pre-AD cases, and 80.5 % of non-AD cases in our sample exhibited NFTs of at least NFT stage I.

Neuritic plaque pathology as determined by the CERAD score [31] showed (by definition) no neuritic plaques in non-AD controls, displayed a moderate frequency of neuritic plaques in pre-AD cases, and showed high frequencies of neuritic plaques in demented individuals with AD (Fig. 1c). Consequently, CERAD scores were higher in AD than in pre-AD cases ($p < 0.002$) and higher in pre-AD than in non-AD cases ($p < 0.002$). Neuritic plaques were observed in 97.3 % of the AD and in 28.4 % of the pre-AD cases.

The NIA-AA degree of AD pathology, a parameter that combines Aβ phase, NFT stage, and CERAD score, likewise distinguished AD, pre-AD, and non-AD control cases (Fig. 1d). NIA-AA degrees of AD pathology were high or intermediate in clinically symptomatic AD cases but low in pre-AD cases ($p < 0.002$). Non-AD control cases had, by definition, no AD pathology. Accordingly, the degree of AD pathology in pre-AD cases was higher than in non-AD controls ($p < 0.002$).

CAA was seen in 5.5 % of non-AD controls, thereby indicating that CAA can precede plaque pathology in a small number of cases (Fig. 1e). About 37.1 % of pre-AD cases had CAA mainly restricted to neocortical areas (CAA stage 1), i.e., CAA was more frequently seen in pre-AD than in non-AD control cases ($p < 0.002$), whereas AD cases had more widely distributed CAA-affected vessels than did pre-AD cases, as indicated by more advanced CAA stages ($p < 0.002$) [41]. CAA was observed in 92.6 % of AD cases.

GVD was found more widely distributed in clinical AD than in pre-AD, as represented by GVD stage ($p < 0.002$; Fig. 1f) [40]. Pre-AD as well as non-AD control cases exhibited early stages of GVD. Although pre-AD and non-AD cases did not vary significantly with respect to GVD stage ($p = 0.075$), there was a trend toward higher GVD stages in pre-AD cases compared with non-AD controls. GVD was found in 96.3 % of AD, in 46.2 % of pre-AD, and in 28.6 % of the non-AD control cases.

Soluble and dispersible Aβ in AD, pre-AD, and non-AD cases

Analysis of the soluble/dispersible fraction of brain homogenates by BN-PAGE showed large amounts of soluble/dispersible, high-molecular-weight Aβ in the neocortex of AD cases (Fig. 2). Here, a strongly labeled smear of $Aβ_{42}$-positive material between ~100 and 1236 kDa was observed. In pre-AD and non-AD cases, such a smear was not present. Pre-AD cases exhibited various patterns of

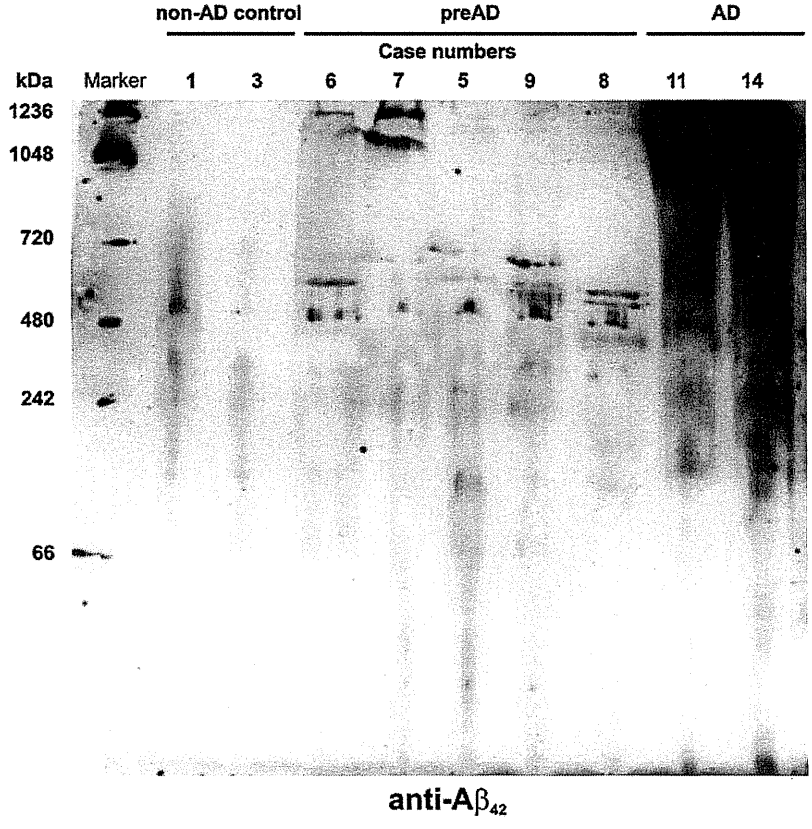

Fig. 2 BN-PAGE and subsequent Western blot analysis of soluble/dispersible Aβ aggregates from human brain homogenates of AD, pre-AD, and non-AD control cases. AD cases show significant high-molecular-weight smears of $Aβ_{42}$-positive aggregates, whereas only distinct oligomer bands between 480 and >1200 kDa were observed in pre-AD cases. Non-AD cases did not exhibit significant $Aβ_{42}$-positive material. Low-molecular-weight Aβ aggregates with a molecular weight lower than 100 kDa were not observed in any cases. Case numbers related to Table 2 are provided

well-defined, mild-to-moderately stained oligomer bands at ~480, ~580, ~600, ~680, ~1100, and ~1200 kDa. The ~1100 and ~1200 kDa bands were observed in only two pre-AD cases (Fig. 2). In non-AD, control cases such bands were not found (Fig. 2).

Discussion

This comparison between AD, pre-AD, and non-AD cases, classified according to the current clinical and neuropathological criteria [20, 30, 39], confirms that clinical AD cases have the most widely distributed AD-related pathologies, namely Aβ plaques, NFTs, neuritic plaques, CAA, and GVD, whereas pre-AD cases have less. Although cases classified as having no AD exhibited fewer NFTs than pre-AD cases and had no plaques, some of them did display very early stages of NFT, GVD pathology, and occasionally of CAA. Since the expansion of GVD pathology is associated with AD but not with other tauopathies [40], we hypothesize that coexisting NFT and GVD pathology in cases classified as non-AD cases may

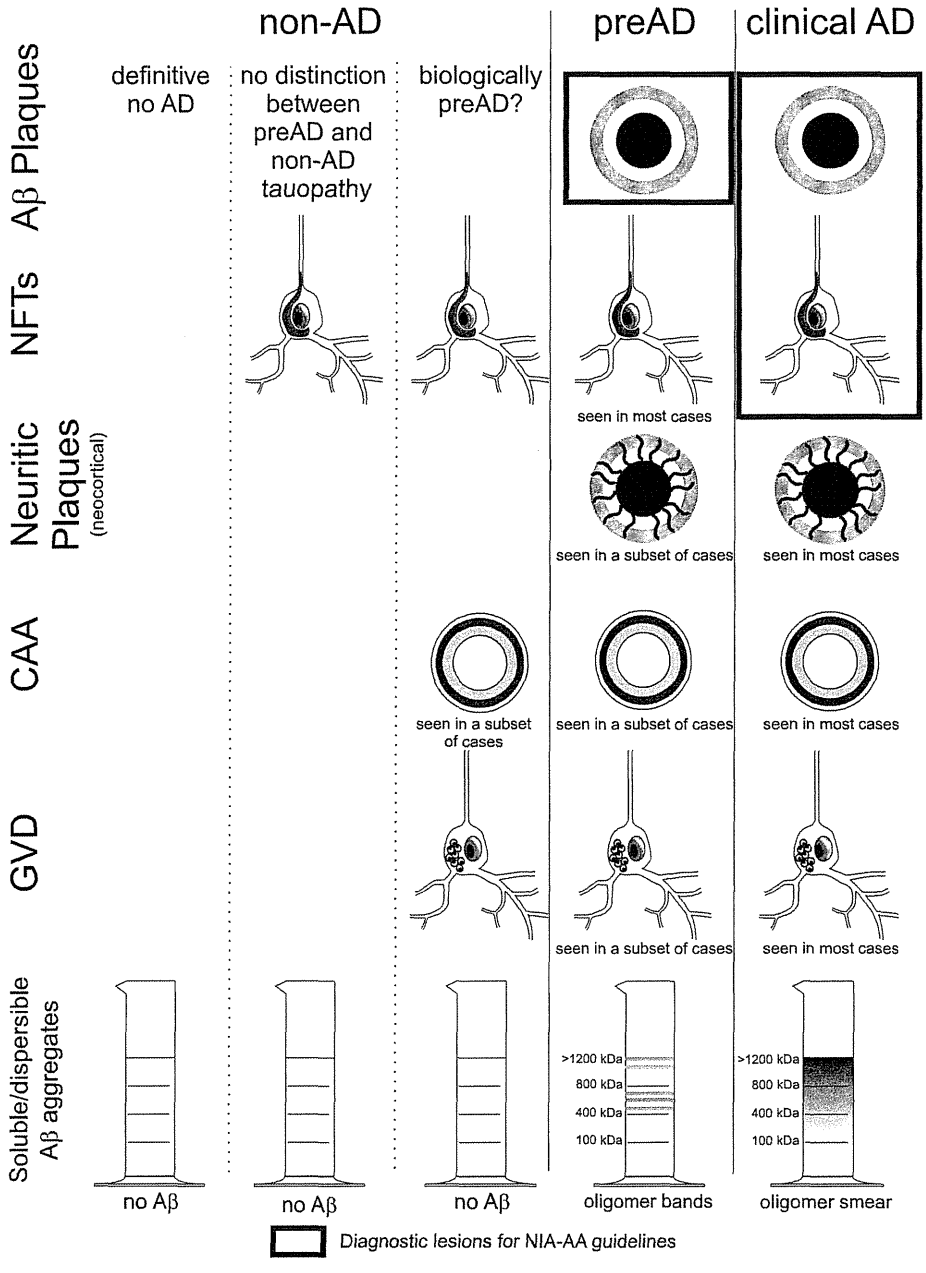

Fig. 3 Schematic representation of AD-related pathological features in non-AD, pre-AD, and AD cases. Obligatory pathologies for AD diagnosis, according to the NIA-AA guidelines [20], are indicated by *boxes*. The presence of CAA, neuritic plaques, and GVD pathology is not obligatory under NIA-AA guidelines, but these features are frequently seen in AD cases. Non-AD cases according to the current NIA-AA criteria were subclassified into possible pre-amyloid plaque stage cases, i.e., biologically pre-AD cases, cases with τ pathology without clear distinction between AD and non-AD changes, and cases with no AD-related lesions at all

also represent early AD-related lesions. That NFT pathology as well as pretangle τ pathology precedes Aβ deposition has already been described in detail [5, 9, 10], but this point is controversial because τ pathology without Aβ deposits could not be definitively distinguished from early lesions of non-AD tauopathies. With GVD as a second AD-specific lesion, in addition to NFTs, in a subset of these cases, it becomes evident that AD pathology indeed starts before the detection of Aβ plaques (Fig. 3). Accordingly, a major conclusion of this study is that cases currently classified as non-AD because of the absence of Aβ plaques may, in fact, represent incipient pre-AD when NFTs and GVD are seen. In addition, CAA can occur in some cases in the absence of parenchymal Aβ, and this is a further argument in favor of the existence of pre-plaque stages of pre-AD. However, CAA varies in its expression in AD and pre-AD cases, depending on the type of AD, and some AD cases do not even show CAA [2, 4, 42].

