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Perspectives

Japanese Alzheimer's Disease Neuroimaging Initiative: present status and future

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Abstract Japanese Alzheimer's Disease Neuroimaging Initiative (J-ADNI) was launched in 2008, aiming at conducting a longitudinal workup of a standardized neuroimaging, biomarker and clinico-psychological surveys. The research protocol was designed to maximize compatibility with that of US-ADNI, including structural MRI analysis for the evaluation of brain atrophy, FDG and amyloid PET, CSF sampling, apoE genotyping, together with a set of clinical and psychometric tests that were prepared to achieve the highest compatibility to those used in the United States. Japanese ADNI has recruited ~340 participants (142 amnestic mild cognitive impairment, ~127 normal aged and 70 mild Alzheimer's disease (AD), as of March 2010). World-wide ADNI activities will establish the rigorous quantitative descriptions of the natural course of AD in its very early stages. The data, as well as the methodologies and infrastructures, will facilitate the clinical trials of disease-modifying therapies for AD using surrogate biomarkers.

Keywords: ■■■

Currently, there is a compelling need to establish novel treatments for Alzheimer's disease (AD), and to demonstrate, as well as track, the efficacy of potential treatments in clinical trials, especially those for disease-modifying drugs that target the pathophysiological mechanism of AD. At this time, clinical trials of AD are conducted in a stage of the disease that is considered late in the trajectory of the pathological process. In addition, clinical studies require large numbers of participants with AD because the statistical power of our currently available measures, that is, clinico-neuropsychological scales, is low because of the large fluctuation in data. Thus, biomarkers, including neuroimaging and body fluid chemistry, hold great promise that would assist in many of these challenges.

To identify such biomarkers, Alzheimer's Disease Neuroimaging Initiative (ADNI) was launched in the United States in 2005. US-ADNI already completed the recruitment and is continuing the longitudinal follow-up of 800 participants including mild cognitive impairment (MCI) as the major target population, a major proportion of which represents the very early stage of AD.

We started discussions about the need for Japanese version of ADNI in 2006 for several reasons. First, there was an urgent need to meet with the requirements for global clinical trials of disease-modifying drugs for AD that were about to start in Japan, although we had little experience in nationwide or global-level clinical studies on AD, despite the relatively high activities of neurologists, psychiatrists, and geriatricians who had been involved in the clinical studies of dementia. Second, we did not have sufficient infrastructures, such as clinical study coordination center like ADCS or imaging data repository like LONI, that are required for clinical studies or trials of AD. Third, we realized that we would be able to improve the Japanese AD clinical sciences to an international level by conducting rigorous and comprehensive clinical study like ADNI, in collaboration with international experts in this field.

In this way, we submitted proposals for Japanese ADNI (J-ADNI) to the two major governmental funding agencies, that is, Ministry of health, labor and welfare (MHLW), and New Energy and Industrial Technology Development Organization (NEDO; a foundation of Ministry of economy, technology, and industry), and got funded in 2007. Seven

URL of J-ADNI: http://www.j-adni.org/.

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domestic pharmas (Astellas, Eisai, Daiichi-Sankyo, Dainippon-Sumitomo, Shionogi, Takeda, Tanabe-Mitsubishi) and four international pharmas (BMS, Eli-Lilly, Merck-Banyu, Pfizer) also decided to contribute one-third of the total budget, the latter amounting to ~500 million yen/year.

We designed the research protocol to maximize the compatibility with that of US-ADNI, including structural MRI analysis, FDG and amyloid PET, CSF sampling, apoE genotyping, combined with a set of clinical and psychometric tests that were prepared to achieve the highest compatibility to those used in US-ADNI. We are going to recruit 300 individuals with amnestic MCI (using logical memory cut off based on education), 150 early AD and 150 cognitively normal individuals by the end of 2010, following them up until 2013 (Fig. 1).

The organization of J-ADNI is shown in Fig. 2. In total, 38 clinical sites participated in J-ADNI.

The clinical core is headed by Takashi Asada (Tsukuba University, Psychiatry) and Hiroyuki Arai (Tohoku University, Gerontology) and is responsible for the registration and clinical evaluation of the participants. The clinical core closely collaborates with the neuropsychology core led by Morihiro Sugishita (Niigata Rehabilitation University). During the preparation stage, Sugishita corrected the Japanese translation as well as the configuration of several major clinical and neuropsychological batteries, including ADAS-COG, MMSE, and Clinical Dementia Rating, to maximize the harmonization between English and Japanese versions. Currently, the compatibility of the test batteries is being demonstrated through the analysis of the baseline data of J-ADNI.

