前頭側頭型認知症(痴呆)

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前頭葉と側頭葉前方部に病変の主座を有する変性(性)認知症(痴呆)性疾患の臨床症候群である前頭側頭型認知症(痴呆)(FTD)の歴史的変遷を含めた概念，頻度，診断基準，画像診断，ならびに治療とケアについて概説した．

概念の変遷(図)[1]

ピック病は病理診断基準をめぐって種々の議論が続いたが，1980年代には再び前方型認知症(痴呆)が注目されるようになり，その後1994年にManchesterとLundのグループが共同で，変性部位に忠実に前頭側頭型認知症(FTD)という新しい概念の臨床ならびに病理学的診断基準を提唱した．これにより，ピック病にまつわる病理学的混乱に捕われることなく臨床症状と画像所見から，脳の前方部に原発性の変性を有する非アルツハイマー型の変性(性)認知症疾患を包括的に捉えられるようになった．このFTDという概念の提出以降，前方型認知症に関する臨床研究は飛躍的に増加した．FTDという字面からは，側頭葉優位の萎縮を呈する前頭側頭部脳変性症も含まれるように思われるが，FTDでは側頭葉の萎縮は前方部にとどまるとされ，初期から失語症状が前景に立つことはないとされている．したがって，FTDという概念の最も大きな問題点は，これまでピック病の前頭葉優位型，側頭葉優位型として同一の疾患とみなされていたものがまったく異なる臨床概念に分類される可能性が生じてきたことであり，その批判に応えるかたちで，1996年にManchesterのグループは，前頭－側頭葉に原発性の変性を有する前頭－側頭部脳変性症例に対し**前頭側頭葉変性症**(FTLD)という包括的概念を新たに提唱した．

頻　度[2]

ロンドンの2地域の初老期発症の認知症(痴呆)を対象とした地域調査では，認知症と診断された185名のうち，アルツハイマー病(AD)34％に対し，FTDは12％であった．Cambridgeのグループが行った最近の地域調査では，初老期発症の認知症108名のうち，AD 25％に対して，FTLDは15.7％であった．また，FTLDのうち29％が，家族歴を有していた．医療機関の受診者を対象とした場合，われわれの高次脳機能外来を受診した連続例の認知症患者330名のうち，ADは215名(65.1％)，脳血管性認知症(痴呆)(VD)は33名(10.0％)，FTLD 42名(12.7％)であった．このうち，FTDは22例であった．したがって，FTDは初老期認知症(痴呆)や専門外来を受診する認知症患者においては，ADと比較してもけっしてまれではない．本邦の報告例には，FTDP-17(本書118頁「FTDP-17」参照)として報告されている少数例を除いて，従来からの報告通り家族歴を有するものは含まれておらず，高頻度に家族歴を認める欧米との大きな違いがある．

診断基準

表は，1998年に示されたFTDの診断基準[3]の一部を抜粋したものである．一応操作的な(operational)診断基準の形式になってはいるが，剖検例による病理学的な妥当性は検証されていない．また，必須とされる主要診断的特徴は，ADやDLBなどの他の認知症性疾患の診断基準とは異なり，専門医以外には抽象的でわかりにくい内容になっているが，全体的には，本書「ピック病」(110頁)

用語解説――前頭側頭葉変性症(fronto-temporal lobar degeneration)
前頭－側頭葉に原発性の変性を有する前頭－側頭部脳萎縮症例に対する包括的な概念である．FTD，Progressive non-fluent Aphasia(PA)，Semantic Dementia(SD)の3型の臨床症候群が含まれる．

Recommended Readings
❶ Ikeda K: Neuropathology 20: 76-82, 2000
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❸ 繁信和恵ほか：生物学的アプローチによる精神科ケア．南江堂，東京，2001, pp.159-174
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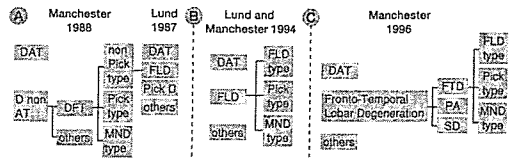

図　変性疾患による認知症の分類の変遷(前方型認知症を中心に)
DAT : Dementia of Alzheimer Type, D non AT : Dementia of non-Alzheimer Type, DFT : Dementia of Frontal Lobe Type, FTD: Fronto-Temporal Dementia, FLD type : Frontal Lobe Degeneration type, MND type : Motor Neuron Disease type, PA : Progressive non-fluent Aphasia, SD : Semantic Dementia

表　FTD の診断的特徴

性格変化と社会的行動の障害(disordered social conduct)が，発症から疾患の経過を通して有意な特徴である． 知覚，空間的能力，行為，記憶といった道具的認知機能は正常か，比較的良好に保たれる．
I 主要診断特徴(すべて必要)
A 潜行性の発症と緩徐な進行 B 社会的対人行動(interpersonal conduct)の早期からの障害 C 早期からの自己行動の統制(regulation of personal conduct)障害 D 早期からの情意鈍麻(emotional blunting) E 早期からの病識の欠如
II 支持的診断特徴
A 行動異常 1. 自己の衛生や身なりの障害 2. 精神の硬直化と柔軟性のなさ 3. 易転導性(distractibility)と維持困難(impersistence) 4. 口唇傾向と食餌嗜好の変化 5. 保続的行動と常同行動 6. 使用行動
III FTLDに共通する支持的診断特徴
A 65歳以前の発症．親兄弟に同症の家族歴 B 球麻痺，筋力低下と萎縮，筋線維束攣縮．保続的行動と常同行動

(文献3より引用)

の項で概説した従来からのピック病の臨床特徴がまとめられている．

病理学的診断基準の問題点に関しては，Ikeda (2000)の総説を参照されたいが，ピック球を有さないが高度のグリオーシスを有する限局性萎縮例は，とりあえずピック型に分類しておくとされ，問題を先送りしている．また，神経病理学的には前頭葉変性型(frontal lobe degeneration type：FLD 型)，ピック型(Pick type：Pick 型)，運動ニューロン病型(motor neuron disease type：MND 型)に分類され，従来の前頭葉優位型ピック病に相当するピック型，神経症状を合併する MND 型に対して，FLD 型に関してはピック型とは臨床症状による鑑別はできないという見解を示している．本邦では，これまでにピック型ならびに MND 型(湯浅・三山病)の報告は多数あるものの，遺伝負因の強いとされる FLD 型と考えられる症例の報告は少なく，なお議論が多い．

画像診断

古典的なピック病(ピック型)に関しては，脳の前方部の限局性葉性萎縮を捉えられるという点で，CT，MRI は有用である．さらに，MRI ではピック型でみられる強いグリオーシスを反映して，T 2 強調画像とプロトン強調画像における白質の信号強度が前頭側頭部で増加するといわれている．機能画像では，萎縮部位に対応するより広範囲の血流・代謝の低下が認められる．一方，FLD 型については，脳萎縮はあまり目立たないが，SPECT や PET 画像上著明な前頭部の血流，代謝の低下を示すので，機能画像所見が診断には重要となる．

治療とケア[4,5]

FTDは，上記のような脱抑制などの特徴的な行動異常により，処遇の最も困難な疾患と考えられている．

有効な薬物療法はなく，興奮や暴力，問題行動に対して抗精神病薬の投与が余儀なくされてきた．しかし，最近になって選択的セロトニン再取り込み阻害薬(SSRI)が，FTD ないし FTLD の脱抑制，常同行動，食行動異常に効果があるという報告がなされている．これらの研究は小規模なオープン試験であり十分な検討ができているとは言い難いが，各種 SSRI の強迫性障害(OCD)や大食症に対する有効性は確認されており，FTD の常同・強迫症状や食行動異常に対しても効果が期待される．また，相対的セロトニン再取り込み阻害薬についても，FTD の反響・反復行動に対する効果が報告されている．

FTD 患者のケアは上述のような精神症状や行動異常によって，AD 患者のそれと比べてはるかに困難を伴うことが多い．しかし AD と異なり，行為自体の解体が無いことや本質的には記憶が保たれていることがケアを検討するうえでは重要である．また常同行動や被影響性の亢進など，特徴的な症状を利用することが可能である．

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関連事項

非アルツハイマー型変性認知症(痴呆) ▶▶ 104 頁
ピック病 ▶▶ 110 頁
ALS を伴う認知症(痴呆)(湯浅・三山型) ▶▶ 112 頁
FTDP-17 ▶▶ 118 頁
非薬物療法 ▶▶ 276 頁

Original article

Nuclear Medicine Communications

Functional interactions between entorhinal cortex and posterior cingulate cortex at the very early stage of Alzheimer's disease using brain perfusion single-photon emission computed tomography

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Objective The cause of the reduced regional cerebral blood flow (rCBF) in the posterior cingulate cortex in the early stage of Alzheimer's disease has not been clarified. In Alzheimer's disease, the posterior cingulate cortex itself shows little neuropathologic degeneration, and a hypothesis explaining such a discrepancy is that the functional impairment in the posterior cingulate cortex reflects remote effects caused by degeneration in distant but connected areas, such as the entorhinal cortex. To test the hypothesis, we investigated the functional connectivity between the entorhinal cortex and posterior cingulate cortex.

