表 1　地域支援事業による基本チェックリストにおける「閉じこもり」の把握

質問項目	質問項目の趣旨
① 週に1回以上は外出していますか。	週によって外出頻度が異なる場合は，過去1カ月の状態を平均して下さい。
② 昨年と比べて外出の回数が減っていますか。	昨年の外出回数と比べて，今年の外出回数が減少傾向にある場合は「はい」となります。

（厚生労働省：地域支援事業の実施について．"基本チェックリスト" より一部抜粋）

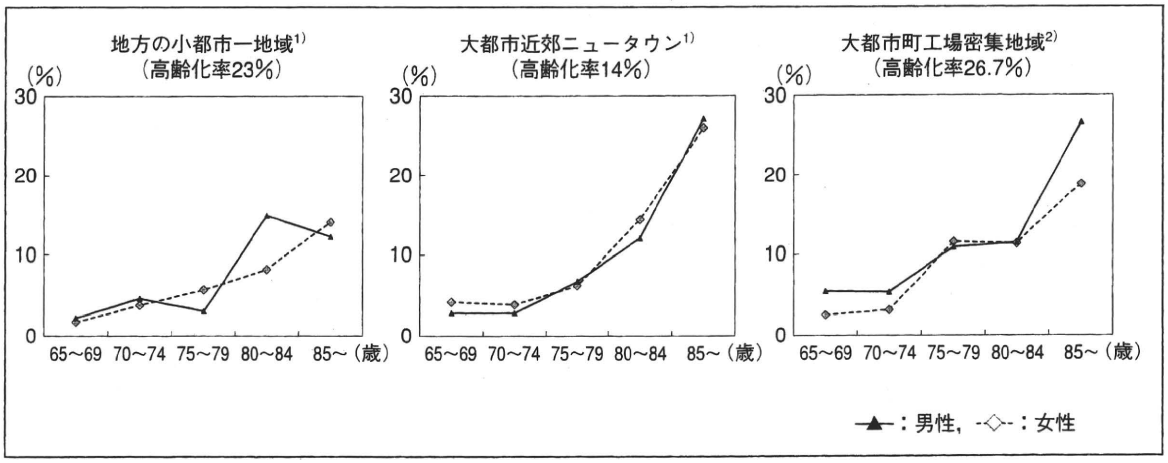

図 1　高齢者における地域特性の違いによる性，年齢階級別にみた「閉じこもり」の出現率

（新開省二，藤田幸司，藤原佳典，ほか：地域高齢者におけるタイプ別閉じこもりの出現頻度とその特徴．日本公衆衛生雑誌，52（6）：449，2005 より一部引用し，著者らによるデータ（2006 年調査）を加え，比較）

域（人口 16968 人，調査回収率 75.6%）の筆者らの調査データを追加したものである。

各地域の全高齢者における「閉じこもり」の出現率は，地方の小都市では 5.4%，大都市近郊ニュータウンでは 6.8%，大都市町工場密集地域では 6.7% であり，地域高齢者における「閉じこもり」の発生率は，約 5～6% 程度と考えられる。また，**図 1** より，高齢になるほど「閉じこもり」が出現しやすく，特に大都市部や近郊ニュータウンなど人々の交流が希薄と考えられる地域では 75 歳以上になると急激に「閉じこもり」の出現率が高まることがわかる。また，高齢者の「閉じこもり」の出現状況は地域特性によって，異なることが推測される。

3 「閉じこもり」の特徴

「閉じこもり」の高齢者は，生活機能が低下している状態であるため，その後の身体的・心理的機能の予後は悪く，要介護状態になりやすいと考えられる。

今までの我が国における追跡調査データにおける「閉じこもり」の高齢者の変化をみると，1 年程度の短期間では「閉じこもり」の高齢者の自己効力感[9)]や意欲[10)]などが低下しやすいことが示されている。さらに長期的な「閉じこもり」の高齢者の変化を追跡したときには，**図 2** のように，「閉じこもり」や「閉じこもり」がちな高齢者は日常生活動作が低下しやすいことが示されている[11)]。このこと

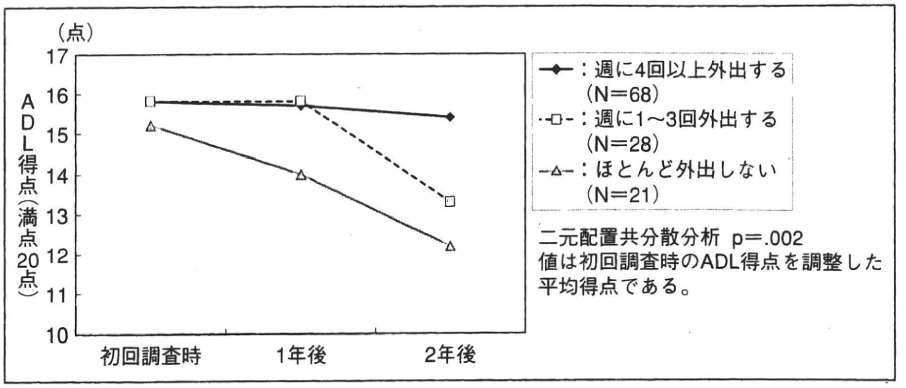

図 2　地域高齢者における外出頻度による2年間のADLの変化
（Kono A, et al.：Archives of Gerontology & Geriatrics 45：233-242, 2007 より引用）

は，他の疫学調査[12~14]においても同様の結果が明らかになっている。

さらには，高齢者が「閉じこもり」になる要因として，住んでいる地域への愛着が少ない[15]，外出に誘ってくれる人[15]や親しい友人がない[16]，低学歴である[15]，高齢である[15]，認知機能が低い[16]，抑うつ傾向である[16]，散歩や体操などの習慣がないこと[16]などが指摘されている。

4 「閉じこもり」に対するケア

1）1次予防

「閉じこもり」への1次予防として，「閉じこもり」の発生を予防するための健康づくりと環境整備を行うために一般住民や健康な高齢者に対して「閉じこもり」に関する意識啓発と高齢者の社会参加を促進していくことが挙げられる。そのためには人々が「閉じこもり」の弊害と予防の必要性を知り，自ら主体的に解決できる方法を考える力がもてるように地域づくりを行うことが必要である。

2）2次予防

2次予防としては，地域高齢者のなかで「閉じこもり」をできるだけ早期に発見し，「閉じこもり」のリスクの高い高齢者に対して，適切な支援を行うことが考えられる。ケアマネジメント，訪問看護，訪問指導，各種相談など個別ケアの中で「閉じこもり」がちな高齢者を把握した場合は，介護予防事業や通所系サービス，ほか地域のグループケア活動などにつなげるように支援する。グループケアを企画運営する場合は，アクティビティ，健康教育などさまざまなプログラムをとおして，高齢者同士または地域の人々との交流を深め，「閉じこもり」を予防することをめざす。グループケアでは，初めての人でも参加しやすく，気軽に参加が継続できる楽しい雰囲気をつくるように配慮し，送迎と会場の設定，参加対象者の集め方，実施頻度や実施期間なども目的や状況に応じて工夫することが大切である。

3）3次予防

3次予防としては，「閉じこもり」の高齢者に対して，機能回復を促し，その生活の質が向上できるようにケアを提供することが挙げられる。すでに「閉じこもり」になった高齢者には，通所系サービスや外出を勧めても高齢者や家族が応じないことが多い。しかし，そのような場合であっても，定期的に訪問をするなど継続的にかかわり，高齢者や家族にサービス利用や外出を無理強いせずに，信頼関係をつくるように努める。高齢者や家族とかかわる中で，身だしなみを整える，ベッドから居間に生活行動範囲を拡げる，庭先まで

