, 27: 8628–8635.
34. Arrieta-Cruz I, Wang J, Pavlides C, Pasinetti GM (2010) Carvedilol Reestablishes Long-Term Potentiation in a Mouse Model of Alzheimer's Disease. J Alzheimers.Dis, 21: 649–54.
35. Lacor PN, Bunie MC, Chang L, Fernandez SJ, Gong Y, et al. (2004) Synaptic Targeting by Alzheimer's-Related Amyloid {beta} Oligomers. J.Neurosci., 24: 10191–10200.
36. Lacor PN, Buniel MC, Furlow PW, Sanz Clemente A, Velasco PT, et al. (2007) A{beta} Oligomer-Induced Aberrations in Synapse Composition, Shape, and Density Provide a Molecular Basis for Loss of Connectivity in Alzheimer's Disease. J.Neurosci., 27: 796–807.
37. Shankar GM, Bloodgood BL, Townsend M, Walsh DM, Selkoe DJ, et al. (2007) Natural Oligomers of the Alzheimer Amyloid-{beta} Protein Induce Reversible Synapse Loss by Modulating an NMDA-Type Glutamate Receptor-Dependent Signaling Pathway. J.Neurosci., 27: 2866–2875.
38. Hajjar I, Brown L, Mack WJ, Chui H (2012) Impact of Angiotensin Receptor Blockers on Alzheimer Disease Neuropathology in a Large Brain Autopsy Series 1. Arch Neurol: 1–7.
39. Reagan-Shaw S, Niha M, Ahmad N (2008) Dose translation from animal to human studies revisited 2. FASEB J, 22: 659–661.

Clinical Neurology and Neurosurgery 115 (2013) 1555–1557

Contents lists available at SciVerse ScienceDirect

Clinical Neurology and Neurosurgery

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

Case report

Autopsy-confirmed progressive supranuclear palsy with decreased uptake of metaiodobenzylguanidine

Tadashi Adachi[a,*], Michio Kitayama[a], Kenji Wada-Isoe[a], Toshiya Nakano[a], Kenji Nakashima[a]

[a] Division of Neurology, Department of Brain and Neurosciences, Faculty of Medicine, Tottori University, Yonago, Japan

ARTICLE INFO

Article history:
Received 4 September 2011
Received in revised form 5 January 2013
Accepted 12 January 2013
Available online 5 February 2013

Keywords:
Progressive supranuclear palsy
MIBG
Pathology

1. Introduction

Progressive supranuclear palsy (PSP) is a clinical syndrome comprising supranuclear gaze palsy, postural instability, and dementia. In clinical practice, it is sometimes difficult to distinguish between PSP, early-stage Parkinson's disease (PD), or multiple system atrophy. In the context of these difficulties, decreased cardiac uptake of metaiodobenzylguanidine (MIBG), a physiological analog of norepinephrine, has been reported in patients with PD and dementia with Lewy bodies [1,2]. Some patients with PSP also show slightly reduced MIBG uptake in comparison to healthy controls [3]; however, pathological analyses of these cases have not been conducted. Here, we investigated a case of autopsy-confirmed PSP with decreased MIBG uptake.

2. Case report

This male patient was age 76 at time of death. He was healthy while employed at an office and there was no family history of neurological disorders. At age 69, he had difficulty in walking and looking downward when he was putting on shoes. At the same time, his family noticed him becoming forgetful. He was initially diagnosed with PD and he received L-DOPA/decarboxylase inhibitor (300 mg/day) without effect. Gradually, his gait became unstable and he fell often. At age 72, he was admitted to our hospital. He showed supranuclear vertical gaze palsy, rigidity of neck and extremities without asymmetry, akinesia, postural instability, and dementia (Mini-mental state examination score: 19/30). He showed no apraxia, agnosia, aphasia, or cerebellar signs. He showed no orthostatic hypotension, but suffered from neurogenic bladder. Brain MRI showed atrophy of the midbrain tegmentum (Fig. 1A). Single-photon emission tomography showed hypoperfusion in the frontal lobe. He was diagnosed with possible PSP according to the National Institute of Neurological Disorders and the Society for PSP criteria [4]. Two years after this diagnosis, the patient could not walk and speak. Hemoglobin A1c level, brain natriuretic peptide level, and cardiothoracic ratio on chest radiography were all within normal limits. Cerebrospinal fluid, electrocardiography, coefficient of variation of the R–R interval, and echocardiography all showed no abnormalities. To confirm whether he had concomitant PD pathology or not, we performed MIBG scintigraphy. MIBG scintigraphy performed one month before his death showed decreased cardiac uptake; the heart-to-mediastinum ratio was 1.71 (mean ratio of control patients in our institute ± SD: 2.23 ± 0.31 [5]) in the early image and 1.32 (2.16 ± 0.41) in the delayed image; washout rate was 45.9% (32.4 ± 7.9) (Fig. 1B and C). Drugs that may affect MIBG uptake, such as tricyclic and tetracyclic antidepressants, serotonin reuptake inhibitors, sympathomimetics, sympatholytics, and calcium channel antagonists, were not administered. Monoamine oxidase inhibitor was administered for one year until the patient was age 75. He died of pneumonia at age 76.

An autopsy was performed 12 h after death. The general autopsy revealed severe pneumonia. There was no myocardial infarction. The brain weighed 1200 g after fixation. Gross examination confirmed mild frontal atrophy. The midbrain tegmentum showed

* Corresponding author at: Division of Neurology, Department of Brain and Neurosciences, Faculty of Medicine, Tottori University, 36-1 Nishi-chou, Yonago 683-8504, Japan. Tel.: +81 859 38 6757; fax: +81 859 38 6759.
E-mail address: adachi.neuro@gmail.com (T. Adachi).

0303-8467/$ – see front matter
http://dx.doi.org/10.1016/j.clineuro.2013.01.004

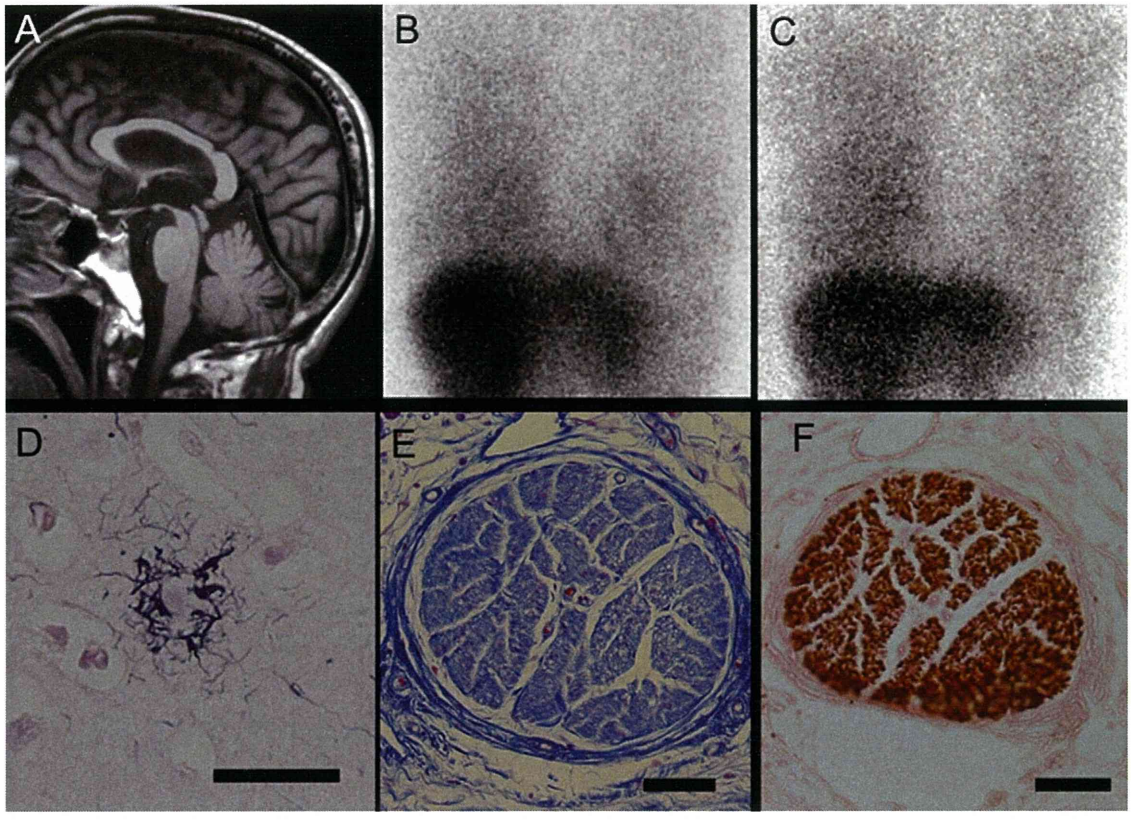

Fig. 1. Clinical images and pathologic findings. (A) Sagittal T2-weighted brain MRI shows severe atrophy of the midbrain tegmentum. The heart-to-mediastinum ratio for the post-injection metaiodobenzylguanidine scan was 1.71 in the early image (B) and 1.32 in the delayed image (C); washout rate was 45.9%. (D) Gallyas–Braak-positive, tuft-shaped astrocytes were present in the putamen; scale bar = 30 μm. Nerve bundles in the left ventricular wall were well preserved as shown by Azan staining (E) and by immunohistochemistry for phosphorylated neurofilament (F); scale bars = 60 μm.

marked atrophy, and the substantia nigra and locus coeruleus showed pigmentation loss. The subthalamic and red nuclei showed atrophy and grayish discoloration. Representative areas of formalin-fixed, paraffin-embedded brain tissue were sectioned and stained with hematoxylin and eosin (HE) and Klüver–Barrera staining. Selected sections were subjected to Gallyas–Braak silver staining. Cardiac left ventricle tissues were sectioned and stained with HE and Azan staining. For immunohistochemistry, we used antibodies to phosphorylated tau (AT8; Innogenetics, Temse, Belgium; 1:1000), β-amyloid 11–28 (12B2; IBL, Maebashi, Japan; 1:1000), phosphorylated α-synuclein (#64; Wako, Osaka, Japan; 1:5000), tyrosine hydroxylase (TH16; Sigma–Aldrich, MO, USA; 1:3000), and phosphorylated neurofilament (SMI-31; Sternberger, Baltimore, USA; 1:10,000). Peroxidase labeling was visualized with diaminobenzidine.

