A

B

C

D

Female + Male, rs713250

[Interaction] $P = 0.8869$
[SNP] $P = 0.985$
[Case-control] $P < 0.0001$

E

Female, rs713250

[Interaction] $P = 0.8907$
[SNP] $P = 0.7024$
[Case-control] $P < 0.0001$

F

Male, rs713250

[Interaction] $P = 0.7203$
[SNP] $P = 0.348$
[Case-control] $P < 0.0001$

Figure 3. Comparison of the plasma levels of Aβ40 and Aβ42, and the Aβ40/42 ratio. The differences in the relative amounts of Aβ40 (**A**) and Aβ42 (**B**), and the Aβ40/42 ratio (**C**) were compared between LOAD patients and controls by means of Mann–Whitney's *U*-test within different gender groups. (**D, E, F**) Correlation between the Aβ40/42 ratio, an associated SNP on *CTNNA3*, and the diagnosis (LOAD or control). Using log-transformed Aβ40/42 ratio values, two-way ANOVA tests were performed after Bartlett's test for the homogeneity of variances and the KS normality test. The results for SNP rs713250 are presented here as being representative of the seven associated SNPs identified in this study. The horizontal line inside each box denotes the median value. The box extends from the 25th and 75th percentiles. The error bars extend down to the lowest value and up to the highest. Genotypes CC, CT and TT represent major-allele homozygotes, heterozygotes and minor-allele homozygotes, respectively.

region including the four SNPs, different LD block structures were observed in Japanese and CEPH subjects (Fig. 2B and Supplementary Material, Fig. S2). As one of the reasons why reproducible association could not be detected for these four SNPs, we mainly consider that an ethnic difference may exist.

High-level gene expression of *CTNNA3* is detected predominantly in heart and testis, and low-level expression in several tissues including brain (29). Coimmunoprecipitation analysis revealed that CTNNA3 binds directly to β-catenin in both a human cell line transfected with *CTNNA3* cDNA, and heart and testis tissue extracts of mouse (30). β-Catenin forms a complex with presenilin 1 (PSEN1) (31,39,40), mutations of which cause familial cases of early-onset AD (EOAD) [Alzheimer Disease & Frontotemporal Dementia Mutation Database (AD&FTDMDB), http://www.molgen.ua. ac.be/ADMutations/]. The expression level of β-catenin is reduced in the brains of EOAD patients with *PSEN1* mutations (31). Intracellular trafficking of β-catenin is affected in human cells bearing *PSEN1* mutations (41), resulting in sustained loss of Wnt/β-catenin signal transduction, which is probably followed by the onset and development of AD (42,43). Although, at present, there is no direct evidence suggesting that CTNNA3 interacts with PSEN1, it is assumed that their genetic polymorphisms or combinations in *CTNNA3* may have a negative influence on the Wnt/β-catenin signaling pathway, leading to potential involvement in the pathogenesis of AD. In this study, it was clarified that seven intronic SNPs on *CTNNA3* were significantly and reproducibly associated with sporadic female cases of LOAD without the *APOE-ε4* allele. Intronic variants are considered to have the potential to directly affect gene-expression levels in some cases (44); therefore, we performed quantitative real-time RT–PCR analysis of *CTNNA3* using the postmortem brains of 19 neuropathologically-confirmed LOAD cases and 22 control ones. Two-way ANOVA revealed that there was no statistically significant interaction between the *CTNNA3* expression level, the associated SNPs identified here and the diagnosis (data not shown). Additionally, although a genotype-dependent transition effect on the plasma Aβ42 level was observed for intronic SNP rs7070570 by Ertekin-Taner *et al.* (32), it was found that none of these SNPs influence the plasma levels of Aβ peptides (Fig. 3D–F).

However, interestingly, by means of a search of a public genome database, the Database of Genomic Variants (http:// projects.tcag.ca/variation/), we discovered that there is copy number variation (CNV) (45) in the genomic region comprising the seven associated SNPs on *CTNNA3*: variation ID 3807 at Locus 2128, which was detected in a Japanese subject (ID, NA18973) (Fig. 2A). CNV, i.e. deletion, insertion and duplication with >1 kb in length of the genomic sequence (46), rather than SNP could cause phenotypic diversity and complex diseases in humans by altering the gene dose or disrupting the coding or regulatory sequences of genes, and may account for the LOAD susceptibility. Regarding our LOAD subjects, we did not examine the presence or absence of CNV within *CTNNA3*. Therefore, in a further study, it is very important to determine whether or not CNV in *CTNNA3* is associated with LOAD.

Recently, in LOAD families, notable evidence was obtained suggesting a maternal parent-of-origin effect on chromosome 10q between microsatellite markers D10S1233 (44.05 Mb) and D10S1225 (64.43 Mb) with a non-parametric LOD score >1.0: the highest LOD score of 3.73 was seen for microsatellite marker D10S1221 (57.20 Mb) (27,28). Moreover, it was found that *CTNNA3* is subject to genomic imprinting with cell-type specificity in placental tissues: biallelic and monoallelic (maternal-allele) expression is observed in extra-villus and villus trophoblasts, respectively (47). Mouse *Ctnna3* (Clone ID 4933408A16 on FANTOM2), orthologous to human *CTNNA3*, has been deposited as a maternal imprinting gene on chromosome 10 in the Expression-based Imprint Candidate Organizer DataBase (48; EICO DB, http:// fantom2.gsc.riken.jp/EICODB/imprinting/), provided by RIKEN (Japan). These findings led us to examine whether or not *CTNNA3* shows allele-specific expression caused by a molecular mechanism such as genomic imprinting in the brain. We conducted real-time RT–PCR analysis with allele-specific amplification using postmortem human brains heterozygous for non-synonymous SNP rs4548513 in exon 13 [LOAD, 7 (female:male = 3:4); control, 8 (female: male = 3:5)]. Unexpectedly, biallelic expression was detected in brain tissues, and there was no significant difference between LOAD patients and control subjects in the expression level of *CTNNA3* (data not shown). Since as in placental tissues, as described above, it is possible that cell-type dependent imprinting for *CTNNA3* may occur in the brain, further expression analysis should be carefully carried out using homogeneous populations of specific cells from brain tissues. Now genome-wide prediction and the discovery of imprinted genes have progressed (49,50), and 600 (2.5%) of 23 788 annotated autosomal genes have been found to be potentially imprinted in the mouse genome by computational estimation: 384 (64%) of these candidate-imprinted genes show maternal-allele expression (50). It is expected that failure of imprinted gene expression in the human brain may lead to cognition and behavior defects such as Alzheimer's disease, schizophrenia, the bipolar affective disorder and epilepsy (51–53). Therefore, it is important and interesting to actively examine imprinted genes present in the genetic linkage region of LOAD.

MATERIALS AND METHODS

Subjects

The Japanese Genetic Study Consortium for AD (JGSCAD) was organized in 2000, and blood samples were collected to survey risk genes for LOAD by means of a genome-wide association study. All individuals included in this study were Japanese. Probable AD cases met the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders. Control subjects who had no signs of dementia and lived in an unassisted manner in the local community were also recruited. Age at onset (AAO) is here defined as the age at which the family and/or individuals first noted cognitive problems during work or in daily activities. The Mini-Mental State Examination (MMSE), and Clinical Dementia Rating and/or the Function Assessment Staging were used for the evaluation of cognitive impairment: MMSE was used for almost every subject.