Hiroshi Matsuda (Saitama Medical University, MRI core PI), in collaboration with Fumio Yamashita (National Center for Neurology and Psychiatry) and other core members, has established an algorithm to achieve the standardization of MRI scans among clinical sites using different MRI equipments from various vendors, based on 3D-MPRAGE scan protocol using ADNI phantom. They also have created programs for the correction and calibration of signal equity or distortion of the images, which enabled the rigorous volumetric analysis.

Kengo Ito (National Institute for Longevity Sciences, PET core PI) and Michio Senda (Institute of Biomedical Research and Innovation, PET quality control PI) also have established the standardized protocol for PET imaging in J-ADNI, in collaboration with Kenji Ishii (Tokyo Metropolitan Institute for Gerontology, amyloid PET PI). Twenty-eight sites are conducting FDG-PET, so far covering ~72% of participants (243 cases). Amyloid PET core has established a standardized protocol for ^{11}C-PiB PET using dynamic scan data acquisition (in addition to late-phase images), as well as that for ^{11}C-BF-227, the latter being developed by Kudo and colleagues in Japan. ^{11}C-PiB PET is being conducted in 15 sites and ^{11}C-BF-227 is used in two sites. Currently ~44% of total participants (150 cases) have undergone amyloid PET scan.

Biomarker core is led by Ryozo Kuwano as PI (Niigata University), with the assistance of Hiroyuki Arai as co-PI. They established the J-ADNI biosample repository in Niigata, based on the nationwide collection network of biofluid samples with the assistance of SRL company. Blood samples were collected from all participants upon every visit. So far,

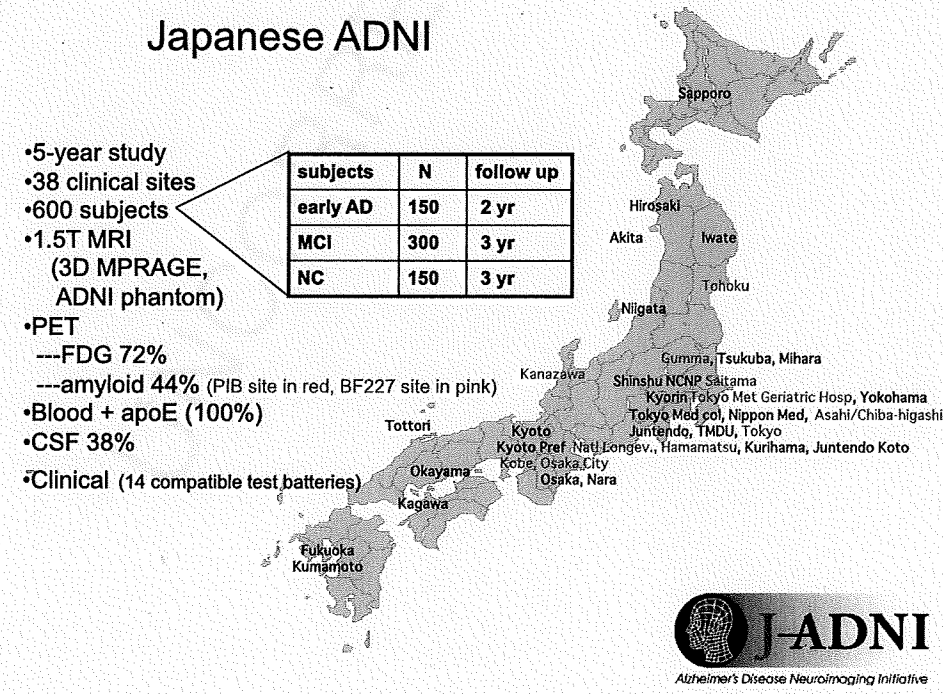

Fig. 1. Overview of J-ADNI.