Microscopy showed neuronal loss and gliosis were severe in the globus pallidus, subthalamic nucleus, substantia nigra, dentate nucleus, and inferior olivary nucleus. Tuft-shaped astrocytes were scattered in the putamen, globus pallidus, red nucleus, and superior colliculus (Fig. 1D). Globoid type neurofibrillary tangles (NFT) were prominent in the midbrain, pons, medulla, and dentate nucleus. The neuropathologic diagnosis was definite PSP. Alzheimer-type pathology was minimal (Braak amyloid stage A and NFT stage I). There was no Lewy body–related α-synucleinopathy in the amygdala, dorsal nucleus of vagus, locus coeruleus, substantia nigra, transentorhinal cortex, hippocampus, or anterior cingulate gyrus. Sympathetic ganglia were not collected at autopsy. Nerve bundles of the epicardium and myocardium were well preserved as shown by azan staining and immunostaining for phosphorylated neurofilament and tyrosine hydroxylase (Fig. 1E and F).

3. Discussion

We present a case of autopsy-confirmed PSP with a clinically identified decrease in cardiac MIBG uptake. In Lewy body disease, cardiac sympathetic denervation precedes neuronal loss in the sympathetic ganglia [2] and decreased MIBG uptake has been established as a biomarker of Lewy body pathology *in vivo*. Decreased MIBG uptake has also been reported in some cases of PSP; concomitant PD pathology, involvement of the autonomic nervous system, and cardiovascular events have been postulated as causes [3]. These causes are unrelated to the present case and pathologically the cardiac nerves were well preserved. Functional abnormalities of the cardiac sympathetic nerve terminal may be responsible for the decreased MIBG uptake. For example, in the early scintigraphy image, dysfunction of noradrenergic transporters or monoamine transporters, or antagonism between MIBG and norepinephrine could be responsible for decreased MIBG uptake. In the delayed image, increased exocytosis due to hyperactivity of sympathetic function, reduced reuptake due to dysfunction of monoamine transporters could be responsible for decreased MIBG uptake. Proving the presence of these conditions with the neuropathological methods currently available is difficult; however, it is possible to evaluate cardiac nerve denervation. These conditions may be present in PSP or in only the akinetic mutism state like in the present case. We should examine many more cases of autopsy-proven PSP cases that include MIBG scintigraphy in clinical practice.

4. Conclusion

This case provides important information about the interpretation of MIBG scintigraphy in clinical practice.

References

[1] Orimo S, Ozawa E, Nakade S, Sugimoto T, Mizusawa H. (123)I-metaiodobenzylguanidine myocardial scintigraphy in Parkinson's disease. Journal of Neurology, Neurosurgery and Psychiatry 1999;67:189–94.
[2] Orimo S, Amino T, Itoh Y, Takahashi A, Kojo T, Uchihara T, et al. Cardiac sympathetic denervation precedes neuronal loss in the sympathetic ganglia in Lewy body disease. Acta Neuropathologica 2005;109:583–8.
[3] Yoshita M. Differentiation of idiopathic Parkinson's disease from striatonigral degeneration and progressive supranuclear palsy using iodine-123 meta-iodobenzylguanidine myocardial scintigraphy. Journal of the Neurological Sciences 1998;155:60–7.
[4] Litvan I, Agid Y, Calne D, Campbell G, Dubois B, Duvoisin RC, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele–Richardson–Olszewski syndrome): report of the NINDS-SPSP international workshop. Neurology 1996;47:1–9.
[5] Wada-Isoe K, Kitayama M, Nakaso K, Nakashima K. Diagnostic markers for diagnosing dementia with Lewy bodies: CSF and MIBG cardiac scintigraphy study. Journal of the Neurological Sciences 2007;260:33–7.

Journal of Alzheimer's Disease 37 (2013) 691–698
DOI 10.3233/JAD-130398
IOS Press

Differences in the Prevalence of Dementia and Mild Cognitive Impairment and Cognitive Functions between Early and Delayed Responders in a Community-Based Study of the Elderly

Moeko Noguchi-Shinohara[a], Sohshi Yuki[a], Chiaki Dohmoto[a], Yoshihisa Ikeda[a], Miharu Samuraki[a], Kazuo Iwasa[a], Masami Yokogawa[b], Kimiko Asai[c], Kiyonobu Komai[d], Hiroyuki Nakamura[e] and Masahito Yamada[a,*]

[a]*Department of Neurology and Neurobiology of Aging, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan*
[b]*Department of Physical Therapy, School of Health Sciences, College of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kanazawa, Japan*
[c]*Bishoen Geriatric Health Services Facility, Suzu, Japan*
[d]*Department of Neurology, Ioh Hospital, National Hospital Organization, Kanazawa, Japan*
[e]*Department of Environmental and Preventive Medicine, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan*

Handling Associate Editor: Robert Friedland

Accepted 29 May 2013

Abstract. Significant differences exist in demographic characteristics between responders and non-responders in population-based studies on mental health and cognitive status, but much less is known regarding differences in the prevalence of dementia and cognitive dysfunction between them. Here we compared the prevalence of dementia and mild cognitive impairment between early responders of a mass brain function examination and delayed responders (non-responders of the mass brain function examination) in a survey of elderly Japanese citizens (≥65 years) to evaluate non-responder bias. All residents in an area of Nakajima, Japan, were considered as potential candidates ($n=783$). Participants of a mass brain function examination were considered as "early responders." The cognitive functions of delayed responders were assessed by home visits. To assess the correlation between sociodemographic characteristics and cognitive functions, the early and delayed responders completed the same questionnaires and neuropsychological tests. Delayed responders ($n=320$) were significantly older and less educated than the early responders ($n=307$). The delayed responders also exhibited a higher frequency of dementia and mild cognitive impairment than the early responders, even when the groups were restricted to the age group 65–89 years. Our results suggest that population-based studies likely underestimate the prevalence of dementia and mild cognitive impairment, especially if the participation rate is low.

Keywords: Bias, dementia, mild cognitive impairment, prevalence, prospective studies

*Correspondence to: Masahito Yamada, Department of Neurology and Neurobiology of Aging, Kanazawa University Graduate School of Medical Science, 13-1 Takara-machi, Kanazawa 920-8640, Japan. Tel.: +81 76 265 2290; Fax: +81 76 265 4253; E-mail: m-yamada@med.kanazawa-u.ac.jp.

ISSN 1387-2877/13/$27.50

INTRODUCTION

The prevalence of dementia is increasing as the population ages, and age-related loss of brain function that occurs with certain diseases has become a serious social problem in most Asian and Western countries [1–3]. The estimated number of people with dementia worldwide is 24.3 million [1]. Dementia prevalence at age >60 years was estimated to be 4.3–6.4%, and that at age >85 years be 22.1–30.1% in Western Europe, North America, and developed regions of Western Pacific [1]. Japanese community-based studies have investigated the age-adjusted prevalence of dementia, with values ranging from 5.9% to 11.6% in the elderly (≥65 years) [4–8], but the accuracy of these estimates is debatable. A population-based cohort study investigated the correlation between lifestyle and the prevalence of dementia [9] from 2006 to 2012 among the residents of Nakajima in the Nanao distinct of Ishikawa Prefecture, Japan. All residents of Nakajima aged ≥60 years were eligible to receive a free annual evaluation of their physical health and brain function using a battery of neurological and cognitive tests to estimate the prevalence of dementia. During the recruitment period from 2006 to 2009, however, more than 60% of those invited to participate did not respond to our invitation, and the prevalence of dementia among the participants of our study was only 1.6%. Considering this high non-participation rate, there is concern that the results of the Nakajima study do not accurately reflect the rates of cognitive and neurological dysfunction in the total elderly population of this region.

Results from population-based studies must be validated by estimating the potential non-responder bias, a type of selection bias. Many authors have discussed the consequences of self-selection and low participation in prospective studies [10, 11]. The effects of self-selection may be especially large in studies estimating the prevalence of dementia, particularly in studies with low participation rates. Many studies have reported differences in the distribution of demographic characteristics between participants and non-participants [12–14]. For example, Miyamoto et al. [15] reported that the prevalence of mild cognitive impairment (MCI) was higher in non-participants than participants. However, the prevalence of dementia in non-participants is difficult to estimate as the influence of self-selection bias remains unknown.

