表1　推奨グレード

A　強い科学的根拠があり，行うよう強く勧められる
B　科学的根拠があり，行うよう勧められる
C1　科学的根拠がないが，行うよう勧められる
C2　科学的根拠がなく，行うよう勧められない
D　無効性あるいは害を示す科学的根拠があり，行わないよう勧められる

文献1より引用

多剤併用をなるべく避け，定期的に薬剤の種類や服薬コンプライアンスを確認することが推奨されている．治療の有効性評価尺度としてNeuropsychiatric Inventory（NPI）やBehavioral Pathologic Rating Scale for Alzheimer's Disease（BEHAVE-AD）などがあり，薬物療法開始前と評価時で比較すれば有用である[1]．

特に，抗精神病薬の投与を行う場合は，非定型抗精神病薬が投与された高齢認知症患者群において，プラセボ群と比較して死亡率が1.6～1.7倍高いという米国食品医薬品局からの勧告や，定型抗精神病薬はさらにリスクが高いという報告[2]を念頭に置き，慎重に投与する必要がある．わが国では，2011年9月28日付けの厚生労働省の通達で，「器質的疾患に伴うせん妄・精神運動興奮状態・易怒性」に対して，クエチアピン，ハロペリドール，ペロスピロン，リスペリドンの保険適応外使用が認められた．リスペリドンでは，「パーキンソン病に伴う幻覚」に対しても保険適応外使用が認められた．これらの抗精神病薬は，抗コリン作用による有害事象と認知機能の低下の可能性も指摘されているので，注意しながら使用する必要がある．なお，抗精神病薬を使用するに当たっては，現時点では保険適応のない治療法であることを，本人ないし家族に十分説明し，必要最低限の量を有害事象に留意しながら使用する[1-3]．

行動異常への薬物療法

1．焦燥性興奮（agitation）

焦燥性興奮（agitation）を改善させる目的では，非定型抗精神病薬であるリスペリドン，クエチアピン，オランザピン，アリピプラゾールが有効である（グレードB）[1]．重症の焦燥性興奮はこれらの薬剤を使用することも多いが，脳血管障害性の有害事象と死亡率の増加を加味して考慮する必要があり，投与も定期的に吟味する必要がある[4]．バルプロ酸やカルバマゼピンの有用性は科学的根拠が不十分であるが，必要な場合は使用を考慮してもよい（グレードC1）[1]．近年，抗認知症薬であるドネペジルとメマンチン併用において，興奮と攻撃に伴う介護負担が有意に低下したとの報告もみられる[5]．

2．暴力・徘徊・不穏

認知症に伴う暴力や攻撃性は介護者を悩ませる大きな要因の1つである．これらの症状に対しては，薬物療法を行う前に，行動異常の内容を明らかにして頻度や重症度を明確にし，その要因を検討し，介入すべき標的症状を決定した上で，行動療法的介入など非薬物療法を実施する．これらの対応だけで不十分な場合に薬物療法が選択される．認知症患者の暴力や不穏に対する薬物療法では，まず，リスペリドンの使用を考慮する（グレードC1）[1]．焦燥性興奮と攻撃性は類縁の症状と考えられ，焦燥性興奮に効果がある薬剤は暴力に対しても効果を期待できる．リスペリドン以外の非定型抗精神病薬，抗てんかん薬（カルバマゼピンやバルプロ酸），コリンエステラーゼ阻害薬の効果も期待できる（グレードC1）[1]．徘徊や不穏に対してはそれぞれの有効性が示された報告はない．

3．性的脱抑制

パロキセチン，トラゾドンといった抗うつ薬

に効果があったという症例報告やクエチアピンの使用報告はあるが，十分なエビデンスはない（グレードなし）[1]．

心理症状への薬物療法

1．幻覚・妄想

認知症にみられる幻覚・妄想は焦燥性興奮など，ほかの症状と併発する場合が多い．幻覚・妄想への対応としてまず行うことは，本人の訴えを傾聴し，否定も肯定もせずに受容的，共感的な態度で接して，安心を与えることが重要である．それでもなお日常生活に支障がある場合に薬物療法を検討する．リスペリドンとオランザピンは幻覚・妄想に改善がみられる（グレードB）[6,7]．クエチアピンがせん妄や幻覚に効果的であったという報告や，アリピプラゾールの効果を示した報告もある（グレードB）[1]．

また，幻覚・妄想はレビー小体型認知症（DLB）を特徴づける症候の1つである．DLBにおけるこれらの症候に対して，ドネペジル，リバスチグミン，メマンチンの有効性が報告されている（グレードB）[1]．クエチアピン，オランザピン，抑肝散の有効性も示されており，これらの使用も考慮してよい（グレードC1）[1]．

2．不安

ベンゾジアゼピン系薬物は軽度の不安を緩和するために，時に有用である．高齢者の場合，長時間作用型より短時間作用型を用いる．しかし，せん妄を誘発しやすく，安易に使用するべき薬物ではない．主な有害事象は過鎮静，運動失調，失見当識，錯乱，脱抑制，筋弛緩作用などである．また，認知症が進行すると有害事象はより顕著となり，中等度から高度の認知症では，ベンゾジアゼピン系薬物により記憶障害が増悪する．また，軽度の認知症患者ではベンゾジアゼピン系薬剤を中止することにより，記憶や注意力が改善する場合もある．これらの理由から，不安に対してベンゾジアゼピン系薬物の使用は推奨されていない[1]．

抗精神病薬の不安に対する検討も多くはないが，低用量のリスペリドンやオランザピンが有効であり（グレードB）[1]，クエチアピンの有効例も認められる（グレードC1）[1]．

3．睡眠障害

睡眠障害に対して，ベンゾジアゼピン系薬物を安易に使用する傾向があるが，高齢者では代謝機能が低下しており，上記に述べた副作用に加えて，夜間転倒の原因になりやすく，その使用を推奨する科学的根拠はないとされている（グレードC1）[1]．なるべく日中の活動を促し，生活リズムが整うように環境調整を第一に考える．それでも，薬物が必要な場合は，成人通常使用量の1/2～1/3程度から開始し，半減期が短い薬剤を使用する．せん妄，徘徊，夕暮れ症候群といった行動障害を伴っている場合は，リスペリドンをはじめとした非定型抗精神病薬の使用も考慮する（グレードC1）[1]．また，認知症の睡眠の質を改善させる目的で，ドネペジルや抑肝散の使用を考慮してもよい（グレードC1）[1]．眠気の副作用がある抗認知症薬のメマンチンを夕食後に投与すると不眠が改善する場合もある．

4．うつ状態

うつ状態に対してはまず，本人の不安を助長させないように，非難や激励，無理強いは行わないように努める．しかし，意欲低下（apathy）との鑑別が必要で，意欲低下であれば，下記の薬物療法よりも，日中の活動性が上がるように環境調整し，引きこもらないよう，活動への参加促しが必要である．

認知症のうつ状態に対して，抗うつ薬の使用は根拠に乏しい．選択的セロトニン再取り込み阻害薬（SSRI）や，ミルタザピンで改善したという報告（グレードC1）[8]，ドネペジルで改善がみられたという報告（グレードC1）[9]などがある．

おわりに

『認知症疾患治療ガイドライン2010』[1]の薬物治療を中心に概説した．現在は，アルツハイマー型認知症（AD）に対する抗認知症薬の有効性

は確立されているが，BPSDに対する薬物のエビデンスは十分とはいえない．近年，DLB患者にみられる幻覚・妄想およびそれらに基づく興奮に対する抗アセチルコリンエステラーゼ阻害薬の効果[10]や，前頭側頭型認知症(FTD)の患者ではアセチルコリン系は比較的保たれているのに対し，セロトニンとドパミン系の神経伝達物質の減少がみられるため[11]，FTD患者の呈する常同行動に対するSSRIの効果が認められるといった報告[12]がなされ始めた．今後，疾患別のBPSDに対する薬物療法も検討していく必要がある．

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ORIGINAL ARTICLE

A comparison of family care infrastructure for demented elderly in inner cities and regional areas in Japan

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Abstract

Background: Family members' observations of daily life are important for the diagnosis and treatment of dementia. However, elderly people are increasingly living alone, and family structures tend to differ between inner-city areas and regional areas. We aimed to compare the family caregiving infrastructure of demented elderly visiting a memory clinic.

Methods: Subjects were consecutive outpatients with dementia at the memory clinic at a university hospital in two different areas. We compared subjects' demographic data, residency status, housemates and companion status at the time of their initial visit.

Results: Patients in the inner-city area (n = 99) had more education and higher Mini-Mental State Examination scores than those in the regional area (n = 172). In both areas, the highest proportion of patients lived with their spouse. In the inner city, patients' housemates were either their spouse (34%) or their child (13%); 22% lived alone. In regional areas, patients lived with their spouse only (39%) or in their child's household (23%); 14% lived alone. At their initial consultation, inner-city patients were accompanied by a family member other than their spouse (49%), a spouse (27%), or they were alone (7%). In the regional area, patients' companions were their spouse (35%) or their spouse and other family members (18%); patients rarely arrived alone. Regression analysis showed that education, diagnosis, housemate state (child only), and companion state (alone) significantly influenced the living area.