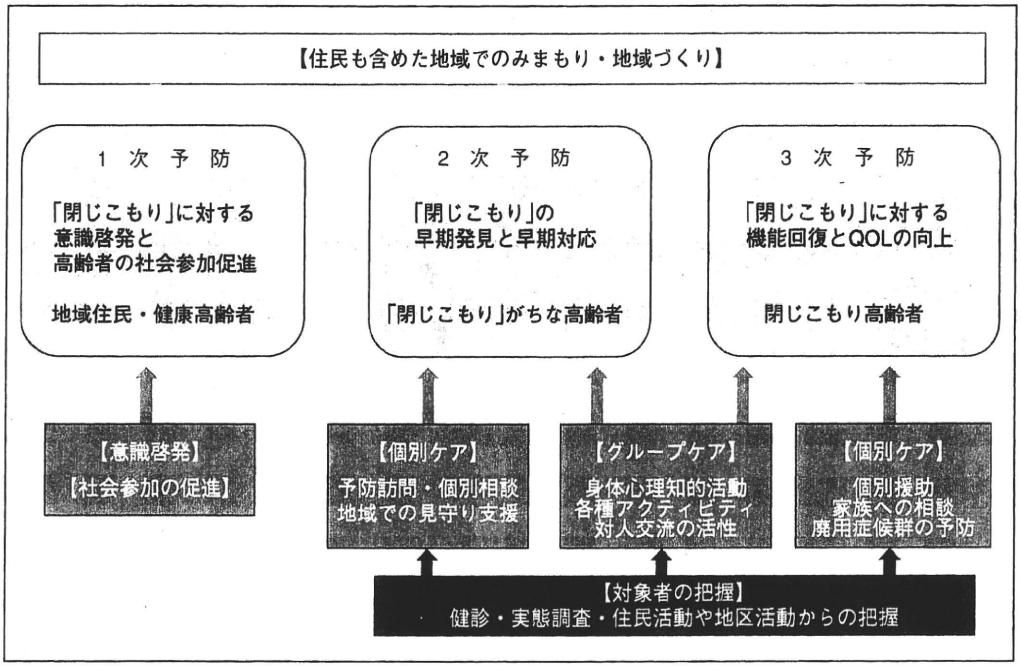

図 3 「閉じこもり」の高齢者への地域ケア

（金川克子，監修，田高悦子・河野あゆみ，編：老年症候群看護ケア関連図＆ケアプロトコル．pp278-279，中央法規出版，2008より許諾を得て一部改変）

でる機会を設ける，近くまで散歩にでかけるなど身近なことを目標におきながら，可能な限り「閉じこもり」を解消する。

4）「閉じこもり」に対するケアの特徴

以上の「閉じこもり」の1次予防から3次予防をふまえ，高齢者の「閉じこもり」に対するケアの概要[17]を**図3**に示す。

「閉じこもり」に対するケアの特徴として，次の3点について工夫するべきと考える。

第1に，地域ケア活動の中で「閉じこもり」の高齢者を適切に効率よく把握することが重要である。その地域で「閉じこもり」を把握するための，簡便で妥当性の高い指標を適切なスクリーニング・方法で活用するようにする。このスクリーニング方法には健診などだけではなく，地域住民から「閉じこもり」の高齢者の情報を直接把握するという保健医療福祉職などの地区活動や実践活動なども含まれる。

第2に，「閉じこもり」は，身体・心理・社会的な要因が多様にかつ，複合的に影響されて起こる生活機能低下状態といえるため，地域ケア活動では，医療，保健，介護，福祉など多分野の特性を生かした学際的なアプローチとケアが必要である。

第3に，**図3**に示すように，「閉じこもり」には，特定のケアのみで予防したり，支援できるものではなく，地域での見まもりや地域づくり，意識啓発，個別ケア，グループケアなど様々なケアを組み合わせながら，包括的なアプローチを行うことが重要と考えられる。

■ 重要ポイント

1. 「閉じこもり」とは高齢者の生理的・身体的・心理的・社会的要因が複合的に関与しておこる生活機能が低下している状態

であり，外出頻度が週１回程度以下の者を操作的に定義することができる。

2. 地域高齢者における「閉じこもり」の発生率は約5〜6%程度であると考えられる。

3. 「閉じこもり」の高齢者の身体的・心理的機能の予後は悪く，要介護状態になりやすい。

4. 「閉じこもり」には１次予防から３次予防まで多様なアプローチが考えられ，地域での見まもりや地域づくり，意識啓発，個別ケア，グループケアなど様々なケアを組み合わせながら包括的アプローチを行うことが重要である。

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Original Research Article

Different Characteristics of Cognitive Impairment in Elderly Schizophrenia and Alzheimer's Disease in the Mild Cognitive Impairment Stage

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Key Words
Alzheimer's disease · Attention deficit · Delayed recall · Executive function · Recent memory · Three-dimensional stereotactic surface projections · Voxel-based specific region analysis · Working memory

Abstract
We compared indices of the revised version of the Wechsler Memory Scale (WMS-R) and scaled scores of the five subtests of the revised version of the Wechsler Adult Intelligence Scale (WAIS-R) in 30 elderly schizophrenia (ES) patients and 25 Alzheimer's disease (AD) patients in the amnestic mild cognitive impairment (aMCI) stage (AD-aMCI). In the WMS-R, attention/concentration was rated lower and delayed recall was rated higher in ES than in AD-aMCI, although general memory was comparable in the two groups. In WAIS-R, digit symbol substitution, similarity, picture completion, and block design scores were significantly lower in ES than in AD-aMCI, but the information scores were comparable between the two groups. Delayed recall and

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forgetfulness were less impaired, and attention, working memory and executive function were more impaired in ES than in AD-aMCI. These results should help clinicians to distinguish ES combined with AD-aMCI from ES alone.

Introduction

Schizophrenia is a common psychiatric disease with onset usually occurring during adolescence or early adulthood. Recently, new atypical antipsychotic drugs for schizophrenia have been developed, and social systems to support schizophrenia patients have been established. As a result, schizophrenia patients are now living longer than they used to [1], and the number of elderly schizophrenia (ES) patients is increasing. The number of Alzheimer's disease (AD) patients has also increased due to the rapid aging of society. Although the incidence of AD rises with age, AD also occurs in younger patients; the prevalence rate of AD in people aged ≤64 years is 0.12 cases per 1,000 people (http://www.mhlw.go.jp/houdou/2009/03/h0319-2.html; Japanese Ministry of Health, Labor and Welfare). Therefore, there are many ES patients who also have AD, and their number is supposed to be increasing. In clinical settings, there is a growing need to differentiate between age-related and AD-related cognitive impairment in patients who have developed schizophrenia in adolescence or middle age.

Because some clinical characteristics of schizophrenia and AD are similar, differentiation between ES and AD can be difficult. Neuropsychiatric symptoms, such as apathy, poverty of speech, and delusional thinking, are common in both types of patients. Neuroimaging studies have shown volume loss in the hippocampus [2] and in the frontal lobe [3] in schizophrenia, and similar losses have been observed in AD [4]. Furthermore, patients with schizophrenia are impaired in various domains of cognition, such as memory, working memory, and executive function [5]. These symptoms are also observed in patients with AD.