We hypothesized that the prevalence of dementia and MCI was higher in non-responders than responders of brain function surveys. To evaluate potential bias caused by self-selection in surveys on brain functions, we studied the differences in the prevalence of dementia and MCI and other associated measures between early responders and delayed responders. For delayed responders, we performed door-to-door examinations to assess brain functions. Therefore, the objective of this study was to evaluate self-selection bias in dementia screening in the general population.

MATERIALS AND METHODS

Study subjects

This cross-sectional study was conducted as a part of the Nakajima project in Nakajima, Ishikawa Prefecture, Japan, between June 2010 and February 2012. The total population of Nakajima in 2010 was 6,795 (3,227 men and 3,568 women), and the number of elderly people aged ≥65 years was 2,331, representing 34.3% of the total population. The proportion of the elderly in Nakajima was higher to that of the whole of Japan in 2010, and would be almost identical with that of the whole of Japan in the future of 30 years later. The total population of the town has been stable for longtime. We targeted all inhabitants who were legally residing in a southern area of Nakajima on the prevalence day (1 April 2010), aged ≥65 years, and the 783 inhabitants (320 men and 463 women) meeting the age requirement were considered potential candidates. The total population of the southern area of Nakajima was 2,116 (1,019 men and 1,097 women). Age distribution and gender ratios of the total population in the southern area were almost similar to those of the entire town of Nakajima. A mass examination of the cognitive functions was conducted in public town halls. Recruitment started in May 2010 by advertising in letters for individuals and flyers around public town halls. Nakajima project was supported by Nanao city, and the information of the residence was used to list target candidates and to send invitations of mass examination. To assess the cognitive function of non-participants, we visited them at home. The home survey included the same questionnaires on personal lifestyle, medical conditions, and activities of daily living (ADL) as well as the same neuropsychological tests used in the mass examination in public town halls. This phase of the Nakajima study was conducted with the help of collaborators of the neighborhood association (local welfare commissioners and chairmen of the neighborhood association) with the hope that their cooperation would encourage participation by the reluctant residents. Before scheduling an in-home examination, a letter was sent

to each potential candidate explaining the objectives of the study. Researchers and collaborators visited individuals at least two times to invite them to participate in the study. Individuals with whom a collaborator of the neighborhood association and the present researchers could not meet or contact despite sending two separate letters were excluded. This research was conducted by six neurologists, two psychologists, five nurses, one physiotherapist, and one occupational therapist, all of whom were specifically trained for this study. Regarding individuals who were institutionalized in a long-term care facility or a hospital, we examined the persons when we obtained the written informed consent to investigate the individual from their families. We visited 31 persons and performed the same examinations used to evaluate the other participants.

Questionnaires and neuropsychological evaluations

Each participant completed a self-administered questionnaire that queried sociodemographic data (including age, gender, and education) and instrumental ADL (IADL) [16]. The completed questionnaires were reviewed by trained researchers to identify inconsistent answers and unanswered items. The IADL inventory asked whether the individual could perform eight ADL tasks "independently," "with some help," or "not at all." The evaluated activities included the following: traveling within walking distance, using the telephone, shopping for groceries and clothes, preparing meals, performing housework, washing clothes, managing medicine, and handling money. These responses were scored "1" for "unable" or "0" for "independently" or "with some help," for a total IADL impairment score of 0–8. To assess the cognitive status, all participants completed neuropsychological tests, including the Mini-Mental State Examination (MMSE) [17] and the Clinical Dementia Rating (CDR) [18–20]. The CDR is a dementia staging instrument used to rate cognitive function along five levels of impairment from none to maximal (rated as 0, 0.5, 1, 2 or 3) in each of the following six domains: memory, orientation, judgment and problem solving, function in community affairs, home and hobbies, and personal care. A global CDR score was calculated using an algorithm that takes into account each subscore. The overall possible range of global CDR score is 0 (indicating a normal healthy individual with no cognitive or functional deficits), 0.5 (a normal healthy individual but with questionable cognitive and/or functional abilities), 1 (mild dementia), 2 (moderate dementia), and 3 (severe dementia).

Diagnosis of dementia and MCI

Diagnosis of dementia was based on the guidelines of the Diagnostic and Statistical Manual of Mental Disorders, third edition, revised (DSM-III-R) [21], whereas diagnosis of MCI was established according to the International Working Group on general criteria for MCI [22], which state that (1) persons should be judged as abnormal using other modalities besides not fulfilling the DSM-III-R dementia criteria, (2) functional activities of the person are mainly preserved or at least impairment is minimal and (3) the person should have evidence of cognitive decline, either by self-assessment and/or the use of an informative report in conjunction with deficits on the objective cognitive tasks. Among participants without dementia, a CDR score of 0.5 was used as the objective cognitive impairment value to denote cognitive and functional impairment consistent with MCI.

Ethical considerations

This study was conducted with the approval of the medical ethics review board of Kanazawa University (Kanazawa, Japan). All participants provided written informed consent using a form that included the purpose and procedures of the research, potential risks and benefits associated with participation, the strict voluntary nature of participation, the right to withdraw from the research without prejudice or penalty, and a guarantee of confidentiality and security of personal data.

Statistical analyses

Prevalence and 95% confidence intervals (CI) were calculated for dementia and MCI. Adjusted prevalence of dementia was estimated with 95% CI by a direct method with five-year age groupings and gender [23], where the total population in Japan in 2010 [24] was used as a standard population. Comparisons between data on groups of subjects (i.e., early responders versus delayed responders) were performed with analysis of variance, chi-square, or Mann–Whitney tests as appropriate. A two-sided p-value of <0.05 was considered statistically significant in all analyses. Taking into account the characteristics, dementia and MCI prevalence associated with response to brain function survey, the multivariate logistic regression model was established using standard statistical modeling. The

SPSS software package (version 12.0J; SPSS Inc., Chicago, IL, USA) was used to perform all statistical analyses.

RESULTS

Of the 783 potential candidates, 58 were excluded: 20 died, eight relocated, and 30 could not be contacted. Thus, the remaining 725 residents were considered as candidates at baseline. A total of 308 candidates participated in the brain function examination at the public town halls (participation rate = 42.5%). These subjects were considered "early responders." Residents who participated in the in-home survey ($n = 322$, 44.4%) were considered "delayed responders." In addition, 31 institutionalized individuals (4.3%) were enrolled. In total, 661 residents (91.2% of candidates at baseline) participated in the present study, and 64 residents who refused to participate in our study were final non-responders (Fig. 1). We excluded eleven subjects; those with psychiatric illnesses ($n = 4$), consciousness disturbances ($n = 3$), cerebral palsy ($n = 1$), or those who failed to complete the cognitive tests ($n = 3$). Finally, data from 650 subjects (263 men and 387 women) were analyzed for the prevalence of dementia.

The sociodemographic characteristics of the study subjects and indices of their cognitive status are presented in Table 1. The mean overall age was 76 years, and the proportion of women was 59.5%. The final non-responder group was significantly older (mean ± SD: 78.4 ± 7.8 years, $p < 0.05$) than overall study subjects. A total of 76 subjects (29 men and 47 women) fulfilled the diagnostic criteria for dementia, yielding a prevalence of dementia of 11.6 cases/100 persons aged ≥65 years (95% CI, 9.3–14.6). The age and gender adjusted prevalence of dementia in Japan in participants aged ≥65 years was estimated to be 10.4 cases/100 persons, according to the data from this study. In total, 107 subjects (41 men and 66 women) fulfilled the diagnostic criteria for MCI, yielding a prevalence of 16.4% (95% CI, 13.6–19.9) in elderly individuals aged ≥65 years. The age and gender adjusted prevalence of MCI in Japan in participants aged ≥65 years was 15.4 cases/100 persons. Of the 76 subjects diagnosed with dementia, seven were assessed with a CDR score of 0.5 (9.2%), 36 with 1 (47.4%), 17 with 2 (22.4%), and 16 with 3 (21.0%). Compared to normal subjects, those with dementia and MCI were significantly older ($p < 0.001$), had significantly fewer years of formal education ($p < 0.001$), and were institutionalized significantly more ($p < 0.001$). The MMSE scores ranged from 5 to 30 points in the study subjects. The Supplementary Fig. 1 illustrated the skewed nature of the distribution of the MMSE scores, with heavy clustering at the higher scores.

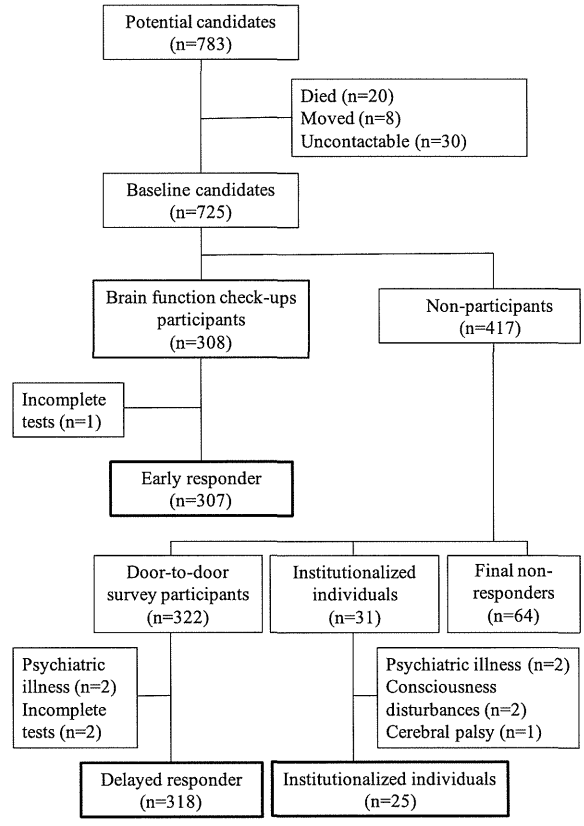

Fig. 1. A flow chart of the survey method conducted at Nakajima, Japan in 2010. The number of subjects involved in each step is shown.