The basic demographics of the LOAD patients and non-demented control subjects are presented in Table 1. A total of 3192 subjects comprising 1526 LOAD patients [female, 1103 (72.3%); male, 423 (27.7%)] and 1666 controls [female, 998 (59.9%); male, 668 (40.1%)], which is referred to as overall sample set All in this study, were used to discover gender-related loci associated with LOAD on chromosome 10q: information on these subjects was also presented in our recent paper, Kuwano *et al.* (26). The mean AAO $\pm$ standard deviation (SD) in the 1526 LOAD patients was 73.5 $\pm$ 6.6 (range 60–93). The mean age at examination (AAE) $\pm$ SD of the control subjects was 73.1 $\pm$ 7.8 (range 60–96). There was no significant difference between AAO in LOAD patients and AAE in control subjects with the unpaired Student's *t*-test (*P*-value = 0.1239). The mean MMSE score in the 1526 LOAD patients was 16.5 (SD 7.0), which was significantly lower (*P*-value with unpaired Student's *t*-test <0.0001) than that in the 1666 controls (mean $\pm$ SD 28.0 $\pm$ 1.8). The numbers (frequency) of *APOE-ε2*2*, *ε2*3*, *ε2*4*, *ε3*3*, *ε3*4* and *ε4*4* in the 1526 LOAD subjects were 1 (0.07%), 49 (3.21%), 17 (1.11%), 699 (45.81%), 613 (40.17%) and 147 (9.63%), and those in the 1666 control subjects were 3 (0.18%), 132 (7.92%), 15 (0.90%), 1243 (74.61%), 256 (15.37%) and 17 (1.02%). The allelic distribution of *APOE* was significantly different between LOAD patients (*ε2*, 68; *ε3*, 2060; *ε4*, 924) and control subjects (*ε2*, 153; *ε3*, 2874; *ε4*, 305), as expected (*P*-value with χ^2 test using a 2×3 contingency table, <0.0001).

The present study was approved by the Institutional Review Board of Niigata University and by all participating institutes. Informed consent was obtained from all controls and appropriate proxies for patients, and all samples were anonymously analyzed for genotyping.

SNPs and genotyping

SNP information was obtained from five open databases: NCBI dbSNP (Build 125, http://www.ncbi.nlm.nih.gov/SNP/), UCSC Genome Bioinformatics (http://genome.ucsc.edu/), International HapMap Project (Rel#20/phaseII on NCBI Build 35.1 assembly and dbSNP Build 125, http://www.hapmap.org/index.html), Ensemble Human (Version 37 on NCBI Build 35.1, http://www.ensembl.org/Homo_sapiens/) and Celera myScience (Version R27 g on NCBI Build 35.1, http://myscience.appliedbiosystems.com/). We selected 1322 SNPs in the region from 60 to 107 Mb on chromosome 10q; mean intermarker distance $\pm$ SD, 34.9 $\pm$ 87.4 kb; 95% CI, 30.2–39.6 kb. The information on all SNPs, including rs or Celera IDs and genomic positions on NCBI build 35.1, used here was presented in detail elsewhere (26). These SNPs consisted of 29 missense mutations, 27 silent mutations, 6 SNPs in the 5′-UTR, 29 SNPs in the 3′-UTR, 921 SNPs in introns, 282 SNPs in intergenic regions and 28 SNPs in four loci shared by two different genes (*CTNNA3/LRRTM3*, *CDH23/C10orf54*, *C10orf55/PLAU* and *PGAM1/EXOSC1*). Among the 1322 SNPs, 28 SNPs could not be genotyped. To examine deviation from HWE of 1294 SNPs, exact tests (details given under Statistical analysis) were performed with both 363 LOAD patients and 337 control subjects (carrying *APOE-ε3*3* in the exploratory sample set, as shown in Table 1). We used 1140 SNPs

that were shown to be actually polymorphic in the Japanese population and showed *P*-values >0.05 with the exact tests; mean intermarker distance $\pm$ SD, 40.5 $\pm$ 96.7 kb; 95% CI, 34.9–46.1 kb.

Genomic DNA was extracted from peripheral blood with a QIAamp DNA Blood Maxi Kit (Qiagen, Duseldorf, Germany) and examined fluorometrically with a PicoGreen dsDNA quantification kit (Molecular Probes, California, USA). SNP genotyping of individual samples was performed with an ABI PRISM 7900HT instrument using TaqMan technology, and TaqMan SNP Genotyping Assays were purchased from Applied Biosystems (California, USA).

Case–control study

To discover gender-related genetic loci on chromosome 10q (60–107 Mb on NCBI build 35.1), allelic association was assessed by means of the χ^2 test based on a 2×2 contingency table in comparison with allele frequencies in LOAD patients and control subjects within different gender groups. For screening, two independent sample sets, Exploratory and Validation, comprising case–control subjects with *APOE-ε3*3* were first used after being stratified as to gender (Table 1). Sample set Exploratory comprising 363 LOAD patients and 337 control subjects was genotyped (26), and SNPs showing significant association (allelic *P*-value <0.01) were then subjected to further examination using another sample set, Validation, comprising 336 LOAD patients and 372 control subjects. Multistage, including two-stage, genotyping designs for large-scale association surveys have been proved to be practically as well as theoretically effective for identifying common genetic variants that predispose to human disease (54–58). Therefore, we considered that replication in both the Exploratory and Validation sample sets implicates an association of particular SNPs with LOAD.

Subsequently, for stratified analysis we increased the number of subjects and constructed an overall sample set, All. Furthermore, to construct three sub-sample sets, overall sample set All was stratified as to the *APOE* carrier status: Negative-ε4, *APOE-ε 2*2*, *2*3* and *3*3*; *ε3*3*, *APOE-ε 3*3*; Positive-ε4, *APOE-ε 2*4*, *3*4* and *4*4* (Table 1). The sample numbers for LOAD patients and controls in All, Negative-ε4, *ε3*3* and Positive-ε4 were 1526 and 1666, 749 and 1378, 699 and 1243, and 777 and 288, respectively. These four sample sets were used for the χ^2 test after being sub-grouped as to gender.

Case–control haplotype analysis with significant SNPs was also performed using the following sample sets: All, Negative-ε4, *ε3*3* and Positive-ε4. These four sample sets were used after being stratified as to gender.

Aβ40 and Aβ42 quantification

For Aβ40 and Aβ42 quantification, 603 subjects consisting of 456 LOAD patients (female, 332; male, 124) and 147 control subjects (female, 95; male, 52) were used. They are included in the All set. The sandwich enzyme-linked immunosorbent assay (59–61) was used to specifically quantify whole plasma Aβ species. The standardization, sensitivity and specificity of the method were described in a previous paper (61).

Briefly, microplates (Immunoplate I; Nunc, Rockilde, Denmark) were pre-coated with monoclonal BNT77 (IgA isotype specific for Aβ11−16) and then sequentially incubated for 24 h at 4°C (100 μl of whole plasma/well), followed by 24 h incubation at 4°C with horseradish-peroxidase-conjugated BA27 (anti-Aβ1−40, specific for Aβ40) or BC05 (anti-Aβ35−43, specific for Aβ42). Color was developed with 3,3′,5,5′-tetramethylbenzidine and evaluated at 450 nm with a microplate reader (Molecular Devices, CA). Synthetic Aβ40 and Aβ42 (Sigma, St Louis, MO) of known concentration (estimated from the amino acid composition) were used as standards. The plates were normalized as to each other by inclusion of three standard plasma samples on all plates.

Statistical analysis

Allele frequencies were calculated by allele counting. To evaluate deviation from the HWE of each SNP marker, we carried out an exact test (62) based on the probability of occurrence of genotypic contingency tables with fixed total numbers of alleles within each sample set (LOAD patients and controls included in two screening sets, Exploratory and Validation). For single SNP case−control analysis, the allelic distributions in LOAD patients and controls were compared by means of χ^2 tests via standard 2×2 contingency tables. Evidence of replication, rather than multiple testing corrections, was used to evaluate the significance of associated SNPs. To comprehensively assess the reproducible SNPs, we conducted a Mantel−Haenszel test, where Exploratory and Validation samples in our case−control study were considered as the strata (63), and computed pooled ORs with 95% CI and P-values from Mantel−Haenszel statistics (Statcel 2; OMS, Tokyo, Japan). Estimation of haplotypes and their frequencies was carried out for LOAD patients and controls separately by the maximum-likelihood method from unphased diploid genotype data using an EM algorithm (64) with the following parameters: iteration counter, 5000; conversion criterion, 0.000001. To assess the differences in haplotype distribution between LOAD patients and controls, a permutation test (65) was performed. In this test, all permutation P-values were empirically computed using 10 000 iterations of random sampling with fixed total numbers of both LOAD and control subjects. OR (95% CI), as an estimate of the relative risk of disease, of each marker or haplotype was calculated from a 2×2 contingency table. For all statistical methods mentioned above, except the Mantel−Haenszel test, we used SNPAlyze software versions 3.2.3 or 6.0.1 (DYNACOM, Chiba, Japan; http://www.dynacom.co.jp/). For calculation of LD measures (D′) and LD block definition by Gabriel et al.'s method (66), we used Haploview version 3.32 (67, http://www.broad.mit.edu/mpg/haploview/index.php).