Acetylcholine esterase inhibitors have been developed for the treatment of AD. Although administration of these agents does not result in a radical improvement of symptoms, their early administration can improve the prognosis of AD patients [6]. In addition, disease-modifying drugs for AD are now being developed. Thus, early diagnosis and early initiation of treatment are important in AD patients. One method to identify early AD with a high probability is the measurement of amnestic mild cognitive impairment (aMCI), which is a syndrome characterized by memory performance below the age norm, while intellectual functioning and activities of daily living are otherwise unimpaired [7]. A substantial proportion of patients with aMCI later develop clinically diagnosable AD [7]. In order to treat early-stage ES patients who have AD in the aMCI stage (AD-aMCI) for AD, it is necessary to differentiate between ES combined with AD, and ES alone. As a first step toward this goal, in this study, we clarified the degree of cognitive impairment in patients with ES compared to patients with AD-aMCI.

Methods

Subjects

All patients in this study were recruited from the Department of Neuropsychiatry of the Osaka University Medical Hospital, which includes Schizophrenia and Neuropsychological Clinics. At both clinics, patients underwent standard neuropsychological examinations as well as routine laboratory tests and cranial magnetic resonance imaging (MRI). Single pho-

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Table 1. Comparison of characteristics of the ES and AD-aMCI groups with and without WAIS-R

Characteristics	ES group			AD-aMCI group		
	with WAIS-R	without WAIS-R	p value	with WAIS-R	without WAIS-R	p value
Sex, male/female	5/9	10/6	0.14	7/6	7/5	0.57
Age, years	56.6 ± 5.5	57.1 ± 5.7	0.79	72.6 ± 6.0	70.2 ± 9.5	0.44
Education, years	13.1 ± 2.6	13.3 ± 2.2	0.79	13.7 ± 3.3	13.4 ± 1.8	0.8
MMSE total score	–	–	–	26.1 ± 1.9	27.0 ± 2.1	0.27
WMS-R GM index	81.3 ± 15.5	79.1 ± 17.0	0.75	80.5 ± 13.1	74.9 ± 6.1	0.19
WMS-R AC index	84.8 ± 10.3	94.8 ± 16.0	0.09	99.8 ± 11.1	97.3 ± 12.7	0.59
WMS-R DR index	75.9 ± 15.9	76.6 ± 18.4	0.92	61.5 ± 9.7	55.8 ± 6.5	0.1

ton emission computed tomography (SPECT) was performed on patients with aMCI at the Neuropsychological Clinic. The clinical and investigative data were collected in a standardized manner and were entered into each registry. In this study, we selected patients with ES and patients with AD-aMCI who met the inclusion criteria mentioned below for each group from the registry. In the Schizophrenia Clinic, we began using the revised version of the Wechsler Adult Intelligence Scale (WAIS-R) in March 2004 and then switched to the third version of the WAIS (WAIS-III) in October 2006. In the Neuropsychological Clinic, we began using five subtests of the WAIS-R in September 2002 and switched to five subtests of the WAIS-III in February 2009. In this study, we selected patients who were evaluated with the WAIS-R, because few patients with AD-aMCI were evaluated with the WAIS-III and then followed up until they reached the dementia stage. The revised version of the Wechsler Memory Scale (WMS-R) has been used in both clinics as a memory test because the third version of the WMS (WMS-III) is not standardized and cannot be used in Japan. In both clinics, the WMS-R was usually used before the WAIS-R. However, in some cases, there was no opportunity to use the WAIS-R.

ES Group

Thirty patients with schizophrenia (15 women and 15 men) were selected from the Schizophrenia Clinic registry. The mean age of the patients was 56.9 ± 5.5 years, and the mean years of education were 13.2 ± 2.3. All subjects in the ES group (1) met the criteria for schizophrenia based on the Structured Clinical Interview of the Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision (DSM-IV-TR); (2) were aged ≥50 years [8]; (3) showed first symptoms of schizophrenia before 65 years of age; (4) had been evaluated by either the WMS-R or the WAIS-R; (5) had no other neurological disease, and (6) had no evidence of focal brain lesions on MRI. Of the 30 patients, 14 were given the WAIS-R (group with WAIS-R) and the other 16 were not given the WAIS-R (group without WAIS-R). There were no significant differences in gender, age, education, or WMS-R indices between the ES groups with and without WAIS-R (table 1). Other demographic data on the ES group are summarized in table 2. Mean duration of hospitalization was short, although mean duration of disease was long. Many patients received atypical antipsychotic drugs at the time of neuropsychological assessment in this study. There were no significant differences between the groups with and without WAIS-R in any of the items except for the positive/negative symptom scores of the Positive and Negative Syndrome Scale (PANSS). Both PANSS scores were higher in the group without WAIS-R than in the group with WAIS-R. Four of the 30 patients with ES were not given the WMS-R.

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Table 2. Characteristics of the ES group

Characteristics	ES with WAIS-R mean ± SD	ES without WAIS-R mean ± SD	p value	Total mean ± SD (range)
Age of disease onset, years	32.3 ± 12.0	30.1 ± 12.3	0.64	31.1 ± 12.0 (19.0–61.0)
Duration of untreated psychosis, years	3.6 ± 6.5	4.1 ± 8.4	0.87	3.9 ± 7.5 (0–26)
Duration of disease, years	23.8 ± 11.7	27.4 ± 10.7	0.41	25.8 ± 11.1 (1–45)
Total duration of hospitalization, months	14.0 ± 12.2	9.7 ± 19.6	0.56	11.4 ± 16.8 (0–72)
Daily dose of antipsychotic drugs (chlorpromazine equivalent), mg	554.7 ± 283.6	469.1 ± 387.6	0.5	509.0 ± 340.0 (0.0–1,300.0)
Daily dose of atypical antipsychotic drugs (chlorpromazine equivalent), mg	485.7 ± 306.6	318.8 ± 379.9	0.2	396.7 ± 352.0 (0.0–1,300.0)
PANSS score				
Positive symptoms	12.3 ± 4.6	16.3 ± 4.4	0.03	14.5 ± 4.8 (5–28)
Negative symptoms	12.3 ± 3.2	18.3 ± 6.5	0.01	15.5 ± 6.0 (7–30)
Overall severity in the Drug-Induced Extra-Pyramidal Symptoms Scale (n = 21)	0.90 ± 1.9	0.86 ± 0.7	0.94	0.88 ± 1.3 (0–6)

AD-aMCI Group

Twenty-five AD-aMCI patients were selected from the Neuropsychological Clinic registry. The number of males exceeded the number of females (14 males and 11 females). The mean age of the patients was 71.4 ± 7.8 years, the mean years of education were 13.6 ± 2.6, and the mean MMSE score was 26.5 ± 2.0. All subjects in the AD-aMCI group met the criteria for aMCI, which included (1) a memory complaint documented by the patient or another source; (2) a score in the story A recall task in the logical memory II subtest of WMS-R which is less than the age-corrected and education-corrected cutoff score; (3) a score of ≥24 on the MMSE; (4) a total Clinical Dementia Rating (CDR) score of 0.5 and a memory CDR score >0; (5) normal basic and instrumental activities of daily living evaluated with Lawton's Physical Self-Maintenance Scale and Instrumental Activities of Daily Living Scale [9], and (6) no symptoms of dementia based on a clinical examination and an extensive interview with a knowledgeable informant. All subjects in this group also (7) had been evaluated by either the WMS-R or the short form of the Japanese version of the WAIS-R, (8) had no other neurological disease, and (9) had no evidence of focal brain lesions on MRI. To confirm that the aMCI patients had AD in the preclinical stage, at least one of the following three criteria had to be fulfilled: (1) atrophy in the entorhinal cortex on MRI, (2) hypoperfusion in the posterior cingulate cortex (PCC) and precuneus on SPECT, or (3) progression to AD during annual follow-ups. Progression to AD was defined as meeting the criteria of the National Institute of Neurological Disease and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) for probable AD and a total CDR score of ≥1.0.

