is usually affected but repetition and motor speech are spared. The consensus neuroimaging markers for naPPA are atrophy and/or functional abnormalities in the left posterior fronto-insular region [2,3]. A consensus meeting developed criteria for these conditions in relation to frontotemporal lobar degeneration (FTLD) [5]. Later, other affected cognitive domains and different accompanying language disorders were recognized. The logopenic variant of PPA (lvPPA) was defined by hesitant speech with word-finding pauses due to impaired single-word retrieval and difficulty in sentence repetition, without object knowledge and motor deficits of speech [6]. For lvPPA, the MRI findings are predominant in left posterior perisylvian or parietal atrophies [6]. Consequently, functional neuroimaging studies have established consistent neuroanatomical correlations in three clinical variants of PPA [7–9]. According to these defining characteristics, an international group of experts published a Consensus Classification of the most accepted three clinical variants of PPA (naPPA, svPPA, lvPPA) [10]. In the last decade, cerebrospinal fluid (CSF) biomarkers [11] and amyloid positron emission tomography (^{11}C PiB-PET) [12,13] have been developed in research settings to elucidate clinical–pathological correlations of Alzheimer's disease (AD). So far, some subgroup of patients with PPA have high association with the CSF diagnostic AD markers [14,15], and the neuroimaging biomarkers of amyloid PET/FDG-PET [7,8,16,17] and MRI [8,9,18].

Materials and methods

Subjects

This study complied with the Declaration of Helsinki and was approved by the Institutional Review Boards (IRB) of Gunma University Graduate School of Medicine, Geriatrics Research Institute and Hospital, and Maebashi Red Cross Hospital. The spouse or family members of each AD patient provided written informed consent for the patient to participate in the study. The subjects who underwent lumbar punctures were recruited at Gunma University Graduate School of Medicine, Geriatrics Research Institute and Hospital, and Maebashi Red Cross Hospital (Maebashi, Gunma, Japan). Upon entering the study, subjects underwent a standardized clinical assessment, including medical history, physical and neurological examinations, Mini-Mental State Examination (MMSE) [19], brain MRI and/or computed tomography (CT) scan. AD was diagnosed for patients scoring 23 points or fewer on the MMSE [20], combined with caregivers' information of patients' daily activities. Diagnostic criteria of the National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [21] were used for AD diagnosis. Subjects were classified as non-demented (ND) if they scored more than 24 points on the MMSE, and if, based upon information on activities of daily living (ADL) provided by the family, they were considered to have a normal daily life not requiring any intellectual assistance. Speech function of patients was estimated by the Standard Language Test of Aphasia (SLTA) [22,23]. SLTA is a test battery originally developed for language function to estimate multi-domains, including "Confrontation naming", "Word repetition", "Sentence repetition", "Auditory single-word comprehension", and "Auditory complex sentence comprehension commands". Three variants of PPA patients were diagnosed clinically, based on the Consensus Classification of the three most accepted PPA clinical variants [10].

Demographics of PPA patients and AD

The number of patients in each study group was as follows: 10 for naPPA, 4 for svPPA, 10 for lvPPA, and 50 for AD patients. Age of onset (AOO, years old, mean ± SD) was 63.50 ± 5.06 in naPPA patients, 62.00 ± 0.82 in svPPA patients, 64.70 ± 4.97 in lvPPA patients and 64.8 ± 8.01 in AD patients. Duration of the disease (years) was 5.60 ± 1.78 in naPPA patients, 4.00 ± 1.83 in svPPA patients, 4.00 ± 1.16 in lvPPA patients and 3.06 ± 1.99 in AD patients. The male ratio to total patient number was 0.50 in naPPA patients, 1.00 in svPPA, 0.50 in lvPPA patients and 0.40 in AD patients. The years of attained education were 11.70 ± 0.95 for naPPA patients, 13.00 ± 2.00 for svPPA patients, 12.10 ± 1.66 for lvPPA patients and 12.25 ± 2.13 in AD patients.

Neuroimaging studies

MRI or CT scan, ^{99m}Tc ECD-SPECT and ^{11}C PiB-PET and FDG-PET neuroimaging studies were performed for the patient study groups. Each MRI and SPECT/PET scan was evaluated by an experienced radiologist or nuclear medicine clinician and two neurologists; all evaluators were blinded to the patients' data on neurological findings, cognition and linguistic assessment (MMSE and SLTA). For each patient in the PPA variant and AD study groups, we assessed the presence or absence of imaging-supported diagnostic biomarkers by MRI, SPECT and FDG-PET [7–10,16–18]: (A) predominant atrophy and/or hypoperfusion/hypometabolism in the left posterior fronto-insular region (naPPA), (B) predominant atrophy and hypoperfusion/hypometabolism in the left anterior temporal lobe (svPPA), (C) predominant atrophy and hypoperfusion/hypometabolism in the left posterior perisylvian or parietal region (lvPPA), (D) hypoperfusion/hypometabolism in bilateral posterior cingulate gyrus and precuneus (AD) (Figure 1A–D).

PiB (2-(4-aminophenyl)-6-hydroxybenzothiazole) was synthesized for ^{11}C PiB-Positron Emission Tomography (^{11}C PiB-PET) [12]. After an intravenous injection of ^{11}C-PiB (550 MBq), a dynamic 70-min scan was acquired in the three-dimensional mode without arterial sampling using an Eminence-B PET scanner (General Electric, CT, USA). CT scans were co-registered with the respective PET images using the PMOD image-fusion tool (PMOD Technologies Ltd., Zurich, Switzerland). The PET images were reconstructed using a filtered back-projection algorithm for attenuation and scatter corrections. According to a previous study [24], in which the frame summation of the dynamic images was recorded for 70 min, Logan graphical analysis was used for determining the regional counts (SUVR)(distribution volume ratio, DVR = binding potential + 1) using the cerebellum as the reference region. For this purpose, the cortical lesions occurring in the frontal and temporal lobes and posterior cingulate gyrus were selected. The mean cortical DVR (MCDVR) was the mean of the DVR values

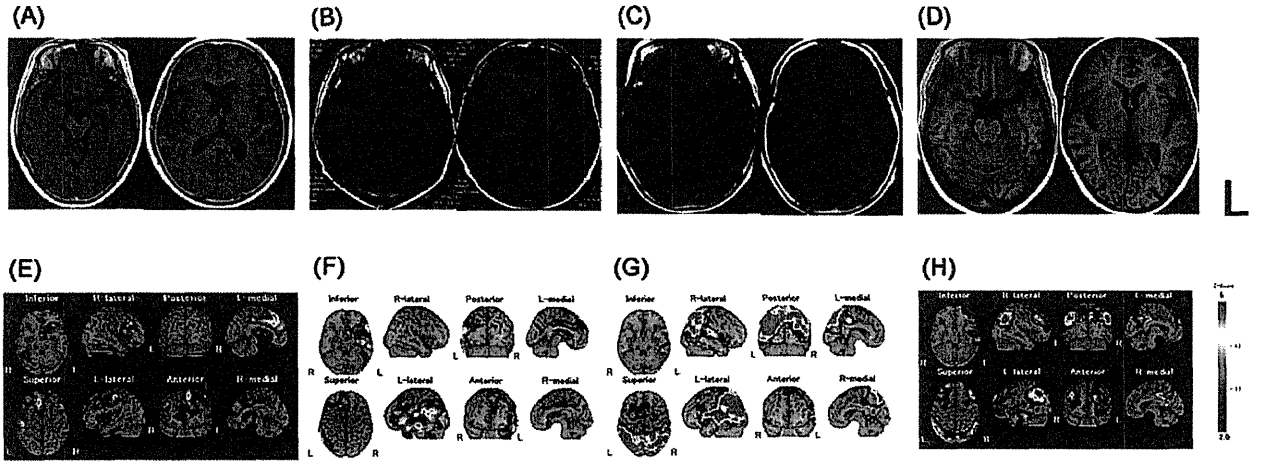

Figure 1. MRI and ^{99m}Tc ECD-SPECT.Brain MRI of PPA patients for naPPA (A), lvPPA (B), svPPA (C) and early-onset AD (D). ^{99m}Tc ECD-SPECT of patients for naPPA (E), lvPPA (F), svPPA (G) and AD (H). naPPA is characterized by predominant atrophy (A) and hypoperfusion (E) in the left posterior fronto-insular region, svPPA by predominant atrophy (B) and hypoperfusion in the left anterior temporal lobe (F), and lvPPA by predominant atrophy (C) and hypoperfusion in the left posterior perisylvian or parietal region (G). An early-onset AD patient showed frontal and temporal lobes atrophy (D), and hypoperfusion in the frontal lobes and parietal lobes cortices and the posterior cingulate (H).

of these lesions. Positive ^{11}C PiB binding indicated that the visible cortical ^{11}C PiB accumulation was higher than that of the white matter or that the MCDVR of the cortex was larger than the cutoff index obtained at our hospital.