Methods Sixty-one patients with probable Alzheimer's disease at a very early stage and 61 age-matched healthy controls underwent both brain structural magnetic resonance imaging (MRI) and single-photon emission computed tomography (SPECT). Voxel-based morphometry was performed on MRI data to identify clusters of significantly reduced grey matter concentration in patients with Alzheimer's disease relative to controls, which were set as volumes of interest (VOIs) for correlation analyses of SPECT images. We then used adjusted rCBF values in the VOIs as covariates of interest in statistical parametric mapping.

Results Voxel-based morphometry demonstrated a significant reduction in grey matter concentration in the bilateral entorhinal cortex in Alzheimer's disease. A positive correlation between rCBF in the entorhinal cortex as VOI and that in the limbic and paralimbic systems, including the posterior cingulate cortex, anterior cingulate cortex, lingual gyri and left middle temporal gyrus ($P<0.001$), was observed in Alzheimer's disease. Control subjects also showed a similar correlation in the limbic and paralimbic systems, but not in the posterior cingulate cortex.

Conclusion These results indicate that rCBF changes in the posterior cingulate cortex may be closely related to those in the entorhinal cortex in patients with Alzheimer's disease, thereby supporting the 'remote effect' hypothesis. *Nucl Med Commun* 27:151–156 © 2006 Lippincott Williams & Wilkins.

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Keywords: Alzheimer's disease, mild cognitive impairment, regional cerebral blood flow, SPECT

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Introduction

Alzheimer's disease is a neurodegenerative disorder leading to amnesia, cognitive impairment and dementia, and is associated with pathological neuronal changes resulting from the accumulation of β-amyloid plaques and neurofibrillary degeneration (NFD) [1]. Delacourte *et al.* [2] reported that NFD with paired helical filaments tau was systematically present in varying amounts in the hippocampal region, not only in the very early stage of Alzheimer's disease, but also in non-demented aged subjects. When NFD was found in other brain areas, it was always along a stereotypical, sequential, hierarchical pathway, and the progression was categorized into several stages according to the brain regions affected. According to this report, the posterior cingulate cortex is not affected by NFD at the early stage of Alzheimer's disease.

Morphological magnetic resonance imaging (MRI) studies have demonstrated that higher atrophy rates in the medial temporal regions, such as the entorhinal cortex and hippocampus, are observed in the very early stage of

Alzheimer's disease [3–6]. Moreover, recent advances in computer-assisted statistical imaging analysis have revealed that subjects with very mild Alzheimer's disease typically show abnormal metabolic and regional cerebral blood flow (rCBF) patterns even at the preclinical stage. Using glucose metabolism positron emission tomography (PET) with a voxel-by-voxel statistical analysis, Minoshima *et al.* [7] reported that the earliest changes observed in very mild Alzheimer's disease occur in the posterior cingulate cortex. This unexpected finding has been replicated by other groups using both glucose metabolism measurements with PET and less sophisticated measurement techniques, such as rCBF measurements with single-photon emission computed tomography (SPECT). Bradley *et al.* [8] reported that reduced perfusion appeared between the entorhinal and limbic stages pathologically defined by Braak and Braak [1] in the posterior cingulate cortex, as well as in the anterior temporal lobe, subcallosal area and precuneus. Our previous rCBF SPECT studies demonstrated significantly decreased rCBF in the posterior cingulate cortex and precunei bilaterally in patients with mild cognitive impairment (MCI), proposed by Petersen *et al.* [9], when compared with controls at least 2 years before they satisfied a clinical diagnosis of Alzheimer's disease [10,11]. We also reported a diagnostic value of reduced rCBF in the posterior cingulate cortex to assist in discriminating between patients with probable Alzheimer's disease at the very early stage and age-matched controls before and after partial volume correction [12]. Furthermore, a PET study demonstrated hypometabolism of the posterior cingulate cortex in young subjects with a high genetic risk of developing Alzheimer's disease [13].

The fact that the posterior cingulate cortex itself shows little degeneration neuropathologically despite the significant reduction in its rCBF or glucose metabolism has been attributed to the possibility that the posterior cingulate cortex reflects remote effects caused by degeneration in distant but connected areas, such as the entorhinal cortex. In a non-human study, Baleydier and Mauguiere [14] reported that, in the monkey, the posterior cingulate cortex receives inputs from the parahippocampal gyrus, especially the entorhinal cortex, as well as from the subiculum and presubiculum. Furthermore, Meguro *et al.* [15] reported that lesions of the entorhinal cortex cause long-lasting, reduced cerebral glucose metabolism in the parietal, temporal and occipital associative cortices, posterior cingulate cortex and the hippocampal regions. Few in-vivo human studies on the functional connections between the entorhinal cortex and the rest of the brain, using neuroimaging techniques, have been published [16], although the association of atrophy of the medial temporal lobe with reduced rCBF in the posterior parietotemporal cortex has been reported in patients with a clinical and pathological diagnosis of Alzheimer's disease [17].

In the present study, using MRI and SPECT, we examined the issue of whether functional connectivity exists between the posterior cingulate cortex and entorhinal cortex in humans, and whether the posterior cingulate cortex is subject to remote effects caused by degeneration in distant but connected areas, such as the entorhinal cortex, in the very early stage of Alzheimer's disease.

Materials and methods

We studied retrospectively 61 patients (32 men and 29 women) with MCI who showed progressive cognitive decline and eventually fulfilled the diagnosis of probable Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria [18] during the subsequent follow-up period of 2–6 years. They were recruited from 350 patients complaining of memory impairment in an Outpatient Memory Clinic at the National Center Hospital for Mental, Nervous and Muscular Disorders, National Center of Neurology and Psychiatry, Tokyo, Japan. They ranged in age from 48 to 87 years with a mean ± standard deviation (SD) of 70.6 ± 8.4 years. At the first visit, they showed selective impairment in delayed recall (more than 1.5 SD below the age-matched normal mean scores) of the word-list learning test, story recall test or Rey-Osterrieth complex test on neuropsychologic examination, without an apparent loss in general cognitive, behavioral or functional status. They corresponded to the MCI criteria and scored 0.5 in the Clinical Dementia Rating [19]. The Mini-Mental State Examination (MMSE) score [20] ranged from 24 to 29 (mean, 26.0 ± 1.5) at the initial visit.

Sixty-one control subjects (30 men and 31 women; age, 54–86 years; mean, 70.2 ± 7.3 years) were healthy volunteers without memory impairment or cognitive disorders. Specifically, their performance was within normal limits (< 1 SD) on both the Wechsler Memory Scale-Revised and Wechsler Adult Intelligence Scale-Revised, and their MMSE score ranged from 26 to 30 (mean, 28.7 ± 1.5). They did not differ significantly in age or education from the Alzheimer's disease patients. Spouses of the patients comprised the control subjects (not only spouses of the present patients but also spouses of other patients with advanced Alzheimer's disease). None of the control subjects manifested cognitive changes during the follow-up period of more than 2 years.

The local ethics committee approved the study for both healthy volunteers and patients with Alzheimer's disease, all of whom gave informed consent to participate. All

subjects were right-handed, were screened by questionnaire with regard to their medical history and were excluded if they had neurological, psychiatric or medical conditions that could potentially affect the central nervous system, such as substance abuse or dependence, atypical headache, head trauma with loss of consciousness, asymptomatic or symptomatic cerebral infarction detected by T2-weighted MRI, hypertension, chronic lung disease, kidney disease, chronic hepatic disease, cancer or diabetes mellitus.

All subjects underwent MRI and brain perfusion SPECT within 2 months after the first visit. The MRI data of a gapless series of thin sagittal sections were obtained using a three-dimensional volumetric acquisition of a T1-weighted MPRage sequence (1.0 T system; Magnetom Impact Expert; Siemens, Erlangen, Germany; echo time/repetition time, 4.4 ms/11.4 ms; flip angle, 15°; acquisition matrix, 256 × 256; one excitation; field of view, 31.5 cm; slice thickness, 1.23 mm). For the pretreatment of voxel-based morphometry (VBM) analysis of the two groups (patients with Alzheimer's disease and controls), image analysis was performed using Statistical Parametric Mapping 2 (SPM2; Wellcome Department of Cognitive Neurology, London, UK) running on MATLAB6.1 (Mathworks, Sherborn, Massachusetts, USA). Using SPM2 software, the original MRI images were first segmented by extraction of only grey matter, and the segmented images were spatially normalized into the standard space of Talairach and Tournoux [21]. Normalized images were then smoothed with a 12 mm full width at half-maximum isotropic Gaussian kernel to accommodate individual variability in the sulcal and gyral anatomy. The VBM analysis between patients with Alzheimer's disease and controls was performed by group analysis of SPM2 to identify clusters of significantly reduced grey matter concentration in patients with Alzheimer's disease relative to controls, which were set as volumes of interest (VOIs) for correlation analyses of SPECT images.