Using SPSS version 13.0 software (SPSS, Chicago, USA), multiple logistic regression analysis (Table 5) was performed to reveal the effects of the *APOE-ε4* [non-carrier of the *ε4* allele (*ε2*2, ε2*3* and *ε3*3*)/carrier of the *ε4* allele (*ε2*4, ε3*4* and *ε4*4*)], gender (male/female), age and significant SNPs identified here (major-allele homozygote/heterozygote/minor-allele homozygote) on the risk for LOAD as well as their second-order interaction terms. The strength of association between these variables and disease status (control/

LOAD) was evaluated with ORs with 95% CI, based on Wald statistics. We examined the four variables by means of a two-step multiple logistic regression analysis according to Akazawa et al. (68). In order to examine which variables explain an association with LOAD independently, we initially carried out stepwise logistic regression analysis (forward selection method) without interaction terms. A significance level of 0.05 was used to enter a variable in the model. Through this analysis, the following multiple logistic regression model was fitted (Model 1 in Table 5): $\log(P/(1 - P)) = \alpha + \beta_1 X1 + \beta_2 X2 + \beta_3 X3 + \beta_4 X4$, where P denotes the probability of having LOAD, α is the intercept, β_i represents the estimated parameters and Xj the independent variables ($X1$, APOE-ε4; $X2$, gender; $X3$, age; $X4$, SNP). We next analyzed the four variables including their second-order interaction terms (SNP_gender, SNP_APOE-ε4, SNP_age, gender_APOE-ε4, gender_age and age_APOE-ε4) by means of a forward stepwise regression method with a significance level of 0.05 for the inclusion of a variable in the model. As a result, the following model was fitted (Model 2 in Table 5): $\log(P/(1 - P)) = \alpha + \beta_1 X1 + \beta_2 X2 + \beta_3 X3 + \beta_4 X4 + \beta_5 X5 + \beta_6 X6 + \beta_7 X7$, where P denotes the probability of having LOAD, α is the intercept, β_i represents the estimated parameters and Xj the independent variables ($X1$, APOE-ε4; $X2$, gender; $X3$, age; $X4$, SNP; $X5$, SNP_gender; $X6$, gender_APOE-ε4; $X7$, age_APOE-ε4). Subjects with undetermined SNP genotype data were omitted for multiple logistic regression analysis.

The Mann−Whitney U-test was applied to compare differences in the levels of Aβ40 and Aβ42, and their ratio (Aβ40/42) between LOAD patients and controls (Prism 4.0b; GraphPad Software, CA, USA). After Bartlett's test for the homogeneity of variances (Statcel 2) and the KS normality test (Prism 4.0b), the effects of three SNP genotypes (minor-allele homozygotes, heterozygotes and major-allele homozygotes) in three sub-groups stratified as to gender (female−male mixture, female or male) were examined as to levels of the plasma Aβ40/42 ratio using two-way ANOVA (Prism 4.0b). To create more normally distributed datasets, the Aβ40/42 ratio was subjected to log transformation [$\log_2$(Aβ40/42 ratio + 1)] before the two-way ANOVA. The statistical significance was set at $P < 0.05$.

SUPPLEMENTARY MATERIAL

Supplementary Material is available at HMG Online.

ACKNOWLEDGEMENTS

follows: All authors on the title page; and Akihiko Nunomura, MD, and Shigeru Chiba, MD, Department of Psychiatry and Neurology, Asahikawa Medical College, Asahikawa; Takeshi Kawarabayashi, MD, Department of Neurology, Neuroscience and Biophysiological Science, Hirosaki University, School of Medicine, Hirosaki; Satoshi Takahashi, MD, Department of Neurology, Iwate Medical University, Morioka; Naoki Tomita, MD, Department of Geriatric and Complementary Medicine, Tohoku University Graduate School of Medicine, Sendai; Jyunzo Ito, MD, Alpine Kawasaki, Kawasaki, Miyagi; Haruo Hanyu, MD, Department of Geriatric Medicine, Tokyo Medical University, Tokyo; Shin Kitamura, MD, Second Department of Internal Medicine, Nippon Medical School, Tokyo; Hitoshi Shinotoh, MD, Asahi Hospital for Neurological Disease, Chiba; Hiroyuki Iwamoto, MD, Department of Neurology, Hatsuishi Hospital, Kashiwa; Masahiko Takahashi, MD, Department of Old Age Psychiatry and Memory Clinic, Tokyo Metropolitan Geriatric Medical; Yasuo Harigaya, MD, Department of Neurology, Maebashi Red Cross Hospital, Gunma; Masaki Ikeda, MD, and Masakuni Amari, MD, Department of Neurology, Gunma University Graduate School of Medicine, Maebashi; Takeo Takahashi, MD, Ina Neurological Hospital, Ina; Ryoichi Nakano, MD, and Masatoyo Nishizawa, MD, Department of Neurology, Brain Research Institute, Niigata University, Niigata; Takeshi Ikeuchi, MD, and Osamu Onodera, MD, Department of Molecular Neuroscience, Bioresource Science Branch, Center for Bioresources, Brain Research Institute, Niigata University, Niigata; Masaichi Suga, MD, Higashi Niigata Hospital, Niigata; Makoto Hasegawa, MD, Niigata Shin-ai Hospital, Niigata; Yasuhiro Kawase, MD, Kawase Neurology Clinic, Sanjo; Kenichi Honda, MD, Honda Hospital, Uonuma; Toshiro Kumanishi, MD, and Yukiyosi Takeuchi, MD, Niigata Longevity Research Institute, Shibata; Atsushi Ishikawa, MD, Department of Neurology, Brain Disease Center, Agano Hospital, Agano; Masahiro Morita, MD, Department of Psychiatry, Mishima Hospital, Mishima; Fumihito Yoshii, MD, Department of Neurology, Tokai University School of Medicine, Isehara; Hiroyasu Akatsu, MD, and Kenji Kosaka, MD, Choju Medical Institute, Fukushimura Hospital, Toyohashi; Masahito Yamada, MD, and Tsuyoshi Hamaguchi, MD, Department of Neurology and Neurobiology of Aging, Kanazawa University Graduate School of Medical Science, Kanazawa; Satoshi Masuzugawa, MD, Department of Neurology, Mie Prefectural Shima Hospital, Shima; Takeo Takao, MD, and Nobuko Ota, Kurashiki Heisei Hospital, Kurashiki; Ken Sasaki, MD, Yoshikatsu Fujisawa, MD, and Kenji Nakata, MD, Kinoko Espoir Hospital, Kasaoka; Ken Watanabe, MD, Watanabe Hospital, Tottori; Yosuke Wakutani, MD, and Kenji Nakashima, MD, Department of Neurology, Institute of Neurological Science, Tottori University, Yonago; Toshiyuki Hayabara, MD, Iwaki Hospital, Kagawa; Terumi Ooya, Town Office, Oonan, Shimane; Mitsuo Takahashi, MD, Department of Clinical Pharmacology, Fukuoka University, Fukuoka; Tatsuo Yamada, MD, Fifth Department of Internal Medicine, Fukuoka University, Fukuoka; Taihei Miyakawa, MD, Labour Welfare Corporation Kumamoto Rosai Hospital, Yatsushiro; Eiichiro Uyama, MD, Department of Neurology, Graduate School of Medical Science, Kumamoto University, Kumamoto; Takefumi Yuzuriha, MD, Department of Psychiatry, National Hospital Organization Hizen Psychiatric Center, Sefuri; and Ryuji Nakagawa, MD, Shizushi Yoshimoto, MD, and Kayoko Serikawa, MD, Ureshino-Onsen Hospital, Saga.