Conclusion: Our results suggest family caregiving infrastructure of demented elderly differ between the two areas. This may reflect changes in social structure and increased awareness regarding dementia in inner-city areas.

Key words: *ageing society, dementia, family care infrastructure, regional comparison.*

INTRODUCTION

The population is rapidly ageing in Japan, and elderly people older than 65 years account for over 20% of the population.[1] As a result, there has been an increase in the number of demented patients to more than 2.2 million. To cope with this increase, clinics have specializing in treatment of dementia, memory clinics, have been established in the past 10 years to facilitate early diagnosis and treatment.[2] Meanwhile, educational activities pertaining to dementia, anti-dementia drugs, and a long-term care insurance system have been developed to assist the increasing number of patients who need assistance. These new programmes and institutions also help diverse cases including those with mild cognitive impairment.[3]

To accurately diagnose dementia, it is necessary to have an understanding of behavioural symptoms observed during daily life by family members and housemates, particularly family caregivers.[4–6] For treatment and care management, cooperation with

these key individuals is necessary. In many cases, the person who accompanies the patient to the initial visit to the memory clinic is the first person who notices abnormal changes in the patient and is the one who becomes the patient's primary caregiver.

However, the rate of elderly people living with younger relatives is on the decline in Japan. Among households with elderly members, the majority were households that included only elderly people.[1] Moreover, spouses who act as caregivers are also ageing along with the patients. Thus, the number of cases in which the elderly patient lives alone or with an elderly spouse is increasing in memory clinics. Furthermore, family structures differ between metropolitan areas and regional cities for many reasons. For example, large metropolitan areas have 'brought-over elderly', where elderly people leave their long-time communities to move closer to their children who live in a metropolitan area.[7] In contrast, in regional cities, there are many households in which the elderly live apart from the younger generation. Therefore, the consulting situation and the infrastructure for family care for elderly people with dementia vary between these two types of areas.

In this study, to gain a better understanding of the present situation in Japan, we focus on these differences and performed a regional comparison of family caregiving infrastructure for demented elderly. Our study was based on residency status, housemates at the time of initial visit, and companion at the time of initial visit in both inner-city areas and regional cities.

METHODS AND MATERIALS

The subjects were consecutive patients with dementia who visited the memory clinic at the Department of Psychiatry, Jikei University Hospital and the Department of Neuropsychiatry Kumamoto University Hospital, between April 2008 and March 2009. Jikei University Hospital is located in Minato-ku, Tokyo, and patients come to the hospital from metropolitan Tokyo and/or neighbouring metropolitan areas. Tokyo is the capital of Japan, and Minato-ku is an area with many government and large corporate offices. According to the 2005 national census, the population of metropolitan Tokyo is 12.576 million, and out of that, the number of elderly people over 65 years old was 2.295 million (18.2%).[8] Kumamoto University Hospital is located in Kumamoto city, Kumamoto Prefecture, and patients come to the hospital from Kumamoto city and its surrounding areas. Kumamoto Prefecture is located on Kyushu, one of Japan's four main islands. The population of Kumamoto Prefecture was 1.842 million according to the 2005 census, and the elderly population is 0.437 million (23.7%), which is typical for a regional city in Japan.

Both clinics are part of university hospitals and are registered with the Japanese Psychogeriatric Society; the institutions offer the same diagnostic training and perform the same neuropsychological examination batteries. All of the patients who visited either memory clinic were examined by a senior neuropsychiatrist who is an expert in dementia. Neuropsychological examinations, routine laboratory tests including thyroid hormone, vitamins B1, B12, and folic acid, and standard neuropsychological examinations, including the Mini-Mental State Examination (MMSE) and Clinical Dementia Rating (CDR) were performed.[9,10] In addition, each patient had brain MRI or CT scan. The clinical, neuropsychological and neuroimaging data collected prospectively in a standardized fashion were entered into the registry of each institution. After receiving a complete description of this database study's procedures, patients or their caregivers provided written informed consent.

Dementia diagnoses were based on the international consensus clinical criteria. The diagnosis of Alzheimer's disease (AD) was based on the criteria for probable AD of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.[11] The diagnosis of vascular dementia was based on the criteria for the probable vascular dementia of the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences or the Alzheimer's Disease Diagnostic and Treatment Centers.[12,13] The diagnosis of dementia with Lewy bodies was based on recent clinical diagnostic criteria.[14] The diagnosis of frontotemporal lobar degeneration was based on international diagnostic criteria.[15] For other types of dementia, diagnosis was based on the consensus criteria.

In the inner-city area, of the 142 patients who underwent consultation during this study, 43 patients were diagnosed as being normal or having mild cognitive impairment or psychiatric disorders; they were not diagnosed with dementia. Of these 142 cases, 99 patients were diagnosed as having dementia. Of the

Table 1 Background data of the consecutive dementia cases in both institutions

	Inner city area (n = 99)	Regional area (n = 172)	P-value
Sex (Men : Women)	42:57	68:104	0.700
Age at the time of initial consultation (years)	76.16 ± 8.26	74.70 ± 9.37	0.202
Education (years)	12.37 ± 3.43	10.62 ± 2.67	0.000
Time before consultation (years)	2.62 ± 2.00	2.41 ± 1.74	0.484
Diagnostic ratio (AD:VaD:DLB:FTLD:others)	68:11:7:2:11	94:15:21:15:27	0.001
MMSE	21.96 ± 5.16	18.96 ± 6.23	0.007
CDR (0.5:1:2:3)	36:44:14:1†	56:82:26:8	0.436

†n = 95. AD, Alzheimer's disease; CDR, Clinical Dementia Rating; DLB, dementia with Lewy bodies; FTLD, frontotemporal lobar degeneration; MMSE, Mini-Mental State Examination; VaD, vascular dementia.

99 dementia patients, 90% lived in the prefectures of Tokyo, Chiba, Saitama, and Kanagawa, all near in the metropolitan Tokyo area. In the regional area, out of the 260 patients who underwent consultation during this study, 88 patients were diagnosed as being normal or having mild cognitive impairment or psychiatric disorders; they were not diagnosed with dementia. Of these 260 patients, 172 patients were diagnosed as having dementia. Of the 172 dementia patients in the regional area, over 90% lived in Kumamoto Prefecture.

During this study, we extracted and compared the following information from the database: the age at the initial visit, sex, education level, diagnosis, time before consultation (years) (i.e. time between start of symptoms and initial consultation), cognitive function by MMSE, severity of dementia according to CDR, residency status, housemates at the initial time of visit and the companion at the initial visit. A housemate was defined as a person who had been living with a patient for more than 3 months. A companion was defined as a person who visited the clinic with the patient.

Statistical analysis was conducted using SPSS 18.0 (SPSS, Inc., Chicago, IL, USA). Student's t-test was used for age, educational history, the amount of time before consultation, and the MMSE score. The χ^2 test and Fisher's exact test were used to compare sex, CDR, residency status, housemate, and companion.

After comparing each item between the two groups, we conducted logistic regression analysis to investigate factors that most affected the living area (inner-city area/ regional area). In the logistic regression analysis, we assumed living area (inner-city area/ regional area) to be a dependent variable and assumed that other significant items were independent variables.

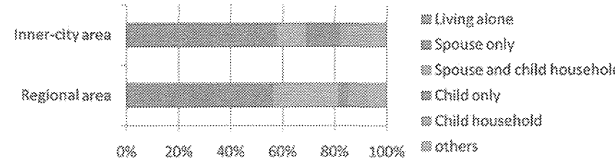

Figure 1 Housemates at the time of initial consultation: inner city area (n = 99), regional area (n = 172), P = 0.004.

RESULTS

The background data and diagnoses of the dementia patients in both institutions are summarized in Table 1 and Figure 1. There were no significant differences in sex, age at the time of initial consultation, disease duration or CDR severity between both groups, but the patients in inner-city areas had significantly more years of education and higher MMSE scores than the patients in the regional area. Moreover, there were considerably more Alzheimer's patients in the inner-city area than the regional area (69% vs 55%).