Before the SPECT scan was performed, all subjects had an intravenous line established. They were injected while lying supine with their eyes closed in a dimly lit quiet room. Each subject received an intravenous injection of 600 MBq of technetium-99m ethyl cysteinate dimer (^{99m}Tc-ECD). Ten minutes after the injection of ^{99m}Tc-ECD, brain SPECT was performed using three-head rotating gamma cameras (Multispect3; Siemens Medical Systems, Inc., Hoffman Estates, Illinois, USA) equipped with high-resolution fan-beam collimators. For each camera, projection data were obtained in a 128 × 128 format for 24 angles at 50 s per angle. A Shepp and Logan Hanning filter was used for SPECT image reconstruction at 0.7 cycles/cm. Attenuation correction was performed using Chang's method. To calculate rCBF, the linearization algorithm of a curvilinear relationship between the brain activity and blood flow was applied, as described in previous reports [22].

Partial volume correction was performed for atrophy correction in SPECT images using the above-mentioned three-dimensional volumetric T1-weighted magnetic resonance images, as described in previous studies [12,23]. In summary, partial volume correction was performed by dividing a grey matter SPECT image by a grey matter magnetic resonance image convoluted with equivalent spatial resolution to SPECT on a voxel-by-voxel basis. In the present study, a fully automated program for the partial volume correction, developed using C^{++} language, was employed.

The SPECT images after partial volume correction were analyzed with SPM2. Using a template for ^{99m}Tc-ECD, the SPECT data were transformed into a standard stereotactic space. The spatial normalization algorithm of SPM2 was used for linear and non-linear transformation. A Gaussian filter (12 mm full width at half-maximum) was used to smooth each image. The effect of global differences in rCBF between scans was removed by proportional scaling with the threshold at 20% of whole brain activity. Using MRIcro (http://www.psychology.nottingham.ac.uk/staff/cr1/mricro.html), we checked the mask image for statistical analysis and verified that medial temporal regions, including the parahippocampal gyrus and hippocampus, were encompassed in the analysis. The rCBF values of the VOIs identified by VBM analysis in SPECT images after partial volume correction were extracted for each subject. The values were then adjusted using the equation, 100 × (rCBF of VOI)/(each global cerebral blood flow), and were treated as covariates of interest. Intercorrelations between different brain regions were analyzed using SPM2 to investigate functional interactions according to Horowitz *et al.* [24].

Results

The VBM analysis demonstrated significant reductions of grey matter concentration in the left (-16 -7 15, x y z; $Z = 7.46$) and right (18 -9 -16, x y z; $Z = 7.45$) entorhinal cortex in the very early stage of Alzheimer's disease compared with controls ($P < 0.001$, corrected for multiple comparisons, Fig. 1). These areas were set as VOIs (1.4 cm^3 for each hemisphere). We used the adjusted rCBF values in these entorhinal cortex VOIs as the covariates of interest for correlation analysis of rCBF SPECT. Adjusted rCBF values in the entorhinal cortex VOIs ranged from 42.3 to 142.1% (mean ± SD, 83.4 ± 17.6%) and from 67.4 to 112.2% (mean ± SD, 88.4 ± 10.5%) for patients with Alzheimer's disease and controls, respectively. Patients with Alzheimer's disease did not show a significant reduction in grey matter concentration in the posterior cingulate cortex compared with controls, even at a lenient threshold ($P < 0.01$).

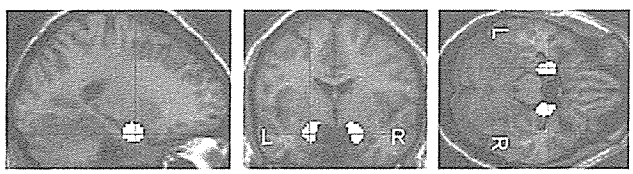
Correlation analysis ($P < 0.001$, corrected for multiple comparisons) revealed positive correlations between rCBF values in the entorhinal cortex and those in the limbic and paralimbic systems, including the posterior cingulate cortex, anterior cingulate cortex, lingual gyri and left middle temporal gyri, in Alzheimer's disease. In contrast, control subjects showed positive correlations in the limbic and paralimbic systems, but not in the posterior cingulate cortex (Table 1, Fig. 2).

Discussion

The VBM analysis demonstrated a significant reduction in grey matter concentration in the bilateral entorhinal cortex in the very early stage of Alzheimer's disease compared with controls. The entorhinal cortex is a well-known site in which pathological changes of Alzheimer's disease occur, even at a very early stage [25]. This result corresponds to previous VBM studies [3–6]. Therefore, we believe that the results of VBM analysis confirm that the profile of SPECT is suitable for the aim of our study: the investigation of the functional interaction between the rCBF in the entorhinal cortex and posterior cingulate cortex at the very early stage of Alzheimer's disease.

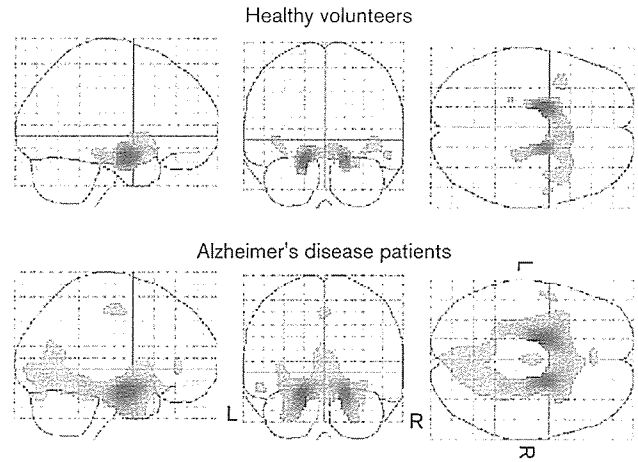
The more limited spatial resolution of SPECT scanners in comparison with PET does not allow an exact measurement of the local radiotracer concentration in brain tissue, as partial volume effects underestimate the activity in small structures of the brain. As focal brain atrophy accentuates the partial volume effect on SPECT measurements, actual rCBF values could be underestimated in the entorhinal cortex in Alzheimer's disease. To obtain accurate rCBF correlation between the entorhinal cortex and other brain areas, rCBF was

Fig. 1



Orthogonal sections of Statistical Parametric Mapping 2 (SPM2) results for significant decline of grey matter concentration in patients with very early Alzheimer's disease compared with age-matched healthy volunteers (−16 −7 15, *x y z*; Z=7.46; 18 −9 −16, *x y z*; Z=7.45). These regions correspond to bilateral Brodmann areas 34 (dorsal entorhinal cortex). Height threshold, <0.001; corrected for multiple comparisons.

Fig. 2



Maximum intensity projections of Statistical Parametric Mapping 2 (SPM2) results for functional connectivities between the entorhinal cortex and the rest of the brain in healthy volunteers (top) and patients with Alzheimer's disease (bottom). Height threshold, <0.001; corrected for multiple comparisons. Local maxima of regions of correlated regional cerebral blood flow (rCBF) are given in Table 1.

Table 1 Local maxima of brain areas in which regional cerebral blood flow (rCBF) is correlated with that in the entorhinal cortex

		Coordinates (mm)			
	Structure	*x*	*y*	*z*	*Z*-score
Healthy volunteers	Left amygdala	−18	−7	−15	Infinite
	Right amygdala	18	−5	−13	Infinite
	Right parahippocampal gyrus (BA35)	24	−26	−14	5.41
	Right superior temporal gyrus (BA21)	53	−2	−10	4.81
	Left insula	−40	10	0	4.8
	Left parahippocampal gyrus (BA36)	−22	−34	−10	4.5
Alzheimer's disease	Left amygdala	−18	−7	−15	Infinite
	Right amygdala	18	−3	−15	Infinite
	Right parahippocampal gyrus (BA36)	22	−36	−13	6.44
	Left parahippocampal gyrus (BA36)	−26	−34	−13	6.03
	Bilateral posterior cingulate cortex (BA23)	0	−63	14	5.66
	Right lingual gyrus (BA18)	12	−72	−3	5.62
	Bilateral dorsal posterior cingulate cortex (BA31)	0	−11	47	5.34
	Left lingual gyrus (BA18)	−4	−72	−3	5.12
	Left anterior cingulate cortex (BA24)	−4	37	0	4.85
	Left middle temporal gyrus (BA21)	−53	−1	−10	4.81

corrected for the partial volume effect in the present study. Although the correction for the partial volume effect has been reported to decrease the regional metabolic or rCBF difference between patients with Alzheimer's disease and control subjects [26], the decrease in intersubject variations of adjusted rCBF values has been reported to increase the statistical significance [12].