CSF biomarkers

Measurement of CSF Aβ1-42, Aβ1-40 and Aβ1-38

CSF was obtained by a lumbar puncture in the L3/L4 or L4/L5 intervertebral space. CSF samples were centrifuged for 10 min at 1800 *g* at 4 °C within 3 h of collection. Samples were divided into aliquots of 0.5 mL in polypropylene tubes and stored at −80 °C until analysis using an ELISA kit for human CSF Aβ1-40 (Wako Pure Chemical Industries, Tokyo, Japan), human CSF Aβ1-42 (Wako Pure Chemical Industries) and human CSF Aβ1-38 (IBL, Gunma, Japan) [25,26].

Measurement of CSF phosphorylated tau 181

Measurement of ptau-181 in CSF was performed by sandwich ELISA (Innogenetics, Ghent, Belgium) as described elsewhere [27].

Genetic analysis of apolipoprotein E

After obtaining informed consent for genetic testing, we purified genomic DNA from lymphocytes in the peripheral blood of affected subjects. For the analysis of apolipoprotein E genotype, purified genomic DNA was examined as previously described [28].

Results

Mini-mental state examination

Scores (full score 30: mean ± S.D.) of mini-mental state examination (MMSE) were 17.20 ± 7.47 in naPPA patients, 6.75 ± 5.56 in svPPA patients, 15.70 ± 4.92 in lvPPA patients and 18.44 ± 4.74 in AD patients. The MMSE score for svPPA patients was lower than those of naPPA and lvPPA patients ($p < 0.0001$, respectively (Table 1).

Standard Language Test of Aphasia

Scores for "Naming" (% correct: mean ± S.D.) from the Standard Language Test of Aphasia (SLTA) were 39.00 ± 19.26 in naPPA patients, 16.25 ± 4.79 in svPPA patients and 59.00 ± 21.58 in lvPPA patients. Scores for "Single-word repetition" (% correct) from the SLTA were 76.00 ± 18.38 in naPPA patients, 75.00 ± 19.15 in svPPA patients and 75.00 ± 23.21 in lvPPA patients. Scores for "Sentence repetition" (% correct) from the SLTA were 30.0 ± 17.00 in naPPA patients, 40.00 ± 43.20 in svPPA patients and 32.00 ± 19.32 in lvPPA patients. Scores for "Auditory single-word comprehension" (% correct) from the SLTA were 76.00 ± 22.71 in naPPA patients, 42.50 ± 38.62 in svPPA patients and 77.00 ± 22.14 in lvPPA patients. Scores for "Auditory sentence comprehension command" (% correct) from the SLTA were 66.00 ± 28.75 in naPPA patients, 15.00 ± 10.00 in svPPA patients and 58.00 ± 30.48 in lvPPA patients. The scores for "Naming" and "Single-word comprehension" in svPPA patients were significantly lower than those of naPPA and lvPPA patients (*$p < 0.001$, **$p < 0.0001$, Mann–Whitney test, Table 1), while the scores for "Auditory single-word comprehension" and "Auditory sentence comprehension command" in svPPA patients were significantly lower than those of naPPA and lvPPA patients (**$p < 0.0001$, Mann–Whitney test, Table 1). The scores for "Calculation" in lvPPA patients were significantly lower than those for naPPA and svPPA patients (**$p < 0.0001$, Mann–Whitney test, Table 1).

Neuroimaging (MRI, ^{99m}Tc ECD-SPECT, FDG-PET and ^{11}C PiB-PET)

The 24 PPA patients were clinically subclassified into 10 naPPA patients, 4 svPPA patients and 10 lvPPA patients according to the Consensus classification of PPA [10]. All the

Table 1. Summary of clinical features, MMSE and SLTA for the 24 PPA patients.

	naPPA ($N=10$)	svPPA ($N=4$)	lvPPA ($N=10$)
Clinical information			
Age of onset (year)	63.50 ± 5.06	62.00 ± 0.82	64.70 ± 4.97
Disease duration (years)	5.60 ± 1.78	4.00 ± 1.83	4.00 ± 1.16
Male gender (%)	50	100	50
Education (years)	11.70 ± 0.95	13.00 ± 2.00	12.10 ± 1.66
MMSE	17.20 ± 7.47	6.75 ± 5.56**	15.70 ± 4.92
SLTA			
Naming (% correct)	39.00 ± 19.26*	16.25 ± 4.79**	59.00 ± 21.58
Single-word repetition (% correct)	76.00 ± 18.38	75.00 ± 19.15	75.00 ± 23.21
Sentence repetition (% correct)	30.00 ± 17.00	40.00 ± 43.20	32.00 ± 19.32
Auditory single-word comprehension (% correct)	76.00 ± 22.71	42.50 ± 38.62**	77.00 ± 22.14
Auditory sentence comprehension (% correct)	66.00 ± 28.75	15.00 ± 10.00**	58.00 ± 30.48
Calculation (% correct)	41.00 ± 27.67	40.00 ± 46.19	28.50 ± 27.79**

Figures indicate means ± SD or number with percentages in parentheses. MMSE = mini-mental state examination; SLTA = standard language test of aphasia. Asterisks denote significantly impaired at $*p<0.001$ and $**p<0.0001$ (Mann–Whitney test).