A second finding of this study is that soluble and dispersible high-molecular-weight $A\beta_{42}$ aggregates obtained by BN-PAGE are most prominent in AD cases, with a smear of $A\beta_{42}$ oligomers of ~100 kDa up to >1200 kDa, whereas pre-AD cases exhibited only distinct bands of high-molecular-weight soluble and dispersible $A\beta_{42}$ aggregates with a molecular weight of 480 kDa and higher. As previously reported for the AD and non-AD control cases included in this study [35], Aβ oligomers with molecular weights lower than 100 kDa are not found in AD, pre-AD, and non-AD cases. The pattern of high-molecular-weight Aβ oligomer bands in pre-AD varied among the cases. This suggests that increasing amounts of soluble and dispersible high-molecular-weight $A\beta_{42}$ aggregates and changes in the pattern of oligomer sizes to a broader spectrum of high-molecular-weight Aβ oligomer types in cortical neuropil play a role in the conversion of pre-AD into AD, which is a critical event in the pathogenesis of AD. A possible mechanism for soluble and dispersible Aβ aggregates to impact conversion from pre-AD to clinical AD is the interaction of Aβ oligomers with synapses, as demonstrated by other authors in in vitro studies [12, 25, 28, 38, 45] as well as the known capacity of Aβ to exacerbate τ pathology [17, 27, 32].

We used BN-PAGE for the detection of soluble and dispersible $A\beta_{42}$ aggregates to avoid artificial dissociation of Aβ aggregates caused by treatment with sodium dodecyl sulfate (SDS) [35, 46], which is required for SDS–PAGE protein analysis. Moreover, in BN-PAGE analysis, high-molecular-weight Aβ aggregates were found to be the predominant type of Aβ aggregates in the soluble/dispersible fraction, whereas low-molecular-weight Aβ oligomers, such as dimers or Aβ*56, were not observed in detectable amounts. We know that BN-PAGE is less sensitive for the detection of Aβ in comparison with SDS–PAGE, especially because $A\beta_{40}$ aggregates are not seen using BN-PAGE in human brain homogenates but are observed using SDS–PAGE [35]. These results have been discussed previously in detail [35]. Here, we did not focus on total Aβ levels or $A\beta_{40}$ in the brain, which correlate with Aβ plaques as shown previously for the human brain and for mouse models of AD [11, 21]. The BN-PAGE analysis of $A\beta_{42}$ aggregates shown here provides additional information about changes in the spectrum and quantity of soluble and dispersed $A\beta_{42}$ oligomers, protofibrils, and fibrils in the cortical neuropil of AD cases in comparison with pre-AD and non-AD cases.

In summary, the findings presented here show that the distinction between AD, pre-AD, and non-AD control cases according to current recommendations provides a valuable tool for identifying pre-AD cases, which are neuropathologically characterized by early stages in the distribution of AD-related pathologies. Moreover, some cases classified as non-AD controls because of an absence of Aβ plaques actually did show early stages of AD-related NFT and GVD pathology, and such cases could also be considered as pre-AD cases from a biological point of view (Fig. 3). The clinically important conversion from pre-AD to AD is not only accompanied by more widespread Aβ plaque deposition, NFT pathology, neuritic plaques, CAA, and GVD, but also by the appearance of large amounts of various soluble/dispersible high-molecular-weight Aβ aggregates in the neuropil of AD cases compared to pre-AD cases and non-AD controls. This indicates that quantitative and qualitative changes in the aggregation status of soluble and dispersed types of Aβ aggregates may play an important role in the conversion from non-demented pre-AD to clinical AD (Fig. 3).

Acknowledgments The authors thank Mrs. Irina Kosterin, Mrs. Monika Riede, and Mrs. Kathrin Pruy for technical help, Dr. Kelly Del Tredici for reading and editing the manuscript and Prof. Dr. Heiko Braak for providing autopsy brains for this study. This study was supported by DFG grants TH624/4-1, TH624/6-1, and Alzheimer Forschung Initiative Grant #10,810 (DRT). Part of this study (JA) was supported by the Dunhill Medical Trust (R173/1110). Tissue for this study was provided by the Newcastle Brain Tissue Resource, which is funded in part by a grant from the UK Medical Research Council (G0400074) and by Brains for Dementia Research, a joint venture between Alzheimer's Society and Alzheimer's Research, UK.

Conflict of interest DRT received a consultant honorarium from Simon-Kucher and Partners (Germany), and GE Healthcare (UK) and collaborated with Novartis Pharma Basel (Switzerland). CAFvA received honoraria for serving on the scientific advisory board of Nutricia GmbH and has received funding for travel and speaker honoraria from Sanofi-Aventis, Novartis, Pfizer, Eisai, and Nutricia GmbH, and has received research support from Heel GmbH.

This article is part of the supplement "Bridging the gap between Neurobiology and Psychosocial Medicine." This supplement was not sponsored by outside commercial interests. It was funded by the German Association for Psychiatry and Psychotherapy (DGPPN).

References

1. Alafuzoff I, Arzberger T, Al-Sarraj S, Bodi I, Bogdanovic N, Braak H, Bugiani O, Del Tredici K, Ferrer I, Gelpi E, Giaccone G, Graeber MB, Ince P, Kamphorst W, King A, Korkolopoulou P, Kovács GG, Larionov S, Meyronet D, Monoranu C, Parchi P, Patsouris E, Roggendorf W, Seilhean D, Tagliavini F, Stadelmann-Nessler C, Streichenberger N, Thal DR, Wharton S, Kretzschmar H (2008) Staging of neurofibrillary pathology in Alzheimer's disease. A study of the BrainNet Europe Consortium. Brain Pathol 18:484–496
2. Allen N, Robinson AC, Snowden J, Davidson YS, Mann DM (2013) Patterns of cerebral amyloid angiopathy define histopathological phenotypes in Alzheimer's disease. Neuropathol Appl Neurobiol. doi:10.1111/nan.12070
3. Arriagada PV, Marzloff K, Hyman BT (1992) Distribution of Alzheimer-type pathologic changes in nondemented elderly individuals matches the pattern in Alzheimer's disease. Neurology 42:1681–1688
4. Attems J, Jellinger KA (2004) Only cerebral capillary amyloid angiopathy correlates with Alzheimer pathology—a pilot study. Acta Neuropathol (Berl) 107:83–90
5. Attems J, Thomas A, Jellinger K (2012) Correlations between cortical and subcortical tau pathology. Neuropathol Appl Neurobiol 38:582–590
6. Braak E, Braak H, Mandelkow EM (1994) A sequence of cytoskeleton changes related to the formation of neurofibrillary tangles and neuropil threads. Acta Neuropathol 87:554–567
7. Braak H, Alafuzoff I, Arzberger T, Kretzschmar H, Del Tredici K (2006) Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. Acta Neuropathol 112:389–404
8. Braak H, Braak E (1991) Neuropathological staging of Alzheimer-related changes. Acta Neuropathol 82:239–259
9. Braak H, Braak E (1997) Frequency of stages of Alzheimer-related lesions in different age categories. Neurobiol Aging 18:351–357
10. Braak H, Thal DR, Ghebremedhin E, Del Tredici K (2011) Stages of the pathological process in Alzheimer's disease: age categories 1 year to 100 years. J Neuropathol Exp Neurol 70:960–969
11. Capetillo-Zarate E, Staufenbiel M, Abramowski D, Haass C, Escher A, Stadelmann C, Yamaguchi H, Wiestler OD, Thal DR (2006) Selective vulnerability of different types of commissural neurons for amyloid beta-protein induced neurodegeneration in APP23 mice correlates with dendritic tree morphology. Brain 129:2992–3005
12. Decker H, Jurgensen S, Adrover MF, Brito-Moreira J, Bomfim TR, Klein WL, Epstein AL, De Felice FG, Jerusalinsky D, Ferreira ST (2010) N-methyl-D-aspartate receptors are required for synaptic targeting of Alzheimer's toxic amyloid-beta peptide oligomers. J Neurochem 115:1520–1529
13. Dickson DW (1997) The pathogenesis of senile plaques. J Neuropathol Exp Neurol 56:321–339
14. Dickson DW, Ksiezak-Reding H, Davies P, Yen SH (1987) A monoclonal antibody that recognizes a phosphorylated epitope in Alzheimer neurofibrillary tangles, neurofilaments and tau proteins immunostains granulovacuolar degeneration. Acta Neuropathol 73:254–258
15. Funk KE, Mrak RE, Kuret J (2011) Granulovacuolar degeneration bodies of Alzheimer's disease resemble late-stage autophagic organelles. Neuropathol Appl Neurobiol 37:295–306
16. Glenner GG, Wong CW (1984) Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. Biochem Biophys Res Commun 120:885–890
17. Gotz J, Chen F, van Dorpe J, Nitsch RM (2001) Formation of neurofibrillary tangles in P301 l tau transgenic mice induced by Abeta 42 fibrils. Science 293:1491–1495
18. Grundke-Iqbal I, Iqbal K, Tung YC, Quinlan M, Wisniewski HM, Binder LI (1986) Abnormal phosphorylation of the microtubule-associated protein tau (tau) in Alzheimer cytoskeletal pathology. Proc Natl Acad Sci USA 83:4913–4917
19. Hoozemans JJ, van Haastert ES, Nijholt DA, Rozemuller AJ, Eikelenboom P, Scheper W (2009) The unfolded protein response is activated in pretangle neurons in Alzheimer's disease hippocampus. Am J Pathol 174:1241–1251
20. Hyman BT, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Carrillo MC, Dickson DW, Duyckaerts C, Frosch MP, Masliah E, Mirra SS, Nelson PT, Schneider JA, Thal DR, Thies B, Trojanowski JQ, Vinters HV, Montine TJ (2012) National Institute on Aging–Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. Alzheimer Dement 8:1–13
21. Ikonomovic MD, Klunk WE, Abrahamson EE, Mathis CA, Price JC, Tsopelas ND, Lopresti BJ, Ziolko S, Bi W, Paljug WR, Debnath ML, Hope CE, Isanski BA, Hamilton RL, Dekosky ST (2008) Post-mortem correlates of in vivo PiB-PET amyloid imaging in a typical case of Alzheimer's disease. Brain 131:1630–1645
22. Joachim CL, Morris JH, Selkoe DJ (1988) Clinically diagnosed Alzheimer's disease: autopsy results in 150 cases. Ann Neurol 24:50–56
23. Kadokura A, Yamazaki T, Kakuda S, Makioka K, Lemere CA, Fujita Y, Takatama M, Okamoto K (2009) Phosphorylation-dependent TDP-43 antibody detects intraneuronal dot-like structures showing morphological characters of granulovacuolar degeneration. Neurosci Lett 463:87–92
24. Kayed R, Head E, Thompson JL, McIntire TM, Milton SC, Cotman CW, Glabe CG (2003) Common structure of soluble amyloid oligomers implies common mechanism of pathogenesis. Science 300:486–489
25. Lacor PN, Buniel MC, Chang L, Fernandez SJ, Gong Y, Viola KL, Lambert MP, Velasco PT, Bigio EH, Finch CE, Krafft GA, Klein WL (2004) Synaptic targeting by Alzheimer's-related amyloid beta oligomers. J Neurosci 24:10191–10200
26. Lesne S, Koh MT, Kotilinek L, Kayed R, Glabe CG, Yang A, Gallagher M, Ashe KH (2006) A specific amyloid-beta protein assembly in the brain impairs memory. Nature 440:352–357
27. Lewis J, McGowan E, Rockwood J, Melrose H, Nacharaju P, Van Slegtenhorst M, Gwinn-Hardy K, Paul Murphy M, Baker M, Yu X, Duff K, Hardy J, Corral A, Lin WL, Yen SH, Dickson DW, Davies P, Hutton M (2000) Neurofibrillary tangles, amyotrophy and progressive motor disturbance in mice expressing mutant (P301L) tau protein. Nat Genet 25:402–405
28. Li S, Jin M, Koeglsperger T, Shepardson NE, Shankar GM, Selkoe DJ (2011) Soluble Abeta oligomers inhibit long-term potentiation through a mechanism involving excessive activation of extrasynaptic NR2B-containing NMDA receptors. J Neurosci 31:6627–6638
29. Masters CL, Simms G, Weinman NA, Multhaup G, McDonald BL, Beyreuther K (1985) Amyloid plaque core protein in Alzheimer disease and Down syndrome. Proc Natl Acad Sci USA 82:4245–4249
30. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH (2011) The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging–Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7:263–269