The comparisons of residency status, housemates, and companion at the initial time of consultation are shown in Figures 1 and 2. There were no significant differences (P = 0.142) within the two groups regarding residency status (at home vs. admitted to a care facility). In both areas, the highest proportion of patients lived with their spouse. In the inner city, patients' housemates were either their spouse (34%) or their child (13%); 22% lived alone. In regional areas, patients lived with their spouse (39%) or with their spouse and child (23%). At their initial consultation, inner-city patients were accompanied by a family member other than a spouse (49%), a spouse (27%), or they were alone (7%). In the regional area, patients were frequently accompanied by multiple family

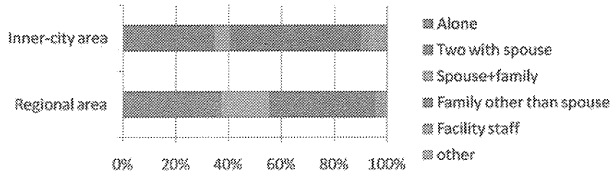

Figure 2 Companion at the time of initial consultation: inner city area (n = 99), regional area (n = 172), P = 0.000.

Table 2 Logistic regression analysis: influence of living area (inner city/regional)

Variables	OR	95%CI	*P*-value
Education (years)	1.35	1.18–1.56	0.001
Diagnosis (AD vs non-AD)	3.07	1.45–6.51	0.006
MMSE	1.09	0.99–1.13	0.084
Housemate status			
Alone	2.69	098–5.25	0.078
Spouse only	1.04	0.58–1.88	0.489
Spouse and child household	0.79	0.38–1.65	0.371
Child only	3.86	1.28–6.39	0.036
Companion status			
Alone	3.13	1.22–6.28	0.041
Two with spouse	0.87	0.32–2.45	0.439
Spouse and family	0.62	0.18–2.08	0.309
Family other than spouse	1.09	0.46–2.59	0.452

AD, Alzheimer's disease; MMSE, Mini-Mental State Examination.

members other than their spouse (40%). Otherwise, patients were accompanied by their spouse (35%) or their spouse and other family members (18%); patients rarely arrived alone (1%).

In the logistic regression analysis, we assumed significant variables by simple comparison (education, diagnosis, MMSE, housemate status and companion status) as an independent variable. Logistic regression showed that the education, diagnosis, housemate status (child only), and companion status (alone) significantly influenced the living area. (inner-city area/ regional area) (Table 2).

DISCUSSION

Our study revealed that there are significant differences in the housemate and companion statuses of elderly demented patients in the inner cities and regional cities in Japan. In the inner-city area, while a relatively large number of demented elderly live with a child, there were many cases where the patient had no companion at their initial consultation. This suggests a difference in the family caregiving infrastructure for demented elderly in the inner cities and regional cities.

According to the national census of 2005, of the households that included elderly people in Tokyo, 30.3% of those had an elderly person living alone and 28.8% were husband-wife households.[8] In Kumamoto, in 21.7% of elderly households a person lived alone and 26.1% were husband-wife households; these proportions are considerably lower than in Tokyo. In our result, relatively high percentages of subjects in the inner-city area lived alone or with their child only; specifically, 34% lived only with their spouse only, 22% lived alone and 13% lived only with their child. This result is consistent with the 2005 census,[8] and a paper on elderly persons by the Japanese Ministry of Health, Labour and Welfare (22.4% lived alone, 29.5% lived only with their spouse, 16.1% lived only with an unmarried child).[1] This data from the inner-city area may be typical of Japanese society today. In the regional area, there were many cases of husband-wife households (39%). This is considerably higher than the 26.1% of spouse only elderly households in Kumamoto according to the census.[8] In regional areas, a high proportion of patients are accompanied by someone when they have a consultation at a memory clinic; this may be because of the strong spouse connection in regional areas.

With regard to companions at the initial consultation, a significantly large number of patients in the inner-city area came alone. Given that patients in the inner-city area had more years of education, it may be said that the education/occupation level was high, and there were many cases where the patients themselves noticed their problems and consulted the clinic themselves. While patients that visited the hospital alone may not necessarily require family caregiving soon, it is important that they have a key person that understands their cognitive and behavioural symptoms in order to postpone the institutional care and to recognize when some kind of intervention is required. Ensuring that family members understand the importance of continued treatment and that one can become the key person in the patient's life may well be essential to the on-going management of the case. Given the role of family members, more educational activities pertaining to dementia are required in the regional areas.

In the inner-city area, there were many cases where patients were accompanied only by their spouse or child. (There were few cases of patients being accompanied by both their spouse and child, but this is not significant in the logistic regression.) This suggests that patients in the inner-city areas only have one key person for support. The isolation of lone caregivers and the mounting care burden can lead to an early homecare breakdown. As such, we think that even in a situation where a key person exists, there may be a need to assign a caregiving aide.

With regard to patient background, inner-city patients had significantly more years of education. This may be caused by regional differences and different employment opportunities. Many inner-city patients were diagnosed with AD; few had other dementias such as frontotemporal lobar degeneration. This may be related to the number of surrounding specialized medical institutions that were able to diagnose the patients rather than a regional difference in the causes of dementia.

This study had a few limitations. Firstly, because we studied continuous cases of dementia, we have included early onset cases involving patients under 65 years of age at the initial visit. In fact, 11 of the 99 cases (11%) in the inner-city area and 31 of 172 cases (18%) in the regional area were under 65 years old at the initial visit. In these cases, a comparison with demographic statistics for elderly persons is difficult. However, this group was important in terms of housemates and companions of dementia patients, so we included these cases in this study. Furthermore, although we excluded early onset patients, housemates and companion at the time of initial visit data do not differ greatly.

Second, because significant differences were observed in housemate status, companion status, education and diagnostic ratio , there is a possibility of influences other than regional differences. There are various factors connected with each other that might have affected when patients visited the memory clinic. Andersen described patients' ways of accessing medical care as the 'Behavioral Model', which consists of 'predisposing characteristics', 'enabling resources', and 'need'.[16] For example, while there are 27 approved institutes of geriatric psychiatry in the Tokyo area, there are only four in Kumamoto Prefecture. For example, Kumamoto University is one of the primary dementia centres in Kumamoto Prefecture, and with its extensive connections to related medical institutions, the university attracts many cases within the prefecture that are difficult to diagnose.[17] Given the availability of medical care, the institutions' varying characteristics come into play. This may influence the number of people visiting the two institutions; there were more people coming to the clinic in the regional area than in the inner city area. It should be noted that we did not assess other factors such as patients' financial situations, religious beliefs and practices, and family members' occupations. This study is a comparison of only two institutions, so it is difficult to generalize our results.

Conclusion

There was a relatively large number of demented elderly who live only with their children in the inner-city area, and there were many cases where patients did not have a companion at the initial consultation. Two factors likely influenced these facts: (i) more elderly people live alone in large metropolitan areas because of changes in social structure; and (ii) increased awareness regarding dementia. As a result, there has been an increase in the number of patients that consult the clinic alone in large metropolitan areas. In these cases, it becomes difficult to introduce treatment based on a family caregiver, so the problem here is how to set up a key person and continue with treatment. The necessity of developing a new system of care has been brought into sharp relief.

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Prevalence and Topography of Small Hypointense Foci Suggesting Microbleeds on 3T Susceptibility-Weighted Imaging in Various Types of Dementia

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ABSTRACT

BACKGROUND AND PURPOSE: The prevalence and topography of small hypointense foci suggesting microbleeds on 3T SWI in various types of dementia have not been systematically investigated. The purpose of this study was to determine the prevalence and topography of SHF on 3T SWI in patients with different dementia subtypes.

MATERIALS AND METHODS: We included 347 consecutive patients (217 women, 130 men; age range, 42–93 years; mean age, 74 years) who attended our memory clinic and underwent 3T SWI. They were divided into 6 groups: subjective complaints, MCI, AD, DLB, VaD, and FTLD. Two neuroradiologists evaluated the number and location of SHF on SWIs. Statistical analyses were performed to evaluate inter- and intragroup differences.

RESULTS: Of the 347 patients, 160 (46.1%) exhibited at least 1 small hypointense focus. This was true in 86% with VaD, 54% with DLB, 48% with AD, 41% with MCI, 27% with FTLD, and 22% with subjective complaints. With the subjective complaints group as a reference, the odds ratio adjusted by age, sex, and arterial hypertension was 9.2 (95% CI, 2.0–43.6) for VaD; 5.4 (95% CI, 1.2–24.3) for AD; 3.1 for DLB (95% CI, 1.1–8.8); 2.0 for MCI (95% CI, 0.5–8.1); and 1.5 for FTLD (95% CI, 0.4–5.4). There was a significant lobar predilection for AD, DLB, and FTLD groups ($P < .05$).

CONCLUSIONS: On 3T SWI, patients with VaD, AD, and DLB manifested a high SHF prevalence. In patients with AD, DLB, and FTLD, the SHF exhibited a lobar predilection.

