

Briefly, microplates (Immunoplate I; Nunc, Rockville, 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 reproducibility of 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 ($\epsilon^2\epsilon^2$, $\epsilon^2\epsilon^3$ and $\epsilon^3\epsilon^3$)/carrier of the *ε4* allele ($\epsilon^2\epsilon^4$, $\epsilon^3\epsilon^4$ and $\epsilon^4\epsilon^4$)], 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): $\log(P/(1-P)) = \alpha + \beta_1X_1 + \beta_2X_2 + \beta_3X_3 + \beta_4X_4$, where *P* denotes the probability of having LOAD, α is the intercept, β_j represents the estimated parameters and *X_j* 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): $\log(P/(1-P)) = \alpha + \beta_1X_1 + \beta_2X_2 + \beta_3X_3 + \beta_4X_4 + \beta_5X_5 + \beta_6X_6 + \beta_7X_7$, where *P* denotes the probability of having LOAD, α is the intercept, β_j represents the estimated parameters and *X_j* 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 homozygote, 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 [$\log_2(\text{A}\beta 40/42 \text{ ratio} + 1)$] before the two-way ANOVA.

The statistical significance was set at *P* < 0.05.

SUPPLEMENTARY MATERIAL

Supplementary Material is available at HMG Online.

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ORIGINAL ARTICLE

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

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Key words: Alzheimer's disease, dementia prevalence, longitudinal study, rural area, vascular dementia.

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

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.

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

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 previously⁸⁻¹⁰ (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



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

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

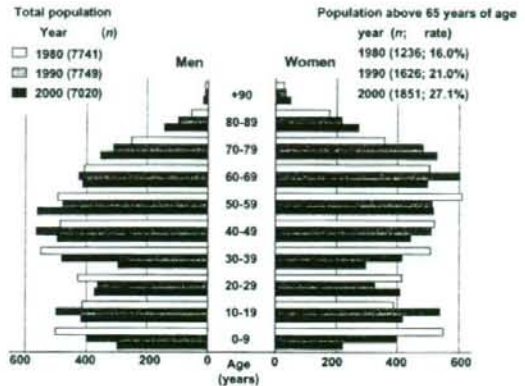


Figure 2 Population structure and the number and ratio of people above 65 years of age in Daisen-cho in 1980, 1990 and 2000.

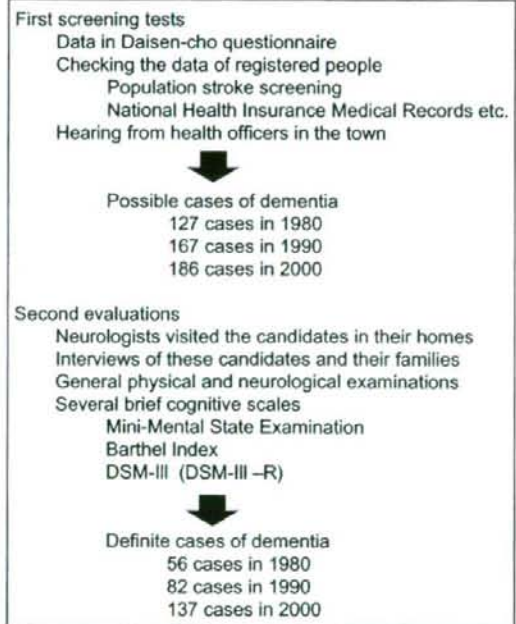


Figure 3 Methods used to investigate dementia.

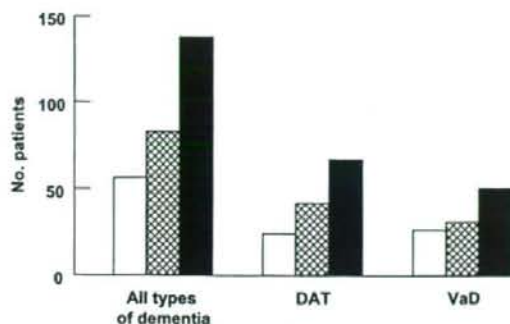


Figure 4 Number of cases of dementia in people over 65 years of age in 1980 (1236; □), 1990 (1626; ▨) and 2000 (1823; ■). DAT, Alzheimer-type dementia; VaD, vascular dementia.