Progression to AD from aMCI during the subsequent follow-ups (up to 8 years) was confirmed in 17 of the 25 patients. Nineteen of the 25 AD-aMCI patients received three-dimensional spoiled gradient echo MRI, which identified atrophy in the entorhinal cortex in 13 of the 19 patients. Twenty-three of the 25 AD-aMCI patients received N-isopropyl-p-[^{123}I]-iodoamphetamine (^{123}I-IMP)-SPECT, and hypoperfusion in either the PCC or precuneus was identified in 12 of the 23 AD-aMCI patients. One patient was recruited due to abnormality on the MRI and 7 patients were recruited due to abnormality on SPECT. Of the 25 patients, 13 were given the five subtests of the WAIS-R (group with WAIS-R) but the other 12 were not (group without WAIS-R). There were no significant differences in gender, age, education,

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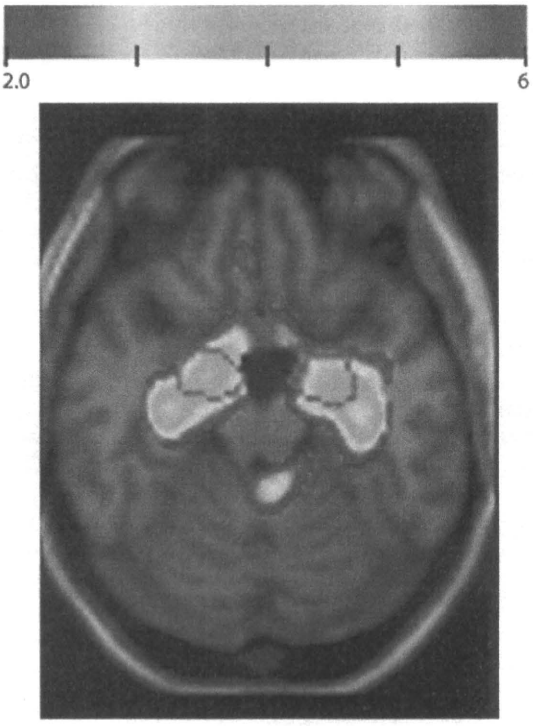

Fig. 1. Z-score map overlaid on an MRI template of a representative patient with AD-aMCI made with VSRAD. This patient was included in the study because of the presence of significant atrophy in the entorhinal cortices on MRI. Parts of the colored areas are in the areas circumscribed by purple lines, indicating significant atrophy in the entorhinal cortices. Purple lines indicate the bilateral entorhinal cortices. Colored areas on MRI are those with a Z-score >2 (significant atrophy). Color bar indicates Z-score.

MMSE score or WMS-R indices between the two groups with and without WAIS-R (table 1). All AD-aMCI patients were administered the WMS-R.

Comparison of Demographic Data in the ES and the AD-aMCI Groups

There was no significant difference between the ES and the AD-aMCI groups in terms of sex ($p = 0.48$, χ^2 test) or education ($p = 0.71$, t test). However, the ES group was significantly younger than the AD-aMCI group ($p < 0.001$, t test).

MRI and SPECT Criteria for the AD-aMCI Group

MRI was performed on a 1.5-tesla system (Signa Excite HD 12x; General Electric Medical Systems, Milwaukee, Wisc., USA). A three-dimensional volumetric acquisition of a T1-weighted gradient echo sequence produced a gapless series of thin sagittal sections that covered the whole calvarium. The operating parameters were as follows: field of view = 240 mm, matrix = 256×256, 124×1.40 mm contiguous sections, TR = 12.55 ms, TE = 4.20 ms, and flip angle = 15°. The three-dimensional T1-weighted MRI data of the patients were analyzed with the voxel-based specific region analysis for AD (VSRAD) [10] (fig. 1). VSRAD contained the MRI data of normal control subjects with a wide age range and could automatically compare the gray matter intensities of the MRI data on a voxel-by-voxel basis between an aMCI patient and age-comparable normal control subjects after a series of steps including segmentation, anatomical standardization and smoothing using Statistical Parametric Mapping 2002 (SPM2; Wellcome Department of Imaging Neuroscience, London, UK). The Z-score is calculated on a voxel-by-voxel basis as (Is – Ic)/SD where Is and Ic are the gray matter intensities of an aMCI patient and the mean of normal control subjects, respectively, and SD is the standard deviation of the gray matter intensities of the normal control subjects. The region of interest was set to the entorhinal cortex in the VSRAD software. Atrophy corresponding to a Z-score >2.0 in the entorhinal cortex was used as a criterion for AD in the VSRAD method.

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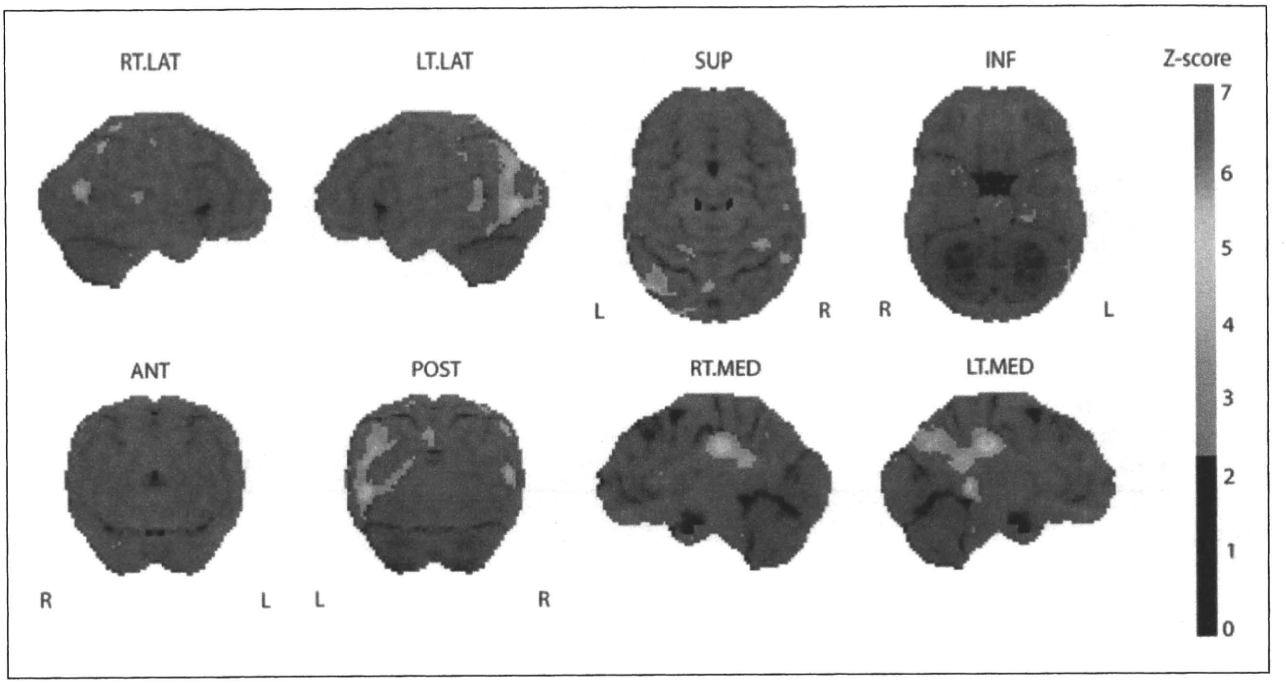

Fig. 2. Z-score map of a representative patient with AD-aMCI made with 3D-SSP. This patient was included in the study because of the presence of hypoperfusion in the PCC and precuneus on SPECT. Colored areas contain PCC and precuneus. Colored areas with significant rCBF reduction with a Z-score of >2.32 were overlaid on original surface images from eight views. Color bar indicates Z-score. RT.LAT = Right lateral; LT.LAT = left lateral; SUP = superior; INF = inferior; ANT = anterior; POST = posterior; RT.MED = right medial; LT.MED = left medial.