In the present study, correlation analysis showed positive correlations between rCBF values in the entorhinal cortex and in the limbic and paralimbic systems, including the posterior cingulate cortex, anterior cingulate cortex and lingual gyri, in Alzheimer's disease. In contrast, control subjects showed a correlation in the limbic and paralimbic systems, but not in the posterior cingulate cortex. Meguro *et al.* [15] reported that lesions of the entorhinal cortex in non-human primates cause a long-lasting reduced cerebral glucose metabolism in the hippocampus, the inferior parietal, posterior temporal and posterior cingulate cortex, and associative occipital cortices. Insausti *et al.* [27] also reported that the entorhinal cortex has connections to the limbic and paralimbic systems, including the anterior cingulate cortex and posterior cingulate cortex, insula in the temporal lobe, parainsula area in the parietal lobe, dorsolateral frontal cortex and an orbital region in the frontal lobe in the monkey. Our results in patients with Alzheimer's disease agreed well with these experimental results. With regard to control subjects, who showed similar correlations in the limbic and paralimbic systems, but not in the posterior cingulate cortex, Meguro *et al.* [15] have demonstrated that the degree of reduced cerebral glucose metabolism in areas that have connections with the entorhinal cortex correlates significantly with the severity of histologically determined damage in the entorhinal cortex. In Alzheimer's disease, the entorhinal cortex may be more markedly damaged than in controls, as adjusted rCBF values in the entorhinal cortex VOIs were approximately 6% lower on average in patients with Alzheimer's disease than in controls. Although our correlation analysis showed connections with the entorhinal cortex more strongly in patients with Alzheimer's disease than in controls, this may simply be due to a smaller range of adjusted rCBF values in the entorhinal cortex VOIs in controls than in patients with Alzheimer's disease. Although Mosconi *et al.* [16] reported the loss of entorhinal cortex correlations with cerebral cortices in glucose metabolism in patients with more advanced Alzheimer's disease, the entorhinal cortex correlation with the posterior cingulate cortex was observed in patients with Alzheimer's disease, but not in healthy control subjects, in a similar manner to the present study.

Conclusion

According to an SPM approach to rCBF SPECT, we found enhanced functional connectivity between the entorhinal cortex and posterior cingulate cortex in Alzheimer's disease at the very early stage. The results indicate that rCBF changes in the posterior cingulate cortex may positively correlate with those in the entorhinal cortex through this functional connectivity. Taken together, our results may support the existence of a 'remote effect'.

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Case report

Efficacy of milnacipran on the depressive state in patients with Alzheimer's disease

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Abstract

An open-labeled study was conducted to examine the efficacy of selective serotonin and noradrenaline reuptake inhibitor (SNRI), milnacipran in treating depression in Alzheimer's disease (AD) patients. Eleven patients with AD showing major depressive symptoms were examined. Ten of 11 patients demonstrated an over 50% decrease in their HAM-D scores from the baseline, and 8 of 11 patients reached remission (HAM-D score ≦ 7) within 12 weeks of the start of milnacipran treatment, and their GAF score was also remarkably improved. Although in 11 patients, two patients showed a mild hypomanic state and one patient showed daytime somnolence, these problems were quickly solved after a decrease in the daily dose or discontinuation of milnacipran. In addition, the treatment had no negative effects on cognitive function of the patients. Our study results suggest that milnacipran is a promising medicine for depressive state in AD patients.

Keywords: Alzheimer's disease; Depression; Milnacipran; SNRI; SSRI

1. Introduction

In Alzheimer's disease (AD) patients, depression is not a rare condition. The prevalence of major depression has been reported to be within the range of 20–25% (Migliorelli et al., 1994; Olin et al., 2002) of AD patients. Depression in AD patients is associated with earlier placement out of the community into a nursing home (Steele et al., 1990), and is also associated with greater impairments in the quality of life (Gonzales-Salvdor et al., 2000) as well as with increased caregiver depression and burden (Gonzales-Salvdor et al., 1999). Although some tricyclic anti-depressants (TCAs) have been found to improve depression in AD, the anti-cholinergic effects of these medicines are critical to cognitive function in AD patients (Teri et al., 1991). Recently, serotonin selective reuptake inhibitors (SSRIs) have been recommended for depression in AD patients due to their minimal anti-cholinergic effects, although their efficacy has remained controversial and further studies are needed.

Milnacipran (1-phenyl-1-diethyl-aminocarbonyl-2-amino-methyl-cyclopropane hydrochloride) is a novel anti-depressant agent that is a selective serotonin and noradrenaline reuptake inhibitor (SNRI) (Puech et al., 1997; Briley, 1998), and is reported to be devoid of any postsynaptic activity (Moret et al., 1985). Although milnacipran has been reported to be effective and safe for elderly depressive patients (Tignol et al., 1988), thus far there has been no study focusing on its effects on depression in AD patients. We describe here the efficacy and safety of milnacipran on depression with AD through its open trial for 11 patients. To our knowledge, this is the first paper reporting SNRI treatment of depression in AD patients.

2. Methods

2.1. Patients

A consecutive series of 11 patients were enrolled in this study, and all 11 participants were recruited from the outpatient

Abbreviations: AD, Alzheimer's disease; CDR, clinical dementia rating; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; FAST, Functional assessment staging; GAF, General assessment of functioning; HAM-D, Hamilton Depression Score; MMSE, Mini-mental state examination; MRI, Magnetic resonance imaging; SNRI, Serotonin and noradrenaline reuptake inhibitor; SPECT, Single photon emission computerized tomography; SSRI, Serotonin selective reuptake inhibitors; TCAs, Tricyclic anti-depressants.

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clinic of Ishizaki Hospital, and provided written informed consent for study participation. The study was carried out in accordance with the ethics and principles embodied in the Declaration of Helsinki of 1975. Clinical diagnosis of AD was made utilizing DSM-IV (American Psychiatric Association, 1994) and NINCDS/ADRDA (McKhann et al., 1984) criteria. In addition, all 11 patients were diagnosed to be consistent with major depressive episode according to DSM-IV criteria, and their Hamilton Depression Score-17 (HAM-D17) (Hamilton, 1960) scores were greater than 12. All patients in this study were able to understand the contents of the interview and to describe their mental conditions.

2.2. Patient assessment

Patients also underwent physical, neurological, and routine laboratory examinations as well as brain magnetic resonance imaging (MRI). Patients were evaluated for cognitive and social function using the mini-mental state examination (MMSE) (Folstein et al., 1975), general assessment of functionning (GAF) according to DSM-IV, functional assessment staging (FAST) (Reisberg, 1988), and stage of the clinical dementia rating (CDR) (Hughes et al., 1982).

2.3. Drug administration

For 11 patients, treatment with milnacipran was begun after all evaluations were done. Seven patients started with milnacipran at 30 mg daily and 4 patients started with 15 mg daily. If patient showed no improvement for two weeks, the dose was increased by 15 mg/day. The participants underwent repeated evaluation for depressive states using the HAM-D every 2 weeks. Cognitive function using MMSE and social function using the GAF were also evaluated every 4 weeks. The average scores of HAM-D, MMSE, and GAF were compared between the baseline and the endpoint, which was defined as the time of 12 weeks after the start of milnacipran treatment. If patients discontinued milnacipran before 12 weeks, the week of the discontinuation was defined as the endpoint. A HAM-D score of 7 or below was defined as remission. Statistical analysis was carried out using the Wilcoxon method. $p<0.05$ is regarded as a significant difference.

3. Results

Eight patients took milnacipran for more than 12 weeks (72.7%); and 3 patients discontinued the treatment within 12 weeks. The reasons for discontinuation were emergence of hypomanic state for one patient (Case 5) and dropout for two patients (Cases 9 and 10). Case 10, however, resumed the treatment of milnacipran due to recurrence of depression thereafter.

Table 1 shows the background characteristics of the 11 patients analyzed. Their mean age was 75.2±9.4 (range 56–84) years. Of the 11 patients, 9 (81.8%) were female. The numbers of subjects for CDR 1 and CDR 2 ratings were 6 and 5, respectively, and the numbers of subjects for FAST 4, 5, and 6 stages were 8, 2, and 1, respectively. The average HAM-D, MMSE, GAF scores of the 11 patients at baseline were 19.8±3.7 (range 14–26), 19.1±4.2 (range 9–23), and 33.4±12.6 (range 21–65), respectively.

Table 1
Demographic characteristics of 11 patients

Variable		p value
Age (y, mean±SD) (range)	75.2±9.4 (56–84)	
Sex		
Male	2	
Female	9	
CDR		
1	6	
2	5	
FAST		
4	8	
5	2	
6	1	
HAM-D (mean±SD)[a]		
Baseline	19.8±3.7 (14–26)	
Endpoint	6.3±3.8 (2–14)	$p=0.0030$
GAF (mean±SD)[a]		
Baseline	33.4±12.6 (21–65)	
Endpoint	56.0±11.8 (30–75)	$p=0.0032$
MMSE (mean±SD)		
Baseline	19.1±4.2 (9–23)	
Endpoint	20.0±4.7(9–24)	$p=0.5368$

[a] Siginificant.