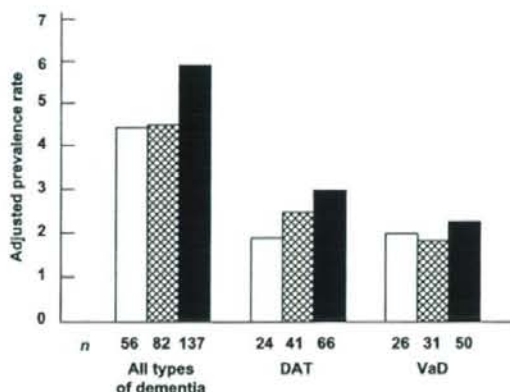


Figure 5 Adjusted prevalence rates of dementia in people over 65 years of age in 1980 (□), 1990 (▨) and 2000 (■). DAT, Alzheimer-type dementia; VaD, vascular dementia.

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-cho and 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

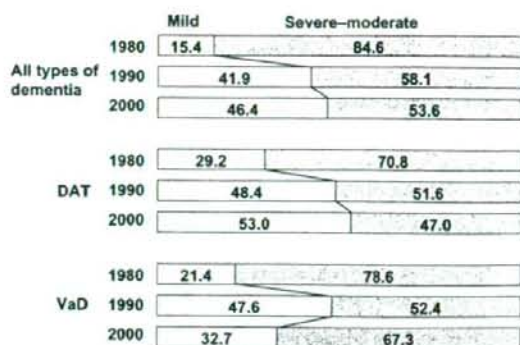


Figure 6 Ratio of mild and severe-moderate cases of dementia in people over 65 years of age in 1980, 1990 and 2000. DAT, Alzheimer-type dementia; VaD, vascular dementia.

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-

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.

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治療

口腔内崩壊錠の意義

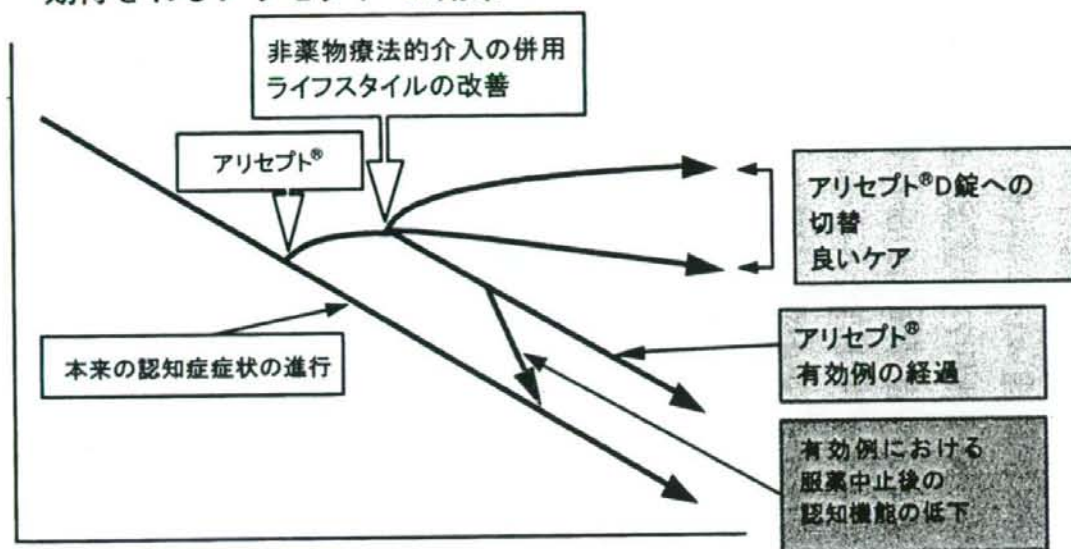
浦上 克哉

塩酸ドネペジルの有効性

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¹⁾。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た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見られている²⁾。しかし、図①のごとく、実際約1年程度を経過してくると徐々にもの忘れが