ABBREVIATIONS: AD = Alzheimer disease; CI = confidence interval; DLB = dementia with Lewy bodies; FTLD = frontotemporal lobar dementia; MCI = mild cognitive impairment; SHF - small hypointense foci; VaD = vascular dementia

Dementia is a growing medical, social, and economic problem. Approximately 24 million individuals have this disease globally, and their number is expected to double every 20 years to reach 81 million by 2040.[1] Among dementias, AD is the most common primary neurodegenerative disease.[2] Patients with amnesic MCI are at high risk for progression to AD.[3] VaD is induced by cerebrovascular disease; it is considered the most common secondary cause of dementia.[4,5] Less common but important causes of dementia are DLB and FTLD.[5,6]

Small hypointense foci in the brain on T2*-weighted gradient recalled-echo and SWI are thought to be microbleeds.[7-9] SHF are associated with symptomatic intracerebral hemorrhage, hypertension, and advanced age.[10-14] Male sex, smoking, and diabetes mellitus may be risk factors for SHF.[10,14,15] On MR imaging, SHF are associated with radiologic signs of small-vessel disease, white-matter hyperintensities, and lacunar infarcts.[11,14,16-18] Histologically, they represent previous extravasation of blood and are related to bleeding-prone microangiopathies of different origins (eg, lipohyalinosis, amyloid deposition).[8] Deep subcortical SHF are thought to be associated with vascular risk factors,[11] and lobar SHF are usually attributed to vascular β-amyloid deposits (cerebral amyloid angiopathy).[11,19-21]

Among patients with cognitive disorders, those with AD, MCI, and VaD tend to have SHF.[22] In healthy subjects, the prevalence of SHF detected by 2D T2*-weighted GRE imaging ranged from 0% to 21%[14,23,24]; it increased to 32% in patients with AD,[25] to 20% in patients with MCI,[22] and to 85% in patients with VaD.[26] Although histologic studies found a relatively high prevalence of

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microhemorrhages in the brains of patients with DLB at postmortem examination,[27] no MR imaging studies examining SHF in patients with DLB have been reported. Although there are a few studies of SHF detected on SWI of control subjects and patients with the limited type of dementia,[21,28] no cohort studies have evaluated the prevalence and topography of SHF on 3T SWI in various types of dementia. The purpose of this study was to investigate the prevalence and topography of SHF on 3T SWI in patients with different dementia subtypes.

MATERIALS AND METHODS

Study Population

All procedures followed the Clinical Study Guidelines of the Ethics Committee of Kumamoto University Hospital and were approved by the internal review board. A complete description of all procedures was provided to the patients, and written informed consent was obtained from them or their caregivers.

We collected data from 592 consecutive patients who attended the Dementia Clinic of the Department of Neuropsychiatry, Kumamoto University Hospital, from January 2008 to February 2010. All patients were examined comprehensively by 2 senior neuropsychiatrists (M.I., M.H.) having sufficient experience in examining patients with dementia. Routine laboratory and standardized neuropsychological tests, such as the Mini-Mental State Examination, brain MR imaging, and single-photon emission tomography were also performed; all results were incorporated into the diagnosis. The diagnoses were made by a team of neuropsychiatrists, neuropsychologists, and radiologists. We excluded 245 patients who met the following exclusion criteria: 1) severe behavioral problems that would make MR imaging difficult; 2) evidence of focal brain lesions on MR imaging such as posttraumatic brain injury or brain tumor; 3) diagnosis of depression, posttraumatic brain injury, idiopathic normal pressure hydrocephalus, or other neurodegenerative diseases (eg, corticobasal degeneration, progressive supranuclear palsy, Parkinson disease with dementia); 4) history of serious psychiatric diseases, substance abuse, or developmental abnormalities; 5) inability to obtain informed consent; or 6) SWI with severe motion or susceptibility artifacts. Consequently, clinical and MR imaging data on 347 patients were used in this prospective study.

All diagnoses were based on pre-established criteria: for AD, fulfilling the criteria for probable AD of the National Institute of Neurologic Disorders and Stroke/Alzheimer Disease and Related Disorders Association[29]; for VaD, fulfilling the criteria for probable VaD of the National Institute of Neurologic Disorders and Stroke/Association Internationale pour la Recherche et l'Enseignement en Neurosciences[30]; for MCI, fulfilling the general criteria of the International Working Group on MCI[31]; for DLB, fulfilling the clinical criteria of the consortium on DLB[32]; and for FTLD, fulfilling the Lund-Manchester criteria for behavioral variant frontotemporal dementia, semantic dementia, or progressive nonfluent aphasia.[33] There were 162 patients (47%) with AD, 51 (15%) with MCI, 41 (12%) with DLB, 33 (10%) with FTLD, and 28 (8%) with VaD. When all clinical investigation results were normal, the patients were recorded as having subjective complaints ($n = 32$, 9%). Hypertension was judged as present when either a systolic pressure of >140 mm Hg or a diastolic pressure of >90 mm Hg was demonstrated on repeat examinations or when a history of treatment for hypertension was present.

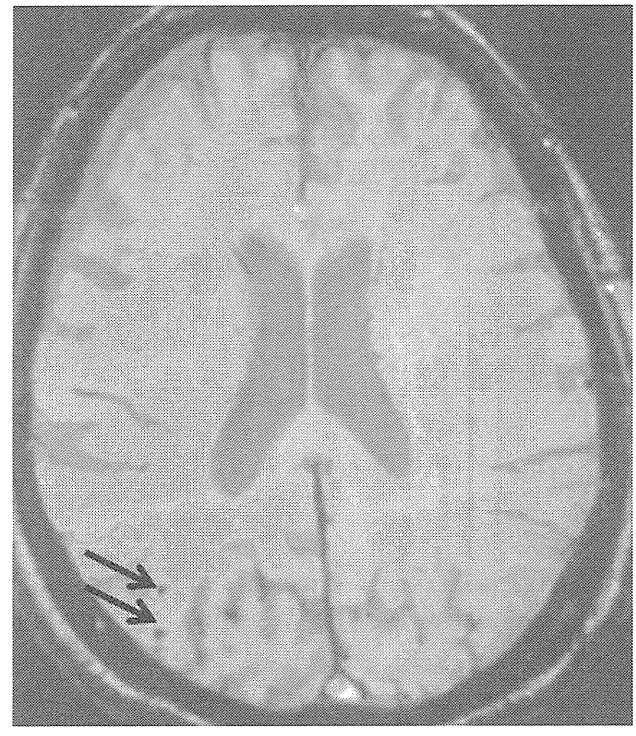

FIG 1. A 78-year-old woman with AD without arterial hypertension. Her Mini-Mental State Examination score was 8. On a 2-mm SWI image, 2 small hypointense foci are seen in the right occipital lobe (*arrows*).

MR Imaging Protocol

MR imaging was performed on a 3T unit (Magnetom Trio; Siemens, Erlangen, Germany). The MR imaging protocol included axial SWI (64 sections per slab, FOV = 230 mm, matrix = 256 × 256, section thickness = 2 mm, voxel size = 0.9 × 0.9 × 2 mm, TE = 20 ms, TR = 27 ms, flip angle = 15°), axial FLAIR, axial T2-weighted turbo spin-echo, 3D T1-weighted magnetization-prepared rapid acquisition of gradient echo sequences and diffusion-weighted imaging, MR spectroscopy, and MR angiography. SWI processing was with software incorporated into the MR imaging system console (Siemens) according to published methods.[34] SWI was constructed by multiplying magnitude by filtered phase images to enhance the susceptibility effect, followed by 16-mm minimum intensity projection reconstruction.

Evaluation of Microbleeds and Other Findings on MR Imaging

On a PACS workstation, all SWI was independently analyzed by 2 neuroradiologists (H.U., T.H.) blinded to clinical data. They reviewed divergent evaluations to reach a consensus. They assessed the number and location of SHF on 2-mm contiguous SWI; 16-mm minimum intensity projection SWI was also used to differentiate SHF from veins. SHF suggesting microbleeds were defined as small (<10 mm diameter), homogeneous, round foci of low signal intensity (Fig 1). Symmetric hypointensities in the globi pallidi or dentate nuclei thought to reflect physiologic calcification or iron deposits, flow void artifacts of pial blood vessels,

Table 1: Patient characteristics and SHF prevalence in each dementia subgroup

	SC (n = 32)	MCI (n = 51)	AD (n = 162)	DLB (n = 41)	FTLD (n = 33)	VaD (n = 28)
Age (mean) (yr)	71 ± 11	76 ± 8	75 ± 9	77 ± 6	68 ± 9	76 ± 8
Men (No.) (%)	6 (19)	22 (43)	54 (33)	20 (49)	14 (42)	14 (50)
MMSE (mean)	28 ± 2	25 ± 2	20 ± 4	19 ± 5	17 ± 7	19 ± 5
Hypertension, (No.) (%)	11 (35)	28 (55)	66 (41)	23 (56)	8 (24)	24 (86)
SHF (No.) (%)	7 (22)	21 (41)	77 (48)	22 (54)	9 (27)	24 (86)
Odds ratio (95% CI)	1 (ref.)	2.5 (0.9–6.8)	3.2 (1.3–7.9)	4.1 (1.5–11.7)	1.3 (0.4–4.2)	21.4 (5.6–82.7)
Adjusted odds ratio[a] (95% CI)	1 (ref.)	2.0 (0.5–8.1)	5.4 (1.2–24.3)[b]	3.1 (1.1–8.8)[b]	1.5 (0.4–5.4)	9.2 (2.0–43.6)[b]

Note:—ref. indicates reference; SC, subjective complaints; MMSE, Mini-Mental State Examination.