Of the 650 subjects enrolled in this study, 307 were early responders, 318 were delayed responders, and 25 were institutionalized. A comparison between the early and delayed responders (Table 2) showed no difference in gender ratio. Compared to the early responder group, the delayed responder group was significantly older ($p = 0.05$) and had significantly fewer years of formal education ($p = 0.01$), significantly lower MMSE score ($p < 0.001$), significantly higher mean CDR and IADL scores ($p < 0.001$ and $p < 0.001$, respectively), and higher frequencies of dementia and MCI ($p < 0.001$ and $p < 0.001$, respectively). In a multivariate logistic regression analysis, MCI and dementia were associated with delayed response [odds ratio (OR) (95% CI, p value): 1.65 (1.03–2.63, 0.037) and 2.39 (1.20–4.77, 0.014), respectively]. In addition, fewer years of formal education was associated with delayed response [OR (95% CI, p value): 0.90

Table 1
Characteristics of study population by cognitive dysfunction

	All subjects ($n=650$)	Normal ($n=467$)	MCI ($n=107$)	Dementia ($n=76$)	p value[#]
Age, years, mean (SD)	76.4 (7.3)	74.2 (6.1)	80.3 (7.7)	84.3 (6.1)	<0.001
Women, %	59.5	58.9	61.7	61.8	N.S
Education, years, mean (SD)	9.6 (2.3)	10.0 (2.3)	8.6 (1.9)	8.3 (1.9)	<0.001
Place of residence, n					<0.001
Home	625	466	106	53	
Health care facility or hospital	25	1	1	23	
MMSE, points, mean (SD)	25.8 (4.5)	27.6 (2.5)	23.3 (3.1)	16.3 (4.9)	<0.001
CDR, n (%)					<0.001
0	467 (71.9)	467 (100)	0	0	
0.5	114 (17.5)	0	107 (100)	7 (9.2)	
>1	69 (10.6)	0	0	69 (90.8)	
IADL, points, mean (SD)	0.54 (1.48)	0.05 (0.38)	0.76 (1.34)	3.47 (2.55)	<0.001

[#]p-value was assessed between subjects with and without dementia.

Table 2
Differences in characteristics, cognitive functions, and dementia and MCI prevalence between early and delayed responders

	All subjects ($n=625$)	Early responder ($n=307$)	Delayed responder ($n=318$)	p value[#]
Age, years, mean (SD)	76.1 (7.2)	75.2 (6.3)	77.0 (7.8)	<0.05
Women, %	60.0	62.2	57.9	N.S
Education, years, mean (SD)	9.6 (2.3)	9.9 (2.4)	9.3 (2.2)	0.01
MMSE, points, mean (SD)	26.0 (4.1)	27.0 (3.3)	25.0 (4.6)	<0.001
CDR, n (%)				<0.001
0	466 (74.6)	254 (82.7)	212 (66.7)	
0.5	113 (18.0)	42 (13.7)	71 (22.3)	
>1	46 (7.4)	11 (3.6)	35 (11.0)	
IADL, points, mean (SD)	0.37 (1.12)	0.15 (0.62)	0.59 (1.43)	<0.001
Dementia, n (%)	53 (8.5)	15 (4.9)	38 (11.9)	<0.001
MCI, n (%)	106 (17.0)	38 (12.4)	68 (21.4)	<0.001

[#]p-value was assessed between the early and delayed responder subjects.

Table 3
Odds ratios for the univariate and multivariate association between variables and delayed response

	Unadjusted models		Adjusted models	
	OR (95% CI)	p	OR (95% CI)	p
Age, years	1.04 (1.01–1.06)	0.002*	1.00 (0.98–1.03)	0.791
Gender (Women)	0.83 (0.61–1.15)	0.267	0.75 (0.53–1.05)	0.097
Education, years	0.88 (0.82–0.94)	0.000*	0.90 (0.83–0.98)	0.013*
Cognitive status				
MCI	2.06 (1.33–3.20)	0.001*	1.65 (1.03–2.63)	0.037*
Dementia	3.00 (1.61–5.61)	0.001*	2.39 (1.20–4.77)	0.014*

*$p<0.05$. Adjusted odds ratios (ORs) were calculated after controlling for age, gender, education and cognitive status. CI, confidence interval.

(0.83–0.98, 0.013)]. There was no association between age or gender and delayed response [OR (95% CI, p value): 1.00 (0.98–1.03, 0.791) and 1.33 (0.95–1.88, 0.097), respectively] (Table 3). Compared to the early responder group, the final non-responder group was significantly older ($p<0.005$). However, the mean age of the final non-responder group did not significantly differ from that in the delayed responder group. We did not have information about either gender or education concerning the final non-responders.

We also analyzed the data from subjects restricted to the age group 65–89 years. As shown in Table 4, the frequencies of dementia and MCI were higher in the age restricted subgroup of the delayed responders compared with that of the age restricted early responders ($p<0.001$ and $p<0.001$, respectively). The age restricted delayed responder subgroup also reported significantly fewer years of formal education ($p<0.005$). The mean MMSE score of the delayed responder subgroup was significantly lower ($p<0.001$)

Table 4
Differences in characteristics, cognitive functions, and dementia and MCI prevalence between early and delayed responders in subjects aged 65–89 years

	All subjects ($n=596$)	Early responder ($n=300$)	Delayed responder ($n=296$)	p value[#]
Age, years, mean (SD)	75.3 (6.3)	74.8 (5.8)	75.8 (6.8)	N.S
Women, %	58.9	62.0	56.1	N.S
Education, years, mean (SD)	9.6 (2.3)	9.9 (2.3)	9.3 (2.1)	<0.005
MMSE, points, mean (SD)	26.3 (3.9)	27.1 (3.2)	25.4 (4.4)	<0.001
CDR, n (%)				<0.001
0	460 (77.2)	253 (84.3)	207 (69.9)	
0.5	98 (16.4)	37 (12.3)	61 (20.6)	
>1	38 (6.4)	10 (3.4)	28 (9.5)	
IADL, points, mean (SD)	0.29 (0.96)	0.13 (0.59)	0.45 (1.22)	<0.001
Dementia, n (%)	45 (7.6)	14 (4.7)	31 (10.5)	<0.001
MCI, n (%)	91 (15.3)	33 (11.0)	58 (19.6)	<0.001

[#]p-value was assessed between the early and delayed responder subjects.

and the CDR and the IADL scores significantly higher than those in the age restricted early responder subgroup ($p<0.001$ and $p<0.001$, respectively).

DISCUSSION

This study found that the prevalence of dementia and MCI was higher in the delayed responders who did not participate to the brain function examination at the public halls compared to the early responders, even when subjects restricted to the age group 65–89 years. Our results suggest that non-responder bias would lead to an underestimation of the prevalence of dementia and MCI in studies with low participation rates.

The proportion of early responders that participated in the mass examination at the public town halls was limited to 42.5% of the candidate population; however, the participation rate increased dramatically by conducting in-home evaluations of the initial non-responders (delayed responders, 44.4% of the candidate population) and by evaluation of institutionalized individuals (4.3% of the candidate population). The present study demonstrated that the age and gender adjusted prevalence of dementia was 10.4% in an elderly general population of Japanese, slightly lower than that in a recent Japanese report showing an age-adjusted prevalence of dementia of 11.6% in 2008 [7]. There are some possible reasons for the lower prevalence of dementia found in our study. The first was that people with dementia who moved to nursing homes in other areas or lived with their families outside the town were excluded in our study. Second, the mean age of final non-responder group was significantly older than overall study subjects. If we could analyze the data including final non-responders, the dementia prevalence rate would be higher than that of the present study. However, there is considerable divergence in the age-adjusted prevalence of dementia reported in previous Japanese community-based studies, with values ranging from 5.9% to 8.8% [4–6], which is lower than that obtained in the present study. A possible reason for this discrepancy is the difference of the year of total population in Japan, which was used as a standard population. The proportion of those aged ≥65 years in the total population ranged from 9.1% to 20.2% in previous studies, which were conducted from 1980 to 2004, as compared with 23.0% in the present study, performed in 2010. The crude prevalence of MCI in the entire cohort was 16.4%, which was lower as compared to previous Japanese studies that reported the crude prevalence of all types of MCI to be 18.9%–23.4% [7, 25]. The prevalence of MCI would vary between reports probably due to different diagnostic criteria as well as disparate assessment procedures [25, 26].