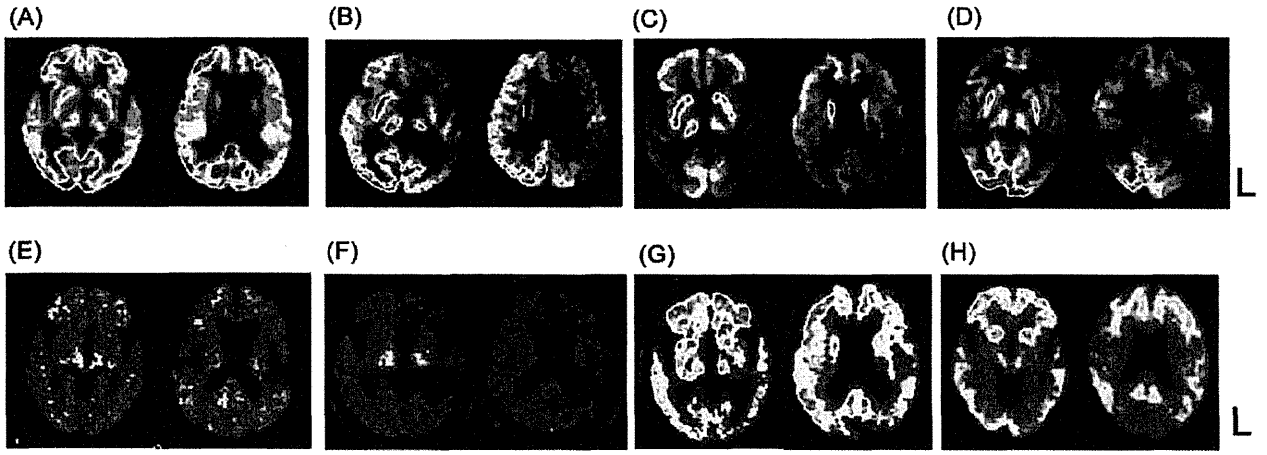

Figure 2. FDG-PET and ^{11}C PiB-PET. (A) In naPPA patients, FDG-PET analysis showed glucose hypometabolism in the left posterior fronto-insular region. (B) ^{11}C PiB-PET showed no abnormal signal lesion in the brain of naPPA patients. (C) In svPPA patients, FDG-PET showed glucose hypometabolism in the left anterior temporal lobe, while no PiB positive signal finding in cerebral cortices (D). (E) While lvPPA patients showed glucose hypometabolism in the left anterior temporal lobe by FDG-PET, ^{11}C PiB-PET showed abnormal high PiB signal findings in cerebral cortices of frontal lobes and temporal lobes and the posterior cingulate (F). (G) An early-onset AD patient showed glucose hypometabolism in bilateral frontal and temporal lobes, presenting abnormal PiB positive signal findings in cerebral cortices and the posterior cingulate in ^{11}C PiB-PET (H).

10 naPPA patients showed brain atrophy in the left posterior fronto-insular region by MRI (Figure 1A: a naPPA case). All the 10 naPPA patients showed hypoperfusion in the left posterior fronto-insular region by ^{99m}Tc ECD-SPECT (Figure 1E: a naPPA case). All the 4 svPPA patients showed atrophy in the left anterior temporal lobe by MRI or CT (Figure 1B: a svPPA case), and ^{99m}Tc ECD-SPECT showed hypoperfusion in the left anterior temporal lobe (Figure 1F: a svPPA case). All the 10 lvPPA patients showed brain atrophy in the left posterior perisylvian and parietal region by MRI or CT (Figure 1C: an lvPPA case) and hypoperfusion in the corresponding lesions by ^{99m}Tc ECD-SPECT (Figure 1G: an lvPPA case). An early-onset AD patient showed bilateral atrophy in the temporal and parietal lobes (Figure 1D), with bilateral hypoperfusion in the temporal and parietal lobes (Figure 1H).

All 7 naPPA patients showed glucose hypometabolism in the left posterior fronto-insular region by FDG-PET (Figure 2A). All 7 naPPA patients showed no abnormal signal lesion by ^{11}C PiB-PET (Figure 2E). All 4 svPPA patients showed glucose hypometabolism in the left anterior temporal lobe by FDG-PET (Figure 2B), while no PiB positive signal was found in the cerebral cortices (Figure 2 F). All 6 lvPPA patients showed glucose hypometabolism in the left anterior temporal lobe by FDG-PET (Figure 2C), and by ^{11}C PiB-PET showed PiB positive signal findings corresponding to Aβ accumulation bilaterally in the cerebral cortices (Figure 2G). By FDG-PET, an early-onset AD patient showed bilateral glucose hypometabolism in the frontal and temporal lobes (Figure 2D), and by ^{11}C PiB-PET presented bilateral PiB positive signal findings in the cerebral cortices of the frontal and temporal lobes, and also in the posterior cingulate (Figure 2H).

Comparative analysis of CSF data

The lvPPA patients showed lower levels of CSF Aβ1-42 and higher levels of CSF ptau-181 than ND. The CSF levels of ptau-181 (mean ± SD) were 33.59 ± 16.09 for naPPA ($N=10$), 42.24 ± 21.26 for svPPA ($N=4$), and

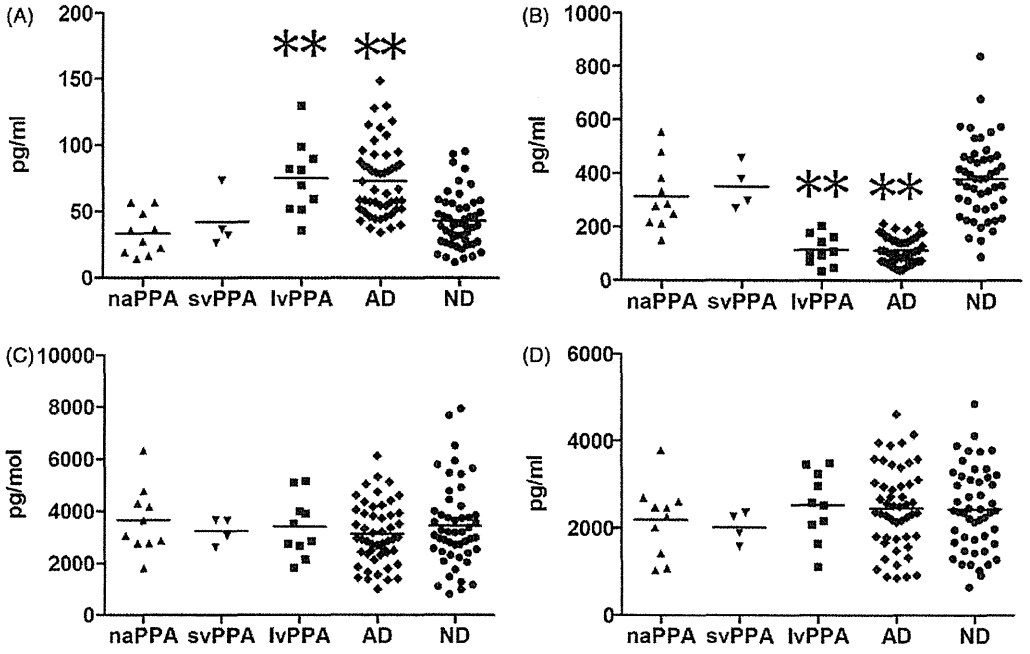

Figure 3. CSF levels of ptau-181, Aβ1-42, Aβ1-40 and Aβ1-38. (A) CSF levels of ptau-181 of lvPPA and AD showed significant increases compared to those of naPPA, svPPA and ND (**$p<0.0001$). (B) CSF levels of Aβ1-42 of lvPPA and AD showed significant decreases compared to those of naPPA, svPPA and ND (**$p<0.0001$). (C) CSF levels of Aβ1-40 were not significantly different amongst naPPA, svPPA, lvPPA and ND. (D) CSF levels of Aβ1-38 were not significantly different amongst naPPA, svPPA, lvPPA and ND. Bar in the Figure shows average data. Asterisks denote significantly impaired (**$p<0.0001$, Mann–Whitney test).

75.38 ± 27.32 for lvPPA ($N=10$), 73.14 ± 27.26 for AD ($N=50$) and 43.19 ± 20.49 for non-demented subjects ($N=50$) (Figure 3A). The CSF levels of ptau-181 for lvPPA and AD were significantly higher than those for naPPA and svPPA (Figure 3A). No abnormal findings for naPPA and svPPA patients were observed in the CSF levels of Aβ1-42, Aβ1-40, Aβ1-38 or ptau-181. In the CSF levels of Aβ1-42, average scores were 314.42 ± 125.83 for naPPA, 351.35 ± 84.21 for svPPA, 115.98 ± 56.46 for lvPPA, 113.82 ± 48.84 for AD and 379.25 ± 144.45 for ND (Figure 3B). The CSF levels of Aβ1-42 for lvPPA and AD were significantly lower than those for naPPA, svPPA and ND (Figure 3B). In the CSF levels of Aβ1-40, average scores were 3647.09 ± 1293.76 for naPPA, 3248.58 ± 504.53 for svPPA, and 3401.29 ± 1151.24 for lvPPA, 3126.24 ± 1185.32 for AD and 3439.24 ± 1611.39 for non-demented subjects (Figure 3C). In the CSF levels of Aβ1-38, average scores were 2190.12 ± 839.47 for naPPA, 2023.82 ± 356.92 for svPPA, and 2535.66 ± 790.99 for lvPPA, 2464.03 ± 946.80 for AD and 2435.37 ± 950.67 for non-demented subjects (Figure 3D). In either CSF levels of Aβ1-38 or Aβ1-40, no significant difference was observed amongst naPPA, svPPA and lvPPA patients (Figure 3C and D).