^{123}I-IMP-SPECT was performed with a SPECT scanner (SPECT-2000H; Hitachi Medical Co., Tokyo, Japan) and a four-head rotating gamma camera. SPECT data were analyzed using three-dimensional stereotactic surface projection (3D-SSP) software [11] (fig. 2). 3D-SSP contained ^{123}I-IMP-SPECT data of normal control subjects with a wide age range and could automatically compare the regional cerebral blood flow (rCBF) between an aMCI patient and age-comparable normal control subjects. The peak cortical values of the SPECT data were projected back and assigned to the original surface images from eight views on a pixel-by-pixel basis. Z-score was calculated on a pixel-by-pixel basis as (Is – Ic)/SD where Is and Ic are the rCBFs of an aMCI patient and the mean of normal control subjects, respectively, and SD is the standard deviation of the rCBF of the normal control subjects. Areas with a Z-score >2.32 (the significance level of the Z-score) were overlaid on original surface images from eight views. With the computer program Stereotactic Extraction Estimation (SEE) we determined which gyri included the regions with a Z-score >2.32 [12]. In SEE, the percentage of areas with a Z-score >2.32 in each gyrus was calculated and the percentage was called the 'extent'. The presence of areas of hypoperfusion, in which both the Z-score was >2.32 and the extent was >10% [13] in either the PCC or precuneus, was used as the inclusion criteria for AD in the aMCI stage.

Assessment of Cognitive Functions

The attention/concentration (AC) index in the WMS-R was used for measuring attention and working memory, the general memory (GM) index was used for recent memory, and the delayed recall (DR) index for delayed memory. For each index, the normal range is

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Table 3. Cognitive impairment in ES and AD-aMC patients

Test/subtest	ES group	AD-aMCI group	p value
WMS-R			
GM index	80.0 ± 16.2	77.8 ± 10.5	0.58
AC index	91.0 ± 14.7	98.6 ± 11.7	0.046
DR index	76.3 ± 17.2	58.8 ± 8.6	<0.001
GM-DR	3.6 ± 10.7	19.9 ± 8.6	<0.001
WAIS-R			
Information	10.1 ± 3.7	11.2 ± 2.8	0.37
Digit symbol substitution	8.0 ± 2.7	11.6 ± 2.3	<0.001
Similarity	9.9 ± 3.2	12.5 ± 2.2	0.024
Picture completion	8.5 ± 4.0	11.2 ± 1.8	0.037
Block design	8.4 ± 2.7	11.5 ± 1.9	0.0018

between 80 and 120 and the mean index of normal subjects is 100. We also defined a new index equal to the GM index minus the DR index (GM-DR), which is a measure of the degree of forgetfulness.

For the WAIS-R, five test data were used in this study. Four of the five subtests were information, digit symbol substitution, similarities, and picture completion, which were selected according to the manual of the short form of the Japanese version of the WAIS-R [14]. Another was a block design to evaluate visuoconstructive function directly, as this dysfunction is a common symptom in AD patients. In each age-corrected score of the subtest, the normal range is between 7 and 13 and the mean score of normal subjects is 10.

Statistical Analyses

Age-corrected scores of both the WMS-R and the five subtests of the WAIS-R were compared between the two groups using a t test. The significance level was set at $p < 0.05$.

Results

Results of the WMS-R

In this study, the mean GM indices in the two groups were around the lower limit of the normal range, and the mean AC indices in ES and AD-aMCI were normal (table 3). The mean DR index of ES was slightly below the normal range, but the mean DR index of AD-aMCI appeared to be significantly lower. The GM indices of the two groups were comparable. The AC index was significantly lower and the DR index was significantly higher in ES than in AD-aMCI. The difference in the GM and DR scores (GM-DR), which is a measure of the degree of forgetfulness, was significantly lower in ES than in AD-aMCI.

Results of the Five Subtests of the WAIS-R

The mean scores of all the subtests of the WAIS-R in this study in both groups were within the normal range (table 3). The information scores of the two groups were comparable, but scores of the digit symbol substitution, similarity, picture completion, and block design subtests were significantly lower in ES than in AD-aMCI.

Dement Geriatr Cogn Disord Extra 2011;1:20–30
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Discussion

We could not confirm that all AD-aMCI patients in this study developed AD to the dementia stage. However, we were able to select aMCI patients that had AD-specific findings on MRI or SPECT in this study. Pathological abnormalities related to AD, neurofibrillary tangles and neuronal loss, were found to be present in the entorhinal cortex of AD in aMCI stage [15], leading to atrophy in the region on MRI [16]. Because the entorhinal cortex is functionally connected to the PCC [17], the reduction of rCBF in the PCC was probably caused by the abnormal pathology in the entorhinal cortex. In addition, atrophy in the entorhinal cortex on MRI [18] and reduction of rCBF in the PCC and precuneus on SPECT [19] predict progression from MCI to AD. We used two reliable and user-independent statistical image-analyzing methods, VSRAD and 3D-SSP, to detect AD-specific abnormalities in the MR and SPECT images.

This is the first report to compare cognitive impairment between ES and AD-aMCI. The WMS-R GM indices of the two groups were comparable, indicating a similarity in the impairment of recent memory between the two groups. Some previous studies compared recent memory in ES and AD at the dementia stage. There is some disagreement on whether recent memory is better [20] or worse [21] in ES than in AD in the dementia stage. aMCI is a relatively homogeneous group with respect to memory impairment, because the definition of aMCI includes the degree of memory impairment. However, the severity of recent memory impairment could vary in patients with ES. The ES patients in this study were mild cases, because they could complete the WMS-R or WAIS-R, which are comprehensive tests, and the mean duration of their hospitalization was short. Thus, the recent memory tests in this study indicated that the recent memory scores of ES patients with mild cognitive impairment were comparable with those of AD-aMCI patients, and, therefore, that recent memory was not useful for distinguishing between ES and AD-aMCI.

The fact that the WMS-R GM indices were comparable in the ES and AD-aMCI groups indicates that the two groups in this study had similar degrees of impairment of recent memory. This narrows down the difference between the two groups to differences in other cognitive impairments, such as forgetfulness, and impairments of DR, attention, working memory and executive function. The WMS-R GM-DR scores were lower and the DR scores were higher in ES than in AD-aMCI, indicating that the degree of forgetfulness was less and DR was better in ES. On the other hand, the AC was lower in ES than in AD-aMCI, indicating that ES patients had more impaired attention and working memory than AD-aMCI patients. DR was found to be better in ES patients than in AD patients in the dementia stage [21], and forgetfulness did not increase in ES patients but increased in AD patients in the dementia stage [20]. The present study confirmed that memory after a short while was retained in ES but not in AD. In addition, we found that the retention in ES patients was better than in AD even at the aMCI stage, which should help to distinguish ES from AD in the very early stage.