The participation rates of community-based studies on the prevalence of dementia have been low (48.0% [3] and 61.8% [27]); the low participation rate has raised suspicion that these studies underestimate the true prevalence of dementia because of the significant potential for bias [11]. In this study, delayed responders who did not participate in the mass brain function examinations conducted at public town halls most seemed reluctant to participate in our study. We found a significantly higher prevalence of dementia and MCI in the delayed responders (11.9% and 19.4%, respectively) compared to the early responders (4.6% and 11.0%, respectively). Even with the exclusion of the institutionalized individuals, the overall prevalence of dementia and MCI (8.5% and 16.6%, respectively) were significantly higher than that of the early responders. Thus, inclusion of the delayed responders greatly increased the estimated prevalence of dementia and

MCI in this study population. However, the mean age of the delayed responder group was also significantly greater, which could lead to a higher incidence of dementia and MCI. Thus, we compared the data restricted to the age groups (subjects aged 65–89 years) of the early and delayed responders and found that the prevalence of dementia and MCI were still significantly higher in the delayed responders. Additionally, multivariate logistic regression analysis revealed that fewer years of formal education and poor cognitive status (MCI or dementia) were associated with delayed response.

To our knowledge, the present study is the first to examine the difference in the estimated prevalence of dementia and MCI between early and delayed responders using a same comprehensive battery of neuropsychological tests. Several previous epidemiological investigations [12–15] have studied the differences in the demographic characteristics between non-responder and responder groups. Two of these studies [12, 14] also examined neuropsychological tests in a part of non-responders. However, these studies did not investigate the prevalence of dementia in non-responders using internationally accepted diagnostic criteria. One of these studies [15] investigated the prevalence of dementia and MCI in delayed responders, who did not respond to the first recruitment, and revealed that the prevalence of MCI was significantly higher for delayed responders aged $\leq$74 years than quick responders who responded to the first recruitment. However, in contrary to our results, there was no difference in the prevalence of dementia between the quick and delayed responders in an adjusted model controlling for age, gender, and years of education. In contrast to our results, a previous study [13] with a high response rate (82.5%) reported that non-responders had no significant influence on the overall prevalence of dementia. In accordance with our results, however, Kahn [11] emphasized that non-responder bias was significant in epidemiologic studies with lower participation rates.

In the present study, the delayed responders and the final non-responders were likely to be older and the delayed responders have fewer years of formal education. Similarly, non-participants in other studies were older [12, 13, 15] and had fewer years of formal education [14, 15]. Also consistent with previous reports [13–15], there were no differences in the participation rates between men and women. On the other hand, the Canadian Study of Health and Aging [12] reported that women were more likely to be non-participants than men.

The delayed responders scored lower on the MMSE and higher on the CDR and IADL in comparison to the early responder group and these differences were also observed between the age restricted subgroups. In accordance with our results, Miyamoto et al. [15] reported that the scores on a Category Cued Recall test [28] and the N geriatric rating scale for ADL [29] were significantly lower (indicating poorer function) for delayed responders than quick responders. In addition, the greater cognitive decline in the delayed responder group in our study agreed with the higher prevalence of dementia and MCI.

One important limitation was the relatively small size of the population surveyed. In addition, we did not evaluate the causes of dementia and MCI with diagnostic tools such as neuroimaging and neuropathology. Further study with neuroimaging and neuropathology is needed to reveal the each prevalence of the cause of dementia and MCI in elderly population and to evaluate the effects of self-selection bias for each cause of dementia.

The strengths of the current study included the population-based study design and a high response rate (>91%). Another strength was a stable population of Nakajima town.

In conclusion, delayed responders in our community survey were associated with more cognitive decline, and higher prevalence of dementia and MCI. Our results indicated that the prevalence of dementia and MCI is likely underestimated in population-based studies with low participation rates.

ACKNOWLEDGMENTS

We wish to thank all of the residents of Nakajima for their participation in the present study. This study was supported by a grant for the Hokuriku Innovation Cluster for Health Science from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=1816).

SUPPLEMENTARY MATERIAL

Supplementary material can be found here: http://dx.doi.org/10.3233/JAD-130398.

REFERENCES

[1] Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Gaunguli M, Hall K, Hasegawa K, Hendrie H, Huang Y, Jorm A, Mathers C, Menezes PR, Rimmer E, Scazufca M, Alzheimer's

Disease International (2005) Global prevalence of dementia: A Delphi consensus study. *Lancet* **366**, 2112-2117.
[2] Lobo A, Launer LJ, Fratiglioni L, Andersen K, Di Carlo A, Breteler MMB, Copeland JRM, Dartigues J-F, Jagger C, Martinez-Lage J, Soininen H, Hofman A (2000) Prevalence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. *Neurology* **54**, S4-S9.
[3] Kukull WA, Higdom R, Bowen JD, McCormick WC, Teri L, Schellenberg GD, Belle G, Jolley L, Larson EB (2002) Dementia and Alzheimer disease incidence. *Arch Neurol* **59**, 1737-1746.
[4] Wakutani Y, Kusumi M, Wada K, Kawashima M, Ishizaki K, Mori M, Mori N, Ijiri T, Adachi Y, Asada Y, Kuno N, Urakami K, Takeshima T, Nakashima K (2007) Longitudinal changes in the prevalence of dementia in a Japanese rural area. *Psychogeriatrics* **7**, 150-154.
[5] Wada-Isoe K, Uemura Y, Suto Y, Doi K, Imamura K, Hayashi A, Kitayama M, Watanabe Y, Adachi Y, Nakashima K (2009) Prevalence of dementia in the rural island town of Ama-cho, Japan. *Neuroepidemiology* **32**, 101-106.
[6] Sekita A, Ninomiya T, Tanizaki Y, Doi Y, Hata J, Yonemoto K, Arima H, Sasaki K, Iida M, Iwaki T, Kanba S, Kiyohara Y (2010) Trends in prevalence of Alzheimer's disease and vascular dementia in Japanese community: The Hisayama Study. *Acta Psychiatr Scand* **122**, 319-325.
[7] Wada-Isoe K, Uemura Y, Nakashita S, Yamawaki M, Tanaka K, Yamamoto M, Shimokata H, Nakashima K (2012) Prevalence of dementia and mild cognitive impairment in the rural island town of Ama-cho, Japan. *Dement Geriatr Cogn Disord Extra* **2**, 190-199.
[8] Ikejima C, Hisanaga A, Meguro K, Yamada T, Ouma S, Kawamuro Y, Hyouki K, Nakashima K, Wada K, Yamada S, Watanabe I, Kakuma T, Aoyama Y, Mizukami K, Asada T (2012) Multicentre population-based dementia prevalence survey in Japan: A preliminary report. *Psychogeriatrics* **12**, 120-123.
[9] Sugano K, Yokogawa M, Yuki S, Dohmoto C, Yoshita M, Hamaguchi T, Yamase D, Iwasa K, Komai K, Yamada M (2012) Effect of cognitive and aerobic training intervention on older adults with mild or no cognitive impairment: A derivative study of the Nakajima Project. *Dement Geriatr Cogn Disord Extra* **2**, 69-80.
[10] Rothman KJ, Greenland S, Lash TL (2008) Modern epidemiology, 3rd edition. Lippincott Williams & Wilkins, Philadelphia.
[11] Kahn H (1983) *An Introduction to Epidemiologic Methods*, Oxford University Press, New York.
[12] Helliwell B, Aylesworth R, McDowell I, Baumgarten M, Sykes E (2001) Correlates of nonparticipation in the Canadian study of health and aging. *Int Psychogeriatrics* **1**(13 Supp), 49-56.
[13] Boersma F, Eefsting JA, Brink WVD, Tilburg W (1997) Characteristics of non-responders and the impact of non-response on prevalence estimates of dementia. *Int J Epidemiol* **26**, 1055-1062.
[14] Launer LJ, Wind AW, Deeg DJH (1994) Nonresponse pattern and bias in a community-based cross-sectional study of cognitive functioning among the elderly. *Am J Epidemiol* **139**, 803-812.
[15] Miyamoto M, Kodama C, Kinoshita T, Yamashita F, Hidaka S, Mizukami K, Kakuma T, Asada T (2009) Dementia and mild cognitive impairment among non-responders to a community survey. *J Clin Neurosci* **16**, 270-276.
[16] Katz S (1983) Assessing self maintenance. Activities of daily living, mobility, and instrumental activities of daily living. *J Am Geriatr Soc* **31**, 721-727.
[17] Folstein MF, Folstein SE, McHugh PR (1975) "Mini-Mental State": A practical method for grading the cognitive state of patients for clinician. *J Psychiatr Res* **12**, 189-198.
[18] Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL (1982) A new clinical scale for the staging of dementia. *Br J Psychiatry* **140**, 566-572.
[19] Morris JC (1993) The Clinical Dementia Rating (CDR): Current version and scoring rules. *Neurology* **43**, 2411-2413.
[20] Morris JC, Storandt M, Miller JP, McKeel DW, Price JL, Rubin EH, Berg L (2001) Mild cognitive impairment represents early-stage Alzheimer disease. *Arch Neurol* **58**, 397-405.
[21] American Psychiatric Association (1987) Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised. American Psychiatric Association, Washington DC.
[22] Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund L-O, Nordberg A, Bäckman L, Albert M, Almkvist O, Arai H, Basun H, Blennow K, Deleon M, Decarli C, Erkinjuntti T, Giacobini E, Graff C, Hardy J, Jack C, Jorm A, Ritchie K, Van Duijn C, Visser P, Petersen RC (2004) Mild cognitive impairment-beyond controversies, towards a consensus: Report of the international working group on mild cognitive impairment. *J Intern Med* **256**, 240-246.
[23] Hennekens CH, Buring JE (1987) Epidemiology in Medicine. Lippincott Williams & Wilkins, Philadelphia, USA.
[24] Total population by age (five-year groups) and sex in Japan according to the results of the national census taken in 2010, http://www.e-stat.go.jp/SG1/estat/eStatTopPortal.do. Accessed December 12, 2012.
[25] Sasaki M, Kodama C, Hidaka S, Yamashita F, Kinoshita T, Nemoto K, Ikejima C, Asada T (2009) Prevalence of four subtypes of mild cognitive impairment and APOE in a Japanese community. *Int J Geriatr Psychiatry* **24**, 1119-1126.
[26] Saxton J, Snitz BE, Lopez OL, Ives DG, Dunn LO, Fitzpatrick A, Carlson MC, Dekosky ST (2009) Functional and cognitive criteria produce different rates of mild cognitive impairment and conversion to dementia. *J Neurol Neurosurg Psychiatry* **80**, 737-743.
[27] Petersen RC, Roberts RO, Knopman DS, Geda YE, Cha RH, Pankratz VS, Boeve BF, Tangalos EG, Ivnik RJ, Rocca WA (2010) Prevalence of mild cognitive impairment is higher in men. *Neurology* **75**, 889-897.
[28] Grober E, Buschke H, Crystal H, Bang S, Dresner R (1988) Screening for dementia by memory testing. *Neurology* **38**, 900-903.
[29] Nishimura T, Kobayashi T, Hariguchi S, Takeda M, Fukunaga T, Inoue O, Kondo H, Niigawa H, Tanaka S, Yamashita M (1993) Scales for mental state and daily living activities for the elderly: Clinical behavioral scales for assessing demented patients. *Int Psychogeriatr* **5**, 117-134.