Ratios of CSF Aβ molecules (Aβ1-42, Aβ1-40 and Aβ1-38) and ptau-181

The ratio of Aβ1-42/Aβ1-40 (mean ± S.D.) was 0.09 ± 0.04 for naPPA, 0.11 ± 0.02 for svPPA, 0.04 ± 0.02 for lvPPA, 0.05 ± 0.04 for AD and 0.14 ± 0.11 for ND. The ratios of Aβ1-42/Aβ1-40 for lvPPA and AD were significantly lower than those for naPPA, svPPA and ND (**$p<0.0001$, respectively, Figure 4A). The ratio of Aβ1-42/Aβ1-38 was 0.16 ± 0.06 for naPPA, 0.17 ± 0.01 for svPPA, 0.05 ± 0.01 for lvPPA, 0.06 ± 0.04 for AD and 6.92 ± 3.37 for ND. The ratios of Aβ1-42/Aβ1-38 for lvPPA and AD were lower than those of those for naPPA, svPPA and ND (**$p<0.0001$, respectively, Figure 4B). The ratio of Aβ1-38/Aβ1-40 was 0.641 ± 0.273 naPPA, 0.64 ± 0.12 for svPPA, 0.81 ± 0.34 for lvPPA, 0.94 ± 0.62 for AD and 0.95 ± 0.92 for ND. No significant difference was observed among these ratios for naPPA, svPPA, lvPPA, AD and ND (data not shown). The ratio of ptau-181/Aβ1-42 was 0.12 ± 0.07 for naPPA, 0.12 ± 0.03 for svPPA, 0.83 ± 0.50 for lvPPA, 0.79 ± 0.54 for AD and 0.14 ± 0.13 for ND. The results of ptau-181/Aβ1-42 for lvPPA and AD were significantly higher than those for naPPA, svPPA and ND (**$p<0.0001$, respectively, Figure 4C). The ratio of ptau-181/Aβ1-38 was 0.02 ± 0.01 for naPPA, 0.02 ± 0.01 for svPPA, 0.03 ± 0.02 for lvPPA, 0.04 ± 0.03 for AD and 0.02 ± 0.01 for ND. The results of ptau-181/Aβ1-38 for lvPPA and AD were significantly higher than those for naPPA, svPPA and ND (**$p<0.0001$, respectively, Figure 4D). The results of Aβ1-42/Aβ1-40, Aβ1-42/Aβ1-38, ptau-181/Aβ1-42 and ptau-181/Aβ1-38 for AD and lvPPA were quite similar to those for EOSAD/LOSAD and ND in previous study [26].

Apolipoprotein E genotypes

The apoE ε4 allele frequency in the patient groups was 0.05 in naPPA, 0 in svPPA and 0.40 in lvPPA. In this study, the frequency of the ApoE ε4 allele in lvPPA is quite similar to

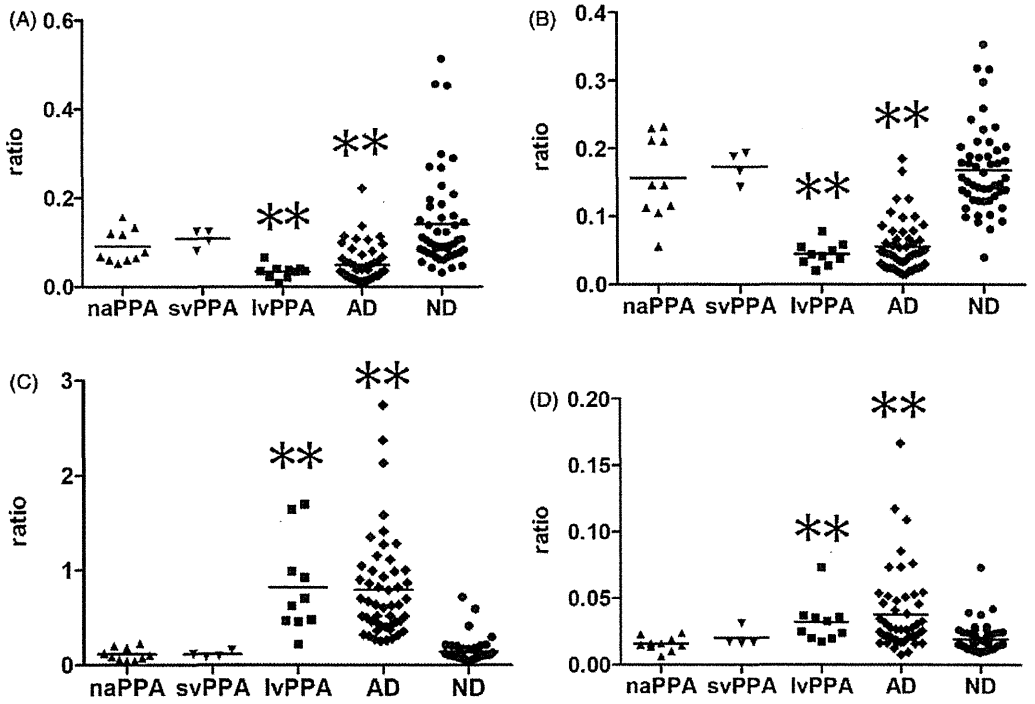

Figure 4. Ratios of CSF Aβ1-42/Aβ1-40, Aβ1-42/Aβ1-38, ptau-181/Aβ1-42 and ptau-181/Aβ1-38. (A) The ratio of Aβ1-42/Aβ1-40 in lvPPA and AD was significantly decreased compared to those of naPPA, svPPA and ND (**$p < 0.0001$). (B) The ratio of Aβ1-42/Aβ1-38 in lvPPA and AD was significantly decreased compared to those naPPA, svPPA and ND (**$p < 0.0001$). (C) The ratio of ptau-181/Aβ1-42 in lvPPA and AD was significantly increased compared to those naPPA, svPPA and ND (**$p < 0.0001$). (D) The ratio of ptau-181/Aβ1-38 in lvPPA and AD was significantly increased in lvPPA and AD compared to those naPPA, svPPA and ND (**$p < 0.0001$). The bar in Figure shows average data. Asterisks denote significantly impaired at **$p < 0.0001$ (Mann–Whitney test).

the frequency of the ApoE ε4 allele in AD patients in Japan [29,30]; however, it appears lower than a previous publication [6].

Discussion

Our study of PPA is based on the analysis of 24 patients diagnosed with a primary progressive language disorder. For the PPA patients in our study, there were clear clinical features, in which, SLTA scores of "Naming", "Word repetition", "Sentence repetition", "Auditory single-word comprehension" and "Auditory sentence comprehension commands" in svPPA were significantly less than those of naPPA and lvPPA. Relatively early age of onset, disease duration and education years were similar among the three clinical variants of PPA. These findings were compatible to those from a previous publication [6,9].

In our study, the MRI of PPA patients generally revealed left-sided dominant brain atrophy, with left posterior frontal lobe and insular atrophy for naPPA, left anterior temporal lobe atrophy for svPPA, and left temporal lobe and perisylvian region atrophy for lvPPA. ^{99m}Tc ECD-SPECT presented hypoperfusion in the left posterior frontal lobe/perisylvian region for naPPA, hypoperfusion in the left anterior temporal lobe for svPPA, and hypoperfusion in the left posterior perisylvian region/parietal lobe for lvPPA. In contrast, an early-onset AD patient showed bilateral hypoperfusion in the posterior cingulate to parietal lobe and frontal lobe. FDG-PET also showed hypometabolism in the left posterior frontal lobe for naPPA, left temporo-anterior lobe for svPPA, and left temporo-parietal lobe and the posterior cingulate for lvPPA. In contrast, an early-onset AD patient showed hypoperfusion/hypometabolism bilaterally in the frontal and temporal lobes and the posterior cingulate to parietal lobe. Our ^{11}C PiB-PET study showed PiB positive findings in the fronto-temporal cortices bilaterally and the posterior cingulate for lvPPA and AD, and PiB negative findings for naPPA and svPPA.