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



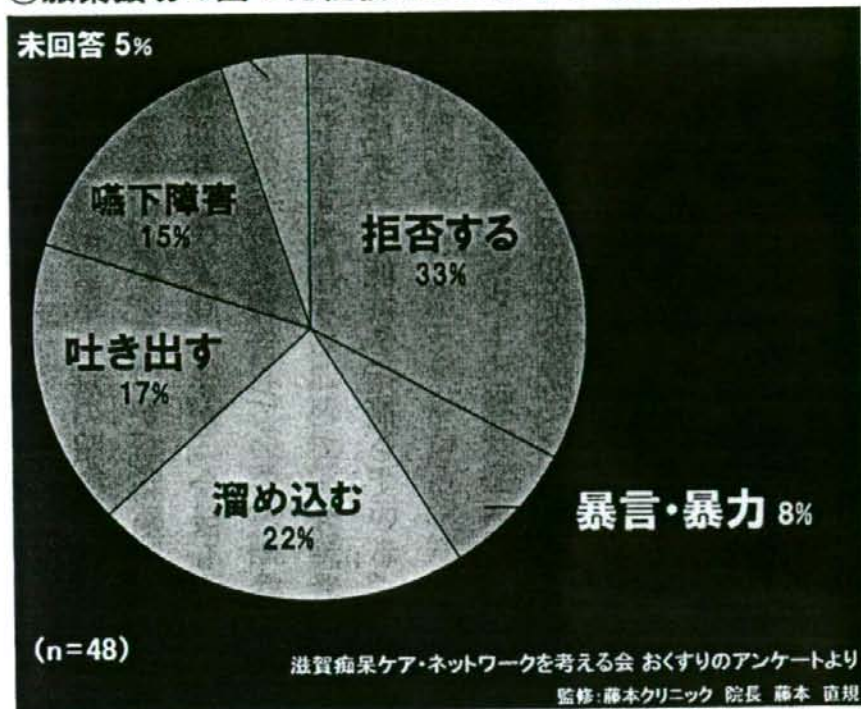
高橋智ら：臨床と研究、77(6)、1084(2000)を一部改変

増えてくる。

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、図②のごとく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の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ふ、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

②服薬援助の困った経験はどのような場合ですか



ンスはよくないのである。また、もの忘れの症状が増えて、そのために薬を飲み忘れる、そしてさらにももの忘れが増えるという悪循環に落ちいつているケースもかなりある。そこで、一つ

の方法としてアリセプト錠[®]からアリセプトD錠[®]への切り替えが考えられる。アリセプトD錠[®]に切り替えてから初めて家族から「実はこれまであまり薬がきちんと飲めていなかったんです。後から飲むと言ってそのまま飲み忘れていたり、口に入れても飲み込まず溜め込み、自分が見ていないところで吐き出したりしていたようなのです。アリセプトD錠[®]に切り替えていただいて、口に溜め込んでいてもそのまま溶けるし、とてもよくなりました。」と話してくださることがよくある。それまでのコンプライアンス不良な状況を、実は遠慮して(?) 医師に伝えていないことがよくあり、変更して初めて気づくことが多いことに驚く。このため、アリセプトD錠[®]への切り替え後にまた症状が改善してくることをしばしば経験する。アリセプト錠[®]の処方で症状が悪化している患者さんに、アリセプトD錠[®]への変更は試してみただきたい方法の一つである。

中村らは、アルツハイマー型認知症患者さんと介護者にアリセプト[®]D錠の服薬感についてアンケート調査を行い、44%が「服薬しやすくなった」と回答し、100%が「今後も服薬を続けたい」と答えたと報告している。今井らはアリセプトD錠を利用することで、介護者家族の負担を軽減する可能性を指摘している。⁴⁾