31. Mirra SS, Heyman A, McKeel D, Sumi SM, Crain BJ, Brownlee LM, Vogel FS, Hughes JP, van Belle G, Berg L (1991) The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. Neurology 41:479–486
32. Oddo S, Billings L, Kesslak JP, Cribbs DH, LaFerla FM (2004) Abeta immunotherapy leads to clearance of early, but not late, hyperphosphorylated tau aggregates via the proteasome. Neuron 43:321–332
33. Price JL, Davis PB, Morris JC, White DL (1991) The distribution of tangles, plaques and related immunohistochemical markers in healthy aging and Alzheimer's disease. Neurobiol Aging 12:295–312
34. Rijal Upadhaya A, Capetillo-Zarate E, Kosterin I, Abramowski D, Kumar S, Yamaguchi H, Walter J, Fändrich M, Staufenbiel M, Thal DR (2012) Dispersible amyloid β-protein oligomers, protofibrils, and fibrils represent diffusible but not soluble aggregates: their role in neurodegeneration in amyloid precursor protein (APP) transgenic mice. Neurobiol Aging 33:2641–2660
35. Rijal Upadhaya A, Lungrin I, Yamaguchi H, Fändrich M, Thal DR (2012) High-molecular weight Aβ-oligomers and protofibrils are the predominant Aβ-species in the native soluble protein fraction of the AD brain. J Cell Mol Med 16:287–295
36. Scholz W (1938) Studien zur Pathologie der Hirngefäße. II. Die drusige Entartung der Hirnarterien und -capillaren. (Eine Form seniler Gefäßerkrankung). Z Ges Neurol Psychiatr 4:694–715
37. Schwab C, DeMaggio AJ, Ghoshal N, Binder LI, Kuret J, McGeer PL (2000) Casein kinase 1 delta is associated with pathological accumulation of tau in several neurodegenerative diseases. Neurobiol Aging 21:503–510
38. Shankar GM, Li S, Mehta TH, Garcia-Munoz A, Shepardson NE, Smith I, Brett FM, Farrell MA, Rowan MJ, Lemere CA, Regan CM, Walsh DM, Sabatini BL, Selkoe DJ (2008) Amyloid-beta protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. Nat Med 14:837–842
39. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, Iwatsubo T, Jack CR Jr, Kaye J, Montine TJ, Park DC, Reiman EM, Rowe CC, Siemers E, Stern Y, Yaffe K, Carrillo MC, Thies B, Morrison-Bogorad M, Wagster MV, Phelps CH (2011) Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging–Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7:280–292
40. Thal DR, Del Tredici K, Ludolph AC, Hoozemans JJ, Rozemuller AJ, Braak H, Knippschild U (2011) Stages of granulovacuolar degeneration: their relation to Alzheimer's disease and chronic stress response. Acta Neuropathol 122:577–589
41. Thal DR, Ghebremedhin E, Orantes M, Wiestler OD (2003) Vascular pathology in Alzheimer's disease: correlation of cerebral amyloid angiopathy and arteriosclerosis/lipohyalinosis with cognitive decline. J Neuropathol Exp Neurol 62:1287–1301
42. Thal DR, Papassotiropoulos A, Saido TC, Griffin WS, Mrak RE, Kölsch H, Del Tredici K, Attems J, Ghebremedhin E (2010) Capillary cerebral amyloid angiopathy identifies a distinct APOE epsilon4-associated subtype of sporadic Alzheimer's disease. Acta Neuropathol 120:169–183
43. Thal DR, Rüb U, Orantes M, Braak H (2002) Phases of Abeta-deposition in the human brain and its relevance for the development of AD. Neurology 58:1791–1800
44. Thal DR, Rüb U, Schultz C, Sassin I, Ghebremedhin E, Del Tredici K, Braak E, Braak H (2000) Sequence of Abeta-protein deposition in the human medial temporal lobe. J Neuropathol Exp Neurol 59:733–748
45. Wang HW, Pasternak JF, Kuo H, Ristic H, Lambert MP, Chromy B, Viola KL, Klein WL, Stine WB, Krafft GA, Trommer BL (2002) Soluble oligomers of beta amyloid (1-42) inhibit long-term potentiation but not long-term depression in rat dentate gyrus. Brain Res 924:133–140
46. Watt AD, Perez KA, Rembach A, Sherrat NA, Hung LW, Johanssen T, McLean CA, Kok WM, Hutton CA, Fodero-Tavoletti M, Masters CL, Villemagne VL, Barnham KJ (2013) Oligomers, fact or artefact? SDS-PAGE induces dimerization of beta-amyloid in human brain samples. Acta Neuropathol 125:549–564
47. Woodard JS (1962) Clinicopathologic significance of granulovacuolar degeneration in Alzheimer's disease. J Neuropathol Exp Neurol 21:85–91
48. Yamaguchi H, Sugihara S, Ogawa A, Saido TC, Ihara Y (1998) Diffuse plaques associated with astroglial amyloid beta protein, possibly showing a disappearing stage of senile plaques. Acta Neuropathol 95:217–222
49. Yamazaki Y, Takahashi T, Hiji M, Kurashige T, Izumi Y, Yamawaki T, Matsumoto M (2010) Immunopositivity for ESCRT-III subunit CHMP2B in granulovacuolar degeneration of neurons in the Alzheimer's disease hippocampus. Neurosci Lett 477:86–90

EXTRA
Dementia
and Geriatric
Cognitive Disorders

Dement Geriatr Cogn Disord Extra 2013;3:131–142
DOI: 10.1159/000350460
Published online: April 30, 2013

1664–5464/13/0031–0131$38.00/0
www.karger.com/dee

Original Research Article

Symptoms of Early Dementia-11 Questionnaire (SED-11Q): A Brief Informant-Operated Screening for Dementia

Yohko Maki[a, b] Tomoharu Yamaguchi[a, c] Haruyasu Yamaguchi[a]

[a]Gunma University School of Health Sciences, [b]Geriatrics Research Institute and Hospital, and [c]Department of Rehabilitation, Gunma University of Health and Welfare, Maebashi, Japan

Key Words
Dementia screening · Dementia · Alzheimer's disease · Activities of daily living · Cognitive deficits · Early detection · Mild cognitive impairment · Non-Alzheimer's disease

Abstract
The aim of this study was to develop a brief informant-based questionnaire, namely the Symptoms of Early Dementia-11 Questionnaire (SED-11Q), for the screening of early dementia. 459 elderly individuals participated, including 39 with mild cognitive impairment in the Clinical Dementia Rating scale (CDR) 0.5, 233 with mild dementia in CDR 1, 106 with moderate dementia in CDR 2, and 81 normal controls in CDR 0. Informants were required to fill out a 13-item questionnaire. Two items were excluded after analyzing sensitivities and specificities. The final version of the SED-11Q assesses memory, daily functioning, social communication, and personality changes. Receiver operator characteristic curves assessed the utility to discriminate between CDR 0 (no dementia) and CDR 1 (mild dementia). The statistically optimal cutoff value of 2/3, which indicated a sensitivity of 0.84 and a specificity of 0.90, can be applied in the clinical setting. In the community setting, a cutoff value of 3/4, which indicated a sensitivity of 0.76 and a specificity of 0.96, is recommended to avoid false positives. The SED-11Q reliably differentiated nondemented from demented individuals when completed by an informant, and thus is practical as a rapid screening tool in general practice, as well as in the community setting, to decide whether to seek further diagnostic confirmation.