The results of AD-CSF biomarkers for the lvPPA patients were quite similar to those for AD patients, presenting significantly higher frequency of the ApoE ε4 allele in lvPPA patients than in naPPA and svPPA patients. Recently, the level of CSF Aβ1-38 for FTD patients was reported to be significantly lower compared to the other diagnostic groups of PPA patients (not classified clinical variants), AD and ND [14]. The AD-CSF markers are reported to be closely correlated to those of the lvPPA patients, while not correlated to those of naPPA and svPPA patients [15].

In our study, we observed no differences between the three PPA variants and AD in the levels of CSF Aβ1-38 and CSF Aβ1-40. Additionally, we have confirmed lower levels of CSF Aβ1-42 and higher levels of CSF ptau-181 and a higher ratio of ptau-181/Aβ1-42 for AD and lvPPA than those for the other two clinical variants (naPPA and svPPA) and ND, as previous reports [8,15,31].

Furthermore, we revealed that lvPPA patients showed significantly lower ratios of Aβ1-42/Aβ1-40 and Aβ1-42/Aβ1-38, whereas the ratios of ptau-181/Aβ1-42 and ptau-181/Aβ1-38 were significantly higher than those of naPPA, svPPA and ND. We observed neither higher levels of

CSF Aβ1-38 for lvPPA nor AD compared to naPPA, svPPA and ND. With a higher frequency of the ApoE ε4 allele in lvPPA, these patients might share a common pathological mechanism of Alzheimer's disease in biochemical pathways and pathology [31,32].

With the results of CSF and neuroimages including ^{11}C PiB-PET, we could diagnose lvPPA for AD and other variants of PPA more exactly. Our findings are the first report in Japan including Asian ethnics whose language structure differs from Western languages; which may support a common pathogenicity worldwide. The lvPPA might have a different pathogenesis from other two variants of PPA and may be a variant of AD in most cases from points of patho-biochemical findings [33]. Migliaccio et al. reported that lvPPA and posterior cortical atrophy (PCA) showed overlapping anatomic and biologic features with early age at onset of Alzheimer's disease [34]. Magnin et al. described that lvPPA is frequently found in PCA and may be associated with poor performance on verbal neuropsychological tasks, especially verbal memory [35]. They suggest that these clinical syndromes represent the spectrum of clinical manifestation of the non-typical form of AD that presents at early age.

Very recently, the use of PBB3 for tau PET study was developed, which enables detection of tau accumulation in mutant tau transgenic mice and AD patients [36]. By detecting the distribution and accumulation of Aβ and tau with ^{11}C PiB-PET and ^{11}C PBB3-PET for PPA patients, we could describe in more detail the correlation of both accumulation of Aβ and tau in brains of PPA patients, and better understand the pathogenesis of speech and dementia.

Conclusions

There were clear clinical features and neuroimaging findings in naPPA, svPPA and lvPPA, as well as changes in AD-CSF biochemical markers (decrease of Aβ1-42 and increase of ptau-181) in lvPPA as well as AD. In our studies, lvPPA showed a higher ratios of ptau-181/Aβ1-42, ptau-181/Aβ1-38 and a higher frequency of the ApoE ε4 allele as compared to naPPA and svPPA; these findings, accompanying the results of neuroimaging including ^{11}C PiB-PET, demonstrate a common mechanism of AD and lvPPA.

Declaration of interest

This study received a Grant-in-Aid for Scientific Research (C) (MI: 23591231, YF: 21591108, TY: 23500426, HY: 23300197, YI: 24591263) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, a funding from the "Japanese Alzheimer's Disease Neuroimaging Initiative (J-ADNI)" of the New Energy and Industrial Technology Development Organization (NEDO) in Japan, and a research grant of "Dominantly Inherited Alzheimer's Network-Japan (DIAN-J)" of the Ministry of Health, Labour and Welfare. Dr Tashiro, Dr Takatama, Dr Amari and Dr Harigaya report no disclosures.

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Short Communication

Lack of Genetic Association Between *TREM2* and Late-Onset Alzheimer's Disease in a Japanese Population

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Abstract. Rare non-synonymous variants of *TREM2* have recently been shown to be associated with Alzheimer's disease (AD) in Caucasians. We here conducted a replication study using a well-characterized Japanese sample set, comprising 2,190 late-onset AD (LOAD) cases and 2,498 controls. We genotyped 10 non-synonymous variants (Q33X, Y38C, R47H, T66M, N68K, D87N, T96K, R98W, H157Y, and L211P) of *TREM2* reported by Guerreiro *et al.* (2013) by means of the TaqMan and dideoxy sequencing methods. Only three variants, R47H, H157Y, and L211P, were polymorphic (range of minor allele frequency [MAF], 0.0002–0.0059); however, no significant association with LOAD was observed in these variants. Considering low MAF of variants examined and our study sample size, further genetic analysis with a larger sample set is needed to firmly evaluate whether or not *TREM2* is associated with LOAD in Japanese.

Keywords: Alzheimer's disease, Japanese, rare variants, SNP, *TREM2*

INTRODUCTION

Alzheimer's disease (AD) is the main cause of dementia in the elderly. AD is thought to be caused by complex interactions between genetic and environmental factors. A twin study demonstrated that the heritability of late-onset AD (LOAD) is approximately 60~80% [1]. It is also assumed that multiple genes/loci contribute to LOAD development [2]. Rare non-synonymous mutations of *APP*, *PSEN1*, and *PSEN2* are well known to cause familial cases of early-onset AD (EOAD) [3], which accounts for several percent of AD. Concerning LOAD, genome-wide association studies with large numbers of subjects have been conducted, based on the common diseases-common variants hypothesis. As a result, over a dozen genes other than *APOE* have been to be associated with the susceptibility to LOAD [4–10].

TREM2 was recently identified as a novel susceptibility gene for LOAD in Caucasians by two independent study groups [11, 12], both studies being performed on the basis of the common diseases-rare variants hypothesis. A noteworthy fact is that the most significant non-synonymous variant, R47H

(rs75932628: CGC⟶CAC; and minor allele frequency [MAF] < about 1%), located within exon 2 of *TREM2*, shows an odds ratio (OR) range of 2.0–5.0 [11, 12], which is almost equal to the risk magnitude for the *APOE*-ε4 allele [13, 14]. The association of this variant with LOAD [15–19] as well as EOAD [20] has been reproducibly confirmed in multiple Caucasian populations. As to Asians, at present there has only been one genetic association study on *TREM2* variants and LOAD, a northern Han Chinese population being involved [21]. In that study, it was demonstrated that no *TREM2* variants, including R47H, examined show significant association with LOAD [21]. It is assumed that *TREM2* may be a Caucasian-specific susceptibility gene for AD. Therefore, in this study we attempted to replicate the association of *TREM2* with LOAD utilizing a Japanese sample set, comprising 4,688 subjects in total.

SUBJECTS AND METHODS

Subjects

This study was approved by the Institutional Review Board of Niigata University and by all participating institutes. All subjects were Japanese and anonymously genotyped.