The hippocampus, parahippocampus, and entorhinal cortex have traditionally been thought of as the principal structures responsible for the consolidation of short-term stores into long-term memory. Significant associations between hippocampal size and memory have not been observed in schizophrenia [22], although size reductions in the hippocampus have been reported in schizophrenia [2]. In addition, memory capabilities were similar to general intellectual abilities in ES [23]. Therefore, damage in the medial temporal lobe may not play an important role in memory impairment in schizophrenia. On the other hand, memory impairment in AD is inversely associated with hippocampal volume [24].

The ES group was more impaired on the digit symbol substitution, similarities, picture completion, and block design subtests of WAIS-R than the AD-aMCI group, and each subtest score in the ES group was below the mean of each score of the general population in this study. Although the block design subtest was used to evaluate visuoconstructive function in

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Published online: January 6, 2011

this study, attention and executive function are required to perform the block design subtest [25]. Thus, these findings confirmed that attention, working memory, and executive function are impaired in ES. Previous studies reported that ES patients were impaired in the WAIS-R digit symbol substitution, similarities, picture completion, and block design subtests [21], and in attention, working memory, and executive function [20]. These studies also reported that impairment in these functions were comparable in ES and AD patients in the dementia stage. The differences in cognitive impairment that we found in ES and AD-aMCI deviate from those found in previous studies. This discrepancy may be due to differences in the severity of cognitive impairments in the AD-aMCI patients in this study compared to the AD patients in the dementia stage in previous studies.

Which region of the brain is responsible for the difference in attention, working memory, and executive function in the two groups? Impairments in cognitive function in patients with schizophrenia were found to be related to dysfunction of the prefrontal cortex (PFC) [26]. On the other hand, gray matter loss on MRI [27] and pathological abnormality [28] in the PFC were not observed in AD-aMCI, and gray matter loss on MRI was observed at the time of progression from aMCI to AD [27]. These results suggest that differences in impairment in attention, working memory, and executive function in the two groups probably reflect the difference in impairment in the PFC.

The WAIS-R information scores of the ES and AD-aMCI groups were comparable and within the normal range, being consistent with those of a previous study [29]. Semantic memory may be preserved in ES and AD-aMCI patients because they have less impairment in the inferior and anterior temporal lobe regions, which crucially contribute to semantic cognition [30].

There were some limitations in this study. First, approximately half of the patients in each group were not given the WAIS-R. Second, the ES patients in this study were younger than the AD-aMCI patients, and cognitive function in schizophrenia patients undergoes a marked decline after 65 years of age [8]. Third, we did not control the effects of medication on the cognitive test scores in ES patients. Most ES subjects in this study had received atypical antipsychotic drugs, which might improve cognitive function [31]. These issues should be taken into consideration before the findings are generalized.

In this study, DR and forgetfulness were less impaired in ES than in AD-aMCI, while attention, working memory, and executive function were more impaired in ES than in AD-aMCI. The results of this study should help clinicians to distinguish patients with ES from patients with AD-aMCI and might also give us some clues for distinguishing ES combined with AD-aMCI from ES alone. The next step is to clarify the difference in the characteristics of cognitive impairment in ES combined with AD-aMCI compared to ES alone.

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Disclosure Statement

The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

Protein synthesis in the posterior cingulate cortex in Alzheimer's disease

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Key words: *Alzheimer's disease, cerebral blood flow, L-[methyl-^{11}C] methionine, positron emission tomography, posterior cingulate cortex, protein synthesis, single photon emission computed tomography.*

Abstract

Background: Neuroimaging studies using ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) and single photon emission computed tomography (SPECT) have shown that the posterior cingulate cortex (PCC) is the primary and most prominent area of cerebral metabolic and perfusional decrement in early Alzheimer's disease (AD). We carried out the present preliminary study to investigate whether a decline of cerebral blood flow (CBF) in the PCC in early to moderate AD was accompanied with that of cerebral protein synthesis (CPS).

Methods: We carried out both N-isopropyl-p-[123I] iodoamphetamine SPECT (IMP-SPECT) and L-[methyl-11C] methionine positron emission tomography (MET-PET) in eight AD patients with apolipoprotein E epsilon 4 allele in the early to moderate stage. We also carried out IMP-SPECT in eight healthy controls (HC). We located 32 regions of interest (ROI), and values of regional MET or IMP uptakes were averaged in five regions; the frontal lobe (FL), the parietal lobe (PL), the medial temporal lobe (MTL), PCC and the occipital lobe. Furthermore, the values in the FL, PL, MTL and PCC were divided by values in the occipital areas, and normalized values of regional CBF (rCBF) and CPS (rCPS) were calculated. Then, the rCBF in the FL, PL, MTL and PCC were compared between AD and HC. In addition, the rCBF and rCPS were compared in the FL, PL, MTL and PCC of AD.

Results: The rCBF in the PCC, but not in the other three regions, was significantly lower in AD than in HC. The rCBF was significantly lower than rCPS in the PCC, but rCBF and rCPS were comparable in the other three regions in AD.

Conclusions: The CBF reduction in the PCC in AD was partly caused by neuronal loss in the PCC and partly supported the hypothesis that CBF reduction in the PCC was a result of functional deafferentation by neural degeneration in areas other than the PCC.

INTRODUCTION

Neuroimaging studies using ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) and single photon emission computed tomography (SPECT) have shown that the posterior cingulate cortex (PCC) is the primary and most prominent area of cerebral metabolic and perfusional decrement in early Alzheimer's disease (AD).[1] However, neurofibrillary tangles, a pathological hallmark of AD, and neuronal loss have not been reported in the PCC in early AD.[2] The reasons for the discrepancy between SPECT and FDG-PET abnormalities, and the absence of

neuronal loss and neurofibrillary tangles in the PCC have not been well explained. The discrepancy has often been attributed to functional deafferentation. Functional deafferentation occurs when a pathologically damaged region of the brain causes functional deactivation in other regions that are remote from, but connected to, the damaged region. In AD, the SPECT and FDG-PET abnormalities in the PCC are a result of damage in the entorhinal cortex. The entorhinal cortex is the first area that is pathologically affected in AD and is strongly connected to the PCC.[3] However, recent new neuroimaging techniques have shown the deposition of β-amyloid (Aβ), another pathological hallmark of AD,[4] and cortical atrophy[5,6] in the PCC in early AD patients. These findings might indicate neuronal loss in the PCC of AD.

L-[methyl-11C] methionine PET (MET-PET), which can visualize cerebral protein synthesis (CPS), is commonly used for detecting brain tumours, because tumours are associated with increased CPS. However, MET-PET can also be used to evaluate the decreased CPS *in vivo*, which could indicate neuronal loss.[7] The neuronal loss in the brain evaluated by MET-PET would mainly indicate loss of neurons, but not glial cells, because neurons synthesize protein at a higher rate than glial cells in the brain.[8] Crossed cerebellar diaschisis (CCD), which is shown in SPECT and FDG-PET images, is a depression of blood flow and oxidative metabolism of glucose in the cerebellum contralateral to a supratentorial brain lesion and is a typical phenomenon of the neural deactivation caused by the remote lesion.[9,10] However, we recently confirmed that CCD was not observed in MET-PET.[10] Thus, MET-PET could evaluate the neuronal loss *in vivo* without being influenced by neural deactivation in other affected regions. This characteristic of MET-PET is useful for evaluating neuronal loss of AD, because AD is a multilesional brain disease.