Introduction

There is widespread underascertainment of Alzheimer's disease (AD) and other dementias [1], and a combination of pharmacological and nonpharmacological treatments could slow disease progression and maintain individuals at their highest level of functioning

Haruyasu Yamaguchi
3-39-15 Showa-machi
Maebashi 371-8514 (Japan)
E-Mail yamaguti@health.gunma-u.ac.jp

Dement Geriatr Cogn Disord Extra 2013;3:131–142
DOI: 10.1159/000350460

when they are at the early stages of disease [2]. For early detection of dementia, a rapid screening test in clinical settings would be extremely useful, as it could help general practitioners with time constraints to decide whether or not to proceed with more in-depth clinical evaluation. Such a screening test is also useful for community health promotion to detect undiagnosed individuals.

An ideal practical screening test should be easy to administer within tight time constraints but must also be accurate enough to detect dementia. There are two general methods to screen for dementia: patient performance-based testing and informant interviews.

Regarding patient performance-based testing, the most widely used brief test is the Mini-Mental State Examination (MMSE) [3]. However, this test is time-consuming to administer in a clinical setting with time constraints. Furthermore, the ceiling effect makes the MMSE insensitive to the early stages of dementia [4], especially for highly educated individuals [5, 6]. In contrast, a brief test such as the MMSE may falsely identify those with low education or poor cognitive functioning as demented. Other brief tests have also been developed. However, because of the requirement of brevity, most of them are limited to a single cognitive domain. For instance, the tests that are weighted towards memory such as the Short Blessed Test [7] and the Memory Impairment Screen [8] may not be sensitive enough for detecting nonamnestic dementias. Another problem is the psychological burden imposed by cognitive tests, as cognitive tests for dementia are themselves stressful [1].

In the community-based setting, performance-based tests may be impractical for detecting underdiagnosed dementia. A lack of self-awareness of cognitive decline is a characteristic of dementia [9, 10], and demented individuals tend to deny their cognitive decline and refuse the test. Ethical issues are also important; using screening tests with low specificity could lead to a misdiagnosis of dementia in elderly individuals, which could cause unnecessary anxiety. The detection of dementia should be conducted without unduly alarming the patient. In this respect, informant-based assessments are preferable.

When evaluating informant-based assessments, the Clinical Dementia Rating scale (CDR) [11] is widely used. CDR meets the requirement of accuracy, but it is not an easily administered screening tool. It is a semistructured interview that has to be carried out by trained practitioners and takes at least 30 min.

In the present study, we introduce a brief informant-based screening questionnaire to identify dementia in both clinical and community-based settings, namely the Symptoms of Early Dementia-11 Questionnaire (SED-11Q). This questionnaire is easily administered and is both patient and informant friendly. Questions addressing early signs of dementia were selected on the basis of clinical experience. The SED-11Q aims to investigate the state of ordinary daily activities often performed by an elderly individual living independently. The questions it asks are not only easy to answer, but are also informative. Quantifying difficulties in daily living may provide more sensitive information about early functional changes rather than questions about cognitive function in a single domain. This is because functional integrity is a key differentiating feature of dementia, and a decline in multifaceted cognitive domains directly leads to functional impairments. In addition, as deficits caused by dementia are manifested in various aspects, the SED-11Q also includes questions on social interaction and personality.

Methods

459 elderly individuals participated, including 39 with mild cognitive impairment (MCI) in CDR 0.5, 233 with mild dementia in CDR 1, 106 with moderate dementia in CDR 2, and 81 normal controls in CDR 0. The demented individuals were outpatients, and of the 81 normal controls, 64 were community dwellers and 17 were outpatients (table 1). The subjects were

Table 1. Demographic data

	CDR 0 (n = 81)	CDR 0.5 (n = 39)	CDR 1 (n = 233)	CDR 2 (n = 106)
Age, years	71.7±6.0	78.7±6.9	79.6±9.7	79.5±13.2
Gender (male/female)	74/7	18/21	82/151	29/77
MMSE	28.5±2.1	26.4±2.2	21.1±4.2	16.1±4.2
SED-11Q	1.00±1.29	3.21±2.14	5.71±2.78	7.25±2.88
Causative diseases				
AD			5.76±2.76 (127)	6.95±2.79 (40)
Others			5.66±2.81 (106)	7.44±2.93 (66)

With the exception of gender (number of patients) values represent mean ± SD. Values in parentheses represent the number of patients. The ages were significantly different between the groups ($p < 0.001$). CDR 0 was detected significantly more frequently in the younger groups. There was no difference between the affected groups of CDR 0.5, CDR 1, and CDR 2.

diagnosed based on criteria for dementia diseases such as NINCDS-ADRDA for AD [12], the third report of the Dementia with Lewy Bodies Consortium for Lewy body dementia [13], criteria by Neary et al. [14] for frontotemporal lobar degeneration, criteria by the NINDS-AIREN International Workshop for vascular dementia [15], and MCI by the report of the International Working Group on Mild Cognitive Impairment [16]. CDR 0.5 was regarded as MCI, although a different classification was proposed, whereby CDR 0.5 encompasses both mild and earlier dementia [17] or it corresponds to very mild dementia [18]. Depression was an exclusive criterion for normal controls in CDR 0 and subjects with MCI in CDR 0.5. The ethics board of the Gunma University School of Health Sciences approved all procedures (No. 21–27), and written informed consent was obtained from the participants.

Originally, the questionnaire consisted of 13 questions, which are shown in table 2. In the clinical and community setting, the informants were required to fill out the questionnaire including the 13 items. Based on the results of the current study, we decided to exclude 2 items: item 2 (misplacing) and item 13 (delusions). The format of the SED-11Q is shown in figure 1. In the present study, informants were limited to family members, and nonfamily caregivers were excluded. Informants had normal cognitive abilities without psychiatric diseases, delirium, or verbal incomprehension including aphasia.

The patients were also tested using the MMSE. All analyses were conducted using the Japanese version of SPSS for Windows version 19.0 (IBM Corp., New York, N.Y., USA). Significance was set at $p < 0.05$.

Results

Demographic data are shown in table 1. The ratio of positive answers in subitems in the quotient is shown in figure 2. In CDR 0, 51% checked item 2, whereas no one checked items 7 and 13. In CDR 1, more than 50% checked items 1, 2, 3, 6, 8, 9, 10, and 11. Sensitivities and specificities of the subitems in CDR 0 and CDR 1 are shown in table 2. Item 2 (misplacing) showed the lowest specificity, i.e. 0.49, out of the 13 items. Item 13 (delusions) showed the lowest sensitivity, i.e. 0.18, although the specificity was 1. Therefore, these 2 items were removed in the SED-11Q. Instead, a notification was added to recommend medical consultation whenever delusions or illusions were detected.

Dement Geriatr Cogn Disord Extra 2013;3:131–142
DOI: 10.1159/000350460

Table 2. Sensitivity and specificity of the 13 subitems in the differentiation between CDR 0 and CDR 1

Item		Sensitivity	Specificity
1	Repetitive talking	0.81	0.79
2	Misplacing	0.85	0.49
3	Context understanding	0.52	0.99
4	Indifference about clothing	0.31	0.91
5	Cleaning up	0.35	0.91
6	Forgetting one of two items	0.60	0.90
7	Self-medication	0.47	1.00
8	Time consuming	0.62	0.88
9	Planning	0.52	0.98
10	Complex topics	0.64	0.93
11	Loss of interest	0.54	0.93
12	Irritable and suspicious	0.33	0.81
13	Delusions	0.18	1.00

Scores were as follows: 1.00 ± 1.29 (mean ± SD) in CDR 0, 3.21 ± 2.14 in CDR 0.5, 5.71 ± 2.78 in CDR 1, and 7.25 ± 2.88 in CDR 2. There was a significant difference among the CDR groups [analysis of variance $F(3, 455) = 106.264$, $p < 0.001$], and post hoc analysis with Bonferroni correction indicated the following significant differences: CDR 2 higher than CDR 1, CDR 1 higher than CDR 0.5, and CDR 0.5 higher than CDR 0 ($p < 0.001$). Modes of the scores were 0 in CDR 0, 2 in CDR 0.5, 5 in CDR 1, and 9/10 in CDR 2 (fig. 3).

Comparing CDR 0 and CDR 1 in the SED-11Q, the area under receiver operating characteristic (ROC) curve was 0.932 [$p < 0.001$, 95% confidence interval (CI): 0.903–0.961]. A cutoff value of 2/3 indicated a sensitivity of 0.841 (95% CI: 0.817–0.857), a specificity of 0.901 (95% CI: 0.830–0.947), a positive predictive value of 0.961 (95% CI: 0.933–0.979), and a negative predictive value of 0.664 (95% CI: 0.611–0.697). A cutoff value of 3/4 indicated a sensitivity of 0.764 (95% CI: 0.743–0.772), a specificity of 0.963 (95% CI: 0.903–0.987), a positive predictive value of 0.983 (95% CI: 0.957–0.994), and a negative predictive value of 0.586 (95% CI: 0.550–0.601) (fig. 4). The correlation coefficient of the SED-11Q and the MMSE was significant: $r = -0.424$ and $r < 0.001$.