We prepared a Japanese sample set, comprising 2,190 LOAD cases (clinically-verified, $n = 1{,}977$; and neuropathologically-characterized, $n = 213$) and 2,498 controls (clinically-verified, $n = 2{,}128$; and neuropathologically-characterized, $n = 370$) (Table 1). From power analysis on the basis of Guerreiro et al.'s study with Caucasians [11], this sample set was estimated to be large enough to detect risk alleles with an OR of 1.1–2.5 (range of risk allele frequency = 0.01–0.99, $\alpha = 0.05$, power = 80%) [29]. A large proportion of the clinically-verified subjects were the same (74.8%) as those in the overall sample set used in our previous genetic study on *GAB2* [22]. The LOAD patients met the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association for a diagnosis of probable AD [23]. Non-dementia controls were recruited from among elderly people living in an unassisted manner in the local community. Mini-Mental State Examination [24], Clinical Dementia Rating [25], and/or Function Assessment Staging [26] were applied to assess the severity of the cognitive impairment. All neuropathologically-characterized subjects were utilized in our recent genetic study on *SORL1* [27].

Extraction and quantification of genomic DNA, and *APOE* genotyping are described elsewhere [27, 28]. The *APOE* alleles exhibited strong association with LOAD, as expected: $p_{\text{allele}} = 6.71\text{E-}171$ with χ^2 test (χ^2 value = 783.7, degree of freedom = 2), and $OR_{\varepsilon 4/\varepsilon 3}$ (95% confidence interval [CI]) = 4.81 (4.26–5.42) and $OR_{\varepsilon 2/\varepsilon 3}$ (95% CI) = 0.59 (0.46–0.76).

TREM2 variants and genotyping

To determine whether or not *TREM2* is associated with LOAD in Japanese, we focused on 12 non-synonymous variants of this gene, which were examined in Guerreiro *et al.*'s study with Caucasians [11]: Q33X (rs104894002), Y38C (rs ID, not available), R47H (rs75932628), R62H (rs143332484), T66M (rs201258663), N68K (rs ID, not available), D87N (rs142232675), T96K (rs2234253), R98W (rs147564421), R136Q (rs149622783), H157Y (rs2234255), and L211P (rs2234256). However, two variants, R62H and R136Q, were excluded since one (R62H) did not satisfy the design criteria for the TaqMan® genotyping assay and the other (R136Q) did not work well on TaqMan® genotyping. Consequently, we determined the genotypes of the remaining ten *TREM2* variants using the TaqMan® method (Table 2, Supplementary Table 1). Heterozygotes were further evaluated by means of dideoxy DNA sequencing. Information on sequencing primers is available on request.

Statistical analysis

To detect genotyping errors, a Hardy-Weinberg equilibrium (HWE) test based on Fisher's exact test was conducted. From a 2×2 contingency table (case-control status and genotype [MM and Mm]), we computed genotypic p (p_{genotype}) based on Fisher's exact test and OR with 95% CI as the relative risk of disease for each polymorphic variant. We further performed multiple variant analysis as one of gene-based case-control association studies: distribution of minor-allele carriers (Mm) and non-carriers (MM) as to three polymorphic variants, R47H, H157Y and L211P, was compared between cases and controls on the basis of χ^2 test from a 2×2 contingency table. Subjects with undetermined genotype data in these variants were omitted for this analysis, with 4,582 subjects remaining. We used SNPAlyze software (DYNACOM, Japan; http://www.dynacom.co.jp/) for these statistical analyses, as described in detail elsewhere [35].

The statistical significance was set at $p < 0.05$.

Table 1
Demographics of the study sample set

	No. of subjects	Age		*APOE* allele frequency		
	(Female %)	Mean (SD)	Range	ε2	ε3	ε4
Cases	2,190 (70.1)	75.2 (6.2)	57–102	0.02	0.67	0.31
Controls	2,498 (54.9)	76.3 (6.6)	65–105	0.05	0.87	0.08

SD, standard deviation.

RESULTS AND DISCUSSION

We attempted to replicate the association of *TREM2* with LOAD in a Japanese sample set, comprising 4,688 subjects in total: cases, $n=2,190$; and controls, $n=2,498$ (Table 1). Three variants, R47H, H157Y, and L211P, were found to be polymorphic; however, the remaining seven, Q33X, Y38C, T66M, N68K, D87N, T96K, and R98W, did not show polymorphisms (Table 2, Supplementary Table 1). The MAF of the variants, R47H, H157Y, and L211P, were less than 0.01 (Supplementary Table 1). Concerning variant R47H [11, 12], three heterozygous subjects were observed: one clinically-verified case (female, age at onset of 76 years old, and *APOE*-ε3*3) and two neuropathologically-characterized controls (one female, age at death of 99 years old, and *APOE*-ε3*3; and one male, age at death of 79 years old, and *APOE*-ε3*3). Variant L211P exhibited the highest MAF among them: 0.0041 in cases and 0.0059 in controls (Supplementary Table 1). Variants R47H, H157Y, and L211P were all in HWE (Supplementary Table 1). In both single and multiple variant analyses, we observed no significant association of *TREM2* with LOAD (Table 2).

TREM2 is mainly expressed in microglia in the brain [30]. This protein directly interacts with a type I transmembrane adapter protein, DAP12 [30]. Recent whole transcriptome analysis of microglia, purified from mouse brains by means of flow cytometry, revealed that *TREM2* belongs to a DAP12-centered protein network, in which multiple microglial marker proteins such as Cd68 are included [31]. A *TREM2*-DAP12 signaling pathway is involved in innate immune responses as well as the differentiation of myeloid progenitor cells into mature microglia [30, 32]. Microglia play an important role in the clearance of amyloid-β protein in the brain [33]. Thus, it is likely that genomic variants of not only *TREM2* but also other genes involved in the *TREM2*-DAP12 signaling pathway may accelerate amyloid plaque deposition through microglial dysfunction [34]. Although none of the rare non-synonymous *TREM2* variants investigated here exhibited association with LOAD in our sample sets (Table 2), we could not rule out the possibility that *TREM2* is one of the crucial proteins for AD from the point of view of biological functions of this protein.

In conclusion, we were not able to detect the significant association of *TREM2* variants examined with LOAD in Japanese, which is consistent with a recent study involving Chinese [21]. On the other hand, *TREM2* has been reproducibly shown to be strongly associated with both LOAD [15–19] and EOAD [20] in multiple Caucasian sample sets. Given these data, *TREM2* may contribute to the susceptibility of LOAD only in Caucasians, i.e., not or only weakly in Asians. However, considering the very low MAF of variants investigated (Table 2, Supplementary Table 1) and our study sample size (Table 1), a large-scale meta-analysis is further needed to comprehensively evaluate whether or not *TREM2* is associated with LOAD in Asians.

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Table 2
Genotypic distribution of three polymorphic variants, R47H, H157Y, and L211P, on *TREM2* in Japanese

Single variant analysis		Allele		Cases (frequency)			Controls (frequency)			$P_{genotype}$ [a]	OR_{Mm} (95% CI)[b]
Variant	dbSNP	M	m	MM	Mm	mm	MM	Mm	mm		
R47H	rs75932628	G	a	2,171 (0.9995)	1 (0.0005)	0 (0.0)	2,477 (0.9992)	2 (0.0008)	0 (0.0)	1.00E+00	0.57 (0.05–6.30)
H157Y	rs2234255	C	t	2,147 (0.9972)	6 (0.0028)	0 (0.0)	2,474 (0.9984)	4 (0.0016)	0 (0.0)	5.29E-01	1.73 (0.49–6.13)
L211P	rs2234256	T	c	2,161 (0.9917)	18 (0.0083)	0 (0.0)	2,461 (0.9884)	29 (0.0116)	0 (0.0)	3.04E-01	0.71 (0.39–1.28)
Multiple variant analysis		Combind genotype		Cases (frequency)			Controls (frequency)			$P_{genotype}$ [c]	OR_{CG-2} (95% CI)[d]
Combind variant	Combind dbSNP	CG-1	CG-2	CG-1	CG-2	others	CG-1	CG-2	others		
R47H-H157Y-L211P	rs75932628-rs2234255-rs2234256	GG-CC-TT	Ga-CC-TT, GG-Ct-TT, GG-CC-Tc	2,104 (0.9883)	25 (0.0117)	0 (0.0)	2,419 (0.9861)	34 (0.0139)	0 (0.0)	5.26E-01	0.85 (0.50–1.42)

In single variant analysis, only three variants, L211P, H157Y, and R47H, are shown here since heterozygotes (Mm) were observed. M, major allele; m, minor allele; MM, major genotype; Mm, heterozygous genotype; mm, minor genotype; CG, combined genotype. [a]Fisher's exact test; [b]OR_{Mm} (95% CI) for the heterozygote (Mm); [c]chi-squared test (degree of freedom = 1); [d]OR_{CG-2} (95% CI) for CG-2 (Ga-CC-TT, GG-Ct-TT, and GG-CC-Tc).