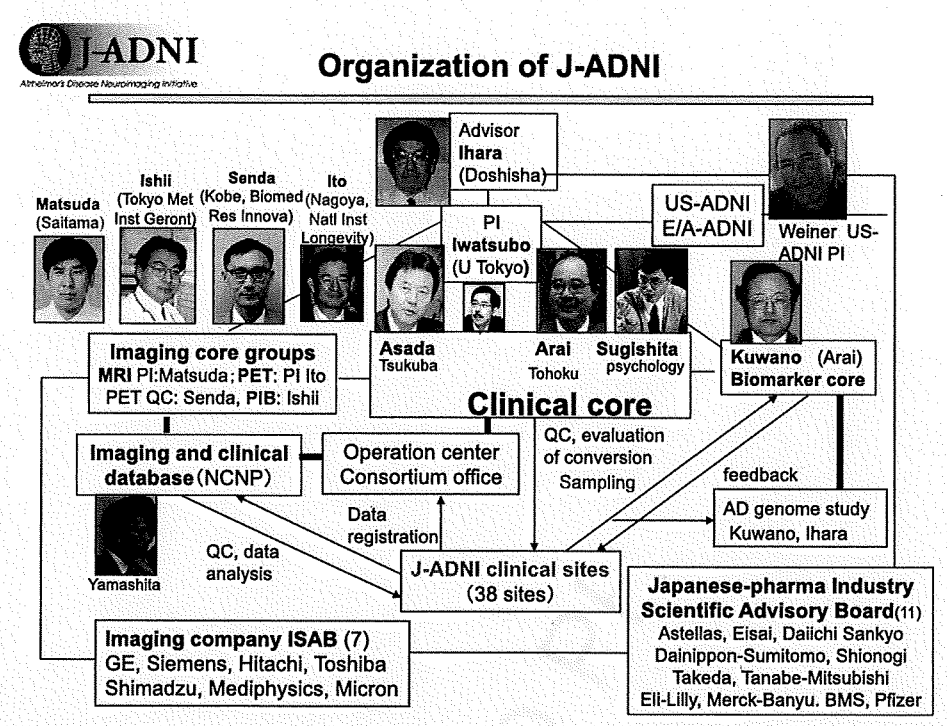

Fig. 2. Organization of J-ADNI.

130 participants (~38% of total) had lumber tap and donated cerebrospinal fluid samples. ApoE genotype also is characterized at the Niigata site.

Until now, 38 clinical sites have screened 469 individuals and enrolled 339 participants who met with the inclusion criteria (142 amnestic MCI, 127 cognitively normal aged, and 70 early AD, as of March 25, 2010). The overall exclusion rate upon screening was 21.7% (9.3% in CN, 28.6% in MCI and 25.5% in AD), which was lower than that in US-ADNI. Currently longitudinal follow-up examination is underway with a relatively low drop-out rate (~6.5%).

Use of highly compatible protocols between J-ADNI and US-ADNI will enable us to establish the rigorous quantitative descriptions of the natural course of AD in its very early stages. The data, as well as the methodologies and infrastructures, will facilitate clinical trials of disease-modifying therapies for AD using surrogate biomarkers, enabling the application of effective therapies to AD/MCI patients, and eventually the prevention of AD.

Acknowledgments

The author thanks all the participants, research members, funding agencies (NEDO, MHLW) and J-ADNI ISAB member companies for their efforts and willingness to foster the J-ADNI research.

Worldwide-ADNI Symposium in Sendai

●2009年11月22～23日　於　仙台

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アルツハイマー病(Alzheimer's disease；AD)のdisease-modifying therapyの研究・開発の急速な進展に伴い，それらの治療効果を適切に評価するためのバイオマーカーの確立が急務となっている。イメージング，体液バイオマーカーなどを臨床指標と組み合わせて，AD発症過程の自然経過の厳密な計量的・経時的評価を実現するために米国で開始されたプロジェクトがADNI(Alzheimer's Disease Neuroimaging Initiative)である。この動きと歩調を合わせて，日本においてもJ-ADNIが立ち上がった。欧米人とは異なる人種的，社会的背景を有する日本人のデータを収集することにより，今後グローバル治験により有効性の検証されていく治療薬を本邦で応用する際に有用なデータが得られるとともに，AD臨床研究の基盤形成にも貢献するとの期待が，J-ADNIには寄せられている。また，同様にヨーロッパ，オーストラリア，中国，韓国においても同様の目標を設定し，ADNIに類した研究プロジェクトが立ち上がりつつある。

今回，日本認知症学会に併催されるかたちで，J-ADNI，US-ADNIが中心となり，NEDO(新エネルギー・産業技術総合開発機構)，長寿科学振興財団，バイオテクノロジー開発技術研究組合の後援を受けて，世界ADNIシンポジウムが開催された。各国におけるADの画像・バイオマーカー研究データを共有し，ADの発症・進行過程を忠実に反映する客観的評価法の世界基準確立を目指して，US-ADNI，J-ADNIの全専門コア主任研究者，さらにはEuropean-ADNI，オーストラリアのAIBL(Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing)，中国，韓国の代表的AD研究者が集結し，熱い議論が繰り広げられた。