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ORIGINAL ARTICLE

Longitudinal changes in the prevalence of dementia in a Japanese rural area

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Received 13 July 2006; accepted 23 February 2007.

Abstract

Background: The increasing number of patients with dementia in Japan, together with the rapid aging of society, is currently considered to have a substantial impact on Japan's medical, economic and sociological systems. Therefore, the longitudinal estimation of changes in the prevalence of dementia based on accurate diagnostic evaluation has important implications.

Methods: We undertook three separate epidemiological studies on long-term changes, 10 years apart (1980, 1990 and 2000), in the prevalence of dementia in an elderly population using identical methods (DSM-III and Hachinski's ischemic score) for the same rural area in Japan (Daisen-cho).

Results: The percentage of the population that was elderly (over 65 years of age) increased steadily from 16.0% in 1980 to 21.7% in 1990 and 27.1% in 2000. The prevalence of dementia (cases/100 people aged 65 years or older, adjusted to the population structure of 1980) in 1980, 1990 and 2000 was 4.4, 4.5 and 5.9, respectively, for all types of dementia, 1.9, 2.5 and 3.6, respectively, for Alzheimer-type dementia (DAT) and 2.0, 1.7 and 2.2, respectively, for vascular dementia (VaD).

Conclusions: These findings of an increase in the number of cases and prevalence of DAT and VaD in a Japanese rural community have important implications for interventional medicine.

INTRODUCTION

One of the most important issues in the public health of Japan is the rapid aging of society. It is highly possible that the increasing number of patients with dementia may become a serious social problem, impacting on Japan medically, economically and sociologically. Therefore, longitudinal estimation of changes in the prevalence of dementia based on accurate diagnostic evaluation has important implications.

It has been reported previously that vascular dementia (VaD) is more predominant than dementia of the Alzheimer type (DAT) among the Japanese population.[1] However, several recent reports have shown that the incidence of DAT is equal to or greater than that of VaD.[2–5] At present, there are few reports that consider longitudinal changes in the prevalence of dementia in Japan.

Several clinical criteria have been developed to standardize the diagnosis of dementia, including DAT and VaD. Significant differences in patient classification have been reported, depending on the criteria used. In particular, recent studies have demonstrated that clinical criteria for VaD are not interchangeable.[6,7] Thus, the use of identical clinical criteria is indispensable for the accurate estimation of changes in the prevalence of dementia. We have been conducting longitudinal prevalence studies of dementia, 10 years

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apart, in the elderly population using identical methods for the same area (Daisen-cho) in Japan.

METHODS

Epidemiological studies were repeated at 10 year intervals (1980, 1990 and 2000) for the entire population of Daisen-cho. Daisen-cho is located in a rural area of western Japan (Fig. 1). The population structure of Daisen-cho in 1980, 1990 and 2000 is shown in Fig. 2. The population was 7741 (3668 men and 4073 women) in 1980, 7749 (3674 men and 4075 women) in 1990 and 7020 (3354 men and 3666 women) in 2000. The number of elderly people over 65 years of age increased over two decades: 1236 (16.0%) in 1980, 1626 (21.0%) in 1990 and 1851 (26.4%) in 2000. The migration rate of the population was approximately 1% or less and is therefore considered very low, especially among the elderly population of Daisen-cho. We examined the prevalence rate of dementia in the elderly population over a 10 year period using methods detailed previously[8-10] (Fig. 3).

First, we performed screening tests of the data obtained from the Daisen-cho questionnaire for all inhabitants over 20 years of age. The Daisen-cho questionnaire data consist of lifestyle items (including occupation and working hours), an abridged medical history (including information about hypertension, hyperlipidemia, diabetes mellitus, cerebrovascular disease, Parkinson's disease, DAT and cancer) and recent subjective symptoms focusing on neurological issues (including amnesia, headache, numbness, weakness and speech and gait disturbances). The total response

rate of the Daisen-cho questionnaire in 2000 was 85.5% and the response rate for the elderly population (over 65 years of age) was 82%. We identified individuals who had cerebrovascular disease, DAT and Parkinson's disease based on their medical history and who
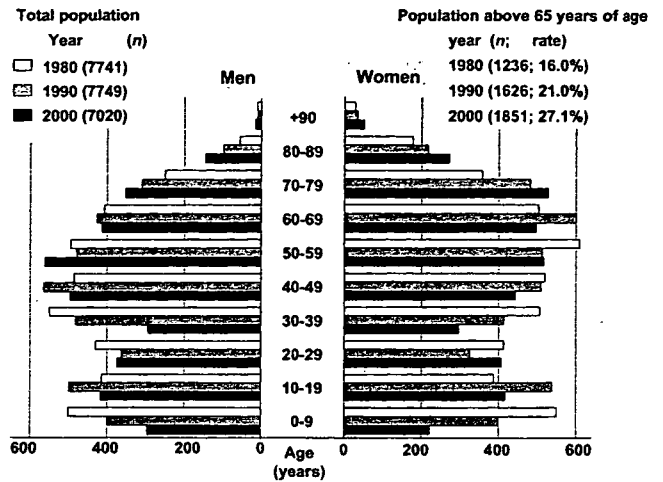

Figure 2 Population structure and the number and ratio of people above 65 years of age in Daisen-cho in 1980, 1990 and 2000.
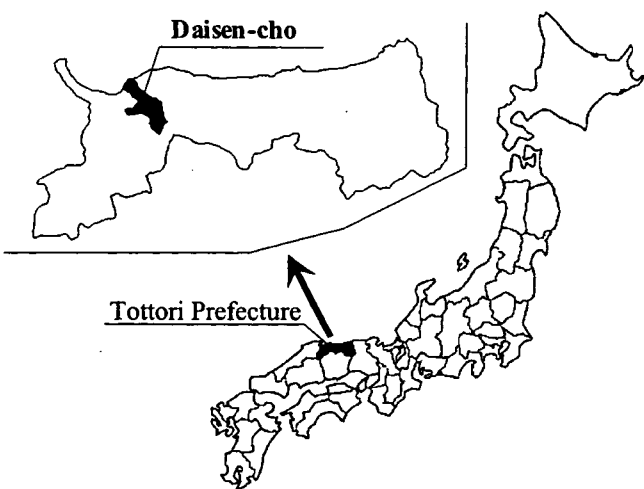

Figure 3 Methods used to investigate dementia.
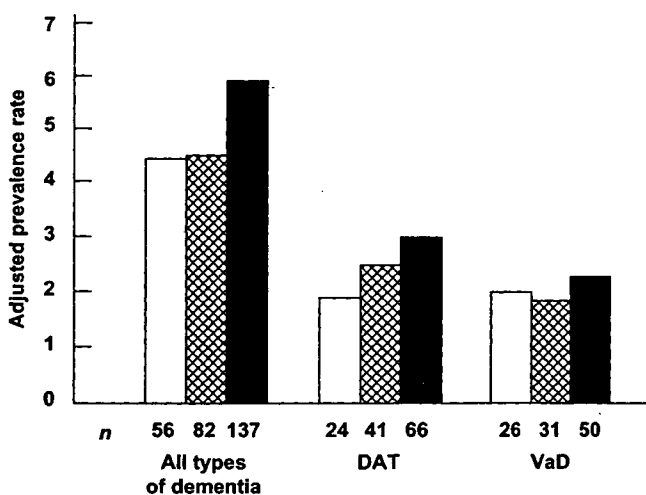

Figure 1 Map of Japan, showing the location of Daisen-cho.