One of 11 patients (Case 3) had a past history of major depressive episode, while the other 10 had no history of psychiatric illness including depression.The maximum average dose of milnacipran within 12 weeks was 41.4±20.4 mg (range 15–75 mg). The endpoint of the average HAM-D and GAF scores of 11 patients were 6.3±3.8 (range 2–14) and 56.0±11.8 (range 30–75), respectively. There is a significant difference in the average HAM-D and GAF scores between the baseline and the endpoint (at 12th week) ($p=0.0030$, $p=0.0032$, respectively). In contrast, there is no significant difference in the average MMSE scores of 11 patients between the baseline and the endpoint ($p=0.5368$). Within 12 weeks, all the 11 patients showed improvement of depressive states, and 10 of 11 patients (except for Case 4) exhibited more than 50% HAM-D score reduction compared with the baseline score (Table 2). In addition, 8 patients reached remission (HAM-D score ≦7) at endpoint (12 weeks) and 5 patients reached remission within 4 weeks (Fig. 1). Broad aspects of depressive states, including depressive mood, anxiety, and psychomotor retardation, were improved by the treatment with milnacipran. Adverse reactions were observed in three patients. Although two patients (Cases 5 and 8) showed a mild hypomanic state and one patient (Case 1) showed daytime somnolence, these problems were quickly solved after a decrease in the daily dose (Cases 1 and 8) or discontinuation (Case 5) of milnacipran. The summary of 11 cases was shown in Table 2.

3.1. Case reports

Case 1 is a 84-year-old man with a 5-year history of cognitive decline and a 1-year history of depressive state,

Table 2
Summary of 11 patients

No.	Age	Sex	Milnacipran (mg/day)		HAM-D			GAF		MMSE		Side effect
			Initial	Maximum	Baseline	Endpoint	% Changes	Baseline	Endpoint	Baseline	Endpoint	
1	84	M	30	60	18	5	−72%	35	45	15	14	Drowsiness
2	78	F	30	50	24	12	−50%	21	55	22	21	
3	79	F	30	30	23	5	−78%	25	60	23	21	
4	79	F	15	30	26	14	−46%	35	50	22	20	
5	71	F	30	30	19	7(4W)	−63%	25	30(4W)	9	9	Hypomanic
6	81	F	15	15	18	6	−67%	45	55	17	18	
7	77	F	30	30	14	4	−71%	65	75	22	24	
8	79	F	15	60	19	2	−89%	31	61	22	24	Hypomanic
9	84	M	15	15	18	8(5W)	−56%	35	65(5W)	21	22	
10	59	F	30	60	16	4(10W)	−75%	25	55(10W)	18	21	
11	56	F	30	75	23	2	−91%	25	65	19	23	
			24.5±7.6	41.4±20.4	19.8±3.7	6.3±3.8		33.4±12.6	56.0±11.8	19.1±4.2	20.0±4.7	

including severe depressive mood and loss of interest and moderate suicidal ideas. His depressive states had persisted despite treatment with fluvoxamine. He was started on 30 mg daily of milnacipran, which was gradually dosed up. At 60 mg he felt sleepiness, which was resolved by reduction to 45 mg. He recovered from his depression within 12 weeks.

Case 5 is a 71-year-old woman with a 4-year history of cognitive decline and a 1-month history of depressive state, with moderate depressive mood, loss of interest, and anxiety. She started on milnacipran at 30 mg daily, then 2 weeks later dosed down to 15 mg, and 4 weeks later discontinued due to slight hypomania. At 4 weeks, her mood disorder had resolved.

Case 8 is a 79-year-old woman with a 2-year history of cognitive decline and a 1 month history of depression characterized by moderate depressive mood, loss of interest, feelings of guilt, and psychomotor retardation. She started on milnacipran at 15 mg/day and dosed up to 60 mg. Her depression remitted within 4 weeks. At 60 mg daily, she showed a transient hypomanic state, which was quickly resolved by dose-down to 45 mg daily.

Case 10 was a 59-year-old woman with a 2-year history of cognitive decline and a 2-month history of depression, including moderate depressive mood, feelings of guilt, suicidal ideas, and anxiety. She was started on a daily dose of 30 mg milnacipran. Milnacipran at 60 mg daily put her depression into remission at 8 weeks. However, her 2-month discontinuation of milnacipran caused her depressive state to recur, and then resumption of 45 mg/day milnacipran again improved her depressive state.

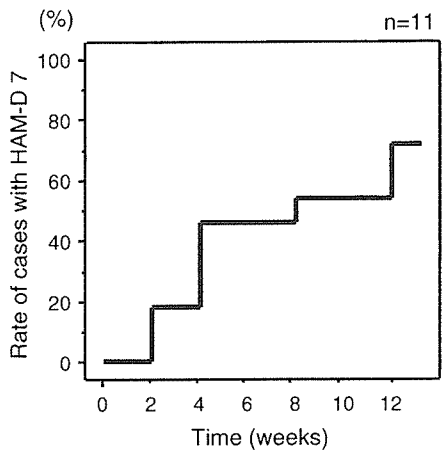

Fig. 1. Graph showing cumulative remission rate of 11 patients. Eight patients reached remission within 12 weeks, and 5 patients reached remission within 4 weeks.

4. Discussion

In our study, all the 11 patients demonstrated a remarkable improvement in depression with milnacipran treatment. Within 12 weeks, 8 of 11 patients reached remission (remission rate, more than 70%). Previous studies on depressive state in AD patients treated with anti-depressants demonstrated that the remission rates using clomipramine and fluoxetine, respectively, are 82% (Petracca et al., 1996) and 47% (Petracca et al., 2001), and that the rate of 30% reduction in HAM-D scores using fluoxetine and amitriptyline is 64% and 50%, respectively (Taragano et al., 1997). Thus, our study using milnacipran appears to have attained a very high remission rate, although there are some limitations to compare the results of our study with the previous studies. In addition, the majority of our patients showed a quick response, and 5 of 11 patients reached remission within 4 weeks. Interestingly, milnacipran has been reported to alleviate the symptoms of post-stroke depression within 1–2 weeks (Kimura et al., 2002). In addition, the onset of action of milnacipran is faster than that of SSRIs such as fluvoxamine and paroxetine (Morishia and Arita, 2003). Collectively, it is reasonable to suppose that milnacipran is effective in treating major depression in AD patients, and its effects appear within a short time interval. In our patients, with the treatment of milnacipran, all the 11 patients showed a remarkable improvement in GAF score according to the improvement of their depressive state, suggesting that milnacipran also has a beneficial impact on social function in AD patients.

Some reports have pointed out the placebo effect in the treatment of depression in AD patients (Petracca et al., 1996, 2001). Also in our study, it is possible that the placebo effect contributed to the improvement of depressive states. However, the remission rate using placebo has been reported to be

approximately 30–35% (Petracca et al., 1996, 2001), and the remission rate in our study is much higher than that expected using placebo. In addition, in Cases 1, 2, and 3, previous antidepressant therapy was ineffective, and after milnacipran treatment their depression improved. Case 10 aggravated her depression by discontinuation of milnacipran and recovered by its resumption. These clinical observations argue against the concern regarding placebo effects, although a further double-blind study is needed.

In our study, no serious adverse reactions were observed, although adverse reactions were noted in three patients, who recovered quickly after discontinuation or a decreased dose. The average MMSE scores of the 11 patients did not change significantly with the treatment of milnacipran, although some variations in the alteration patterns of MMSE scores were observed in each patient. It has been reported that depressive AD patients taking TCAs such as imipramine and clomipramine demonstrate decreased MMSE scores compared with depressive AD patients taking a placebo (Teri et al., 1991; Petracca et al., 1996). Milnacipran has a lack of anti-cholinergic and sedative effects (Moret et al., 1985), and it is reported to be free from disruptive effects on cognitive function in elderly healthy volunteers (Hindmarch et al., 2000) as well as elderly depressive patients (Tignol et al., 1988). Our study suggests that milnacipran is also a safe medicine for the cognitive function of AD patients. However, it has been reported that dysuria is observed significantly more frequently with milnacipran than with TCAs and SSRIs (Puech et al., 1997; Tignol et al., 1988). Thus, it is important to watch for the development of dysuria during the treatment, especially in the case of elderly male patients.

Nowadays, SSRIs are recommended as a first-line medicine for depression in AD because of their efficacy and safety (Taragano et al., 1997; Lyketsos et al., 2003), although some studies have failed to show their efficacy (Petracca et al., 2001; Magai et al., 2000). It has been documented that in those aged 50 years or older, milnacipran has a tendency to be more effective than SSRIs such as fluvoxamine and paroxetine (Morishita and Arita, 2004). Furthermore, milnacipran has metabolic advantages over SSRIs, since the latter are metabolized via and inhibit cytochrome P450 isoenzymes and therefore have an important interactive potential, while milnacipran has no inhibition on any cytochrome P450 isoenzymes (Puozzo and Leonard, 1996), thus reducing the risk of adverse effects due to drug interactions. In addition, postmortem studies have shown that depression in AD has been associated with a selective loss of noradrenergic cells in the locus ceruleus (Zubenko et al., 1990). Taking these findings together, milnacipran is expected to be better than SSRIs with regard to efficacy and safety in treating depression in AD patients.