おわりに

いま臨床医は認知症診療において、使用可能なアリセプトをいかに、少しでも有効に使うかが問われている。また、その努力はきたるべきアルツハイマー型認知症の根本治療薬が使用可能になったときに大きな力になると考えられる。セクレターゼ阻害剤やアミロイドβ蛋白のワクチン療法などが開発の最先端を行っているが、これらの開発状況を見てみると本当に近い将来に使用可能となると思われる。アルツハイマー型認知症は「不治の病」から「治療可能な病気」

へと大きく変貌しようとしている。多くの臨床医の先生方に認知症診療に関心を持っていただきたいと考える。

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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 の改善をもたらす多くの恩恵を与えている。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。

A 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¹⁾。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たことが多くなっただけでなく、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 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かみあわ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²⁾。

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10mg/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。

B 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らが提唱した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

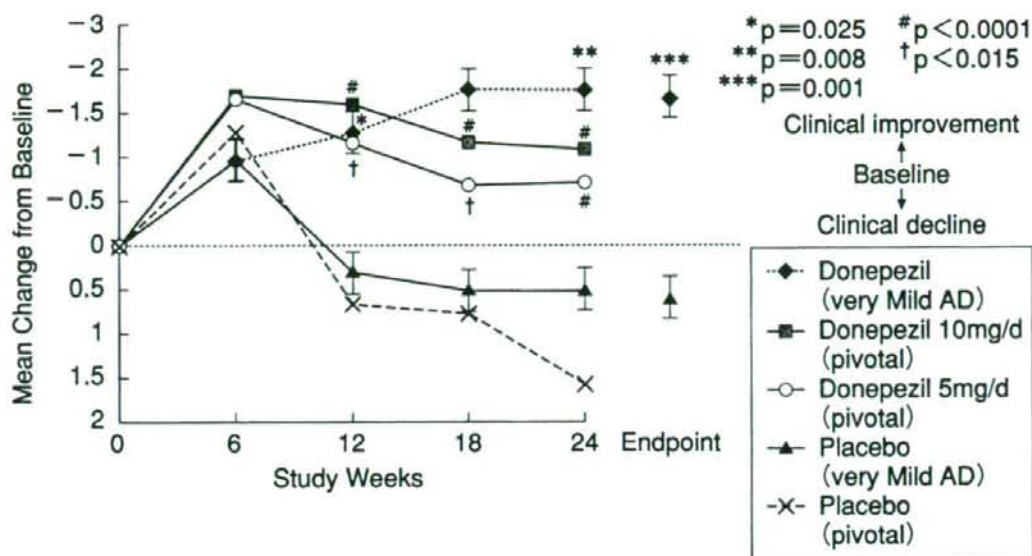


図 9-1 Modified ADAS-cog Total Score

認知機能が特に改善されている。(Rogers, Farlow, Doody, et al. Data on File. Eisai Inc., NJ; Teaneck; 1998.)

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 の定義には現在のところ一致した見解がえられていないが、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、長谷川式簡易知的機能検査—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悪化例はプラセボ群に多く、ドネペジル投与群では改善例が多いという結果が得られている (図 9-2)³⁾。