筆者の1人(林)は東京大学薬学部学生の立場で，本シンポジウムに参加する機会を得た。以下筆者らが関心をもったいくつかの研究について紹介したい。

I US-ADNIの進展状況

まずUS-ADNIにおける臨床研究の概要が，Clinical Coreのprincipal investigator(PI)のRon Petersenから発表された。これまでに全被験者の組み入れが完了しており，内訳は健常者(NC)229例，軽度認知障害(mild cognitive impariment；MCI)398例，ADが192例であった。MCIからNCへのreversionは14例，NCからMCIへのconversionは4例，ADからMCIへのreversionは1例，そしてMCIからADへのconversion(臨床的な観察における主要なエンドポイントとされる)は119例であった。すなわち，NCのMCIへの進行率は観察期間中1.4%，MCIからADへの移行率は16%/年，24%/2年であり，従来の健忘型MCIでの観察結果に一致した。これらの被験者を対象とする認知機能検査の結果が報告された。ADAS-Cogでは，AD>MCI>NC，MMSEではNC>MCI>ADとスコアは予想どおりの差を示し，縦断観察ではNCではほぼ変化はなかったが，MCI，ADでは経過とともに増悪，ADはMCIに比して高い変化率を示した。その他のテスト[CDR，AVLT(Auditory Verbal Learning Test)]においても同様の傾向がみられ，認知機能テストは臨床経過を忠実に反映することが確認されたが，個人間，計測時点間の大きなばらつきが問題点として示された。髄液Aβ42レベルと認知機能の関係についてみると，髄液Aβ42はAD<MCI<NCの順に低値を示したが，Aβ42とADAS-Cogスコアをプロットすると，両者の間には相関がみられた。すなわち，

Aβ42が低値であるほどADAS-Cogの成績が悪く，12ヵ月間の縦断観察における低下率も大きいことが示された。髄液Aβ42は脳アミロイド蓄積と逆相関することが示されているので，アミロイド蓄積がすでに存在する場合には，脳機能低下が進行しつつあることを示すものであろう。

現在米国では，現行の5年間のADNI研究に引き続いて，次の5年間をカバーするADNI2研究が計画され，現在グラントが申請され審査中とのことである。ADNI2はADの進行過程のより早期段階に照準を当てている。現在のADNIではMCIを記憶障害の重いlate MCIが対象とされているのに対し，ADNI2では，エピソード記憶の障害が軽度の段階の'early MCI'をも対象とし，追跡研究を行う。Early MCIはlate MCIに比して進行がより緩徐であることが，縦断研究において変化率を検出するうえで問題となると思われるが，病理学的変化が早期状態にあるほどdisease-modifying therapy，ことに抗Aβ療法のよりよい対象となると想定されることからも，早期を目指した研究は重要な方向性である。ADNI2研究により今後，NCがMCIへ進行する際のバイオマーカー評価が実現することが期待される。

図1　船上での国際交流

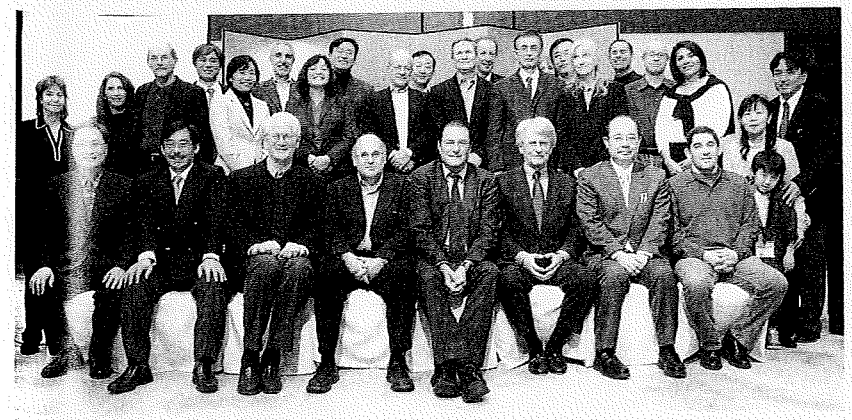

図2　世界ADNI研究代表の集結

John MorrisはUS-ADNIにおいてNeuropathology Core PIの責務を負っているが，ワシントン大学セントルイス校における'preclinical AD'研究についても言及した。Morrisらセントルイス学派は，ADの早期状態に対してMCIの概念を適用せず，preclinical ADとの診断を用いる立場をとることで知られているが，今回超早期のpreclinical AD例において，視覚性空間認知機能の低下が記憶機能の低下に先行して顕在化することを報告し，記憶機能のみに依拠した評価の問題点を指摘した。