PSYCHOGERIATRICS
The Official Journal of the Japanese Psychogeriatric Society

doi:10.1111/psyg.12012 *PSYCHOGERIATRICS* 2013; **13:** 199–205

ORIGINAL ARTICLE

Clinical utility of the Functional Independence Measure for assessment of patients with Alzheimer's disease and vascular dementia

Naofumi TANAKA,[1,2] Masahiro NAKATSUKA,[1] Hiroshi ISHII,[1,2] Rie NAKAYAMA,[2] Ryoko HOSAKA[2] and Kenichi MEGURO[1]

[1]Department of Geriatric Behavioral Neurology, Tohoku University Graduate School of Medicine, Sendai, and [2]Department of Rehabilitation Medicine and Neurology, Kawasaki Kokoro Hospital, Kawasaki, Japan

Correspondence: Dr Kenichi Meguro MD, Department of Geriatric Behavioral Neurology, Tohoku University Graduate School of Medicine, Sendai 980-8575, Japan. Email: k-meg@umin.ac.jp

Received 1 May 2012; revision received 8 July 2012; accepted 14 March 2013.

Abstract

Aim: The aim of this study was to investigate the clinical utility of the Functional Independence Measure (FIM), and especially FIM-Cognition (FIM-C) scores, in patients with Alzheimer's disease (AD) and vascular dementia (VaD), and to determine the influence of behavioural and psychological symptoms of dementia (BPSD) on FIM-C scores.

Methods: This was a cross-sectional survey of 37 AD and 40 VaD patients. Cognitive function was assessed with the Cognitive Abilities Screening Instrument. Activities of daily living were evaluated with the FIM and the Barthel Index. BPSD were assessed with the Behavioural Pathology in Alzheimer's Disease Frequency Weighted Severity Scale.

Results: For both groups, Spearman's correlations were found between FIM-Motor and Barthel Index scores and between FIM-C and Mini Mental State Examination scores. Each FIM-C subscore was correlated with Cognitive Abilities Screening Instrument scores in both groups, except for the FIM-C *Social interaction* subscore in VaD. VaD patients showing *Activity Disturbance* and *Aggressiveness* on the Behavioural Pathology in Alzheimer's Disease Frequency Weighted Severity Scale had significantly lower FIM-C *Memory* and *Social interaction* subscores than those without BPSD.

Conclusion: The results suggest that the FIM-Motor and FIM-C scales are useful measures of physical and cognitive disabilities in patients with AD and VaD. The FIM-C profile of AD may reflect global cognitive function, while that of VaD may be more influenced by BPSD.

Key words: *activities of daily living, Alzheimer's disease, behavioural symptoms, dementia, vascular dementia.*

INTRODUCTION

Dementia is becoming increasingly common as the population of older adults grows,[1] and patients with dementia are often encountered in rehabilitation settings such as those for stroke or fracture. Rehabilitation medicine aims to improve impaired activities of daily living (ADL) and should be available as a therapeutic option for ADL disabilities in patients with dementia. Assessment of ADL is an important outcome measure in these patients, but ADL in dementia are disturbed not simply by motor dysfunction, such as that due to accompanying hemiparesis, but by primary symptoms of cognitive deterioration.[2] Thus, a method that can assess cognitive function, as well as ADL levels, is required in rehabilitation medicine for dementia.

The Functional Independence Measure (FIM) and Barthel Index (BI) are well-known observational ADL scales in rehabilitation medicine.[3,4] The FIM measures a patient's ability to function independently in ADL, and it can assess both physical and cognitive functions.[5,6] It consists of 18 subscales that are divided into two main categories: 13 motor (FIM-Motor: FIM-M) and 5 cognitive (FIM-Cognition: FIM-C) subscales with 7 severity levels each. The 13 FIM-M subscales are part of four larger categories: *Self-care* (feeding, grooming, and dressing), *Sphincter control* (bladder and bowel management), *Mobility* (transferring in and

out or on and off a bed, toilet, or tub), and *Locomotion* (walking or wheelchair use, and use of stairs). The FIM-C consists of five subscales: *Comprehension*, *Expression*, *Social interaction*, *Problem solving*, and *Memory*. All item scores range from 1 (total assistance, the lowest possible score) to 7 (complete independence, the best possible score). The FIM-M has been validated with the BI,[7] which is designed to evaluate a patient's self-care abilities.

Surprisingly, only a few studies have applied the FIM to dementia patients, for whom cognitive dysfunction and ADL disturbance are the main clinical problems.[8,9] To our knowledge, the relationships between FIM-C subscales and cognitive domains assessed by neuropsychological tests have not been examined, although several studies have reported that the FIM-C score is correlated with the Mini-Mental State Examination (MMSE) score in stroke patients and patients with hip fractures.[10–12] However, assessment of these relationships would be improved by use of a more detailed neuropsychological test than the MMSE.

Abnormal behaviours such as wandering or agitation,[13,14] which have recently been referred to as behavioural and psychological symptoms of dementia (BPSD),[15] may also affect ADL. Clinically, it is well known that BPSD can inflict a heavy burden on caregivers. It is also likely that BPSD affects FIM-C scores, but to our knowledge these relationships have not been examined. Therefore, the aim of this study was to evaluate the clinical utility of the FIM, and especially the FIM-C, and to examine the influence of BPSD on FIM-C scores in patients with Alzheimer's disease (AD) and vascular dementia (VaD), the first and second most common dementing diseases.[1]

METHODS

Facility

The study was conducted at the Kawasaki Kokoro Hospital (Kawasaki City, Japan). This hospital has 200 beds, including 50 special beds for dementia patients, and provides long-term care for these patients. Magnetic resonance imaging facilities are available, and these can help with the differential diagnosis of dementing diseases.

Patients

The subjects were in-patients with AD and VaD. Brain magnetic resonance imaging with a 1.5-T Excelart scanner (Toshiba Medical Systems, Tochigi, Japan) was used to confirm the diagnosis. The inclusion criteria were diagnosis of probable AD or probable VaD based on National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria.[16,17] The exclusion criteria were the presence of an ADL disability such as hip fracture and a history of cerebral contusion or other systematic disorders that could affect the central nervous system function, such as hypothyroidism or decreases in vitamin B_1, B_6 or B_{12}.

Thirty-seven AD patients and 40 VaD patients were enrolled in the study. The clinical demographics of these patients are shown in Table 1. The groups were similar in age, sex, and years of education (*t*-test, χ^2 test, and *t*-test, respectively; all $P > 0.05$). The AD group tended to have lower MMSE scores than the VaD group, and the VaD group tended to have more hypertensive patients, but the difference was not significant. All assessments were completed within 6 months in each patient.

FIM

Per the standardized manual of FIM,[3] a board-certified physicist (N.T.) scored all patients' FIM scales.

Ethics

Written informed consent was obtained from all patients and from family members according to the Declaration of Helsinki. The study protocol was approved by the Ethical Committees of Tohoku University School of Medicine (Sendai, Japan) and Kawasaki Kokoro Hospital.