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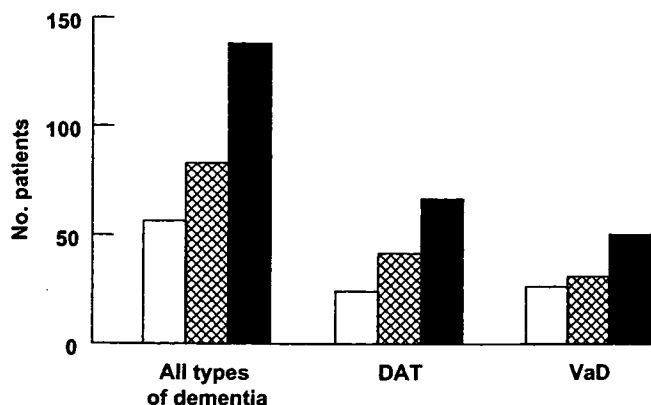
Figure 4 Number of cases of dementia in people over 65 years of age in 1980 (1236; □), 1990 (1626; ▨) and 2000 (1823; ■). DAT, Alzheimer-type dementia; VaD, vascular dementia.

Figure 5 Adjusted prevalence rates of dementia in people over 65 years of age in 1980 (□), 1990 (▨) and 2000 (■). DAT, Alzheimer-type dementia; VaD, vascular dementia.

may have had amnesiac episodes or other neurological signs based on subjective symptoms.

We conducted further documentary searches, including the population stroke screening record, National Health Insurance Medical Records and nursing care insurance records. Volunteer health officers operate in each small community in Daisen-choand we interviewed them to determine whether there are any individuals with neurological disabilities, including amnesiac symptoms, in their communities. There were 127, 167 and 186 possible cases of dementia in 1980, 1990 and 2000, respectively.

For supplementary evaluation of dementia, qualified neurologists visited the candidates and their

family member(s) in their homes or met with them in the official day-care center of Daisen-cho. The supplementary evaluation consisted of assessment of these patients based on a thorough medical history, physical examination, including a drug inventory, neurological examination, comprehensive cognitive evaluation using the Mini-Mental State Examination,[11] activity of daily life evaluation with the Barthel Index,[12] psychosocial assessment of the patient's environment and routine laboratory tests. Patients who satisfied the DSM-III and those scoring 4 points or less on Hachinski's ischemic score were diagnosed as having DAT.[13,14] Patients who satisfied the DSM-III and those scoring 7 points or more on Hachinski's ischemic score were diagnosed as having VaD. The degree of dementia (mild, moderate or severe) was assessed according to a functional assessment staging of Alzheimer's disease (FAST).[15]

RESULTS

The progressive aging of society was clearly evident in Daisen-cho. The percentage of individuals over 65 years of age was 16.0% in 1980, 21.0% in 1990 and 26.4% in 2000. The number of all types of dementia was 56 of 1236 people aged 65 years or more in 1980, 82 of 1626 persons in 1990 and 137 of 1823 persons in 2000. Therefore, the number of all types of dementia in 1990 and 2000 had increased approximately 1.5- and 2.4-fold, respectively, compared with that in 1980 (Fig. 4).

Unadjusted prevalence rates for dementia in the elderly population were 4.4 per 100 population in 1980, 4.9 in 1990 and 7.4 in 2000. The age-adjusted prevalence rate in those aged 65 years or more compared with the 1980s population structure in Daisen-cho was 4.5 per 100 population in 1990 and 5.9 in 2000. The number of DAT cases was 24 in 1980, 41 in 1990 and 66 in 2000. The adjusted prevalence rates of DAT were 1.9 in 1980, 2.3 in 1990 and 2.8 in 2000. There were 26 cases of VaD in 1980, 31 cases in 1990 and 56 cases in 2000. The adjusted prevalence rates of VaD were 2.0 in 1980, 1.7 in 1990 and 2.2 in 2000 (Fig. 5). The ratio of VaD to DAT was 1.1 in 1980, 0.8 in 1990 and 0.8 in 2000, indicating that DAT had clearly become more prevalent than VaD over the two decades.

Dividing the cases of dementia into two groups according to FAST severity, the ratio of mildly demented patients had increased over the two

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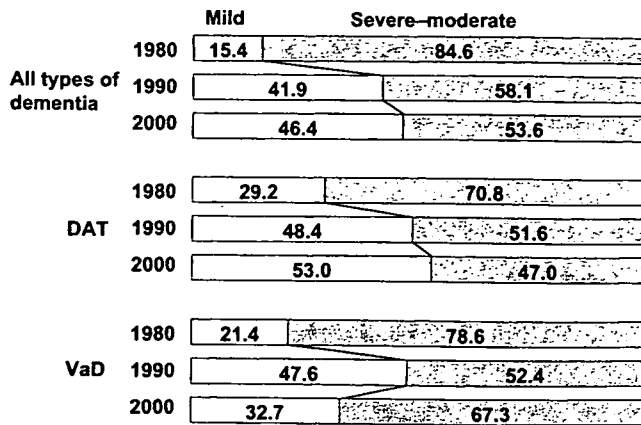
Figure 6 Ratio of mild and severe–moderate cases of dementia in people over 65 years of age in 1980, 1990 and 2000. DAT, Alzheimer-type dementia; VaD, vascular dementia.

decades. In particular, the increase in the ratio of mildly demented DAT patients was obvious through the two decades, whereas the ratio of mildly demented VaD patients increased from 1980 to 1990 and decreased from 1990 to 2000 (Fig. 6).

DISCUSSION

The present study shows the longitudinal transition of the prevalence of dementia in the population over 65 years of age in a community (Daisen-cho) situated in a rural area of western Japan. Because Daisen-cho was an evidently stable population, it was suitable for investigations of longitudinal changes in the prevalence of dementia patients. Further, to avoid discrepancy of the longitudinal prevalence owing to differences in patient collection methods and diagnostic criteria, we used identical methods throughout the present study. We used DSM-III criteria for dementia evaluation and Hachinski's ischemic score to differentiate DAT and VaD.

The progressive aging of the population was shown to be significant in Daisen-cho. As predicted, the number of dementia patients increased steadily. Unadjusted prevalence rates for dementia in the elderly population aged 65 years or more were 4.4 per 100 population in 1980, 4.9 in 1990 and 7.5 in 2000, indicating that the progressive aging of the population has had an impact on the increased number of dementia patients. The unadjusted prevalence rate for dementia in Daisen-cho in 2000 substantially agrees with the recently developed epidemiological study of

dementia in Japan.[2–5] Furthermore, the age-adjusted prevalence of dementia obviously increased in 2000 compared with 1980 and 1990. Recent epidemiological studies in Japan have demonstrated that the prevalence of DAT exceeds that of VaD.[2–5]

Although it is predicted that the Japanese lifestyle (particularly dietary habits), even in rural areas, is closely associated with the increased ratio of DAT, the precise factors responsible are yet to be identified. The increased number and prevalence of VaD in Daisen-cho is consistent with the recent results of a computed tomography based study conducted in another rural area in Japan.[4] Although the precise factor(s) explaining the increasing prevalence of dementia, DAT and VaD in Daisen-cho remains unknown, the increasing ratio of moderate or severe VaD may reflect reduced mortality from cerebrovascular diseases and the increase in disease duration in Japan. Moreover, owing to the therapeutic progress in Japan for aging-related diseases, such as infectious diseases (e.g. pneumonia), lifestyle-related diseases (e.g. hypertension, diabetes mellitus, hyperlipidemia, coronary heart diseases, chronic cardiac failure and cerebrovascular diseases), orthopedic diseases (e.g. bone fractures) and cancers, the number of elderly people having (or surviving) those diseases has increased in the Japanese population and this issue may lead to increased numbers of elderly people 'at risk' of developing dementia. Recent epidemiological studies have shown that hypertension, diabetes mellitus or other atherosclerosis-related factors (e.g. increased plasma levels of homocysteine) are important risk factors in the elderly population for the development of dementia, VaD and DAT.[16–19] Assuming that not only vascular factors, but also other unidentified factors (e.g. alterations in hormonal homeostasis) based on these diseases are closely related to the pathogenesis of DAT, the decrease in acute and mortal vascular diseases (cardiovascular diseases or cerebrovascular diseases) as a result of effective therapies could be inversely associated with the increase in the prevalence of chronic brain diseases, especially DAT.