There were some limitations in this study. First, it was an open-label study and not a double-blind study with a placebo. Second, the number of patients was small. To confirm the efficacy of milnacipran in treating depression in AD patients, these limitations must be addressed in future studies.

In conclusion, our preliminary study suggests that milnacipran is a promising medicine for depression with Alzheimer's disease due to its efficacy and safety, although further studies, including a double-blind placebo control study, are needed.

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Efficacy of perospirone in the management of aggressive behavior associated with dementia

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Abstract

We assessed the efficacy of the serotonin dopamine antagonist, perospirone (PER) on aggressive and agitated behavior in demented patients. Eighteen outpatients with dementia diagnosed according to the DSM-IV were enrolled in this study, and their behavioral symptoms and cognitive impairments were assessed with the Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) and Mini-Mental State Examination (MMSE) instruments for a period of 6 weeks. The maximum benefit of PER was achieved at a mean dose of 7.4 mg/day. Post-hoc analysis showed significant improvement in verbal outbursts after 4 weeks and in agitation scores after 4 and 6 weeks. Only 2 patients dropped out of the study, because of adverse effects, and no serious adverse effect was observed. The data suggest that PER is effective in improving aggressive and agitated behavioral symptoms in demented patients and that it is safe to use in elderly patients.

Keywords: Aggressive behavior; Behavioral and psychological symptoms of dementia; Dementia; Perospirone

1. Introduction

The behavioral and psychological symptoms of dementia (BPSD), which include aggression, agitation, screaming, wandering, hallucination, and delusion, have a negative impact on patients' activities of daily living and on caregivers' quality of life. Among the BPSD, aggression and agitation are especially serious and problematic symptoms for family caregivers, and these symptoms are often the primary cause of hospital admission or institutional care (American Psychiatric Association, 1997; Schneider et al., 1996). In addition, it is reported that aggression and agitation occur in about 20–80% of patients with Alzheimer's disease (AD) (Burns et al., 1990; Cooper et al., 1990; Lyketsos et al., 2000; Mega et al., 1996), and that patients with vascular dementia (VD) also often exhibit aggression and agitation (Cohen et al., 1993).

Although non-pharmacological interventions, such as the verbal environmental intervention, should be first-line for milder BPSD (American Psychiatric Association, 1997; Asada et al., 2000), many psychotropic agents (e.g. conventional antipsychotics, benzodiazepines, antidepressants, anticonvulsants, and beta-blockers) have been used to manage aggressive behavior. However, their efficacy is insufficient (Cohen et al., 1993; Schneider et al., 1996) and their use has been limited because of adverse effects such as orthostatic hypotension, arrhythmia, extrapyramidal symptoms (EPS), urinary retention, constipation, sedation, and delirium (Brodaty et al., 2003; De Deyn et al., 1999; Katz et al., 1990; Schneider et al., 1996). Recently, newer atypical antipsychotics, characterized by the serotonin (5-HT2) and dopamine (D2) antagonists, have been used for the treatment of aggression in demented patients. Double-blind, placebo-controlled trials have demonstrated that

Abbreviations: AD, Alzheimer's disease; ANOVA, analysis of variance; BEHAVE-AD, Behavioral Pathology in Alzheimer's Disease; BPSD, behavioral and psychological symptoms of dementia; CDR, Clinical Dementia Rating; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, fourth edition; EPS, extrapyramidal symptoms; MMSE, Mini-Mental State Examination; VD, vascular dementia.

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some atypical neuroleptics, such as risperidone and olanzapine, have beneficial effects and are well tolerated (American Psychiatric Association, 1997; Brodaty et al., 2003; De Deyn et al., 1999; Schneider et al., 1996; Street et al., 2000) in the treatment of aggression and agitation in demented patients.

Perospirone(*cis*-*N*-[4-[4-(1,2-benzisothiazole-3-yl)-1-piperazinyl]butyl]cyclohexane-1,2-dicarboximide monohydrochloride) (PER) is a novel antipsychotic agent available in Japan for the treatment of schizophrenia. PER has a unique pharmacologic profile and acts as a serotonin-dopamine antagonist (Onrust and McClellan, 2001) as well as a partial serotonin (5-HT1A) agonist (de Paulis, 2002). Buspirone, which exhibits 5-HT1A agonist effects, has been reported to be effective in the treatment of aggressive and agitated behaviors associated with dementia (Cantillon et al., 1996; Hermann and Eryavec, 1993; Sakauye et al., 1993). Previous studies demonstrating buspirone efficacy led us to hypothesize that PER would be effective and safe in the treatment of aggressive and agitated behaviors in patients with dementia. We previously reported six patients with dementia, in whom PER reduced aggression (Sato et al., 2006). This article further presents the effects of PER on aggressive and agitated behaviors associated with dementia.

2. Methods

2.1. Patient population

A consecutive series of 18 patients were enrolled in this study. All patients were referred to the outpatient clinic of Ishizaki Hospital between April 2003 and March 2004. Eligibility criteria for the present study were: meeting the diagnosis of dementia of the Alzheimer's type (AD) or vascular type (VD) according to DSM-IV (American Psychiatric Association, 1994); and exhibiting moderate to severe agitation or aggressive behavior requiring pharmacotherapy for at least 1 month. This study protocol was approved by the Internal Review Board of Ishizaki Hospital. Patients and their caregivers provided written informed consent for study participation. However, if the patient was lack of ability to give it, we obtained it from only their caregivers. The patients underwent physical, neurologic, and laboratory examinations as well as brain magnetic resonance imaging. If they had a serious physical illness or a past history of mental disorders, they were excluded from the study.

2.2. Drug administration

Initially, the administration of PER started at 8 mg/day divided into morning and evening doses. If efficacy was deemed insufficient, the dose was increased weekly by 4 mg/day. However, if the initial dosage of PER was associated with any adverse effects, the dose was decreased weekly by 2 or 4 mg/day. The maximum effective dose was determined based on clinical judgment and the BEHAVE-AD scores.

Basically, the patients treated with PER monotherapy during the study period. However, 9 cases had previously received other medications (sodium valproate 6 cases, tiapride 4 cases, donepezil 3 cases, risperidone 1 case, olanzapine 1 case). In these cases, risperidone and olanzapine were discontinued, while the other previous medications were continued, and their dosage was unchanged during the study.

2.3. Study design and assessment instruments

The patients were assessed four times, at baseline and at 2, 4 and 6 weeks after the start of PER administration. The Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and the Clinical Dementia Rating (CDR) (Hughes et al., 1982) were used to assess the severity of cognitive deficits. Psychiatric and behavioral symptoms were evaluated with the Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) instrument (Reisberg et al., 1987). The BEHAVE-AD scale measures behavioral disturbances in the seven major categories of "paranoid and delusional ideation," "hallucination," "activity disturbances," "aggressiveness," "diurnal rhythm disturbances," "affective disturbances," and "anxieties and phobias." In this study, the change in the total score and aggressiveness score including "verbal outbursts," "physical threats and violence," and "agitation" subscales of the BEHAVE-AD were evaluated.

2.4. Data analysis

Initial and end-point MMSE scores were compared using the Wilcoxon signed-rank test. Changes in the total BEHAVE-AD scores and each subscale of BEHAVE-AD at each time point were analyzed by means of repeated-measures analysis of variance (ANOVA). Dunnett test was used for Post-hoc analysis of ANOVA comparing baseline and 2, 4 and 6 weeks after scores. The significant level was set at $p<0.05$.

3. Results

The 6-week course of treatment was completed by 16 patients (88.9%); and 2 patients discontinued PER due to adverse effects. Table 1 shows the background characteristics of

Table 1
Demographic characteristics of 18 patients

	Variable
Age (years, mean ± SD) (range)	78.1 ± 6.6 (65–89)
Sex	
Male	7
Female	11
Diagnosis	
AD	15
VD	3
MMSE (mean ± SD)*	
Baseline	12.3 ± 6.3
End-point ($n=16$)	15.6 ± 8.9
CDR (mean ± SD)	2.2 ± 0.4
Perospirone dose (mg/day, mean ± SD) (range) ($n=16$)	7.4 ± 3.5 (2–12)

AD: Alzheimer's disease.
VD: vascular dementia.
MMSE: Mini-Mental State Examination.
CDR: Clinical Dementia Rating.
* Not significant, Wilcoxon signed-rank test.