MET-PET has previously been used to show decreases of CPS in the frontal lobe[11] and temporoparietal area in patients with AD.[12] However, the characteristics of patients with AD in these studies were not well described. Furthermore, these studies set the regions of interest (ROI) directly on the patient's MET-PET images, which inevitably reduced reproducibility as a result of differences in human expertise and intraobserver variations. In addition, the ROI was not set at the PCC in these studies.

In the present study, we carried out both N-isopropyl-p-[123I] iodoamphetamine (IMP)-SPECT and MET-PET in eight patients with mild to moderate AD to assess whether the hypoperfusion was accompanied by the loss of CPS. The apolipoprotein E (ApoE) epsilon 4 allele is associated with a higher risk of AD and hypometabolism in the PCC.[13] In the present study, to increase the number of AD patients who have dysfunction in the PCC, we recruited only AD patients with the ApoE epsilon 4 allele.

SUBJECTS AND METHODS

Patients group

We recruited eight patients (4 females and 4 males) from consecutive outpatients who visited the neuropsychological clinic in the Department of Neuropsychiatry of Osaka University Medical Hospital between April and July in 2006. The inclusion criteria were: (i) a clinical diagnosis of probable AD based on National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria;[14] (ii) scores of less than 24 in the Mini-Mental State Examination (MMSE),[15] and >10 in the Alzheimer's Disease Assessment Scale-Cognitive Component-Japanese version (ADAS J-cog);[16] (iii) a score of 1 or 2 in the Clinical Dementia Ratings (CDR)[17] for the assessment of severity of the disease; (iv) no abnormal findings that caused dementia in the neurological examination and blood chemistry; (v) having the ApoE epsilon 4 allele; and (vi) no other abnormal findings than cerebral atrophy on magnetic resonance imaging (MRI) or computed tomography. The eight patients had a mean age of 73.0 years (SD = 5.4), a mean age of onset 67.8 years (SD = 5.0), a mean duration of illness of 5.3 years (SD = 2.3), and a mean level of education of 10.9 years (SD = 1.5). Their mean MMSE score was 19.3 (SD = 3.3) and their mean ADAS-Jcog. score was 21.3 (SD = 6.5). The scores of the CDR were 1 for three patients and 2 for five patients. The ApoE status was four homozygotes and four heterozygotes.

Healthy control group

Eight healthy control (HC) subjects (6 female and 2 male) were recruited from the community and were comparable to AD subjects on age and educational attainment. They had normal cognitive functions (MMSE score >25), normal findings in the physical and

neurological examinations, no history of psychiatric disorders and head trauma with loss of consciousness, no abnormal findings on MRI other than insignificant leucoaraiosis, and no risk factors for cerebrovascular disease (hypertension, heart disease and diabetes mellitus). Their mean age was 72.5 years (SD = 5.8), their mean level of education was 11.0 years (SD = 1.4) and their mean MMSE score was 28.6 (SD = 1.4).

The AD and HC groups did not significantly differ in age, education ($t = 0.18$, $P = 0.86$; $t = 0.17$, $P = 0.86$, respectively, Student's t-test) or sex ($P = 0.30$, Fisher's exact probability test). However, the AD group had significantly lower MMSE scores than the HC group ($t = 7.42$, $P < 0.001$, Student's t-test).

The present study was approved by the Ethics Committee of Osaka University Hospital. Before their enrollment, the subjects were given detailed explanations of the purpose of the study and all the procedures used. Written informed consent was obtained from all subjects.

PET and SPECT procedures

All AD patients underwent both MET-PET and IMP-SPECT scans with an interval period ranging from 24 to 97 days (59 ± 21 days); there were no clinical changes in any of the patients during this interval period. The HC subjects underwent only IMP-SPECT scans.

MET-PET images were carried out using a Headtome V PET scanner (Shimadzu, Kyoto, Japan) with retractable septa. Scans of all subjects was carried out in the stationary mode with septa in, which allowed acquisition of 63 contiguous transverse slices with a spatial resolution of 3.7 mm full width at half-maximum (FWHM) in the transaxial direction and 5 mm in the axial direction. The patient's head was fixed in place with a head holder and was positioned with light beams to obtain transaxial slices parallel to the orbitomeatal line. The images were acquired with the patient resting in the supine position, with their eye closed. Corrections for absorption were carried out with attenuation measured in a transmission scan using a retractable rotating rod source. MET were given intravenously at the dose of 555–740 MBq. Regional emission images of the brain were obtained for 10 min, beginning 20 min after the MET injection. Scan data were reconstructed with an ordered-subset expectation maximization algorithm (12 iterations with 4 ordered subsets).

IMP-SPECT images were obtained with a four-head rotating gamma camera fitted with a low-energy, general purpose, parallel-hole collimator with a spatial resolution of 13.0 mm full-width-at-half-maximum (Gamma View SPECT 2000H, Hitachi Medical, Tokyo, Japan). Data were acquired in a continuous rotating mode in reciprocal directions at 20 s per revolution for 66 min from 96 directions in a 64 × 64 matrix. The SPECT scan was started 15 min after intravenous injection of 167 MBq of 123I-IMP (Perfusamine, Nihon Medi-Physics, Hyogo, Japan). The transaxial images were reconstructed using a filtered back projection algorithm and a Butterworth prefilter.

Data analyses

Image data of individual IMP-SPECT or MET-PET scans were stereotactically standardized with Neurological Statistical Image Analysis Software (NEUROSTAT; University of Michigan. Ann Arbor, MI, USA) on a windows personal computer[18,19] in order to remove the difference of the individual's brain size and to minimize the regional anatomical differences. NEUROSTAT has been shown to be suitable for anatomical standardization of the brain with atrophy in AD.[20]

One investigator (T.Y.), who specializes in neuroimaging and who was blind to the subject's clinical information, placed a total of 32 circular ROI of 12-mm diameter on the five cortical areas on the MRI template image of NEUROSTAT; the frontal lobe (FL), the parietal lobe (PL), the medial temporal lobe (MTL), PCC and the occipital lobe bilaterally. Figure 1 shows the ROI on the templates and the anatomical areas. Subsequently, the same ROI were transferred to the standardized MET-PET and IMP-SPECT images.

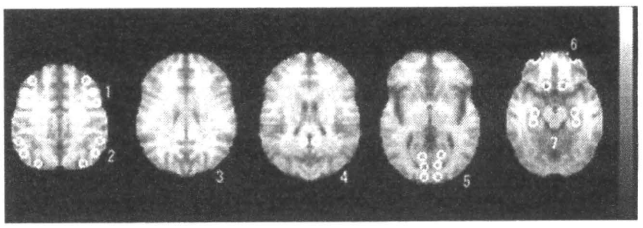

Figure 1 Regions of interest (ROI) on the magnetic resonance imaging (MRI) template images. The ROI shown on the horizontal MRI template images of Neurological Statistical Image Analysis Software (University of Michigan. Ann Arbor, MI, USA)). The anatomical locations of ROI are as follows: 1 and 6, frontal lobe; 2, parietal lobe; 3 and 4, posterior cingulate cortex; 5, occipital lobe; 7, medial temporal lobe.