[a] Logistic regression analyses adjusted for age, sex, and arterial hypertension were performed in the SC group and each of the dementia groups.

[b] Statistically significant difference, $P < .05$.

and hyposignals inside a lesion compatible with an infarct were not recorded as SHF suggesting microbleeds because they could reflect hemorrhagic transformations. Because SWI has skull base artifacts that limit the view of the base of the brain, we excluded the evaluation of SHF in that location. SHF were counted throughout the brain and categorized as SHF in the basal ganglia/thalamus (including the internal and external capsule), infratentorial (brain stem and cerebellum), and lobar (cerebral cortex and subcortical and periventricular white matter) regions. SHF in the lobar region were subgrouped as frontal, temporal, parietal, and occipital. When at least 1 small hypointense focus was detected, the region or area of the brain was defined as SHF-positive.

With regard to assessment of small-vessel disease on MR imaging, image analysis was performed in consensus by 2 radiologists (H.U., T.H.). Lacunar infarcts were defined as small round- or oval-shaped infarcts of <15 mm in diameter, with high signal intensity on T2-weighted images; low signal intensity on magnetization-prepared rapid acquisition of gradient echo and FLAIR sequences, ruling out enlarged perivascular spaces; and patchy leukoaraiosis. Lacunar infarcts were considered present or absent when there was at least 1 in the basal ganglia/thalamus or brain stem. White matter hyperintensities were graded on FLAIR sequences by using a previously described method as grades 0–3 (absent, punctuate, early confluent, or confluent abnormalities).[35]

Statistical Analyses

Statistical analyses were performed with the Statistical Package for the Social Sciences, Version 19 (SPSS, Chicago, Illinois). Interobserver agreement between 2 readers of SWI with respect to the number of SHF-positive regions was determined by calculating the κ coefficient ($\kappa < 0.20$, poor; $\kappa = 0.21–0.40$, fair; $\kappa = 0.41–0.60$, moderate; $\kappa = 0.61–0.80$, good; $\kappa = 0.81–0.90$, very good; and $\kappa > 0.90$, excellent agreement). Inter- and intragroup differences were assessed with the χ^2, Fisher exact, or Student t test. Group comparisons with respect to the number of SHF were performed by using the Kruskal-Wallis test. Crude and adjusted odds ratios and the accompanying 95% confidence interval were calculated for every diagnostic group by using the patients with subjective complaints as the reference group. To adjust for age, sex, and arterial hypertension, we performed logistic regression analyses between the subjective complaints group and each of the other groups. Differences of $P < .05$ were considered statistically significant.

RESULTS

Prevalence of Microbleeds

Interobserver agreement between 2 readers of SWI with respect to the number of SHF-positive regions was very good ($\kappa = 0.87$). Among the 347 patients, 160 (46.1%) had at least 1 small hypointense focus, 30% had one, 17% had two, 20% had 3–5, and 33% had >5 SHF. The mean patient age at the time of the MR imaging study was 74.3 ± 8.8 years; 130 (37.5%) were men. The mean Mini-Mental State Examination score was 21.0 ± 5.3. The prevalence of SHF differed significantly with age, sex, hypertension, and Mini-Mental State Examination ($P < .05$). Among patients 75 years or older ($n = 204$), 55% harbored SHF compared with 33% in patients younger than 75 years ($n = 143$) ($\chi^2 = 16.27$, $P = .0001$). Men had a higher prevalence than women (57% versus 40%) ($\chi^2 = 9.10$, $P = .0026$); 66% of patients with and 29% of those without hypertension manifested SHF ($\chi^2 = 44.06$, $P < .0001$). There was a significant difference between microbleeds and Mini-Mental State Examination (SHF-positive: mean, 20.3 ± 5.2; microbleed-negative, mean, 21.7 ± 5.4; $t = 2.44$, $P = .015$). The median number of SHF (interquartile range) for each group was subjective complaints = 1 (1–2), MCI = 2 (1–7), AD = 3 (1–7), DLB = 2 (1–5), FTLD = 3 (2–5), and VaD = 15 (2–32).

As shown in Table 1, the prevalence of SHF among the groups differed significantly ($P < .0001$); 86% with VaD, 54% with DLB, 48% with AD, 41% of MCI, and 27% with FTLD harbored SHF. Of our patients with subjective complaints, 22% manifested SHF. Logistic regression analysis, adjusted for age, sex, and hypertension, showed that the adjusted odds ratio (95% CI) for SHF, by using the subjective complaints group as a reference, was 9.2 (2.0–43.6) for VaD, 5.4 (1.2–24.3) for AD, 3.1 (1.1–8.8) for DLB, 2.0 (0.5–8.1) for MCI, and 1.5 (0.4–5.4) for FTLD. There was a statistically significant difference between the subjective complaints and the VaD, AD, or DLB group ($P < .05$).

Topography of Microbleeds

The lobar region was the most frequent site of SHF in each group (Table 2 and Fig 2); 136 (39.2%) of the 347 patients were found to have at least 1 small hypointense focus in this region. The SHF prevalence of lobar, basal ganglia/thalamus, and infratentorial regions was 41%, 15%, and 14% for patients with AD; 44%, 12%, and 17% for those with DLB; and 27%, 6%, and 6% for those with FTLD, respectively. For these 3 groups, there was a significant difference in the SHF prevalence in the lobar versus basal ganglia/thalamus or infratentorial regions ($P < .05$) (Fig 2). This was not

Table 2: Topography of SHF in each dementia subgroup[a]

	Total (n = 347)	SC (n = 32)	MCI (n = 51)	AD (n = 162)	DLB (n = 41)	FTLD (n = 33)	VaD (n = 28)
Whole brain	160 (46)	7 (22)	21 (41)	77 (48)	22 (54)	9 (27)	24 (86)
BG/T region	62 (48)	2 (6)	10 (20)	25 (15)	5 (12)	2 (6)	18 (64)
IT region	64 (18)	2 (6)	11 (22)	23 (14)	7 (17)	2 (6)	19 (68)
Brain stem	32 (9)	1 (3)	7 (14)	9 (6)	2 (5)	1 (3)	12 (43)
Cerebellum	48 (14)	1 (3)	7 (14)	18 (11)	6 (15)	1 (3)	15 (54)
Lobar region	136 (39)	5 (16)	16 (31)	66 (41)	18 (44)	9 (27)	22 (79)
Frontal	69 (20)	2 (6)	9 (18)	30 (19)	9 (22)	5 (15)	14 (50)
Temporal	65 (19)	3 (9)	8 (16)	27 (17)	7 (17)	3 (9)	17 (61)
Parietal	78 (22)	3 (9)	10 (20)	31 (19)	14 (34)	3 (9)	17 (61)
Occipital	63 (18)	1 (3)	8 (16)	32 (20)	5 (12)	4 (12)	13 (46)

Note:—SC indicates subjective complaints; BG/T, basal ganglia/thalamus; IT, infratentorial.

[a] Data are the number of small hypointense foci–positive areas, regions, or brain, with percentages in parentheses.

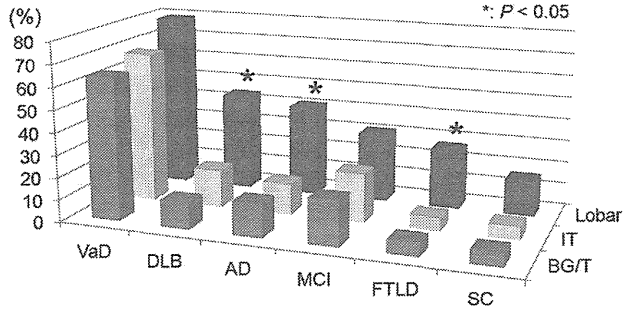

FIG 2. Graph of the topography of small hypointense foci in the different dementia subgroups. Boxes illustrate the percentage of SHF in each region. In each group, the lobar region was the most frequent site of SHF. *In patients with DLB, AD, or FTLD, the prevalence of SHF in the 3 regions of the brain was significantly different ($P < .05$). BG/T indicates the basal ganglia/thalamus region; IT, infratentorial region; Lobar, lobar region.

the case in patients with VaD, MCI, and subjective complaints. There were no statistically significant intragroup differences with respect to involvement of the frontal, temporal, parietal, and occipital areas in any of the groups.