Discussion

The SED-11Q reliably differentiated nondemented from demented individuals. The area under the ROC curve was 93%, suggesting good discrimination between the 2 groups. In the clinical setting with physicians and other medical staff, the statistically optimal cutoff value of 2/3, which indicates a sensitivity of 0.841 and a specificity of 0.901, can be applied. In the community setting, where community-dwelling elderly individuals are screened for detecting dementia, a cutoff value of 3/4, which indicates a sensitivity of 0.764 and a specificity of 0.963, is recommended because of high specificity and positive predictive values. Medical consultation is recommended whenever delusions or illusions are detected. In general, the SED-11Q was revealed to be practical as a rapid screening tool in general practice to decide whether or not to seek further diagnostic confirmation.

Consideration of Subitems

The 2 items that assessed memory function, item 1 (repetitive talking) and item 2 (misplacing), showed high sensitivities of 0.8 and more comparing CDR 0 to CDR 1. Amnestic disorder is one of the earliest signs of AD, and the reason for this could be the fact that the

Symptoms of Early Dementia-11 Questionnaire (SED-11Q)

Date(MM/DD/YYYY) / /

Patient Name : Patient ID :

Respondent Name : Relationship

Respondent-completed / Interview by Name:

How has the patient's daily life been for the last month?
Please answer the following questions by circling the appropriate responses
(Exclude any difficulties caused by physical issues, e.g., pain).
Please ask for any help if needed.

He/she talks and asks about the same things repeatedly.	YES	NO	N/A Don't know
He/she has become unable to understand the context of facts.	YES	NO	N/A
He/she has become indifferent about clothing and other personal concerns.	YES	NO	N/A
He/she has begun to forget to turn off the faucet and/or close the door, and/or has become unable to clean up properly.	YES	NO	N/A
When doing two things at the same time, he/she forgets one of them.	YES	NO	N/A
He/she has become unable to take medication under proper management.	YES	NO	N/A
He/she has begun to take a longer time to do work (e.g., household chores), which could be done quickly before.	YES	NO	N/A
He/she has become unable to make a plan.	YES	NO	N/A
He/she cannot understand complex topics.	YES	NO	N/A
He/she has become less interested and willing, and stopped hobbies, etc.	YES	NO	N/A
He/she has become more irritable and suspicious than before.	YES	NO	N/A
TOTAL SED-11Q SCORE			

He/she has delusions, e.g., claims to have had valuables stolen.	YES	NO	N/A
He/she has illusions, e.g., sees something that isn't there.	YES	NO	N/A

If the answer is "yes" to either of these 2 questions, then a more comprehensive medical consultation is recommended.

Fig. 1. Format of the SED-11Q. The questionnaire represents an informant-based screening and should not be used as a patient-completed screening questionnaire. The total SED-11Q score is the sum of the items marked 'Yes'.

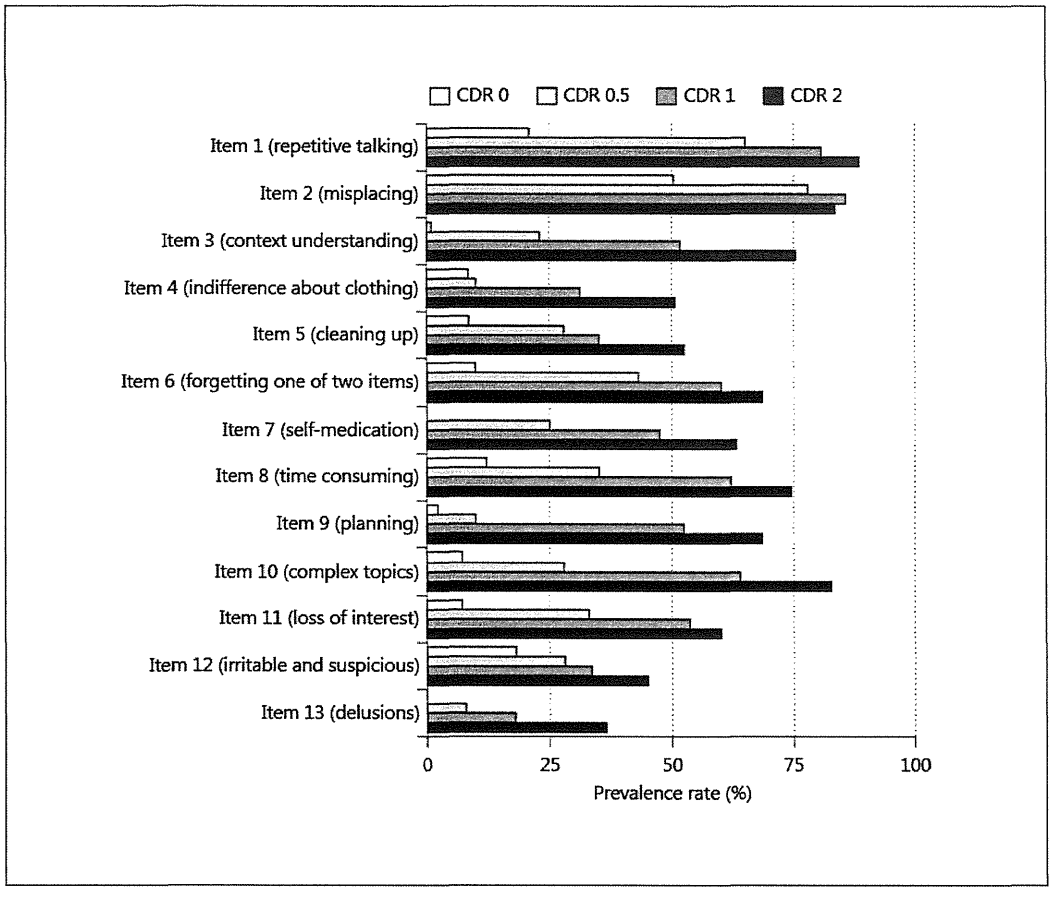

Fig. 2. The ratio of positive answers in the subitems (quotients) according to the CDR groups.

majority of the patients were those with AD in the present study. Item 2 (misplacing) was excluded from the SED-11Q because the specificity was 0.49, which suggested a danger of false positivity.

In CDR 1, deficits in instrumental activities of daily living (IADL) become obvious. In the present study, 4 items, item 3 (context understanding), item 6 (forgetting one of two items), item 8 (time-consuming), and item 9 (planning), showed sensitivities of 0.5 and more and specificities of 0.85 and more in the comparison between CDR 0 and CDR 1. It becomes difficult for the patients in CDR 1 to function independently, even if compensatory strategies are employed, and deficits can be noticed in cooperative activities and conversations in daily living.

The other 2 items regarding IADL, item 4 (indifference about clothing) and item 5 (cleaning up), showed sensitivities of less than 0.5, while specificities were 0.9 and more in the comparison between CDR 0 and CDR 1. It is possible that informants tend to pay little attention and overlook the deficits because of slow and gradual changes. These items remained in the list, considering a community-based use, as it could help elderly individuals if symptoms of dementia other than memory deficits are detected by using the questionnaire. Item 4 (indifference about clothing) could gradually lead to an apathetic attitude to life, which is one of the psychological behavioral symptoms of dementia and aggravates cognitive function.

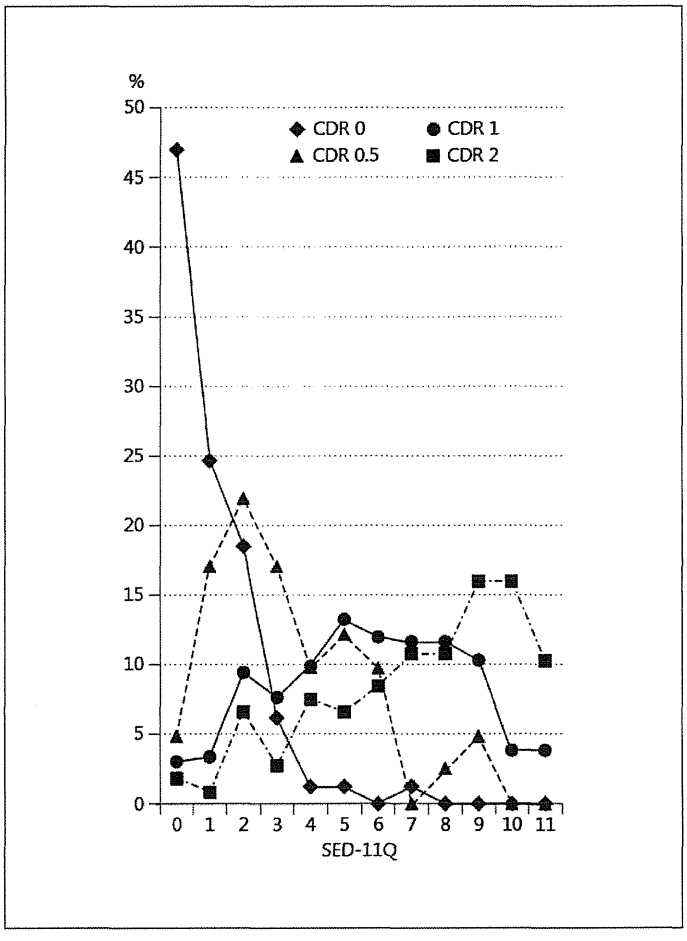

Fig. 3. Distribution according to the severity of dementia. The distribution is shown in the quotients. Modes of scores were 0 in CDR 0, 1 in CDR 0.5, 5 in CDR 1, and 9/10 in CDR 2.

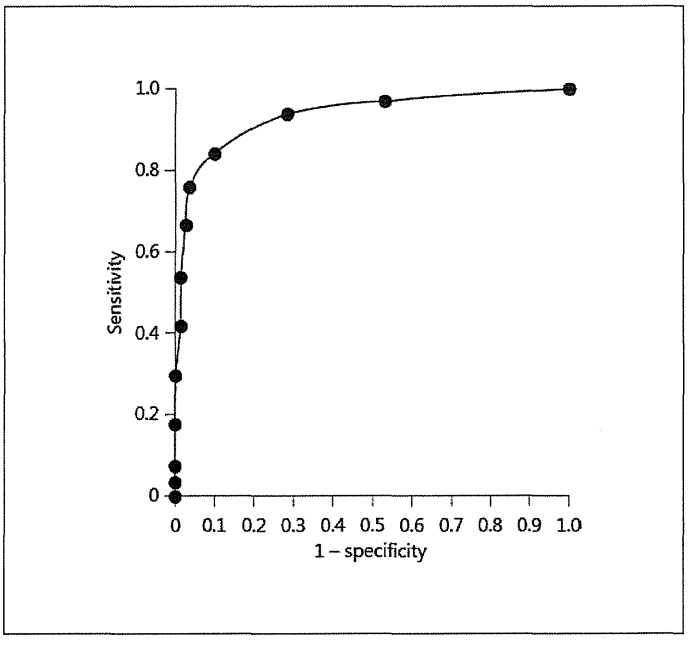

Fig. 4. The ROC curve of the SED-11Q in the differentiation between CDR 0 and CDR 1. The area under the curve is 0.932 ($p < 0.001$, 95% CI: 0.903–0.961). The statistically optimal cutoff value of 2/3 indicated a sensitivity of 0.841 and a specificity of 0.901.