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SUPPLEMENTARY MATERIAL

The supplementary table is available in the electronic version of this article: http://dx.doi.org/10.3233/JAD-140225.

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REVIEW ARTICLE

Early detection of dementia in the community under a community-based integrated care system

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Early detection of dementia is recommended in the stages from mild cognitive impairment to early dementia, excluding the asymptomatic stage. The advantages of early detection for patients and their caregivers include early receipt of pharmacological and non-pharmacological therapies, and early access to appropriate agencies and/or support networks. The disadvantages include psychological damage related to anxiety and depression, and risk of stigmatization and/or social exclusion. The possibility of false positive diagnoses is also problematic. For detection of dementia, various screening tests and questionnaires have been developed. However, none of these techniques are sensitive and specific enough to avoid false positives. Thus, these screening tools are recommended for assessment of the severity of functional decline after sufficient information has been gathered to suspect dementia. In terms of social services, early detection might delay institutionalization. However, implementation of early detection would add a heavy burden on social resources, especially human resources. For effective implementation of early diagnosis and management of dementia, measures are required to improve social and human resources, including the following: improvement of the diagnostic abilities of general practitioners, improvement of necessary care and support systems after diagnosis, and organizing volunteers to support local communities. Under a community-based integrated care system, each community will create a "tailored" system that meets the health needs, health status and values of the community. Promoting social participation and community involvement of the residents should be one of the key strategies to address the shortage of human resources. **Geriatr Gerontol Int 2014; 14 (Suppl. 2): 2–10.**

Keywords: community-based integrated care systems, early detection of dementia, social support, social resources, stigma and social exclusion.

Introduction

Early detection of dementia is encouraged for individuals with dementia and their caregivers to ensure the benefits of accessing treatment, care and support; earlier detection and intervention is one of the main policies of the Five-Year Plan for Promotion of Measures against Dementia in Japan (Orange Plan; 2013–2017). However, there are disadvantages of early detection, as well as various advantages (Table 1). The most serious issue is the shortage of social resources, particularly human resources, as a result of an enormous increase in the number of demented individuals. Early diagnosis is beneficial only when effective treatment and appropriate social services are available; for treatment and care of dementia, medication alone is not sufficient, and social services and support are crucial. The present article aims to overview the advantages and disadvantages from the perspectives of the patients, their caregivers and social services, and then to consider implementation under a community-based integrated care system.

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Early detection of dementia: at which stage of dementia should treatment be started?

There is a lack of consensus regarding at which stage of dementia treatment should be started: asymptomatic stage, symptomatic prodromal stage of dementia (mild cognitive impairment [MCI]) or early-stage dementia after the onset of the disease.

Asymptomatic stage

Research study trends are moving to earlier detection of dementia, at the asymptomatic stage, aiming at the prevention of dementia. Most of these studies have focused on Alzheimer's disease (AD); clinical and epidemiological evidence generally suggests the presence of a cognitive continuum from an asymptomatic phase to onset of AD, and the pathophysiological process of AD is thought to begin many years before the diagnosis of AD dementia.[1]

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Table 1 Advantages and disadvantages of early diagnosis

	Advantages	Disadvantages
Patients	Receiving pharmacological and non-pharmacological therapies	Psychological damage of anxiety and depression
	Access to appropriate agencies and support networks	Risk of withdrawal, isolation, stigma and social exclusion
	Prevention of behavioral and psychological symptoms of dementia	Risk of false positive diagnosis
Families and caregivers	Mental preparation for disease progression	Stigma and exclusion
	Access to appropriate agencies and support networks	Care burden from early stages
Social services	Net cost reduction effects including delay of institutionalized care	Shortage of social resources, including human resources

However, detection of AD in the asymptomatic stage is still in the research phase, and many challenges remain to be overcome. First of all, a firm link has not been shown between the appearance of any specific biomarker in the asymptomatic stage and the subsequent emergence of clinical symptoms of AD. As an associated issue, not all individuals who have evidence of AD pathology will necessarily progress to clinical AD dementia.[2] Regarding treatment, individuals might be left untreated with a high risk of developing AD without disease-modifying drugs. In addition, there has been little research on other causative diseases of dementia. Further research is required, because identification and classification of syndromes that will progress to subtypes of dementia are critical for the management of the diseases when modifiable therapies are available. The issue of costs cannot be ignored. In the asymptomatic stage, detection requires examination of biomarkers using costly brain-imaging techniques, such as positron emission tomography, glucose metabolism or β-amyloid accumulation.

Symptomatic prodromal stage of dementia

MCI is a prodromal stage of dementia characterized by cognitive decline greater than age-related changes, but the condition does not interfere notably with activities of daily living.[3] *The Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5), refers to a spectrum of cognitive and functional impairments, from mild neurocognitive disorders (mild NCD) to major neurocognitive disorders (major NCD). In major NCD, deterioration of cognitive function is severe enough to interfere with independence in everyday activities, whereas capacity for independence still remains in minor NCD.[4]

With optimal intervention during the stage of MCI, development to AD could be avoided or delayed, although MCI shows a high risk of progression to dementia, particularly of the AD type; according to one report, conversion rates to AD were 41% after 1 year, and 64% after 2 years.[5] Thus, detection at the MCI stage could be meaningful for prevention of dementia, or at least to delay the onset of dementia.

Early-stage dementia after the onset of the disease

Once dementia has developed, the best that can be done is to slow the progression of the disease. In the present article, "early" detection is considered as detection at the stage from MCI to very early-stage dementia, excluding the asymptomatic stage.

Advantages and disadvantages of early detection of dementia

Advantages and disadvantages for patients

Advantages for patients include optimizing the use of pharmacological and non-pharmacological therapies, as well as appropriate agencies and support networks provided as required after diagnosis. Early diagnosis is associated with a higher probability of prevention of behavioral and psychological symptoms of dementia (BPSD),[6] and detection of treatable causes, such as normal pressure hydrocephalus. Lifestyle-related diseases, which increase the risk of cognitive decline, might be treated from the perspective of control of the progression of dementia. Detection at the stage of MCI provides the possibility of preventing and/or slowing the development of dementia.

However, it should be noted that there is no conclusive evidence that early treatment with antidementia medication is more effective than late treatment,[7] and it is still unclear whether MCI and early-stage dementia should be medicated or not. In addition, further research is required to clarify the side-effects to the central nervous system.

The greatest disadvantages for patients are psychological damage and stigmatized labeling. A diagnosis of dementia is inevitably associated with deterioration of self-esteem and feelings of helplessness, which might be accelerated by potential loss or diminution of roles, and abrogation of control of property, money and possessions.[8,9] A diagnosis of dementia can lead to depression and anxiety, which are risk factors for developing cognitive deterioration. Regarding the influence of stress on AD pathology, the transgenic mouse model of AD showed that a synthesized adrenocortical hormone of a dexamethasone injection induced β-amyloid deposition and tau accumulation.[10] Indeed, many patients report feeling abandoned and unsupported after diagnosis.[7] A patient's mental health after diagnosis should be carefully considered, and appropriate mental support should be arranged, because an early diagnosis can accelerate the development of dementia.