Prevalence of White Matter Hyperintensities and Lacunar Infarcts

The prevalence of white matter hyperintensities and lacunar infarcts in each dementia subgroup is shown in Table 3. Lacunar infarcts were observed in 71 of 347 (20%) patients. In patients with dementia, 82% with VaD, 26% with MCI, 17% with DLB, 16% with AD, and 6% with FTLD harbored lacunar infarcts. Our patients with subjective complaints did not have lacunar infarcts. With regard to white matter hyperintensities, confluent white matter hyperintensities were seen in 42 of 347 (12%) patients. Confluent white matter hyperintensities were observed in 54% of patients with VaD, 16% with MCI, 9% with AD, 5% with DLB, and 3% with FTLD. Of our patients with subjective complaints, 3% manifested confluent white matter hyperintensities.

DISCUSSION

Our 3T SWI study disclosed a high prevalence of SHF among patients; 22% with subjective complaints, 27% with FTLD, 41% with MCI, 48% with AD, 54% with DLB, and 86% with VaD harbored SHF. Ours is the first study documenting the prevalence of SHF on SWI in patients with DLB and FTLD, to our knowledge. In healthy subjects or patients with subjective complaints, the prevalence of SHF depicted on 2D T2*-weighted gradient recalled-echo images ranged from 0% to 21%.[14,23,24] It ranged from 18% to 32% in AD[22,25] and from 65% to 85% in VaD[22,26]; in patients with MCI, it was reported to be 20%.[22] On a 1.5T SWI study by Goos et al,[28] the prevalence of SHF was 30% in subjective complaints, 39% in AD, and 44% in MCI. The sensitivity of SWI for microbleeds was reported to be 3–6 times higher than that of T2*-weighted gradient recalled-echo imaging.[9,36] The depiction of microbleeds on SWI is reported to be more enhanced at 3T and 7T than at 1.5T.[9,37] However, the prevalence of SHF on 3T SWI in our patients did not increase markedly compared with that on 1.5T SWI in the previous report.[28] Although the exact reason is unknown, the difference in patient characteristics (eg, sex, arterial hypertension) might have affected the results.

The relative prevalence of SHF was different among our diagnostic groups. The adjusted odds ratio for SHF by using patients with subjective complaints as the reference was 9.2 for VaD, 5.4 for AD, 3.1 for DLB, 2.0 for MCI, and 1.5 for FTLD. A statistically significant difference was found between the subjective complaints and the VaD, AD, or DLB group. Cordonnier et al[22] reported the relative prevalence of SHF in a cohort of patients attending a memory clinic. Their odds ratio for microbleeds using patients with subjective complaints as the reference was 15.9 for VaD, 2.1 for AD, and 2.3 for MCI. Because there are some differences between their study and ours, it may be difficult to compare the relative prevalence of SHF between the 2 studies. They used T2*-weighted gradient recalled-echo imaging at 1T, and the mean age of their subgroups was lower than ours. In addition, they did not adjust the odds ratios for age, sex, and hypertension, and they did not perform subgroup analysis of patients with DLB and FTLD.

Carbon 11 Pittsburgh Compound B studies revealed high β-amyloid cortical binding in almost all patients with AD,[38,39] in 60% of those with MCI,[39] and in >50% those with DLB[40,41]; in 25% of patients with FTLD, binding was low.[42] Among the neurodegenerative dementia groups, the order of the prevalence of β-amyloid binding was similar to that of the relative prevalence of SHF in our study. On the basis of neuropathologic studies,[23,43] microbleeds are frequently observed in the brains of patients with AD and are mainly related to β-amyloid pathology (cerebral amyloid angiopathy). Moreover, a neuropathologic study showed a relatively high prevalence of β-amyloid pathology and cortical microhemorrhages in the brains of patients with DLB[27,44] and a

Table 3: Prevalence of white matter hypertensities and lacunar infarcts in each dementia subgroup[a]

	Total (n = 347)	SC (n = 32)	MCI (n = 51)	AD (n = 162)	DLB (n = 41)	FTLD (n = 33)	VaD (n = 28)
White matter hypertensities							
Absent	32 (9)	5 (16)	3 (6)	17 (10)	1 (2)	6 (18)	0 (0)
Punctate	166 (48)	17 (53)	28 (55)	81 (50)	19 (46)	17 (52)	4 (14)
Early confluent	107 (31)	9 (28)	12 (24)	49 (30)	19 (46)	9 (27)	9 (32)
Confluent	42 (12)	1 (3)	8 (16)	15 (9)	2 (5)	1 (3)	15 (54)
Lacunar infarcts	71 (20)	0 (0)	13 (26)	26 (16)	7 (17)	2 (6)	23 (82)

Note:—SC indicates subjective complaints; WMH, white matter hyperintensities.

[a] Data are the number or presence of MR imaging findings, with percentages in parentheses.

low prevalence of β-amyloid pathology in patients with FTLD.[27,45] We suggest that SHF on SWI may be associated with β-amyloid pathology in these diseases.

In all of our patient groups, the lobar region was the most frequent site of SHF. Although in patients with AD, DLB, and FTLD, there was a significant predilection for the lobar region, this was not the case in patients with VaD, MCI, and subjective complaints. SHF in the basal ganglia/thalamus or infratentorial region tend to be associated with vascular risk factors.[11] In patients with MCI, the distribution pattern of SHF was more similar to VaD than AD. Staekenborg et al[46] demonstrated that microbleeds, lacunar infarctions, and severe white matter hyperintensities in MCI were associated with progression to non-AD dementia such as VaD. In our patients with MCI, lacunar infarctions and confluent white matter hypertensities were seen in 26% and 16% of patients, respectively. Although we did not evaluate the progression of MCI to dementia in this study, the patients with small-vessel disease may have affected the distribution pattern of the microbleeds in MCI.

We observed that in patients with VaD, their SHF were almost equally distributed among the lobar, basal ganglia/thalamus, and infratentorial regions. This SHF distribution may be explained as follows: Because cerebral amyloid angiopathy has a lobar predilection and is associated with advancing age,[47] it may have coexisted with lipohyalinosis in our elderly patients with VaD. Then, lobar SHF do not include periventricular or deep white matter according to the Microbleed Anatomical Rating Scale.[48] Because we defined periventricular or deep white matter SHF as a lobar region, the definition may have affected the anatomic prevalence. In addition, our observers scaled a region as SHF-positive if they identified at least 1 small hypointense focus in an area or region. This assessment method may have influenced our results.

The distribution pattern of the microbleeds in patients with FTLD was similar to that in AD. A study of postmortem MR imaging by De Reuck et al[49] demonstrated that microbleeds in patients with FTLD had a lobar prevalence. Their pathologic study revealed that cerebral amyloid angiopathy does not explain all of the microbleeds in the brain. Although the exact causes of microbleeds in patients with FTLD are not known, they suggested that microbleeds were associated with disturbances of the blood-brain barrier due to the severity of neurodegeneration.

Our study confirms earlier reports that documented the lobar distribution of SHF in AD.[19,22,23,25] According to Pettersen et al,[19] in patients with AD, SHF are primarily found at occipital sites. Among our patients with AD, there was no significant difference in the location of SHF in frontal, temporal, parietal, and occipital areas. When our observers identified at least 1 small hypointense focus, the area was recorded as SHF-positive. Our evaluation method differed from theirs, and this discrepancy may account for the difference. We did not evaluate the degree of accumulation of SHF in a specific area of the brain.

In our study, SHF were topographically similar in patients with AD and DLB because they manifested a predilection for the lobar region. We cannot explain the apparent preference for this region in patients with DLB. Earlier neuropathologic studies showed a relatively high prevalence of AD pathology and lobar microhemorrhages, including cerebral amyloid angiopathy pathology, in individuals with DLB.[27,44] These findings support ours. Because our DLB group was of the most advanced mean age, the age factor might have played a role in the induction of cerebral amyloid angiopathy pathology in this group.

Our study has some limitations. First, patients with subjective complaints served as the control. In our subjective complaints group, lacunar infarcts were not observed and the frequency of confluent white matter hyperintensities was very low. Therefore, we think that the effect of small-vessel disease in our patients with subjective complaints was small. The prevalence of lobar SHF among elderly healthy controls with a mean age of 74.6 years reported by Yates et al,[21] who used 3T SWI, was similar to ours. The mean age of our patients with subjective complaints was slightly lower than theirs. Subjective memory symptoms might be related to preclinical AD and, therefore, may be artificially increasing the number of microbleeds expected in the control group. Second, the number of patients in our subgroups was relatively small, and 3T SWI studies on larger populations are needed to elucidate the prevalence and topography of SHF in patients with dementia. Third, our study had a lack of pathologic confirmation of microbleeds. Schrag et al[50] reported a correlative study of 3T SWI-identified hypointense foci to tissue pathology in postmortem brains of patients with AD. The correlation showed a variety of cerebral amyloid angiopathy–related pathologies: acute microhemorrhage, hemosiderin residua of old hemorrhages, and small lacunes ringed by hemosiderin. Their study suggests that hypointense foci on SWI in patients with AD indicate a variety of cerebral amyloid angiopathy–related pathologies. Finally, all diagnoses were based on pre-established clinical criteria without biomarker support of amyloid pathology or pathologic confirmation. This may create some errors in the associations.