Item 5 (cleaning up) is a typical behavior of demented individuals with attentional deficits and difficulties in executive function.

A relatively low sensitivity of 0.47 in item 7 (self-medication) is rather unexpected, because previous studies suggested that self-medication is one of the early signs of dementia [19–24]. Possible causes for this discrepancy could be that some patients may have developed long-term habits of medication, e.g., antihypertensive drugs, while others may not have taken any medications, as the questionnaire was filled out at the initial visit. A specificity of 100% suggested that self-medication could be a robust sign of dementia, and follow-up is needed to observe whether those already affected by dementia can acquire a habit of self-medication or not.

For item 10 (complex topics), cognitive decline is associated with difficulties in social interaction. Socially active lifestyles have a protective influence on mental decline: social isolation is associated with an increased risk of mental decline [25, 26], whereas a rich social network and interaction may protect against mental decline [27, 28]. It becomes difficult for patients to maintain socially active lives, and thus it is desirable that families and caregivers help the patients keep up social interaction.

Changes in interests are also characteristic of the early stages of dementia, as assessed by item 11 (loss of interest) in this questionnaire. Due to cognitive decline, patients are confronted with the loss of mental capacity. They have difficulty in doing what they could easily do and have enjoyed doing previously. Consequently, they lose their motivation and tend to be apathetic. Item 11 (loss of interest) is also related to social interaction; it becomes difficult to maintain social interaction even with those sharing the same hobbies. Families and caregivers should watch for changes because apathy and inaction are related to increased functional disability [29].

Personal changes are also observed in individuals with dementias other than AD, and the SED-11Q aims to detect these dementias. Item 12 asks about changes relating to irritability and suspicion, which are observed in frontotemporal lobar degeneration and are early signs of disease. Items 4 and 11 are associated with apathetic changes, which are more prominent in vascular dementia than in AD [30]. These 2 items could lead to depressive tendencies, which is a frequent symptom of Lewy body dementia [31].

Concerning item 13 (delusions), sensitivity was low, whereas specificity was 100%. Thus, it could be regarded as a determining factor in the diagnosis of dementia or other psychiatric diseases. In the SED-11Q, item 13 was excluded and notification was added to recommend medical consultation whenever delusions or illusions are detected.

Discriminative Ability of the SED-11Q

In the clinical setting, a statistically optimal cutoff value of 2/3 can be applied, whereas in the community setting, a cutoff value of 3/4 is recommended (fig. 4). In the clinical setting, medical staff can determine whether the informants are reliable or not, and they can interview the informants and patients if necessary, whereas in the community setting, such screening is often conducted without medical staff.

In general, during screening, false positives may be preferable to false negatives because failure of early detection could result in a lack of early intervention. However, considering the characteristics of dementia, false negatives are preferable in brief screening. Disease-modifying drugs have not been developed and cognitive and functional capacity would inevitably decline as the disease progresses. The US Preventive Services Task Force (USPSTF) warned that labeling an individual with dementia could potentially cause unnecessary anxiety, which is a risk factor for cognitive decline [32]. Therefore, physicians should perform a careful examination to make a definitive diagnosis, but cognitive tests for dementia are inherently potentially stressful. In this way, not only an incorrect diagnosis of dementia, but also the

notification of the probability of dementia could lead to negative psychosocial consequences. Thus, it makes sense to value specificity more than sensitivity, especially in community settings.

The SED-11Q should not be used to detect MCI (CDR 0.5), as the screening of asymptomatic stages should be conducted carefully. The results of the present study showed a wide distribution of scores in CDR 0.5, and considering the negative psychosocial consequences which result from a false-positive judgment, a diagnosis of MCI should be carefully made.

Self-Rating Scales

Self-rating scales are not appropriate to detect dementia, because subjective cognitive impairment and memory complaints are common in elderly individuals [33–36]. It is controversial whether subjective complaints are associated with cognitive decline [37, 38], and it has been reported that such complaints are correlated with depressive symptoms or personality traits, rather than cognitive decline [39, 40]. In addition, those who are already demented tend to overestimate their functions, and their self-awareness of cognitive impairments diminishes as disease progresses, especially in memory [9, 10].

Other Informant-Based Questionnaires

Other informant-based questionnaires have been developed. In 1989, the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE; available in 26- and 16-item formats) [41] was proposed. It requires an intrapersonal comparison between the present states and those of 10 years ago. However, memories of 10 years ago are vague, and normally aging individuals experience cognitive declines. Thus, the IQCODE can result in false-positive diagnoses, and age-related changes are often misdiagnosed as symptoms of dementia. Furthermore, the IQCODE includes questions on symptoms associated with rather advanced stages, e.g., not recognizing the faces of family members, not remembering the names of family members, not remembering things that happened to him/her when he/she was young, and not remembering things he/she learned when he/she was young.

Another example is the Observation List of Possible Early Signs of Dementia (OLD) [42]. This test focuses on cognitive decline, and questions about daily functioning are not included. Combined questionnaires that ask about cognitive function and daily functioning are desirable [43], as daily functioning requires multifaceted cognitive abilities, and deficits in functional integrity represent a key feature of dementia.

A brief scale combining a single-item informant report of memory problems and a 4-item IADL scale has also been proposed [44]. Although the test itself is easy and brief, the scoring system is complicated and arbitrary, and the test has not been validated with a large cohort.

Another scale that combines questions on cognitive abilities and daily functioning is the 8-item questionnaire, AD8 [43]. AD8 consists of questions about the patient's memory, orientation, and functional abilities by placing emphasis on intraindividual, rather than interindividual comparisons. However, the time frame for change is set as the last several years (an exact time frame is not required). Most of the informants whom we meet in daily practice tend to overlook longitudinal change. It would be more practical to ask about the patient's state during a short period, such as the last month. The validity and reliability were confirmed in early dementia; a score of 2 or more points suggested that cognitive impairment is likely present with a sensitivity over 84% and a specificity over 80%. The negative predictive value was around 70%, and thus there is a risk of overdiagnosis. AD8 was also recommended for detection of MCI, but screening of MCI using such brief tests could result in unnecessary false-positive judgment, as stated above. In the absence of informants, the authors recommend AD8 as a self-completion questionnaire, as they reported that self-rating of AD8 differentiated nondemented from demented individuals with the same specificity as informant ratings [45].

However, the results have not been validated in other cohorts. As stated above in the 'Self-rating scales' section, it is debatable whether self-ratings should be considered as reliable as informants' reports.

Limitations

Reliable informants are not always available. In cases with no reliable informants, a detailed medical interview and examination should be conducted. It is inadvisable to rely on data derived from the SED-11Q when it has been used for self-rating for the reasons stated above. Moreover, it should be noted that scores can be biased by informant depression, care burden, and the relationship with the patient. False positivity is possible for those with depression, as depression, even without comorbid dementia, causes cognitive deficits. It might be necessary to rule out depression at the initial screening using the SED-11Q. Differentiation of dementia from depression requires careful examination, and depression itself is an important risk factor for dementia [46–48]. Another limitation is that this study included few cases of dementias other than AD, and samples should be collected to confirm the reliability of this test in other dementias.

The questionnaire should be validated in a multisite study in both practical and community settings.

Acknowledgements

The authors thank all the study participants, Dr. Masamitsu Takatama (Geriatrics Research Institute and Hospital, Maebashi), and Rumi Shinohara and Yuko Tsunoda (Gunma University, Maebashi) for their support. Dr. Haruyasu Yamaguchi was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, Culture, and Technology, Japan (23300197 and 22650123) and a Grant-in-Aid for Scientific Research (H22-Ninchisho-Ippan-004) from the Ministry of Health, Labor, and Welfare, Japan.

References

1 Holsinger T, Deveau J, Boustani M, Williams JW Jr: Does this patient have dementia? JAMA 2007;297:2391–2404.
2 Boustani M, Peterson B, Hanson L, Harris R, Lohr KN: Screening for dementia in primary care: a summary of the evidence for the US Preventive Services Task Force. Ann Intern Med 2003;138:927–937.
3 Folstein MF, Folstein SE, McHugh PR: 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
4 Lawrence J, Davidoff D, Katt-Lloyd D, Auerbach M, Hennen J: A pilot program of improved methods for community-based screening for dementia. Am J Geriatr Psychiatry 2001;9:205–211.
5 Espino DV, Lichtenstein MJ, Palmer RF, Hazuda HP: Evaluation of the mini-mental state examination's internal consistency in a community-based sample of Mexican-American and European-American elders: results from the San Antonio Longitudinal Study of Aging. J Am Geriatr Soc 2004;52:822–827.
6 Lorentz WJ, Scanlan JM, Borson S: Brief screening tests for dementia. Can J Psychiatry 2002;47:723–733.
7 Katzman R, Brown T, Fuld P, Peck A, Schechter R, Schimmel H: Validation of a short Orientation-Memory-Concentration Test of cognitive impairment. Am J Psychiatry 1983;140:734–739.
8 Kuslansky G, Buschke H, Katz M, Sliwinski M, Lipton RB: Screening for Alzheimer's disease: the memory impairment screen versus the conventional three-word memory test. J Am Geriatr Soc 2002;50:1086–1091.
9 Mograbi DC, Brown RG, Morris RG: Anosognosia in Alzheimer's disease – the petrified self. Conscious Cogn 2009;18:989–1003.
10 Maki Y, Amari M, Yamaguchi T, Nakaaki S, Yamaguchi H: Anosognosia: patients' distress and self-awareness of deficits in Alzheimer's disease. Am J Alzheimers Dis Other Demen 2012;27:339–345.
11 Morris JC: The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 1993;43:2412–2414.