Table 1 Regional cerebral blood flow and regional cerebral protein synthesis in Alzheimer's disease and regional cerebral blood flow in healthy controls

Region	HC rCBF	AD rCBF	AD rCPS	rCBF in HC *vs* in AD *P*-value	rCBF *vs* rCPS in AD *P*-value
FL	0.80 ± 0.06	0.82 ± 0.09	0.80 ± 0.05	0.999	0.962
PL	0.84 ± 0.08	0.79 ± 0.11	0.80 ± 0.09	0.981	1.000
MTL	0.76 ± 0.03	0.63 ± 0.11†	0.71 ± 0.10	0.442	0.132
PCC	0.84 ± 0.11	0.60 ± 0.11†	0.70 ± 0.08‡	0.026	0.045

†Significantly lower than regional cerebral blood flow (rCBF) in the frontal lobe (FL) and parietal lobe (PL; post-hoc Tukey's HSD test). ‡Significantly lower than regional cerebral protein synthesis (rCPS) in FL and PL (post-hoc Tukey's HSD test). Data are given as mean ± SD. AD, Alzheimer's disease; HC, healthy controls; MTL, medial temporal lobe; PCC, posterior cingulate cortex.

Then, we evaluated the tracer uptake with the semi-quantitative method. We divided the averaged value of each of the four areas (FL, PL, MTL and PCC) out of five ROI areas by the mean values of the bilateral occipital areas; that is, we calculated the cerebral blood flow (CBF) or CPS ratio using the regional-to-occipital cortical ratio, to increase the reliability and to remove the intersubject difference in baseline metabolism or perfusion.[21] The normalized values of the regional MET and IMP uptake ratios (rCBF and rCPS) were relative values, which made it possible to compare them directly.

Statistical analyses

The averaged rCBF or rCPS of the right and left sides were used for the analyses, because averaging both sides would increase the reliability of the measurement. To compare the rCBF between HC and AD, the difference of rCBF was analyzed by using two-way analysis of variance (ANOVA) for repeated measures, with one between-factor (group: HC and AD) and one within-factor (region: FL, PL, MTL and PCC) and post-hoc Tukey's HSD test for comparisons between each pair of regions.

To compare between rCBF and rCPS in AD, the difference of tracer uptakes was analyzed by using two-way ANOVA for repeated measures, with two within-factors (isotope: IMP and MET, and region: 4 regions as aforementioned), and post-hoc Tukey's HSD test. The significance level was set at $P < 0.05$ in all statistical analyses.

RESULTS

As for the comparison of rCBF between HC and AD, two-way ANOVA showed a significant group effect ($F(1,14) = 10.8$, $P = 0.005$), region effect ($F(3, 42) = 11.7$, $P < 0.001$) and a significant group × region interaction ($F(3,42) = 8.8$, $P < 0.001$). The rCBF in the PCC was significantly lower in AD than in HC ($P = 0.026$). In the HC group, the rCBF in the different regions were not significantly different by post-hoc analyses. In the AD group, the rCBF in the MTL and PCC were significantly lower than those in the FL and PL, but there were no significant difference of the rCBF between the MTL and PCC (Table 1).

In the comparison between rCBF and rCPS in AD, two-way ANOVA with repeated measures showed a significant region effect ($F(3,21) = 14.1$, $P < 0.001$) and a significant isotope × region interaction ($F(3,21) = 4.3$, $P = 0.016$), but did not show a significant isotope effect ($F(1,7) = 1.8$, $P = 0.22$). rCBF was significantly lower than rCPS in the PCC, but no significant differences were observed in other regions. In the AD group, rCPS was significantly lower in the PCC than in the FL and PL. rCPS in the MTL was lower, but not significantly, than those in the FL and PL ($P = 0.10$ and $P = 0.058$, respectively). rCPS values in the other regions were not significantly different from each other.

DISCUSSION

Both the rCBF and rCPS in the PCC were significantly lower compared with those in the FL and PL in the AD group in the study. The rCBF in the PCC was significantly lower in the AD group than in the HC group in the present study, which was consistent with previous reports of a clear decline of rCBF in PCC in the early to moderate stages of AD.[22] Because we could not carry out MET-PET scans of the HC group, we could not compare the rCPS between HC and AD directly or evaluate whether the rCPS decreased in the PCC of AD in the present study. However, we could approximately calculate the regional-to-occipital cortical ratios of MET-PET in normal subjects from the data of

Coope DJ *et al.*[23] Their study reported that the mean ratios in normal subjects are approximately 0.8–0.9 in all areas examined in the present study. The CPS of the frontal and the temporal cortices in normal subjects measured by Salmon E *et al.*[12] was consistent with those of Coope DJ *et al.*[23] Therefore, we assumed that the rCPS in normal subjects are comparable among the ROI in the four brain areas in the present study and were approximately 0.8–0.9. The rCPS in the PCC appeared to be lower in the AD group in the present study than the normal subjects in the report of Coope DJ *et al.*[23] Thus, protein synthesis in the PCC of the AD patients in the present study appeared to be decreased.

Our finding that rCPS was significantly higher than rCBF in the PCC shows that CBF was more severely decreased than the neuronal loss in PCC. This appears to support the hypothesis that the more severe reduction of the CBF arises from functional deafferentation caused by primary neural degeneration of other brain areas, such as the entorhinal cortex.[24] Thus, the decrease of CBF in the PCC would reflect both the neuronal loss and remote functional hypoperfusion.

The AD patients in the present study had CDR scores of 1 or 2, which are frequently associated with neuropathological Braak stages III and IV.[25] In Braak stages III and IV, MTL is preferably affected with mild neocortical pathology.[25] The neuropathological evidence is consistent with the finding of the present study that the rCPS in the MTL could be lower in the AD group than in the normal subjects in the study of Coope DJ *et al.*[23] The rCBF in the MTL was also lower in the AD group than in the HC group in the present study, although the difference did not reach the significant level. The lack of significant difference might be as a result of a type II error because of the small sample size of the present study. Neuronal loss and neurofibrillary tangles are not common in the PCC in AD patients in Braak stages III and IV.[25] However, recent studies with new neuroimaging techniques showed the presence of pathological changes in the PCC in early AD patients. Neuroimaging studies with [11C] Pittsburgh compound B (PiB)-PET showed Aβ deposition in the PCC[4], which might induce local atrophy of the PCC.[26] MRI studies using voxel-based morphometry (VBM) have shown a regional grey matter loss in the PCC of mild AD.[5,6] Diffusion tensor MRI using the VBM technique showed increased diffusivity in the PCC of AD in the early stage, which might indicate a pathological abnormality.[27] Furthermore, Vogt BA *et al.*[28] reported that neuronal loss in the PCC of AD was accompanied by laminar degeneration. They also found that the ApoE epsilon 4 allele was positively associated with the severity of the pathological change in the PCC, leading to a variable degree of pathological change in PCC among AD patients. In the present study, there was a clear decrease in rCPS in the PCC in AD patients, because the AD patients were limited to those who had the ApoE epsilon 4 allele. Further studies are needed to determine whether the ApoE epsilon 4 allele is associated with neuronal loss in the PCC.

The present study had some limitations. The sample size of this study was small, because we intended to recruit homogenous patients with ApoE epsilon 4 allele. The analyses of the homogenous patients could clarify the significant difference between rCBF and rCPS in the PCC, despite the small sample size of this study. A second limitation is that by limiting the subjects of the present study to AD patients with the ApoE epsilon 4 allele, the results might not apply to AD patients with other ApoE alleles. A possible third limitation is that we used the ROI method rather than a voxel-by-voxel analysis in stereotactic space. The ROI method is not bias-free but could be used in a study with a small sample size. Future studies that use a large number of subjects and a voxel-by-voxel analysis are needed to confirm the present findings.

Our MET-PET results suggest that the hypoperfusion in the PCC observed by SPECT is partially a result of the neuronal loss, which would be indicated by the impairment of CPS, and partially a result of the apparent reduction of CBF. Although the neuronal loss assumed by the MET-PET was not pathologically confirmed, the MET-PET could evaluate the regional neuronal loss in AD *in vivo*.

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