Table 1 *Demographic data of the subjects*

	AD	VaD
n	37	40
Sex (women/men)	22/15	21/19
Age, mean ±SD (year)	82.2 ± 6.9	79.3 ± 8.4
Education, mean ± SD (year)	8.6 ± 2.5	8.5 ± 2.8
MMSE, mean ± SD	7.9 ± 6.2	10.9 ± 6.9
Right/Left hemiparesis	0/0	5/4
Vascular risk factors		
Hypertension	8	21
Diabetes mellitus	4	9
Dyslipidemia	4	4
Ischemic heart disease, Arrhythmias	6	4
Antipsychotics use	18	19

Data are shown as mean ± SD. There were no significant differences between the two groups.
AD, Alzheimer's disease; MMSE, Mini-Mental State Examination; VaD, vascular dementia.

Cognitive assessments

Tests were administered by trained neuropsychologists blinded to the diagnosis and FIM findings. Cognitive functions were assessed with the MMSE and the Cognitive Abilities Screening Instrument (CASI).[18] Using the CASI, we previously evaluated the features of mild cognitive impairment and AD,[19] together with patients' neurological background.[20] The test includes the following domains: C1: *Remote memory*, personal semantic memory and general semantic memory; C2: *Recent memory*, immediate and delayed recall of three words and immediate recall of five objects presented visually; C3: *Attention*, repeating three words and two sentences; C4: *Mental manipulation and concentration*, repeating a digit span backwards and serial subtraction of 3 from 100; C5: *Orientation*, age, temporal and spatial orientation; C6: *Figure copying*, copying two intersecting pentagons; C7: *Abstraction and judgement*, abstracting and judging similarities between pairs of items; C8: *List-generating fluency*, generating names of four-legged animals; and C9: *Language*, executing a simple written command, writing a simple dictated sentence, following a three-step oral command, and naming.

Evaluation of BPSD

A standardized Japanese version of the Behavioural Pathology in Alzheimer's Disease Frequency Weighted Severity Scale (BEHAVE-AD-FW) was used to assess BPSD. The assessment was performed by one of the trained nursing staff, who took care of the patients and was blinded to the FIM and cognitive assessments.[21] The BEHAVE-AD-FW consists of seven subcategories: *Paranoid and Delusional Ideation*; *Hallucinations*; *Activity Disturbances* (such as wandering and meaningless behaviour); *Aggressiveness* (including violent behaviour towards others); *Diurnal Rhythm Disturbances* (including disturbance in daily sleeping/waking rhythm); *Affective Disturbance*; and *Anxieties and Phobias*. The total scores were calculated for each category by multiplying the rating severity (0–3) by the frequency (1–4).

Statistical Analyses

FIM-M and ADL scale

To reveal the clinical utility of the FIM-M subscale for assessing ADL, Spearman's correlation analysis was performed between FIM-M and BI scores in the AD and VaD groups.

FIM-C and cognitive scale

To reveal the clinical utility of the FIM-C subscale for assessing cognitive function, Spearman's correlation analysis was performed between FIM-C and both MMSE and CASI scores in the AD and VaD groups. Correlations with each CASI domain were also analysed.

FIM-C and BPSD

To investigate the effects of BPSD on FIM-C subscores, positive and negative differences in these subscores between groups and for each BEHAVE-AD-FW category were compared with an unpaired *t*-test.

Functional differences between AD and VaD groups

To examine different patterns of FIM-M and FIM-C subscores between AD and VaD groups, as well as the cognitive and behavioural variables associated with AD or VaD based on the results of the above analyses, forward stepwise logistic regression analysis were undertaken.

For all analyses, $P < 0.05$ was considered to be significant. A Bonferroni-adjusted comparison was used for multiple comparisons. Statistical analyses were performed using SPSS software v. 17 (IMB, Chicago, IL, USA).

RESULTS

FIM scores

For the AD group, the mean ± SD scores of FIM-M and FIM-C were 73.3 ± 34.8 and 18.1 ± 8.9, respectively, whereas those for the VaD group were 59.9 ± 25.5 and 21.1 ± 7.9, respectively. There were no significant group difference for both FIM scores (*t*-test, $P > 0.05$).

Analysis 1: FIM-M and ADL scale

FIM-M scores were correlated significantly with BI scores in the AD group (rs = 0.90, 95% confidence interval (CI): 0.82–0.95, $P < 0.001$) and in the VaD group (rs = 0.93, 95%CI = 0.88–0.97, $P < 0.001$). These significant correlations had a biologically meaningful basis.

Analysis 2: FIM-C and cognitive scale

FIM-C scores were correlated significantly with MMSE scores in the AD group (rs = 0.86, 95%CI =

0.74–0.93, $P < 0.001$) and in the VaD group (rs = 0.61, 95%CI = 0.37–0.78, $P < 0.001$). Spearman's correlations between FIM-C subscores and MMSE and CASI total scores are shown in Table 2. In the AD group, all FIM-C subscores were significantly correlated with the MMSE and CASI total scores, whereas in the VaD group, all except the *Social interaction* subscore, were correlated. The significant correlations were all biologically meaningful.

Correlations between FIM-C subscores and CASI domains in the AD group are shown in in Table 3. All correlations, except for that between FIM-C *Social interaction* and CASI domain C6 (*Figure copying*), were found to be significant. Correlations between FIM-C subscores and CASI domains in the VaD group are shown in Table 4. All correlations, except for the horizontal line of FIM-C *Social interaction* and the vertical line of CASI domain C3 (*Attention*), were found to be significant. The significant correlations were all biologically meaningful.

Analysis 3: FIM-C and BPSD

In the AD group, there were no differences in FIM-C subscores between patients with and without BPSD; that is, the amount of care required was not associated with BPSD. In the VaD group, there were significant associations of FIM-C subscores with BEHAVE-AD-FW *Activity Disturbances* and *Aggressiveness*, as shown in Table 5. VaD patients with *Activity Disturbances* had significantly lower FIM-C subscores (i.e. higher needs of care) than those without *Activity Disturbances*, except for *Social*

Table 2 Correlations between FIM-C subscores and MMSE and CASI total scores

	AD		VaD	
FIM-C	MMSE	CASI total	MMSE	CASI total
Comprehension	0.76* (0.58–0.87)	0.79* (0.62–0.89)	0.60* (0.36–0.77)	0.63* (0.40–0.79)
Expression	0.83* (0.69–0.91)	0.85* (0.72–0.92)	0.66* (0.44–0.81)	0.70* (0.50–0.83)
Social interaction	0.70* (0.48–0.83)	0.69* (0.47–0.83)	0.32 (0.01–0.57)	0.35 (0.05–0.60)
Problem solving	0.78* (0.62–0.88)	0.80* (0.64–0.89)	0.54* (0.27–0.73)	0.59* (0.34–0.76)
Memory	0.81* (0.65–0.90)	0.85* (0.73–0.92)	0.53* (0.26–0.72)	0.56* (0.31–0.75)

Cells showing significant correlations are shaded (*$P < 0.05$, Spearman's rank correlation with Bonferroni-adjusted comparison). Range of values presented in parentheses is the 95% confidence interval of the correlation.
AD, Alzheimer's disease; CASI, Cognitive Abilities Screening Instrument; FIM-C, Functional Independence Measure-Cognition; MMSE, Mini-Mental State Examination; VaD, vascular dementia.

Table 3 Correlations between FIM-C subscores and CASI domains in patients with Alzheimer's disease

	CASI domains								
FIM-C	C1	C2	C3	C4	C5	C6	C7	C8	C9
Comprehension	0.80* (0.64–0.89)	0.69* (0.47–0.83)	0.74* (0.55–0.86)	0.67* (0.44–0.82)	0.71* (0.50–0.84)	0.59* (0.33–0.77)	0.67* (0.45–0.82)	0.69* (0.47–0.83)	0.77* (0.60–0.88)
Expression	0.76* (0.58–0.87)	0.75* (0.57–0.87)	0.74* (0.55–0.86)	0.72* (0.52–0.85)	0.75* (0.57–0.87)	0.65* (0.42–0.81)	0.76* (0.58–0.87)	0.79* (0.62–0.89)	0.80* (0.64–0.89)
Social interaction	0.60* (0.35–0.78)	0.60* (0.34–0.77)	0.60* (0.34–0.77)	0.58* (0.32–0.76)	0.61* (0.36–0.78)	0.42_ (0.11–0.66)	0.56* (0.28–0.75)	0.55* (0.28–0.74)	0.63* (0.38–0.79)
Problem solving	0.66* (0.43–0.81)	0.75* (0.57–0.87)	0.66* (0.43–0.81)	0.66* (0.42–0.81)	0.65* (0.41–0.80)	0.75* (0.56–0.86)	0.71* (0.51–0.84)	0.73* (0.53–0.85)	0.77* (0.60–0.88)
Memory	0.71* (0.51–0.84)	0.81* (0.65–0.90)	0.70* (0.48–0.83)	0.64* (0.40–0.80)	0.71* (0.51–0.84)	0.75* (0.56–0.86)	0.71* (0.50–0.86)	0.80* (0.50–0.84)	0.82* (0.68–0.91)

Cells showing significant correlations are shaded (*$P < 0.05$, Spearman's rank correlation with Bonferroni-adjusted comparison). Range of values presented in parentheses is the 95% confidence interval of the correlation.
C1, *Remote memory*; C2, *Recent memory*; C3, *Attention*; C4, *Mental manipulation and concentration*; C5, *Orientation*; C6, *Figure copying*; C7, *Abstraction and judgement*; C8, *List-generating fluency*; C9, *Language*; CASI, Cognitive Abilities Screening Instrument; FIM-C, Functional Independence Measure-Cognition.