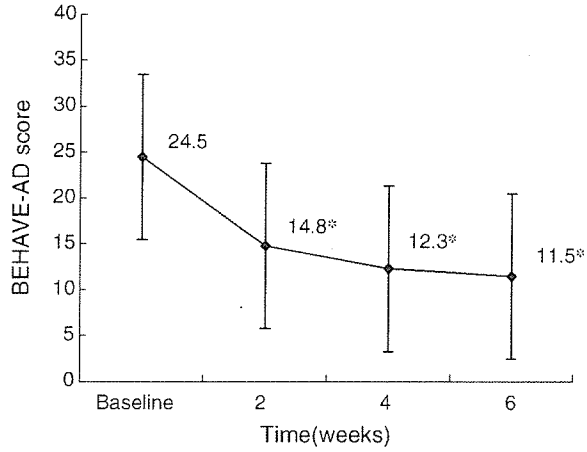

Fig. 1. Changes in total BEHAVE-AD score in patients with dementia during PER treatment. Post-hoc analysis showed significant total score reductions after 2, 4 and 6 weeks (*$p<0.05$).

the 18 patients analyzed. Their mean age was 78.1±6.6 (range 65–89) years. Of the original 18 patients, 11 (61.1%) were women. Among the patients analyzed, 15 (83.3%) had AD, while 3 (16.7%) had VD.

The patients' mean±SD baseline MMSE score was 12.3 ±6.3 (range 0–22) and the severity of dementia (on the CDR) was moderate (mean±SD 2.2±0.4, range 2–3). There were no significant differences in MMSE score between baseline and end-point. The maximum benefit of PER was seen in the dose range of 2–12 mg/day (mean dosage±SD 7.4±3.5 mg/day).

Two patients dropped out of this study because of adverse effects. One was an 82-year-old man diagnosed with AD. After receiving PER 8 mg/day for 2 weeks, he began to show an unsteady gait and tendency to stumble. The other patient was a 76-year-old man with AD. After 3-week administration of PER 12 mg/day, he had muscle weakness and fell repeatedly. Both patients quickly recovered from these adverse symptoms after the discontinuation of PER. In addition, although slight sedation (2 patients) and slight muscle weakness (5 patients) were observed during improvement of aggressive behavior, these adverse effects were quickly resolved after modification of dosage. No serious adverse effect was observed in this study.

Analysis of variables in the total BEHAVE-AD score showed a significant improvement with PER treatment ($F=6.03$, $p=0.007$). Post-hoc analysis revealed that there were significant score reductions at 2, 4 and 6 weeks after the initiation of PER administration (Fig. 1). The analysis also showed a significant improvement in the subscale scores for verbal outbursts after 6 weeks and for agitation after 4 and 6 weeks (Fig. 2). Physical threat and/or violence scores did not change significantly.

4. Case report

A 74-year-old woman with AD was referred to our outpatient unit for psychiatric evaluation. She had a 13-year history of gradually progressive cognitive impairment. She did not have any history of marked physical or psychiatric problems. At the age of 72 years, she easily became angry and excited by inconsequential matters and exhibited aggressive and violent behavior against her family. On her first visit, her total BEHAVE-AD and MMSE scores were 21 and 18, respectively. She was administered PER 8 mg/day. One week later, her agitation, excitement, and violent speech had markedly decreased. Her aggressive behavior disappeared in 4 weeks and she became better able to perform housekeeping tasks than previously.

5. Discussion

In the present study, PER at low doses (mean dose 7.4 mg/day) significantly improved aggression and agitation in demented patients. No serious adverse effects were observed in this study. Only 2 of 18 patients dropped out of the study because of adverse effects such as muscle weakness and unsteady gait, which were not serious and resolved quickly after the discontinuation of PER. In addition, anticholinergic effects, EPS, or decline in cognitive function as measured using the MMSE were not observed. PER displays the characteristics of

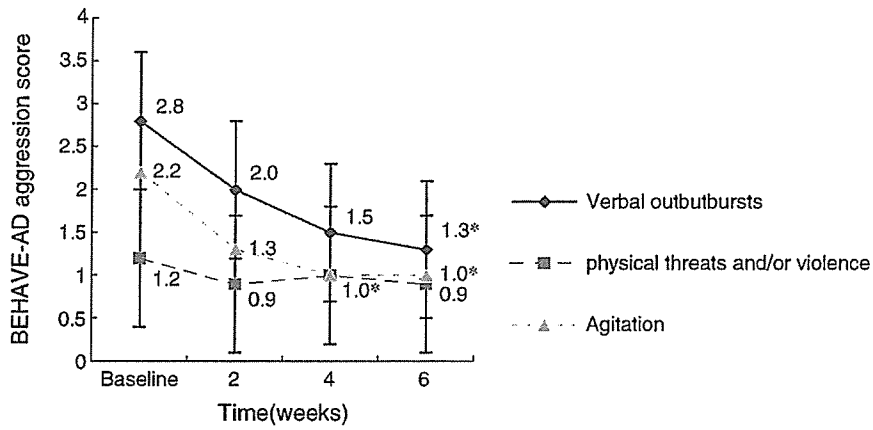

Fig. 2. Changes in BEHAVE-AD aggression scores in patients with dementia during PER treatment. Post-hoc analysis showed significant reductions after 6 weeks (*$p<0.05$) in verbal outburst and, after 4 and 6 weeks (*$p<0.05$) in agitation scores.

an atypical antipsychotic agent, and is better tolerated than haloperidol (Onrust and McClellan, 2001; de Paulis, 2002). In particular, EPS tended to occur less often and were generally milder with PER than with haloperidol (Murasaki et al., 1997) or mosapramine (Kudo et al., 1997). Ichikawa et al. (2001) pointed out that 5-HT1A agonists reduce neuroleptic adverse effects such as EPS. Moreover, some studies reported that PER therapy improved psychotic symptoms with few side effects (Kudo et al., 1997; Murasaki et al., 1997; Masui et al., 2003) in elderly (more than 60 years of age) patients with schizophrenia. The results of this study suggest that PER is well tolerated also in elderly demented patients.

It is noteworthy that low-dose PER exerted its effects immediately, as shown by the reduction in the BEHAVE-AD aggression score. The scores for verbal outbursts and agitation were reduced within 4 or 6 weeks after the initiation of treatment.

De Deyn et al. (1999) pointed out that risperidone may have a direct effect on aggression in treating dementia-related behavioral problems. They explained that the antipsychotic effects of risperidone caused by serotonin-dopamine blockade improved behavioral disturbances in demented patients. Furthermore, PER is not only a serotonin-dopamine antagonist but also a serotonin 5-HT1A partial agonist. A growing body of evidence suggests that there is a correlation between decreased cerebrospinal fluid serotonin levels and aggressive behavior (Lai et al., 2002; Linnoila et al., 1983; Mintzer, 2001; Stanislav et al., 1994). Lai et al. (2002) reported that 5-HT1A receptor density in the brains of Alzheimer's disease patients correlated negatively with the maladaptive behavior of aggression. There are numerous reports that buspirone, a serotonin 5-HT1A partial agonist, inhibits aggression and agitation in demented patients (Cantillon et al., 1996; Hermann and Eryavec, 1993; Sakauye et al., 1993). Cantillon et al. (1996) conducted a double-blind trial of buspirone (15 mg/day) and haloperidol (1.5 mg/day). They reported that the tension subscale scores of the Brief Psychiatric Rating Scale in patients receiving buspirone were more significantly reduced than those in patients receiving haloperidol. They concluded that some behavioral symptoms, especially agitation, observed in demented patients may be linked to a serotonergic system and be well managed with the 5HT-1A partial agonist buspirone. However, randomized placebo-controlled trials are required to determine the efficacy of buspirone on agitation and aggressive behavour in demented patients.

Taking the cumulative results together, it can be assumed that PER, acting as a serotonin-dopamine antagonist as well as serotonin 5-HT1A partial agonist, is effective and safe in the management of aggression and agitation in demented patients due to its unique pharmacologic properties.

In April 2005, The Food and Drug Administration (2005) issued a warning that the use of atypical antipsychotic medications in elderly patients with dementia may be associated with an increased mortality, while Liperoti et al. (2005) suggested that there was no increased risk for arrhythmias or cardiac arrest with the use of atypical antipsychotics in a case-control study. Therefore, before the start of pharmacotherapy with atypical antipsychotics for elderly patients with dementia, it is inevitable to carefully judge the necessity of the pharamacotherapy in consideration of the balance between benefits and risks associated with the therapy, and to carefully monitor the occurrence of adverse effects during the therapy.

There were some limitations in this study. First, it was an open-label study and not a double-blind study with a placebo. Thus, our findings cannot be generalized to all demented patients with agitation and aggressive behavior. Second, the number of patients was small and included those with both AD and VD. However, De Deyn et al. (1999) reported that there were no differences among diagnostic groups in the results of risperidone treatment for aggressive behavior. When we divided our patients into the AD and VD groups and analyzed each subgroup, the results demonstrated that aggression and agitation were significantly reduced only in AD patients, while VD patients failed to show a significant difference in those scores. This result may be attributable to the small number of patients. To confirm the efficacy of PER in treating aggression and agitation in demented patients, these limitations must be addressed in future studies.