Regarding stigma, it is undeniable that a diagnosis of dementia is stigmatizing, and can result in social exclusion and restriction of an individual's rights.[11–14] Withdrawal is also problematic. It is possible for individuals with MCI and very early-stage dementia to continue their social activities with the understanding of people around them. However, because of the prejudices of others, individuals with MCI or dementia tend to withdraw from social activities. In cases where the patients still work, early diagnosis might damage household income, especially with early-onset dementia. Even if the patients are capable enough to work, continuation can become difficult because of prejudices, and they might stop working.

Doctors should note that early diagnosis is not always welcomed because of the fear of negative consequences of stigmatization and isolation, despite the benefits of support and assistance. In association with stigma, risks of misdiagnosis cannot be overlooked. False positives can lead to an unjustified acquisition of a stigmatizing label and patient distress. Misdiagnosis is also associated with missing the opportunity to address treatable conditions, such as depression.

A diagnosis can change the relationships among family members, who might become overly preoccupied and burdened by the dementia. Family members might set restrictions on activities, deprive the patient's roles at home and become hypervigilant with the patient.[8]

Disclosure of a diagnosis is a controversial issue. It has been reported that one in five general practitioners (GPs) regard disclosure as more harmful than helpful.[15,16] One study reported that 51% of people with dementia reacted poorly to the diagnosis, whereas 46% reacted positively.[17] The negative impacts of disclosure identified for individuals with dementia mainly regard psychological damage as aforementioned, whereas the positive impacts include putting an end to uncertainty, confirmation of suspicions and increased understanding of problems.[8]

Advantages and disadvantages for family members and caregivers

Family members and caregivers will play vital roles in at-home care. Advantages for family members and caregivers include the provision of time to make advanced preparations. Informing the family members of the prognosis and the disease course can allow them to set up social support and make legal arrangements for the disease progression. Knowledge and anticipation of the disease can be helpful in preventing a decline of quality of life, and social support might also be helpful in alleviating distress that caregivers may experience.[18]

Regarding disadvantages, family members and caregivers will also be confronted with stigmatized labeling and exclusion. Because of prejudiced views of dementia, family members might be labeled as a "caregiver of a demented family member". If the diagnosis had a negative impact on the patient and resulted in BPSD, including depression and apathy, the psychological burden of caring might increase.

Providing adequate support to caregivers should be a part of the total care at all stages. Receiving a diagnosis of dementia can be a devastating event, and the family members of the diagnosed patient will also require careful support and assistance. In addition to mental care and support, family members and caregivers will require financial and legal advice, and other kinds of practical assistance.

Advantages and disadvantages for social services

Regarding advantages, some reports suggest cost reductions associated with early detection of dementia. An early diagnosis can result in less intensive treatment, especially that associated with BPSD, and can delay nursing home admission when patients are appropriately treated.[19,20]

A shortage of social resources, particularly human resources, is a serious concern; an increased number of patients will strain workloads across all disciplines, and many patients could be diagnosed and not receive appropriate services. Indeed, patients diagnosed in the absence of sufficient local resources report feeling abandoned and unsupported after the diagnosis.[7] To meet these demands, health practitioner education and training are an urgent issue.

Screening of cognitive decline for early detection of dementia

The first step for detection of dementia is screening for symptoms of dementia. In this section, screening measures are considered.

Screening measures

Screening is important in deciding whether or not to proceed with more specific consultation. Requirements of screening include high sensitivity and specificity, brevity, and ease of administration. As an ethical matter, psychological burden should be taken into consideration. There are two general methods to screen for dementia: patient performance-based testing and informant interviews.

Patient performance-based testing

The most widely used brief test is the Mini-Mental State Examination, which covers different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, calculations, and orientation, and a total score represents overall cognitive status.[21] As a similar test, the Montreal Cognitive Assessment was developed for evaluation of MCI,[22] and there are a number of alternatives, such as the six-item Cognitive Impairment Test the General Practitioner Assessment of Cognition and the 7-Minute Screen.[23]

These tests are not without problems. The major problem of such brief tests is variability of their sensitivity according to age and education level.[24,25] Furthermore, the ceiling effect makes these tests insensitive to the very early stages of dementia,[26] especially for highly educated individuals.[27,28] In addition, these tests falsely identify those with low education, poor cognitive functioning, aphasia or depression as demented. The fact that these tests are time-consuming is also problematic; the time to administer the Montreal Cognitive Assessment is approximately 10 min. Another serious problem is the psychological burden on patients, as cognitive tests for dementia themselves are stressful for patients.[29]

Informant interview

It should be noted that self-rating scales are not reliable for dementia detection, because subjective cognitive impairment and memory complaints are common in elderly individuals, and such complaints are correlated with depressive symptoms or personality traits, rather than cognitive decline.[30] In addition, those who are already demented tend to overestimate their function and their self-awareness of cognitive impairments diminishes as the disease progresses, especially memory.[31,32] Such deficits in self-awareness of a disease, anosognosia, is one of the typical symptoms in AD, and DSM-5 explicitly gives a warning about excessive focus on subjective symptoms because of the danger of failing to diagnose in individuals with poor insight.[4]

Regarding informant-based assessment, the Clinical Dementia Rating (CDR)[33] scale is widely used. CDR meets the requirement of accuracy, but it is not an easily administered screening tool. It is a semi-structured interview that requires trained practitioners and takes at least 30 min, which is not easily administered under time-constraint situations.

We propose a brief informant-based screening questionnaire for identifying dementia in both clinical and community-based settings: Symptoms of Early Dementia-11 Questionnaire (SED-11Q; Fig. 1).[34] This questionnaire is easily administered, and is both patient and informant friendly. Questions on early signs of dementia were selected based on clinical experiences. SED-11Q inquires about the state of ordinary daily activities often carried out by an elderly individual living independently. Quantifying difficulties in daily living can provide more sensitive information about early functional changes rather than questions on cognitive function in a single domain, as functional integrity is a key differentiating feature of dementia, and decline in multifaceted cognitive domains directly leads to functional impairments. In addition, as deficits caused by dementia are manifested in various aspects, SED-11Q includes questions on social interaction and personality. The statistically optimal cut-off value of 2/3 indicates sensitivity of 0.84 and specificity of 0.90.[34] SED-11Q is also useful to estimate deficits in self-awareness of a disease, anosognosia. Caregivers and patients are required to answer the same questions, and discrepancies between caregiver and patient assessments show the severity of anosognosia.[35]

Another brief scale including questions on cognitive abilities and daily functioning is the eight-item questionnaire, AD8.[36] AD8 consists of questions of change in memory, orientation and functional abilities by placing emphasis on intra-individual, rather than inter-individual comparisons. The statistically optimal cut-off value of 2/3 shows sensitivity of 0.74 and specificity of 0.86.

Detection of dementia should be carried out without unduly alarming the patient. Therefore, informant-based assessments are preferable. DSM-5 recommends a combination of cognitive tests and questionnaires to complement each other. However, even in combination use, it should be noted that these tests and questionnaire are not sensitive or specific enough to avoid false positives.

Methods of screening: population screening and case findings

In the community setting, two pathways for detection can be considered: community-wide population screening, and case findings at primary care and other clinics, including cases where family members notice changes in daily living and take the person suspected with dementia to a doctor.

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.

Figure 1 The (a) Symptoms of Early Dementia-11 Questionnaire (SED-11Q) and (b) SED-11Q for patients (SED-11Qp), cited from Maki *et al.*[34,35]). (a) The statistically optimal cut-off value of 2/3, which showed sensitivity of 0.84 and specificity of 0.90, can be applied in the clinical setting. In the community setting, a cut-off value of 3/4, which showed sensitivity of 0.76 and specificity of 0.96, is recommended to reduce the danger of false positives. Medical consultation is recommended whenever delusions or illusions are detected. (b) SED-11Qp asks the same questions as SED-11Q. However, the title was changed to avoid using the word "dementia". "Patient Name" and "Patient ID" have been changed to "Name" and "ID". Two additional questions on delusions and illusions were not included in SED-11Qp. The questionnaires can be completed by interview.