Table 4 Correlations between FIM-C subscores and CASI domains in patients with vascular dementia

	CASI domains								
FIM-C	C1	C2	C3	C4	C5	C6	C7	C8	C9
Comprehension	0.48* (0.20–0.69)	0.51* (0.24–0.71)	0.42 (0.13–0.65)	0.53* (0.26–0.72)	0.54* (0.27–0.73)	0.53* (0.26–0.72)	0.62* (0.39–0.78)	0.56* (0.31–0.74)	0.61* (0.37–0.77)
Expression	0.57* (0.31–0.75)	0.45* (0.17–0.67)	0.44* (0.15–0.66)	0.64* (0.41–0.79)	0.60* (0.36–0.77)	0.51* (0.23–0.77)	0.65* (0.43–0.80)	0.61* (0.37–0.78)	0.66* (0.43–0.80)
Social interaction	0.38– (0.07–0.62)	0.50* (0.23–0.70)	0.18– (–0.14–0.46)	0.25 (–0.07–0.52)	0.23– (–0.09–0.51)	0.35– (0.04–0.60)	0.48* (0.19–0.69)	0.37– (0.06–0.61)	0.45* (0.16–0.70)
Problem solving	0.59* (0.34–0.76)	0.48* (0.20–0.69)	0.35– (0.04–0.60)	0.48* (0.20–0.69)	0.55* (0.29–0.74)	0.51* (0.24–0.71)	0.57* (0.31–0.75)	0.56* (0.29–0.74)	0.56* (0.30–0.74)
Memory	0.49* (0.21–0.70)	0.51* (0.24–0.71)	0.44* (0.15–0.66)	0.48* (0.20–0.69)	0.48* (0.20–0.69)	0.54* (0.28–0.73)	0.47* (0.19–0.68)	0.58* (0.33–0.76)	0.53* (0.26–0.72)

Cells showing significant correlations are shaded (*$P < 0.05$, Spearman's rank correlation with Bonferroni-adjusted comparison). Range of values presented in parentheses is the 95% confidence interval of the correlation.
C1, *Remote memory*; C2, *Recent memory*; C3, *Attention*; C4, *Mental manipulation and concentration*; C5, *Orientation*; C6, *Figure copying*; C7, *Abstraction and judgement*; C8, *List-generating fluency*; C9, *Language*; CASI, Cognitive Abilities Screening Instrument; FIM-C, Functional Independence Measure-Cognition.

Table 5 FIM-C subscores with or without BPSD in patients with vascular dementia

	BEHAVE-AD-FW			
	Activity disturbances		Aggressiveness	
FIM-C	With (n = 13)	Without (n = 27)	With (n = 15)	Without (n = 25)
Comprehension	5.0 (3.5–5.0)*	6.0 (5.0–6.5)*	5.0 (3.8–5.0)	5.5 (5.0–6.0)
Expression	4.0 (2.5–5.0)*	5.0 (4.0–7.0)*	4.5 (2.8–5.0)	5.0 (3.0–6.8)
Social interaction	5.0 (2.5–6.0)	6.0 (4.5–7.0)	4.0 (3.0–4.3)*	6.5 (6.0–7.0)*
Problem solving	2.0 (1.0–4.0)*	5.0 (4.0–5.0)*	2.5 (1.0–5.0)	5.0 (3.3–5.0)
Memory	3.0 (2.5–3.0)*	4.0 (3.0–5.5)*	3.0 (3.0–4.3)	4.0 (3.0–5.8)

Cells showing significant correlations are shaded (*$P < 0.05$, Spearman's rank correlation with Bonferroni-adjusted comparison). BEHAVE-AD-FW, Behavioural Pathology in Alzheimer's Disease Frequency Weighted Severity Scale; BPSD, behavioural and psychological symptoms of dementia; FIM-C, Functional Independence Measure-Cognition.

interaction. VaD patients with *Aggressiveness* had a significantly lower FIM-C *Social interaction* subscore than those without *Aggressiveness*. The significant differences were all biologically meaningful.

Analysis 4: Functional differences between AD and VaD groups

In addition to the FIM-M and the FIM-C subscores, age, sex (men = 0; women = 1), years of education, MMSE score, and BEHAVE-AD-FW *Activity Disturbances* and *Aggressiveness* (absence = 0; presence = 1) were included as independent variables for forward stepwise logistic regression analysis with the two diagnostic groups as dependent variable (VaD = 0; AD = 1). Results showed that the FIM-C subscore (β = –0.31, Wald's χ^2 (1) = 13.45, $P < 0.001$, odds ratio = 0.74, 95%CI = 0.62–0.87) and the FIM-M subscore (β = 0.12, Wald's χ^2 (1) = 15.32, $P < 0.001$, odds ratio = 1.12, 95%CI = 1.06–1.19) together classified 71.4% of the cases correctly. As the FIM-C subscores increased, patients were more likely to have AD; as the FIM-M subscore decreased, they were more likely to have VaD. Stepwise backward variable selection did not significantly alter the results.

DISCUSSION

Our results show that the FIM is a useful tool for assessing both physical and cognitive function in patients with AD and VaD who manifest physical and cognitive disabilities. Although many previous studies have shown that total FIM-C scores are correlated with general cognitive function assessed by the MMSE, this is the first study to demonstrate relationships between specific FIM-C subscores and specific cognitive domains assessed with the CASI. There have been a few studies that have evaluated functional disabilities of patients with AD and VaD using the FIM.[8,9] Shiau *et al.* showed that the Clinical

Dementia Rating had the highest predictive ability, followed by subtypes of dementia, to predict the FIM-M, the FIM-C, and the total FIM scores using multiple regression analysis.[8] Unlike our results, both the FIM-M and FIM-C scores of VaD patients were lower than those of AD patients. Although they classified severity of dementia by the Clinical Dementia Rating whereas we used the MMSE, this difference in results may be explained by the fact that the patients in the earlier study seemed to have less severe dementia than our patients. Zekry *et al*. found no significant differences between patients with AD and VaD for most of the factors considered, including age, gender, years of education, MMSE, and the FIM total score.[9] However, they did not compare FIM-M and FIM-C subscores.

In the AD group, we also found a correlation with each CASI domain for all FIM-C subscores except for one pair (FIM-C *Social interaction* vs CASI domain C6). Significant correlations in the VaD group were more limited than those in the AD group. These results may reflect the heterogeneity of VaD as a disorder with several underlying vascular pathologies, while AD pathology progresses in a relatively consistent manner, usually beginning in the medial temporal lobe and then spreading to the temporoparietal region and other cortical areas. We analysed the effect of the areas and sizes of vascular lesions on these correlations, but this analysis was unsuccessful (data not shown). A further investigation using functional neuroimaging such as single-photon emission computed tomography or positron emission tomography is likely to provide more information on neurological background.

We found that the distribution of the FIM-M and FIM-C subscores differed between AD and VaD groups (71% correct classification). Although the cognitive domains and the presence of BPSD had a significant impact on the FIM-C scoring in our sample, these variables were not selected by the stepwise logistic regression procedure. AD patients were more likely to have a higher FIM-C score and a lower FIM-M score than VaD patients. Because VaD was likely to be accompanied with physical disability, such as hemiparalysis causally related to stroke, cognitive disability of VaD could be preserved more than in AD patients at the same physical disability level. If the FIM consisted of motor and cognitive parts, it would be useful to grossly measure functional dependency characteristics of dementia type.

Our results indicated that the FIM-C has no obvious floor effects, even in patients with low MMSE scores. Compared to the MMSE, the FIM-C seems to evaluate a different aspect of cognitive function that is weighted towards verbal and memory skills, even in patients with severe dementia. VaD patients may have aphasia, but in AD patents syntax and phonology remain relatively intact, although semantic abilities are impaired.[22] AD patients with a low MMSE score can possess preserved language abilities according to a study using the language subscale of the Severe Impairment Battery, a neuropsychiatric test.[23] With these findings in mind, the FIM seems to have the advantages that it is easy to administer and can be used to evaluate language disorders in both AD and VaD patients.

One of the unique characteristics of the FIM-C is that the scores do not reflect the accuracy of a patient's statements. Our results demonstrated that FIM-C subscores do not reflect the presence of BPSD, including delusion, in AD patients. Thus, the FIM-C can evaluate AD patients' ability to express their 'inner world', and it is possible to use the FIM-C as an outcome measure for validation therapy, which considers the 'inner world' of an AD patient to be meaningful. To illustrate this, we present a brief case of a patient with AD, who was not one of the study subjects.

For the clinical utility, we herein report the case of a 79-year-old woman with 8 years of education who was admitted to our hospital. Since she was 72 years old, she had been unable to live on her own because of her forgetfulness. She had severe dementia and had been diagnosed with probable AD based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria. Despite her severe dementia, she was able to express basic needs and concepts about 60–70% of the time without prompting, such as 'it's hot' and 'I have a pain in the buttocks'. She also was able to comprehend a simple sentence more than 50% of the time. Her MMSE and CASI scores were 0; however, her FIM-C subscores were 3 points on *Comprehension*, 4 points on *Social interaction*, 1 point on *Problem solving*, and 1 point on *Memory*.

CONCLUSIONS

The FIM scale was shown to be a useful measure of both physical and cognitive disabilities in AD and VaD