CONCLUSIONS

The prevalence of SHF suggesting microbleeds on 3T SWI among the groups differed significantly; 86% of those with VaD, 54% of those with DLB, 48% of those with AD, 41% of those with MCI, 27% of those with FTLD, and 22% of those with subjective complaints harbored SHF. The adjusted odds ratio for SHF by using the subjective complaints group as a reference was 9.2 for VaD, 5.4

for AD, 3.1 for DLB, 2.0 for MCI, and 1.5 for FTLD. Patients with AD, DLB, and FTLD manifested a lobar predilection. Our findings provide further evidence not only for the involvement of vascular factors in these neurodegenerative diseases but also that SHF may even relate to amyloid pathology in specific diseases. Further studies are necessary to investigate the relationship of microbleeds to the disease pathogenesis, disease progression, and prognosis.

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Donepezil for Dementia with Lewy Bodies: A Randomized, Placebo-Controlled Trial

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on behalf of the Donepezil-DLB Study Investigators

Objective: Because cholinergic deficits are prominent in dementia with Lewy bodies (DLB), we investigated the effects of a cholinesterase inhibitor, donepezil, in such patients in a randomized, double-blind, placebo-controlled exploratory phase 2 trial.
Methods: One-hundred forty patients with DLB, recruited from 48 specialty centers in Japan, were randomly assigned to receive placebo or 3, 5, or 10mg of donepezil hydrochloride daily for 12 weeks (n = 35, 35, 33, and 37, respectively). Effects on cognitive function were assessed using the Mini-Mental State Examination (MMSE) and several domain-specific neuropsychological tests. Changes in behavior were evaluated using the Neuropsychiatric Inventory, caregiver burden using the Zarit Caregiver Burden Interview, and global function using the Clinician's Interview-Based Impression of Change-plus Caregiver Input (CIBIC-plus). Safety measures included the Unified Parkinson's Disease Rating Scale part III.
Results: Donepezil at 5 and 10mg/day was significantly superior to placebo on both the MMSE (5mg: mean difference, 3.8; 95% confidence interval [CI], 2.3–5.3; $p < 0.001$; 10 mg: mean difference, 2.4; 95% CI, 0.9–3.9; $p = 0.001$) and CIBIC-plus ($p < 0.001$ for each); 3mg/day was significantly superior to placebo on CIBIC-plus ($p < 0.001$), but not on the MMSE ($p = 0.017$). Significant improvements were found also in behavioral measures ($p < 0.001$) at 5 and 10mg/day and caregiver burden ($p = 0.004$) at 10 mg/day. The safety results were consistent with the known profile of donepezil and similar among groups.
Interpretation: Donepezil at 5 and 10mg/day produces significant cognitive, behavioral, and global improvements that last at least 12 weeks in DLB patients, reducing caregiver burden at the highest dose. Donepezil is safe and well tolerated.

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Dementia with Lewy bodies (DLB) is a common form of dementia in the elderly, and constitutes the second largest group of patients with dementia after Alzheimer disease (AD).[1] The core clinical features of DLB include neuropsychiatric symptoms and motor symptoms of parkinsonism as well as cognitive impairment characterized by deficits of attention, executive function, and visual perception.[2] Fluctuating cognition, hallucinations, and delusions are major sources of difficulties and distress for both patients and caregivers. The motor and autonomic features further impair activities of daily living and lead to poorer quality of life.[3,4] However, pharmacological management of DLB remains challenging, because it is complicated by the risk of adverse reactions to medication.[5] Treatments for one aspect of the disease may exacerbate other symptoms. It is well recognized that DLB patients can be exquisitely sensitive to antipsychotic agents and can develop life-threatening sensitivity reactions.[6] Antiparkinson medication given to improve motor symptoms can exacerbate neuropsychiatric symptoms such as hallucinations. There are no approved treatments for DLB.

Cholinergic loss in DLB is associated with deficits in attention and cognition, and also with neuropsychiatric symptoms.[7] Neuropathological and neuroimaging studies have demonstrated that cholinergic neurotransmission is more defective in DLB than in AD.[8] Although cholinergic losses in DLB affect both brainstem and basal

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The Donepezil-DLB Study Investigators are listed in the Appendix on page xxx.

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forebrain presynaptic nuclei, in contrast to AD, postsynaptic cortical muscarinic and nicotinic receptors are more functionally intact,[9] suggesting that cholinesterase inhibitors (ChEIs) may be potent for DLB. Case reports and open-label studies have demonstrated the benefit of galantamine, rivastigmine, and donepezil on cognitive and behavioral symptoms in DLB.[10–14] However, only 1 randomized placebo-controlled trial (RCT) has been reported, in which it was suggested that rivastigmine improved attentional and behavioral symptoms.[15] Memantine, an N-methyl-D-aspartate receptor antagonist, was also tested in 2 RCTs including DLB patients; however, the results were equivocal.[16,17] Therefore, there is very little evidence for pharmacotherapy in this group. The aim of this phase 2 study was to exploratively investigate the efficacy and safety of donepezil hydrochloride, in 3 different doses compared to placebo, in patients with DLB. This study was registered as number NCT00543855.

Patients and Methods

Patients

Patients who met the consensus diagnostic criteria[2] for probable DLB were recruited from 48 psychiatric or neurological specialty centers throughout Japan from October 2007 to February 2010. Diagnosis of each patient was validated after discussion by the central committee. Outpatients (≥50 years old) with mild to moderate–severe dementia (10–26 on the Mini-Mental State Examination [MMSE][18] and Clinical Dementia Rating[19] ≥0.5) and with behavioral symptoms (Neuropsychiatric Inventory-plus [NPI-plus] ≥8) were eligible. NPI-plus is a 12-item version of the NPI, with the original 10 items supplemented by 2 DLB-relevant domains of sleep and cognitive fluctuation.[11,20,21] Patients had caregivers who routinely stayed with them at least 3 days per week and 4 hours per day, provided information for this study, assisted compliance with treatment, and escorted patients to required visits.

Exclusion criteria included Parkinson disease diagnosed at least 1 year prior to the onset of dementia; focal vascular lesions on magnetic resonance imaging or computed tomography that might cause cognitive impairment; other neurological or psychiatric diseases; clinically significant systemic disease; complications or history of severe gastrointestinal ulcer, severe asthma, or obstructive pulmonary disease; systolic hypotension (<90mmHg); bradycardia ($<50 m^{-1}$); sick sinus syndrome; atrial or atrioventricular conduction block; QT interval prolongation (≥450 milliseconds); hypersensitivity to donepezil or piperidine derivatives; severe parkinsonism (Hoehn and Yahr score ≥ IV)[22]; and treatment with ChEIs or any investigational drug within 3 months prior to screening. ChEIs, antipsychotic agents, and antiparkinson drugs other than L-dopa or dopamine agonists were not allowed during the study.

Written informed consent was obtained from the patient (if at all possible) and his/her caregiver before initiating the study procedures. The study was conducted in accordance with the principles of the Declaration of Helsinki. The protocol was approved by the institutional review board at each center.

Randomization and Masking

This was a multicenter, randomized, double-blind, parallel-group, placebo-controlled study. Treatment lasted 14 weeks, including a 2-week prerandomization period followed by a 12-week randomization period. All participants were given placebo tablets during the prerandomization period, after which the patients were randomly assigned in a 1:1:1:1 ratio to placebo, 3, 5, or 10mg of donepezil. The randomization list was computer-generated using a randomized block design to allocate several blocks (size 4) to each center. Patients were sequentially assigned to the lowest randomization number available at the time of each enrollment at each center. The randomization list was securely managed by an allocation officer, who was independent of all parties concerned with the study, at Bellsystem24, Tokyo, Japan, until study completion. Access to the list was not allowed except in emergency. Study personnel and participants were unaware of the treatment assignment. During the study period, the code was broken for 2 patients: 1 each in the placebo and 3mg arms because of serious adverse events (pelvic fracture and subarachnoid hemorrhage, respectively).

Patients received 2 study drug tablets, which were composed of a combination of 3mg, 5mg, or matched placebo tablets with the same physical appearance, once daily in the morning. Dosage was titrated at the beginning of the randomization period in the 5 and 10mg groups. In the 5mg group, treatment began with 3mg for 2 weeks, and then the dose was increased to 5mg. The 10mg group started with 3mg for 2 weeks, followed by 5mg for 4 weeks, after which the 10mg dose was provided for 6 weeks. The dose was escalated after patient safety was confirmed by telephone interview.

Procedures

This study had no formal predefined primary endpoint. However, cognition, behavior, global function, and caregiver burden were determined as core efficacy outcomes prior to the study initiation.