Conversely, in the severity analysis based on FAST staging, an increased ratio of mild dementia cases, in particular DAT cases, was observed. Although it may be predicted that recent developments in Japan in medical and social intervention for the aging-related diseases mentioned above could also have a benefi-

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cial impact on the progression of DAT, leading to an increased ratio of mild cases, these predicted aspects will need to be investigated in the future.

In conclusion, we have shown an increased prevalence of dementia, in particular DAT, in a Japanese rural area using clinical criteria. We did not have neuroradiological or pathological evidence of the dementia subtype in our patients. However, our data have important implications for future interventional medicine for dementia in Japan.
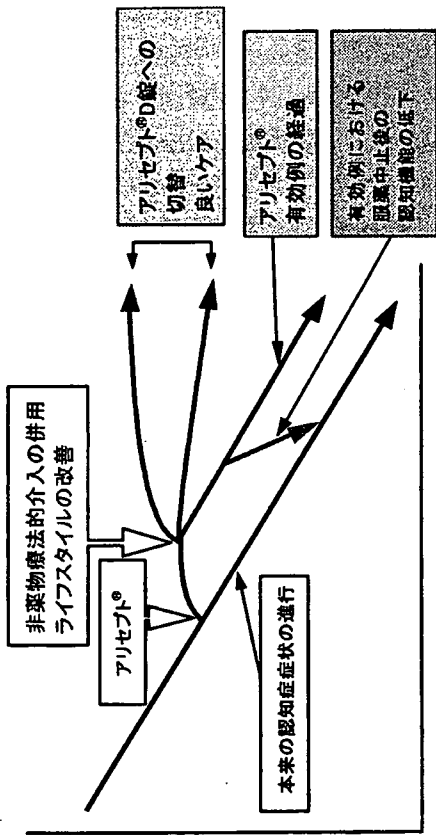
ACKNOWLEDGMENTS

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治療

口腔内崩壊錠の意義

浦上　克哉

塩酸ドネペジルの有効性

現在、アルツハイマー型認知症治療薬として本邦で現在使用可能な薬剤は塩酸ドネペジル(商品名：アリセプト®)しかない。この現状の中、臨床医に求められることは、この薬剤をいかに有効に使用するかである。自験例での有効性をまとめると、49%(21例)に改善が見られ、不変が35%(15例)、悪化7%(3例)、中止9%(4例)であった。この結果は、国内におけるその

他の報告とも一致している。改善例の中には、行きつけの店へも買い物に行けなくなった70歳代半ばの女性が、塩酸ドネペジル内服により忘れずに覚えていることが多くなっただけではなく、幼稚園の先生をしている娘さんの仕事の手伝いをきちんとできるようになった著効例もある。また、現在、塩酸ドネペジルは軽度から中等度のADに適応となっているが、高度な症例でも有効例がある。われわれは会話がほとんど咬み合わなくなった例で、塩酸ドネペジルの投与により意欲的となって会話の内容も咬み合うようになり、さらに絵を描けるようになった症例を経験した。最初は色を塗りつぶすだけであったが、次第に線が書け、次いで丸が書けるようになり、形を成すようになった。その後3年を経過した現在も絵を描き続けており、クレヨンから絵の具へと使う道具にも進歩が見られている。しかし、図①のごとく、実際

①アルツハイマー型認知症の臨床症状の経過と期待されるアリセプト®の効果

本来の認知症状の進行

非薬物療法的介入の併用 ライフスタイルの改善

アリセプト®

アリセプト®D錠への切替 良いケア

アリセプト® 有効例の経過

有効の例にみられる服薬中止後の認知機能の低下

高橋智ら：臨床と研究、77(6)、1084(2000)を一部改変

約1年程度を経過してくると徐々にものの忘れが増えている。

アリセプト®D錠の意義

有効に使うための一つの手段として挙げられるのが、口腔内崩壊錠であるアリセプト®D錠の処方である。アリセプト®D錠はアルツハイマー型認知症患者さんの服薬支援を目的に「つまみやすさ」「飲み込みやすさ」などの工夫がされている。実際にアリセプト®治療中において服薬ができていないケースは意外と多い。外来通院中のアルツハイマー型認知症患者さんで症状が悪化してきて、家族から「何か他に有効な薬はありませんか？」などとよく相談を受ける。その際、詳しく服薬状況を確認してみると薬の飲み忘れや薬が内服できていないことが分かることが少なくない。理由は、図②のように服薬を拒否する、薬を口の中に溜め込むそして吐き出してしまう、などが多い。医師が思っているほど、患者さんの薬のコンプライア

アリセプト®D錠はそのまま飲むことが望ましいが、実は「アリセプト®D錠から普通錠への切り替えが考えられる」こともある。初めからそのまま飲み込む、または口に溜めて飲み込むことができず、口に溜めていることが多くあるアリセプト®D錠を、普通錠に切り替えてうまく飲み込めることがある。アリセプト®D錠の切り替え後にまた症状が悪化した場合には、アリセプト®D錠のもとの処方に変更することも試してよい。

アリセプト®D錠から普通錠への切り替えを行う場合には、患者さんやご家族から初めて飲むことへの不安を伝えられることが多く、医師や薬剤師から十分に説明していただくことがよい。アリセプト®D錠を口に溜め込んでしまうことなどに気づいたら、自分が見ているところで飲んでいただくこと、また飲み込んだことを確認することが大切である。アリセプト®D錠の症状が改善した経験もしばしばある。

（3）医師や薬剤師の方が、実は遠慮して変更しないことに驚くことが多く、実は症状がよくなることがよくある状況を、実は経験することがある。

型認知症は使用可能か

型認知症は、使用可能な開発治療などが阻害されているため、今後の開発が待たれる。アリセプト®は「不治の病」から「治る病気」「進行を遅らせる、また本当に近い将来に「治療可能な病気」へと認知症を行うことができる。そのためにもその根本の努力をしていただいているが、少し臨床に携わっている認知症治療のドクターとしても、本治療に有効な使用ができる。

型認知症にも使われる治療などは使われているまだかなり、型認知症の臨床医は理解されにくいことがある。本治療の根本への大きな治療となる。型認知症治療にその有効な使用が開発可能

フが問われているまだいないことがわかる。まだわずかな、型認知症の臨床医は理解されにくいことがある。アリセプトを使われている認知症治療における本治療に有効に使用可能

おわりに

負担を軽減するアリセプト®D錠の服薬を利用することで、利用するアリセプト®D錠を服用し、今後も服薬をしやすくアリセプト®D錠を試していただきたい。介護する家族には、今村はアリセプト®D錠と回答し調査を行っている。型認知症の患者の約44%が服用し、型認知症の患者の「服薬」が、今後も服薬をしやすくアリセプト®D錠を服用していただきたい。介護する家族は、今村らの調査で中村は「服薬」

②服薬援助の困った経験はどのような場合ですか

（n=48）

最言・暴力 8%
溜め込む 22%
吐き出す 17%
嚥下困難 15%
拒否する 33%
未回答 5%

滋賀摂食ケア・ネットワークのおくすりのアンケートより
監修 藤本クリニック院長 藤本直規

もし一度に落ちて、その症状の悪化により、これがさらに悪循環に陥る。とくにこの薬を飲むことであれば、そのことをよく忘れてしまうが、その忘れによるのである。また、薬を増やしたとしても、そのことをよく忘れてしまうことが、よりいっそう症状を悪化させてしまう。

おわりに

認知症は使用可能な開発治療などが今後の開発が待たれる。

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（鳥取大学医学部 保健学科 環境保健学講座 生体制御学分野 教授・きたむらただし）

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9　認知症の薬物治療

はじめに

本邦で現在市販されている認知症の中核症状に有効な薬剤は、アルツハイマー型認知症（以下、AD）に対する塩酸ドネペジルのみである。塩酸ドネペジルは単に認知機能の改善だけではなく QOL の改善をもたらし多くの恩恵をを与えている。今後より有効な薬剤が市販されると考えられるが、現時点ではこの塩酸ドネペジルを効果的に使うことができるかが、われわれ臨床家に問われるところである。そこで本稿では、塩酸ドネペジルの効果、使い方、注意点、AD 以外の認知症への効果などを紹介し、今後の展望について述べる。