6. Conclusion

Although this was a preliminary, open study, it appears that the serotonin-dopamine antagonist PER may be effective in controlling the aggressive and agitated behavior associated with dementia and be well tolerated. More patients must be analyzed in a randomized, placebo-controlled trial of the efficacy of PER for the treatment of aggression and behavioral disturbances associated with dementias.

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Relationship between antisocial behavior and regional cerebral blood flow in frontotemporal dementia

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Objective: **To examine the relationship between antisocial behaviors and reduction of regional cerebral blood flow (rCBF) in patients with frontotemporal dementia (FTD).**

Methods: **Brain perfusion single photon emission computed tomography (SPECT) was performed in 22 patients with FTD and 76 age-matched healthy volunteers. The statistical analysis was conducted using the SPM99 software. The antisocial behavioral symptoms were assessed independently by three geriatric psychiatrists, who had not been given the information of the SPECT images.**

Results: **Compared with normal controls, FTD patients showed significant reduction of rCBF in the widespread frontal cortical areas. The correlation analysis showed that antisocial behavioral symptoms are associated with reduction of rCBF in the orbitofrontal cortex.**

Conclusion: **The functional decline of orbitofrontal cortex is related to antisocial behavioral symptoms in patients with FTD.**

Keywords: Frontotempotal dementia; Antisocial behaviors; SPECT; Regional cerebral blood flow

Introduction

Frontotemporal lobar degeneration (FTLD) is composed of a spectrum of dementing disorders with degeneration of the frontal lobes, the anterior temporal lobes, or the both (Neary et al., 1998). Frontotemporal dementia (FTD) is the main FTLD syndrome and manifests as prominent personality and behavioral disturbances. Behavioral symptoms such as antisocial behaviors are observed in patients with FTD, and presence of them often makes it difficult to care for such patients. Moreover, such symptoms will prompt their institutionalization. Development of appropriate management methods for the behavioral symptoms may lessen the care-giving burden and lead to postponement of institutionalization. Evaluation of antisocial behavioral symptoms in FTD patients must be the basis for such development.

Systematic functional neuroimaging studies using single photon emission computed tomography (SPECT) or positron computed tomography (PET) have demonstrated that patients with FTD show hypoperfusion of anterior cerebral cortex with relative sparing of posterior cortex (Ishii et al., 1998; Miller and Gearhart, 1999; Charpentier et al., 2000; Hodges, 2001; Lojkowska et al., 2002). These evidences have become useful to make clinical diagnosis of FTD. However, systemic studies examining the association between antisocial behavior and regional cerebral blood flow (rCBF) in patients with FTD are few and mostly based on visual inspection (Mychack et al., 2001) using the region of interest (ROI) method. Although this approach has been popular, accuracy depends on the observer's experience and working-hypothesis, thus such evaluation is apt to lack morphological accuracy of brain regions and leaves large areas of the brain unexplored. An alternative method is voxel-by-voxel analysis of stereotactic space, which adopts the principle of data-driven analysis and can avoid subjectivity. Such an approach is well established in the field of functional neuroimaging analysis; a software package known as statistical parametric mapping (SPM), that not only spatially normalizes PET or SPECT images to a standardized stereotactic space but also statistically analyzes group of images, has been

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developed (Frackowiack et al., 1997). The objective of this study is to evaluate the relationship between antisocial behavior and rCBF abnormalities in FTD patients by application of SPM to brain perfusion SPECT images.

Materials and methods

Subjects

Twenty-two consecutive patients (14 men, 8 women; age range, 58–74 years; mean age, 62.9 years) newly referred to the memory disorder clinic of the National Center Hospital for Mental, Nervous, and Muscular Disorders, National Center of Neurology and Psychiatry, Tokyo, Japan, between 1994 and 2003, were enrolled. The mean age at onset was 57.5 years (range, 47–68 years). The clinical diagnosis of FTD was based on the Lund and Manchester criteria and the more recent consensus criteria (Neary et al., 1998) after detailed examination, including magnetic resonance imaging (MRI), SPECT, and neuropsychological examination. The clinical criteria of FTD are reported to have high diagnostic specificities (Rosen et al., 2002). The neuropsychological battery consisted of tests that have been shown to be useful in the differential diagnosis of FTD and other dementia. The following tests were employed: Mini Mental State Examination (MMSE) (Folstein et al., 1975), Revised Version of Hasegawa's Dementia Scale (HDS-R) (Imai and Hasegawa, 1999), Raven's Colored Progressive Matrices (RCPM) (Hodges, 1993), Digit Span Task, learning of a list of 10 words and Story Recall (Hodges, 1993), Ray-Osterrieth Complex Figure Test (Hodges, 1993), Stroop Test, and Trail Making Test (Anne and Stephan, 1969). All tests were performed and scored according to the standard protocols. The demographic characteristics of the patients including age, sex, MMSE, and HDS-R at the time of the first evaluation are listed in Table 1.

Seventy-six normal healthy volunteers (37 men, 39 women; age range, 67–87 years; mean age ± SD, 71.0 ± 7.1 years) were also studied. They had no neurologic or psychiatric disorders, including alcoholism, substance abuse, atypical headache, head trauma with loss of consciousness, and asymptomatic cerebral infarction detected by T2-weighted MRI. They did not significantly differ in age, sex, or education from the FTD patients.

SPECT image data of the normal healthy volunteers in the present study have previously been reported (Imabayashi et al., 2004).

Written informed consent was obtained from all the participants or their family according to the Declaration of Helsinki. The study was approved by the Ethical Committee of the National Center of Neurology and Psychiatry.

Assessment of antisocial behaviors

Semi-structured interviews with the family members were conducted to obtain information regarding the behaviors of interest. For the interview, we used the modified version of Neuropsychiatric Inventory (NPI) (Cummings et al., 1994). By applying the method of NPI, which assesses the Behavioral and Psychological Symptoms of Dementia (BPSD) in patients basically with Alzheimer's disease, the antisocial behaviors were evaluated as follows. The frequency and severity were respectively graded for the 5 behavioral symptoms based on the study by Miller et al. (1997): (1) stealing, (2) traffic accident (e.g. hit and run), (3) physical assault, (4) sexual comments/advances, and (5) public urination. The frequency was assessed on the basis of the observation during the previous 2 months (1 = once in 2 months, 2 = once per month, 3 = 2 or 3 times per month, 4 = once or more every week). The severity was assessed according to the degree of patient's awareness of his or her own antisocial behaviors (0 = full awareness, 1 = moderate awareness, 2 = mild awareness, 3 = no awareness). The NPI assesses BPSD on the basis of both frequency and severity; BPSD scores are obtained by multiplying the severity and the frequency scores. Therefore, the frequency and the severity scores were multiplied for each behavior, respectively, and then summed (maximum score = 60) to be used as covariate factor for SPM analysis in this study.

Table 1
Demographic variables of FTD patients

n	22	
Age (year)	62.9 (5.9)	Range: 52–74
Sex (M/F)	14/8	
Duration of illness (years)	4.1 (1.8)	Range: 2–9
Mini mental state examination (MMSE)	14.8 (7.7)	Range: 0–26
Hasegawa's dementia scale revised (HDS-R)	13.8 (7.1)	Range: 0–24
Raven's colored progressive matrices (RCPM)	22 (8.7)	Range: 5–33
Digit span		
Forward	4.6 (1.0)	Range: 3–7
Backward	2.3 (1.5)	Range: 0–4
Word learning (10 words)		
Immediate recall	1.6 (1.6)	Range: 0–4
Delayed recall (30 min)	1.1 (1.7)	Range: 0–4
Story recall (15 elements)		
Immediate recall	2.3 (2.4)	Range: 0–7.5
Delayed recall (30 min)	0.2 (0.6)	Range: 0–2
Ray-Osterrieth complex figure test		
Copy	27.5 (11.0)	Range: 5.5–36
Immediate recall	4.9 (6.9)	Range: 0–23
Delayed recall (30 min)	3.6 (7.1)	Range: 0–24
Stroop test		
Dot	58 (sec) (44.5)	Range: 19–132 (sec)
Word	120.7 (sec) (82.2)	Range: 27–165 (sec)
Word-dot	63.1 (sec) (47.4)	Range: 38–134 (sec)
Trail making		
Set A	335.6 (sec) (130.2)	Range: 255–621 (sec)

Note. Values are expressed as mean and (standard deviation). M = male, F = female, *n* = size, sec = second.

These antisocial behaviors were assessed independently by three geriatric psychiatrists (TA, SH, NK), who had not been given the information of the SPECT images. Whenever the scores were different among the psychiatrists, the mean score of the three psychiatrists was employed.

Brain SPECT procedure

Each subjects received an intravenous injection of 600 MBq of ^{99m}Tc-ECD while lying supine with eyes closed in a dimly lit, quiet