Efficacy was assessed at baseline and weeks 4, 8, and 12. Cognition was assessed using the MMSE.[18] In addition, 3 cognitive domains (attentive, executive, and visuoperceptual functions) relevant to DLB were assessed using the Wechsler Memory Scale-Revised (WMS-R) attention/concentration subscale,[23] the Verbal Fluency test (category and letter),[24] the Wechsler Adult Intelligence Scale (WAIS-III) symbol digit modalities subscale,[25] and the Visual Perception Test for Agnosia form discrimination and overlapping figure identification subscales.[26]

Behavior was assessed using the NPI-plus (the original NPI-10 consisting of 10 behavioral domains; ie, delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, and aberrant motor behavior, supplemented by 2 DLB-relevant domains of sleep and cognitive fluctuation).[11,20,21] The questions in the cognitive fluctuation domain were arranged according to those reported in the literature.[27,28] In addition to the NPI-10 and each

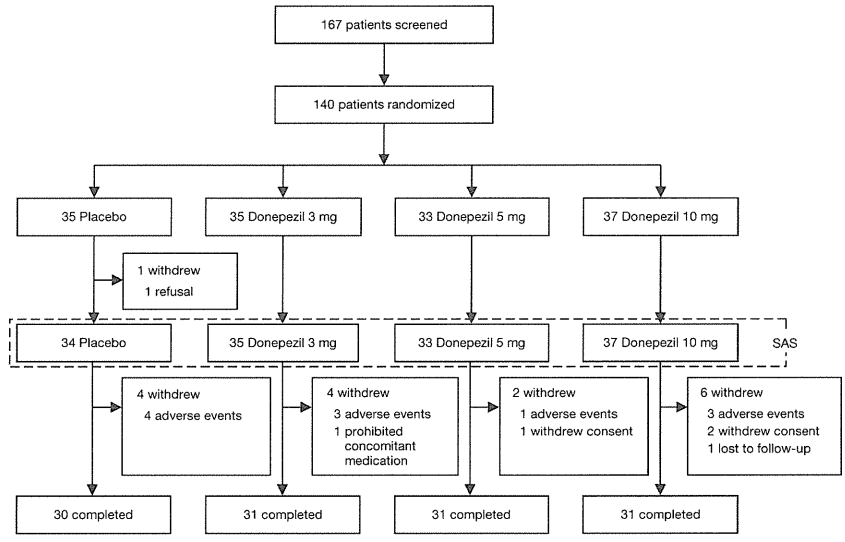

FIGURE 1: Patient disposition. SAS = safety analysis set.

domain of the NPI-plus, a 2-item subscore (NPI-2) was calculated as the sum of scores for hallucinations and cognitive fluctuation, which correspond to the core features of DLB in the consensus criteria, and a 4-item subscore (NPI-4) calculated as the sum of scores for delusions, hallucinations, apathy, and depression, which were reported as the main DLB symptom cluster in the previous rivastigmine study.[15]

Changes in global clinical status were assessed by an experienced clinician who was not involved in patient management or other assessments, using the Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC-plus), with 7 grades ranging from Marked Improvement to Marked Worsening.[29]

Caregiver burden was assessed using the Zarit Caregiver Burden Interview (ZBI), which evaluates the physical, psychological, and social consequences of caring activities.[30] The ZBI contains 22 items scored from 0 (best) to 4 (worst), from which a total score from 0 to 88 is calculated.

Motor function was assessed as a safety measure using the Unified Parkinson's Disease Rating Scale (UPDRS) part III at baseline and week 12.[31] Safety was also assessed on the basis of adverse events (AEs), vital signs, electrocardiogram, and laboratory tests.

Statistical Analyses

The sample size was originally defined as 160 patients (40 in each arm) on the basis of feasibility considerations. However, because of recruitment difficulties, the sample size was reduced to 140. Although no formal calculation of power was performed, this number of patients should have provided a roughly 80% power to detect a 40% difference in responder rates (see definition below) between the active and placebo arms with a 2-sided significance level of 0.0167.

The safety analysis set comprised all patients who received at least 1 dose and had a postbaseline safety assessment. Efficacy analyses were performed on the full analysis set, which consisted of all patients who had at least 1 valid postbaseline assessment on any of the efficacy scales, with the last observation carried forward (LOCF).

Imbalances in baseline demographics and background characteristics were assessed by analysis of variance (ANOVA), Kruskal-Wallis test, or chi-square test, with a 2-sided significance level of 0.15.

For efficacy, mean changes from the baseline in each outcome measure other than CIBIC-plus were compared between each active group and placebo by both Student t test and analysis of covariance (ANCOVA), with baseline values (sex, weight, and each test score) as covariates. In addition to the LOCF analysis, the mixed-effect model for repeated measures was applied to analyze data with dropouts as the secondary approach. For CIBIC-plus, the Wilcoxon rank sum test was used to compare the grade distributions between each active group and placebo. In addition, the MMSE and CIBIC-plus were analyzed by number of responders, defined as a $\geq$3 point improvement on the MMSE and as "minimal improvement" or better on the CIBIC-plus. Fisher exact probability test was used to compare each active group to placebo. The dose–response relationship (linear or 5mg saturation) across the 3 doses was also analyzed, as a secondary analysis, by ANOVA with contrasts for the MMSE and NPI, and by Cochran–Armitage test with contrasts for the CIBIC-plus. Significance levels were set at 2-sided 0.0167 for comparison with placebo (multiplicity adjustment by Bonferroni method) and 2-sided 0.05 for trend analysis.

The incidence of AEs was calculated, and group differences were examined by Fisher exact probability test. For laboratory parameters and vital signs, descriptive statistics and frequency distributions were calculated. UPDRS part III scores were compared between each active group and placebo by both Student t test and ANCOVA, with baseline values as covariates. Significance level was set at 2-sided 0.05 for safety analysis.

All analyses were made on SAS version 9.1.3 (SAS Institute, Cary, NC).

TABLE 1: Baseline Characteristics of Patients (Full Analysis Set)

Characteristic	Treatment Group				*p*
	Placebo, n = 32	Donepezil			
		3mg, n = 35	5mg, n = 32	10mg, n = 36	
Age, yr	78.6 (4.7)	79.6 (4.5)	77.9 (6.8)	78.6 (6.1)	0.663
Sex					0.001
Male	9 (28.1%)	17 (48.6%)	16 (50.0%)	4 (11.1%)	
Female	23 (71.9%)	18 (51.4%)	16 (50.0%)	32 (88.9%)	
Weight, kg	47.5 (9.0)	51.3 (10.1)	49.6 (9.6)	44.9 (9.2)	0.035
CDR					0.643
0	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
0.5	8 (25.0%)	10 (28.6%)	12 (37.5%)	9 (25.0%)	
1	20 (62.5%)	18 (51.4%)	16 (50.0%)	20 (55.6%)	
2	3 (9.4%)	7 (20.0%)	4 (12.5%)	7 (19.4%)	
3	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Core features					
Fluctuating cognition	31 (96.9%)	34 (97.1%)	30 (93.8%)	35 (97.2%)	0.856
Visual hallucination	28 (87.5%)	28 (80.0%)	26 (81.3%)	29 (80.6%)	0.845
Parkinsonism	28 (87.5%)	31 (88.6%)	27 (84.4%)	29 (80.6%)	0.781
Hoehn & Yahr					
I	5 (15.6%)	5 (14.3%)	2 (6.3%)	5 (13.9%)	
II	7 (21.9%)	14 (40.0%)	12 (37.5%)	9 (25.0%)	
III	16 (50.0%)	12 (34.3%)	13 (40.6%)	15 (41.7%)	
IV, V	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Suggestive features					
REM sleep behavior disorder	11 (34.4%)	17 (48.6%)	12 (37.5%)	12 (33.3%)	0.542
Severe neuroleptic sensitivity	3 (9.4%)	1 (2.9%)	0 (0.0%)	3 (8.3%)	0.261
Supportive features					
Repeated falls and syncope	8 (25.0%)	7 (20.0%)	6 (18.8%)	8 (22.2%)	0.933
Transient loss of consciousness	5 (15.6%)	2 (5.7%)	4 (12.5%)	0 (0.0%)	0.083
Severe autonomic dysfunction	7 (21.9%)	5 (14.3%)	7 (21.9%)	8 (22.2%)	0.809
Hallucinations in other modalities	10 (31.3%)	14 (40.0%)	12 (37.5%)	17 (47.2%)	0.600
Systematized delusion	9 (28.1%)	11 (31.4%)	11 (34.4%)	13 (36.1%)	0.905
Depression	11 (34.4%)	16 (45.7%)	9 (28.1%)	19 (52.8%)	0.160
Low occipital perfusion[a]	18 (85.7%)	19 (82.6%)	19 (82.6%)	18 (85.7%)	
Low MIBG uptake[a]	6 (100.0%)	7 (87.5%)	11 (91.7%)	7 (63.6%)	