Dement Geriatr Cogn Disord Extra 2013;3:131–142
DOI: 10.1159/000350460

12 Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, Delacourte A, Galasko D, Gauthier S, Jicha G, Meguro K, O'Brien J, Pasquier F, Robert P, Rossor M, Salloway S, Stern Y, Visser PJ, Scheltens P: Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol 2007;6:734–746.
13 McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, Cummings J, Duda JE, Lippa C, Perry EK, Aarsland D, Arai H, Ballard CG, Boeve B, Burn DJ, Costa D, Del Ser T, Dubois B, Galasko D, Gauthier S, Goetz CG, Gomez-Tortosa E, Halliday G, Hansen LA, Hardy J, Iwatsubo T, Kalaria RN, Kaufer D, Kenny RA, Korczyn A, Kosaka K, Lee VM, Lees A, Litvan I, Londos E, Lopez OL, Minoshima S, Mizuno Y, Molina JA, Mukaetova-Ladinska EB, Pasquier F, Perry RH, Schulz JB, Trojanowski JQ, Yamada M, Consortium on DLB: Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 2005;65:1863–1872.
14 Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, Freedman M, Kertesz A, Robert PH, Albert M, Boone K, Miller BL, Cummings J, Benson DF: Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 1998;51:1546–1554.
15 Román GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, Amaducci L, Orgogozo JM, Brun A, Hofman A, et al: Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology 1993;43:250–260.
16 Reisberg B, Ferris SH, Kluger A, Franssen E, Wegiel J, de Leon MJ: Mild cognitive impairment (MCI): a historical perspective. Int Psychogeriatr 2008;20:18–31.
17 Grundman M, Petersen RC, Ferris SH, Thomas RG, Aisen PS, Bennett DA, Foster NL, Jack CR Jr, Galasko DR, Doody R, Kaye J, Sano M, Mohs R, Gauthier S, Kim HT, Jin S, Schultz AN, Schafer K, Mulnard R, van Dyck CH, Mintzer J, Zamrini EY, Cahn-Weiner D, Thal LJ, Alzheimer's Disease Cooperative Study: Mild cognitive impairment can be distinguished from Alzheimer disease and normal aging for clinical trials. Arch Neurol 2004;61:59–66.
18 Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, Nordberg A, Bäckman L, Albert M, Almkvist O, Arai H, Basun H, Blennow K, de Leon M, DeCarli C, Erkinjuntti T, Giacobini E, Graff C, Hardy J, Jack C, Jorm A, Ritchie K, van Duijn C, Visser P, Petersen RC: Mild cognitive impairment – beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med 2004;256:240–246.
19 Barberger-Gateau P, Dartigues JF, Letenneur L: Four Instrumental Activities of Daily Living Score as a predictor of one-year incident dementia. Age Ageing 1993;22:457–463.
20 Edelberg HK, Shallenberger E, Wei JY: Medication management capacity in highly functioning community-living older adults: detection of early deficits. J Am Geriatr Soc 1999;47:592–596.
21 Edelberg HK, Shallenberger E, Hausdorff JM, Wei JY: One-year follow-up of medication management capacity in highly functioning older adults: J Gerontol A Biol Sci Med Sci 2000;55:M550–M553.
22 Hutchison LC, Jones SK, West DS, Wei JY: Assessment of medication management by community-living elderly persons with two standardized assessment tools: a cross-sectional study. Am J Geriatr Pharmacother 2006;4:144–153.
23 Lieto JM, Schmidt KS: Reduced ability to self-administer medication is associated with assisted living placement in a continuing care retirement community. J Am Med Dir Assoc 2005;6:246–249.
24 Schmidt KS, Lieto JM: Validity of the Medication Administration Test among older adults with and without dementia. Am J Geriatr Pharmacother 2005;3:255–261.
25 Bassuk SS, Glass TA, Berkman LF: Social disengagement and incident cognitive decline in community-dwelling elderly persons. Ann Intern Med 1999;131:165–173.
26 Wilson RS, Krueger KR, Arnold SE, Schneider JA, Kelly JF, Barnes LL, Tang Y, Bennett DA: Loneliness and risk of Alzheimer disease. Arch Gen Psychiatry 2007;64:234–240.
27 Fratiglioni L, Wang HX, Ericsson K, Maytan M, Winblad B: Influence of social network on occurrence of dementia: a community-based longitudinal study. Lancet 2000;355:1315–1319.
28 Wang HX, Karp A, Winblad B, Fratiglioni L: Late-life engagement in social and leisure activities is associated with a decreased risk of dementia: a longitudinal study from the Kungsholmen project. Am J Epidemiol 2002;155:1081–1087.
29 Vilalta-Franch J, Calvo-Perxas L, Garre-Olmo J, Turro-Garriga O, Lopez-Pousa S: Apathy syndrome in Alzheimer's disease epidemiology: prevalence, incidence, persistence, and risk and mortality factors. J Alzheimers Dis 2013;33:535–543.
30 D'Onofrio G, Sancarlo D, Panza F, Copetti M, Cascavilla L, Paris F, Seripa D, Matera MG, Solfrizzi V, Pellegrini F, Pilotto A: Neuropsychiatric symptoms and functional status in Alzheimer's disease and vascular dementia patients. Curr Alzheimer Res 2012;9:759–771.
31 Weisman D, McKeith I: Dementia with Lewy bodies. Semin Neurol 2007;27:42–47.
32 Middleton LE, Yaffe K: Promising strategies for the prevention of dementia. Arch Neurol 2009;66:1210–1215.
33 Bassett SS, Folstein MF: Memory complaint, memory performance, and psychiatric diagnosis: a community study. J Geriatr Psychiatry Neurol 1993;6:105–111.
34 Tobiansky R, Blizard R, Livingston G, Mann A: The Gospel Oak Study stage IV: the clinical relevance of subjective memory impairment in older people. Psychol Med 1995;25:779–786.
35 Jonker C, Geerlings MI, Schmand B: Are memory complaints predictive for dementia? A review of clinical and population-based studies. Int J Geriatr Psychiatry 2000;15:983–991.

36 Riedel-Heller SG, Matschinger H, Schork A, Angermeyer MC: Do memory complaints indicate the presence of cognitive impairment? Results of a field study. Eur Arch Psychiatry Clin Neurosci 1999;249:197–204.
37 Geerlings MI, Jonker C, Bouter LM, Ader HJ, Schmand B: Association between memory complaints and incident Alzheimer's disease in elderly people with normal baseline cognition. Am J Psychiatry 1999;156:531–537.
38 St John P, Montgomery P: Is subjective memory loss correlated with MMSE scores or dementia? J Geriatr Psychiatry Neurol 2003;16:80–83.
39 Carr DB, Gray S, Baty J, Morris JC: The value of informant versus individual's complaints of memory impairment in early dementia. Neurology 2000;55:1724–1726.
40 Pearman A, Storandt M: Predictors of subjective memory in older adults. J Gerontol B Psychol Sci Soc Sci 2004; 59:4–6.
41 Jorm AF, Jacomb PA: The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): socio-demographic correlates, reliability, validity and some norms. Psychol Med 1989;19:1015–1022.
42 Hopman-Rock M, Tak EC, Staats PG: Development and validation of the Observation List for early signs of Dementia (OLD). Int J Geriatr Psychiatry 2001;16:406–414.
43 Galvin JE, Roe CM, Powlishta KK, Coats MA, Muich SJ, Grant E, Miller JP, Storandt M, Morris JC: The AD8: a brief informant interview to detect dementia. Neurology 2005;65:559–564.
44 Li M, Ng TP, Kua EH, Ko SM: Brief informant screening test for mild cognitive impairment and early Alzheimer's disease. Dement Geriatr Cogn Disord 2006;21:392–402.
45 Galvin JE, Roe CM, Coats MA, Morris JC: Patient's rating of cognitive ability: using the AD8, a brief informant interview, as a self-rating tool to detect dementia. Arch Neurol 2007;64:725–730.
46 Rapp MA, Dahlman K, Sano M, Grossman HT, Haroutunian V, Gorman JM: Neuropsychological differences between late-onset and recurrent geriatric major depression. Am J Psychiatry 2005;162:691–698.
47 Baune BT, Suslow T, Arolt V, Berger K: The relationship between psychological dimensions of depressive symptoms and cognitive functioning in the elderly – the MEMO-Study. J Psychiatr Res 2007;41:247–254.
48 Porter RJ, Gallagher P, Thompson JM, Young AH: Neurocognitive impairment in drug-free patients with major depressive disorder. Br J Psychiatry 2003;182:214–220.

Geriatrics Gerontology Medline Indexed

Geriatr Gerontol Int 2013

ORIGINAL ARTICLE

Intensive rehabilitation for dementia improved cognitive function and reduced behavioral disturbance in geriatric health service facilities in Japan

Kenji Toba,[1] Yu Nakamura,[2] Hidetoshi Endo,[1] Jiro Okochi,[3] Yukiko Tanaka,[3] Chiyako Inaniwa,[3] Akira Takahashi,[3] Naoko Tsunoda,[3] Kentaro Higashi,[3] Motoharu Hirai,[3] Hiroyuki Hirakawa,[3] Shizuru Yamada,[3] Yohko Maki,[4] Tomoharu Yamaguchi[4] and Haruyasu Yamaguchi[4]

[1]National Center for Geriatrics and Gerontology, Ohbu, [2]Department of Psychiatry, Kagawa University, Takamatsu, [3]Japan Association of Geriatric Health Service Facilities, Tokyo, and [4]Graduate School of Health Sciences, Gunma University, Maebashi, Japan

Aim: To examine the efficacy of rehabilitation for elderly individuals with dementia at intermediate facilities between hospitals and home, based on the policies for elderly individuals to promote community-based care at home and dehospitalization.