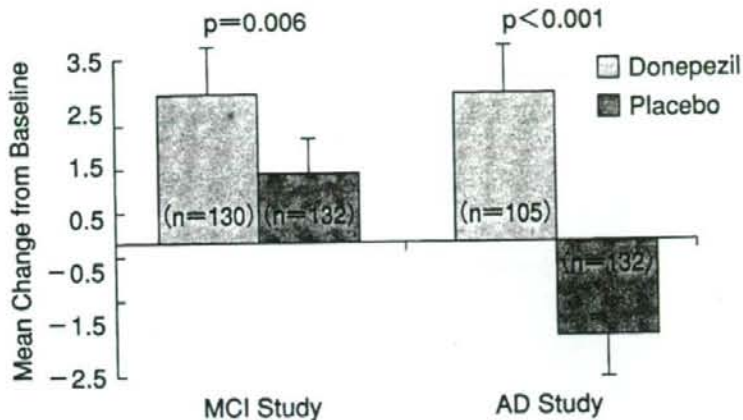


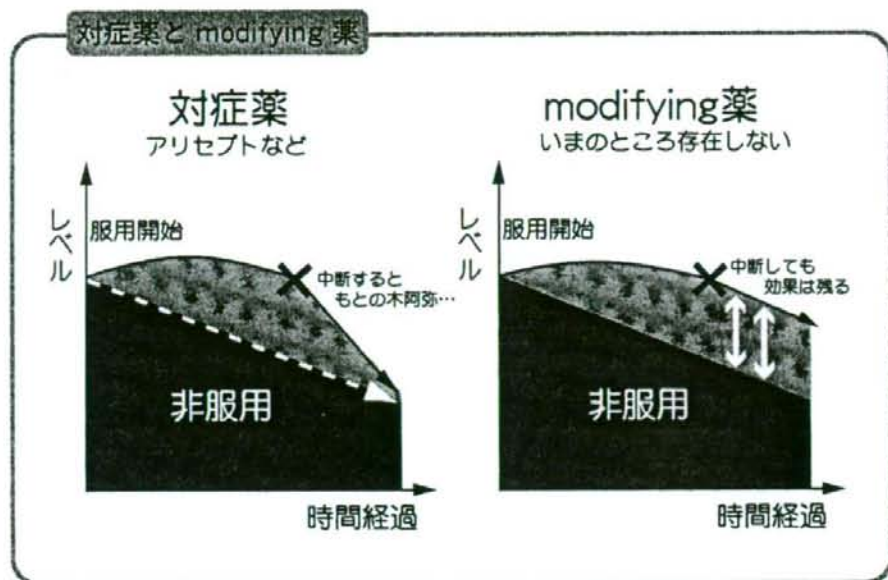
図 9-2 Modified ADAS-cog total score at Week 24

D 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) では欧米で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。

E 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⁾でなどである。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 ($A\beta$) 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きている中で、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ス役、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対症療法薬が不要になる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、この対症療法薬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。このような事実からも、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。

F 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、食事から摂取した場合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が得られていない。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

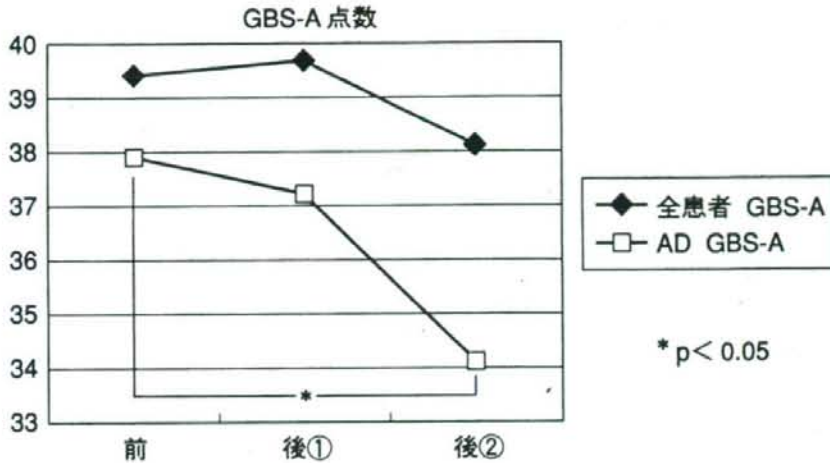


図 9-3 知的機能 (GBS-A) 結果

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⁷⁾。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⁾。そのような観点から、さまざまな非薬物療法が試みられており、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。非薬物療法的介入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いつで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、AchR α 7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、AchR α 7 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。

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