アルツハイマー病に対する塩酸ドネペジルの効果

塩酸ドネペジルは、AD の脳内で減少したアセチルコリン（Ach）を増やすことによって記憶を改善する対症療法薬と位置づけられる。

自験例での有効性をまとめると、49%（21例）に改善がみられ、不変が 35%（15例）、悪化 7%（3例）、中止 9%（4例）であった"。この結果は、国内におけるその他の報告とも一致している。改善例の中には、行きつけの店へも買い物に行けなくなった 74 歳の女性が、塩酸ドネペジル内服により忘れずに覚えていることが多くなったりできるようになったという著効例もある。幼稚園の先生をしている娘さんの仕事の手伝いをきちんとできるようになった著効例もある。

また、現在、塩酸ドネペジルは軽度から中等度の AD が適応となっているが、重症例でも有効例がある。われわれは会話がほとんどみられなくなった重症例で、塩酸ドネペジルの投与により意欲的となって会話の内容もかみ

あうようになり、さらに絵を描けるようになった症例を経験した。最初は色を塗りつぶすだけであったが、次第に線が引け、次いで丸が描けるようになり、形を成すようになった。その後、3 年を経過した現在も絵を続けて描いていて、しかもクレヨンから絵の具へと使う道具にも進歩がみられている"。

AD は進行性の病気であり、"不変"の考え方が重要である。例えば腹痛など通常の病気であれば、不変は改善していないことになるが、AD では不変イコール進行抑制と考えることができる。また、塩酸ドネペジル投与後、約 1 年経過すると徐々に悪化してくるといわれているが、全例がそうなるわけではなく、良好な状態が維持される症例もある。そういう点からも塩酸ドネペジルによる症状の進行抑制は QOL の維持、通院加療期間の延長などにつながり、医療経済学的にみても非常に有用である。

B　Very early AD に対する塩酸ドネペジルの効果

Very early AD を対象とした多施設臨床試験が最近米国でなされ、大変興味ある結果が得られた。153 例の very early AD を対象として、塩酸ドネペジル 10 mg/日で 24 週間投与する randomized, double-blind, placebo-controlled study が施行された。対象の選定基準としては、CDR 0.5～1.0 で、MMSE は 21～26 点とし、有効性の評価は Modified ADAS cog と MMSE を用いている。その結果、Modified ADAS cog の total score, MMSE ともに塩酸ドネペジル投与群でプラセボ群と比較して有意な改善がみられた。最も興味深いのは図 9-1 に示すごとく Modified ADAS cog の Cognitive performance において、とくに very early AD 群で最も良い改善効果を示したことである。また、MMSE でも同様の結果を示した。塩酸ドネペジルを AD のより早期から投与する意義が証明されたものと考えられる。

C　MCI に対する塩酸ドネペジルの効果

AD の前段階として MCI という概念が提唱されている。Petersen らが提唱して MCI の定義は① 自覚的な物忘れの訴えがある、② 客観的な記憶障害を認める、③ 記憶障害以外の高次機能障害がない、④ 日常生活動作は保たれ
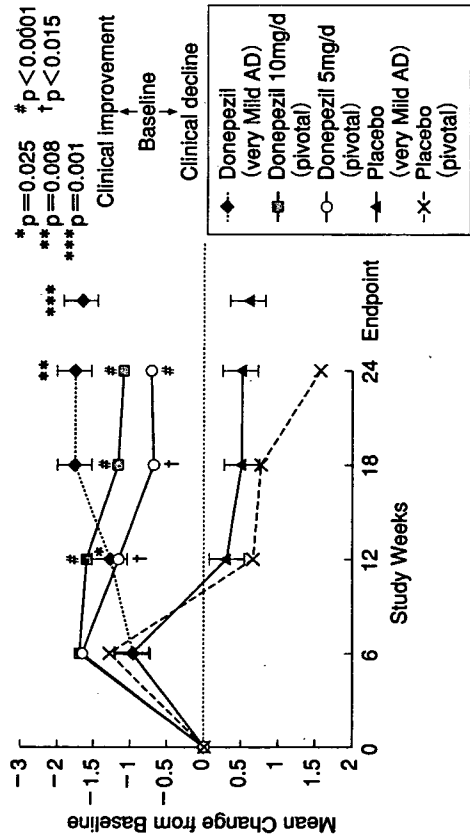
図 9-1　Modified ADAS-cog Total Score.　(Rogers, Farlow, Doody, et al. Data on File. Eisai Inc, NJ; Teaneck; 1998.)

認知機能が特に改善されている。

ている、⑤認知症の診断基準を満たさない、というものである。この MCI の定義は現在のところ一致した見解が得られていないが、少なくとも正常と AD の間に移行期のような状態が存在することは確かであり、認知症の前段階あるいはきわめて早期の AD をとらえられている可能性がある。

わが国では MCI に対する塩酸ドネペジルの適応はないが、自験例で「物忘れが改善した」あるいは「頭がスッキリした」という自覚が得られ、長谷川式簡易知能機能検査－改訂版（HDS-R）あるいは mini-mental state examination（MMSE）などのスコアの改善もみられた症例を経験した。

欧米では塩酸ドネペジルをはじめ各種薬剤の MCI に対する臨床試験が行われている。米国での MCI 患者 270 例を対象とした多施設共同二重盲検プラセボ対照比較試験では、プラセボ投与群に比し塩酸ドネペジル投与群で 24 週後の ADAS-Cog スコアが有意に改善することが示された。また、患者の全般評価においてもプラセボ投与群に比べドネペジル投与群に有意に多く、ドネペジル投与群では改善例が多く、悪化例はプラセボ群に相対的に多いという結果が得られている（図 9-2）[3]。
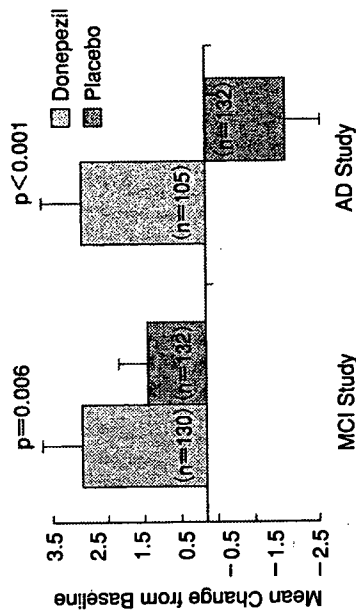
図 9-2　Modified ADAS-cog total score at Week 24

アルツハイマー型認知症以外の認知症への効果

レビー小体型認知症（DLB）では AD 同様にアセチルコリン系神経系が障害されており、このため塩酸ドネペジルが有効と考えられている[4]。脳血管性認知症（VD）では欧米にて二重盲検比較試験がすでに行われており、有意な改善効果が報告されている[5]。統合失調症やダウン症候群の認知機能低下にも改善効果がみられたとする報告もなされている。