Methods: Participants were older adults with dementia newly admitted to intermediate facilities. A total of 158 in the intervention group who claimed Long-Term Care Insurance for three consecutive months, and 54 in the control group were included in the analysis. The interventions were carried out in a tailor-made manner to meet individual needs. The personal sessions were carried out three times a week for 3 months after admission by physical, occupational or speech therapists. Outcome measures were cognitive tests (Hasegawa Dementia Scale revised [HDS-R] and Mini-Mental State Examination), and observational assessments of dementia severity, activities of daily living (ADL), social activities, behavioral and psychological symptoms of dementia (BPSD) using a short version of the Dementia Disturbance Scale (DBD13), depressive mood, and vitality.

Results: Significant improvement in the intervention group was shown in cognitive function measured by HDS-R (interaction $F[1, 196] = 5.190$, $P = 0.024$), observational evaluation of dementia severity ($F[1,198] = 9.550$, $P = 0.002$) and BPSD (DBD13; $F[1,197] = 4.506$, $P = 0.035$). Vitality, social activities, depressive mood and ADL were significantly improved only in the intervention group, although interaction was not significant.

Conclusions: Significant improvement by intervention was shown in multiple domains including cognitive function and BPSD. Cognitive decline and worsening of BPSD are predictors of care burden and hospitalization, thus intensive rehabilitation for dementia was beneficial for both individuals with dementia and their caregivers. **Geriatr Gerontol Int 2013; ••: ••–••.**

Keywords: behavioral and psychological symptoms of dementia, clinical medicine, Dementia Disturbance Scale short version, dementia, geriatric medicine, rehabilitation, tailor-made.

Introduction

Promoting community-based care at home and dehospitalization is one of the main policies for elderly individuals. In order to reduce the length of hospital stay, it is recommended to establish a rehabilitation and care system for the elderly just after leaving hospital. Thus, the Japanese government established the "Geriatric Health Service Facility" in 1986 (Long-Term Care Health Facility after 2000; Roken), which is a transitional facility between hospital and home or nursing home to provide medical treatment, nursing care, and rehabilitation. Elderly individuals are admitted to Roken after their condition has become stable in hospital, and stay until they are ready to return home. After returning home, Roken offers community-based rehabilitation and various care services to support home-based care, and facilitates networks for intraregional exchanges among municipalities, local healthcare and social welfare services.

Since Roken was launched, the number of inpatients with dementia has markedly increased. Hospitalization

Accepted for publication 20 March 2013.

Correspondence: Dr Kenji Toba MD PhD, National Center for Geriatrics and Gerontology, 35 Gengo, Morioka-cho, Ohbu-city, Aichi Japan 474-8511. Email: toba@ncgg.go.jp

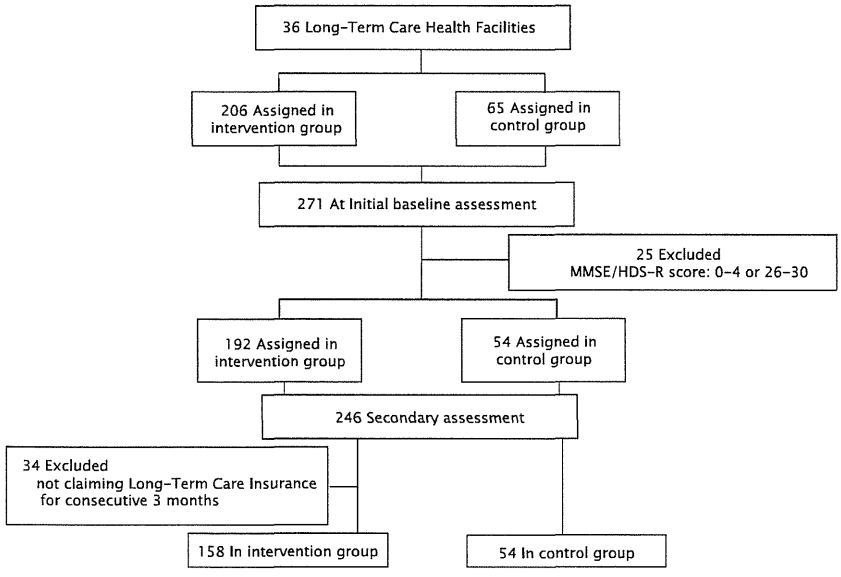

Figure 1 Flow of participants in the intervention and control groups. HDS-R, Hasegawa Dementia Scale revised. MMSE, Mini-Mental State Examination.

itself can cause cognitive deterioration, even during a hospital stay for diseases other than dementia, and patients are often not expected to recover to their pre-hospitalization level.[1] Other predictors of hospitalization are caregivers' burden and the interrelationship with caregivers.[2] Behavioral and psychological symptoms of dementia (BPSD) are a source of distress for caregivers and a major reason for hospitalization.[3,4] Additionally, disuse syndrome is triggered by psychological factors associated with dementia, such as a depressive and apathetic mood.[5–9] Disuse syndrome can lead to deterioration of cognitive and physical function, which can result in repeated hospitalization.

To break the vicious cycle of repeated hospitalization, effective rehabilitation just after discharge from hospital is required, and Roken was singled out as the appropriate facility for the rehabilitation. Thus, in 2006, the Japanese Long-term Care Insurance system introduced intensive rehabilitation for individuals with dementia who were newly admitted to Roken, consisting of personal rehabilitation three times a week for 3 months. This rehabilitation has become widely practiced since its introduction. However, the efficacy has not been examined, although the rehabilitation is payable under long-term insurance. Thus, a model project was organized to examine the efficacy of the rehabilitation for dementia in Roken throughout Japan.

Methods

Study members

Study committee members were researchers excluding stakeholders of any Roken, and committee observers were staff of the Health and Welfare Bureau for the Elderly, Ministry of Health, Labour and Welfare. The committee designed the research, selected 36 Rokens, and interpreted the data. Data were collected by rehabilitation staff in the 36 Rokens.

Participants

The study was carried out between July 2007 and February 2008. The flow of participants is shown in Figure 1. Survey slips were sent to the facilities in July 2007. The facilities were required to send them back after the pre-intervention and post-intervention assessment, respectively. Inclusion criteria of the intervention group were: (i) newly admitted patients with dementia diagnosed by *The Diagnostic and Statistical Manual of Mental Disorders IV*; (ii) with Mini-Mental State Examination (MMSE) or Hasegawa Dementia Scale revised (HDS-R) score between 5 and 25 at pre-intervention assessment; and (iii) who claimed Long-Term Care Insurance for three consecutive months. Inclusion criteria of the control group were: (i) and (ii), and (iii) who did not receive interventions. The participants were not randomized. We received 271 responses, and among them, 212 individuals met the inclusion criteria (158 in intervention group and 54 in control group; Table 1). Informed consent was given from all participants or their responsible care giver. The research plan was approved by the Ethics Board of the Japan Association of Geriatric Health Services Facilities.

Assessment

The assessment was minimized to reduce the burden of facilities staff. As the interventions were carried out by therapists during working time, it would have been

Table 1 Demographic data

		Intervention	Control	
n		158	54	
Male/female (%)		30.2/69.8	39.6/60.4	NS
Age		84.1 ± 7.1	87.3 ± 7.1	P = 0.005†
Dementia	AD	22	7	NS
	VD	52	15	NS
	DLB	3	0	NS
	FTD	2	0	NS
	Others/unknown	79	32	NS

†Significant difference by two-sample *t*-test. AD, Alzheimer's disease; DLB, dementia with Lewy bodies; FTD, front-temporal dementia; M/F, male/female; NS, no significant difference by χ^2-test; VD, vascular dementia.

difficult to collect many data if the assessment were complicated. The assessment scales were chosen based on preliminary studies, which were carried out in the last 2 years.

Cognitive tests

The MMSE and HDS-R were carried out. HDS-R is similar to MMSE, but lays more weight on memory than does MMSE.

Questionnaires

For the assessment of subjective mood, the participants were required to answer the interview of a short version of the Geriatric Depression Scale (GDS;[10] scores are between 0–5, high scores indicate more depressive mood). Facility care staff assessed activities of daily living (ADL), BPSD, N-Memory Scale (NM),[11] vitality index[12] and the Social Activity Scale. ADL was assessed using the Barthel Index (scoring was changed: total assistance of 0 to independence of 3 for each item, and full score of 15).[13] In addition to ADL, the capacity for social interaction was measured using the Social Activity Scale, whose sub-items were conversation with facility staff members, conversation with other residents, organizing own belongings, participation in recreational activities, and outings (total assistance of 0 to independence of 3 for each item, and full score of 15). BPSD was evaluated using a short version of the Dementia Behavior Disturbance Scale (DBD;[13] "never" of 0 to "usually" of 3 for each item and full score of 48).[14] The NM Scale is an observational scale, which evaluates the stages of dementia in five domains: housework, social interaction and interest, communication, memory, and orientation ("impossible" of 0 to "normal" of 10 and full score of 50). The Vitality Index evaluates motivation in daily living, with sub-items of waking up, greetings, having meals, elimination, and participation in rehabilitation and/or recreation ("indifferent" of 0 to "voluntarily" of 2 and full score of 10).

Intervention

Before commencement of the study, a training workshop was held to introduce the intervention methods, whose efficacy was suggested by previous studies: such as reminiscence, reality orientation, memory rehabilitation, music therapy, physical exercise, occupational therapy, speech communication therapy and learning sessions.

The intervention was carried out in an individualized tailor-made manner.[15] First, the individual functional profiles were assessed with regard to both abilities and disabilities to evaluate how to enhance the abilities and compensate for disabilities. Second, training activities were selected; the decision was shared between therapists and participants. Each personal session was took place three times a week for 3 months after admission by physical, occupational or speech therapists. Individuals in the control group took usual group therapies including exercise, singing songs and games.

Analysis of data

The data were analyzed using the Japanese version of SPSS for Windows version 19.0 (IBM Corporation, Armonk, NY, USA). For an initial baseline comparison between the intervention and control groups, two-sample *t*-tests were carried out; there was no significant difference between the two groups for any outcome measure. Participants who underwent the initial baseline and post-intervention assessments were included in the final analysis; dropout participants were excluded from the analysis. Repeated measures analysis of covariance (ANCOVA) with the covariate of age was used to analyze the completed cases. Age was used as a covariate, because the ages were significantly different between the two groups (Table 1). The interaction was examined to assess the differential effect between the intervention and control groups, and post-hoc "within subjects" analysis was carried out with Bonferroni correction. Regarding the measures where significant