期待される根本治療薬と塩酸ドネペジルの将来的意義

近年、AD の治療薬開発は根本的な治療を目指した研究が世界的規模で、きわめて精力的に行われている。現在最も先端をいっているのはβおよびγセクレターゼ阻害剤とアミロイドβ蛋白ワクチン療法[6]などである。どちらも AD の最も早期病変と考えられるアミロイドβ蛋白（Aβ）の沈着を防ぐ、あるいは消去する治療的アプローチである。詳細は本書別項で述べられるので、そちらを参照されたい。このような根本治療薬開発がなされている中で、塩酸ドネペジルの将来的意義としては、①きたるべき根本治療薬への重要なリリーフ役、②対症療法薬として今後も重要な役割をもつ、の2つがあると考えられる。①については塩酸ドネペジルは症状の進行抑制効果であるが、少しでも進行を防ぐことができれば、きたるべき根本治療薬に間に合う可能
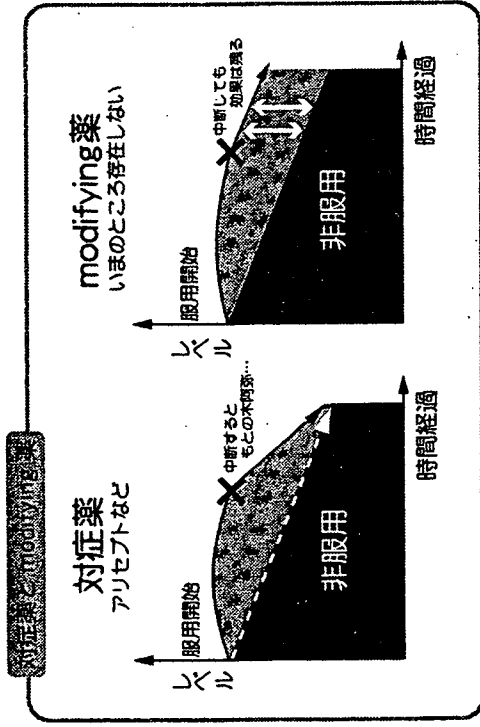
性が出てくるということである。②については、根本治療薬ができても対症療法薬が不要になるということはないということである。神経内科領域では、重症筋無力症という病気があるが、すでに胸腺摘出術やステロイド療法といった根本療法が確立されているが、対症療法であるアセチルコリンエステラーゼ阻害薬は不要になっていない。実際、この対症療法であるアセチルコリンエステラーゼ阻害薬を投与した時が患者さんにとって筋力回復を自覚でき、最も喜ばれるのであるから、対症療法薬である塩酸ドネペジルは今後も重要な役割を担っていくと考えられる。

サプリメント

酸化ストレスがAD発症・進展に関与するとの報告があり、このためビタミンC、ビタミンE、カロテン類などの抗酸化物質が有用とする報告がなされている。ただ、抗酸化物質を食事から摂取した場合とサプリメントとして摂取した場合を比較してみると、食事から摂取するとADリスクを低下させるとの報告が多いが、サプリメントの場合は一致した見解は得られていない。また、ビタミンEをサプリメントとして用いた研究報告では、比較的高容量
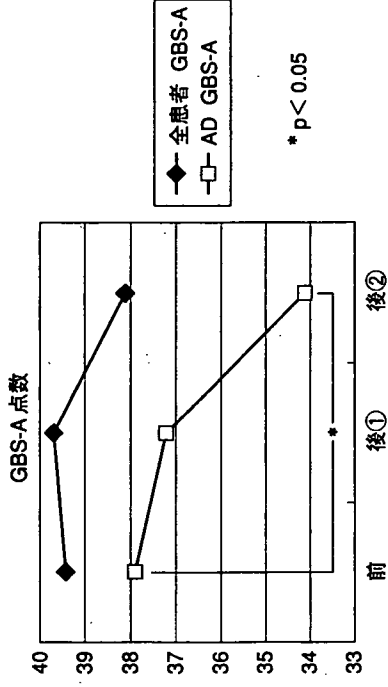

対症療法とmodifying療法

対症薬　アリセプトなど

modifying薬　いまのところ存在しない

図9-3　知的機能（GBS-A）結果

のビタミンEをサプリメントとして摂取した場合、プラセボ群と比較して統計学的に有意に死亡率が高かったとしている⁹⁾。このことから、特にビタミンE摂取に関しては、サプリメントによる摂取は推奨されないと考えられる。
緑茶摂取が認知機能障害の予防に役立つとする報告がなされている。緑茶を1日2杯以上飲んでいる人は、週に3杯以下しか飲まない人より認知機能障害の有病率が低いという結果である⁸⁾。この結果が、直接ADのリスクを軽減させるとはいえないが、今後の検討が期待されるところである。

今後の検討課題

ADの治療では、薬物療法だけではなく非薬物療法との併用が有効である可能性がある⁹⁾。そのためわれわれもアロマセラピーについて検討した。その結果、軽度から中等度のAD患者において、自発性および感情機能のみならず知的機能にも改善傾向が示された（図9-3）。今後はさらに多数例で検討していきたいと考えている。非薬物療法と個人の薬物療法との併用効果について明らかにしていくことも大切である。
前述のように根本治療薬の開発が進んでいるが、対症療法は根本治療が可能になったとしても必要なものであり、塩酸ドネペジルはリリース

役としても重要な役割を担っている。しかし、現時点ではADに対する効果に関して、反応が良好な群 (responder) と良好でない群 (non-responder) の存在が知られており、その差異の解明が大きな課題となっている。われわれはAch受容体 (AchR) に着目し、AchRα7の遺伝子多型の検討によりnon-responder群に比しresponder群でヘテロの頻度が有意に多いことを明らかにした[10]。まだ例数が少なくさらなる検討が必要であるが、AchRα7遺伝子多型の検査が塩酸ドネペジルの有効性の予知に役立つ可能性が示唆される。今後、真のresponderとnon-responderを区別するパラメーターの解明が必要である。

〈浦上克哉〉

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トピックス　アルツハイマー病患者に対するアロマセラピーの有用性

(木村育希, 他. Dementia Japan. 2005; 19: 77-85)
認知症患者を対象としてアロマセラピーを施行した。アロマセラピーはアロマディフューザーを用いる方法で、午前中2時間レモンとローズマリーの香りを、夜2時間ラベンダーとオレンジの香りをたいてもらい、28日間施行し評価した。結果は、認知症の中でも特にアルツハイマー病患者の認知機能改善に有効である可能性が示唆された。コストも安く、予防的にも使える可能性があり、今後期待される療法の一つと考えられる。

〈浦上克哉〉

アルツハイマー病の臨床診断—バイオマーカー

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アルツハイマー病の臨床診断 —バイオマーカー

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■ ポイント

● 髄液中リン酸化タウ蛋白測定は，現在最も精度の高いバイオマーカーと考えられる．
● 髄液中 WGA 結合糖蛋白はアルツハイマー病とタウオパチーの鑑別に役立つ可能性がある．
● タッチパネル式コンピュータを用いた認知症の簡易スクリーニング法は，負担が少なく，容易に検査が可能で，認知症のスクリーニングに有用である．

　アルツハイマー病は近年本邦でも増加してきており，認知症性疾患の約半数を占めている[1]．また，近年塩酸ドネペジル(アリセプト®)が発売され，治療が可能となり，有用性が報告されている．このことから，アルツハイマー病の診断が早期に，かつ的確にできるか否かが重要なポイントとなってくる．しかし，現在のアルツハイマー病診断は徹底した除外診断に基づいてなされており，より容易に誰でもできるバイオマーカーの開発が望まれている．

　本稿では，より確定診断に近いバイオマーカー，スクリーニングに使えるバイオマーカー，治療評価に役立つバイオマーカーに分けて，現状と今後の展望について述べる．

より確定診断に役立つバイオマーカー

■ リン酸化タウ蛋白

　アルツハイマー病撲滅のために設立されたレーガン研究所は，アルツハイマー病の生物学的診断マーカーの条件として，病態をよく反映し，患者への侵襲性が少なく，他の認知症性疾患を区別して診断する精度が高いこと，つまりアルツハイマー病患者を検出する率(感度)と非患者を検出しない率(特異度)がともに80％を超えることを要求している．髄液中総タウ蛋白は上記基準をかなり満たすが，感度と特異度がともに80％以上は難しく，アミロイドβ蛋白と組み合わせることにより，アルツハイマー病インデックス(AD index)，アルツハイマー病ユニット(AD unit)という表現を用いているが，感度と特異度がともに80％以上という結果が得られている．総タウ蛋白で特に問題なのは，髄膜脳炎や Creutzfeldt-Jakob 病などで極端に高値を示すことである．そこで，単独でこの基準をクリアする方法はないかと考え，髄液中リン酸化タウ蛋白を検討した．

　アルツハイマー病患者脳にみられる神経原線維変化のタウ蛋白は高度にリン酸化されている．このため，リン酸化タウ蛋白を選択的に測定できれば，総タウ蛋白よりよい結果が期待できる．そこで，筆者らのグループはセリン199のリン酸化部位に着目してリン酸化タウ蛋白

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