PIB(Pittsburgh compound-B)によるアミロイド蓄積の検出とADのリスクファクターの関連について，ワシントン大学の241例の健常高齢者の検討の結果が示された。PIB陽性率は，50歳台では13%/0%(ε4+/−，以下同じ)，60歳台では36.7%/8.2%，70歳台では52.9%/15.6%，80歳台では75.0%/16%と，まさしく年齢，APOEε4という2つのリスクファクターと強い相関があることをMorrisは明示した(Morris JC, et al. Ann Neurol 67, 122-131, 2010)。J-ADNIのデータについても全く同じ傾向が見られることが，Amyloid Imaging Core PIの石井賢二から本シンポジウムで発表され，この一致は興味深い。

さらにpreclinical ADの脳脊髄液Aβ42値の低下は脳萎縮と相関すること，PIBによるアミロイド陽性が認知機能の進行性低下，局所的な脳萎縮，大脳皮質の菲薄化と相関することが示され，アミロイド陽性で臨床徴候に乏しいpreclinical ADは決して非進行性の良性病態ではないことが強調された。今後，加齢やAPOEε4アレルの存在に伴って増加する脳Aβ蓄積に着目することによりpreclinical ADの検出が進めば，より早期の段階でAD発症を予防的に治療できる可能性があり，その重要性が強調された。Morrisらのデータは ADNIに先行してセントルイスで蓄積されたものであり，その先進性と質量に圧倒される思いであった。

II MRIを中心とする長期縦断脳画像研究の成果

ADNIの目的の1つは，AD患者とそうでない人の違いはどこにあるのか，またこの2群を区別する際に最も有用なバイオマーカーは何かを知ることにある。ADと非AD患者の鑑別にあたり，視覚的判断の根拠としても，MRIによる画像診断は有効である。US-ADNI MRI Core PIのClifford Jackは，MRI Coreの方向性と成果について講演した。

MRI Coreは，Mayo Clinicをセンターとして，全米59ヵ所の臨床サイトからMRIデータを収集し，解析を行った。電子プロトコールの各サイトへの提供，結果の即時公開，スキャナーの品質管理などもMRI Coreが担当した。画像データは，7ヵ所の専門家によりそれぞれ異なる手法(voxel based morphometryなど)を用いて解析され，結果が比較された。

これまでのMRI画像解析の結果，tensor based morphometry，boundary shift integral，free surferの3つの手法を用いた解析は，長期縦断研究で変化率を検出するパワーを有していること，また1.5テスラ画像と3テスラ画像ではパワーに優劣はみられないことが示された。一定の変化率をアウトカムとして検出する能力を比較すると，MCI，AD両群ともに，MRIによる脳容量の変化は，FDG-PETよりも検出能が高かった。縦断的な変化の検出能は，予想どおり，MRI，FDG-PETのほうがADAS-Cog，MMSE，CDRなどの認知機能よりも勝っていた。一方，ADAS-Cogのスコアの悪化の予想能については，FDG-PETのほうがMRIよりも優れていた。このように，MRI，FDG-PETはそれぞれ異なる役割をもった指標となりうると考えられた。

2009年に米国では景気刺激策としてGeneral Opportunity(GO)グラントと称する大型科学研究費が公募され，ADNIに関しては2,400万ドル/2年間の延長プログラムが採択された。このADNI-GOや，申請中のADNI2におけるMRIプロトコールとしては，現行ADNIからの継続観察例では同じ1.5テスラのスキャナーと，同じプロトコールを用いて縦断研究を進展させ，新規例では3テスラスキャナーを用い，新たなMRIプロトコールに沿った研究が計画されている。ANDI2では，arterial spin labeling perfusion法やdiffusion tensor imagingなどの探索的な手法の併用も計画されているようである。

III 生物統計学的研究

US-ADNI Biostatistics Core PIのLaurel Beckettらは，ADNIで得られた各種認知機能，バイオマーカーデータの統計学的解析について述べた。統計学コアは，研究グループ全体に対して，認知機能測定やバイオマーカーデータの横断的サマリー，追跡中の被験者数，変化率，反復計測のモデルや経時変化の「スパゲティプロット」グラフなどのデータを提供し，ことにノイズの大きな臨床データで高い統計学的パワーを達成しつつ，治験計画のサイズを縮小し，治療効果の検出能力を高めるための手法を開発している。US-ADNIのこれまでの統計解析の結果，まだ根拠が不十分ではあるものの，臨床治験におけるサロゲートエンドポイントとしてどのようにバイオマーカーを用いるのがよいか，また組み入れ基準や組分け，解析における共変数の取り方などについて，有益な情報が得られている。また統計学的な問題点として，認知機能指標のノイズの大きさ，NC群での変化の乏しさ，多変数解析に用いるには被験者数(サンプル数)が小さすぎることなども指摘された。

世界のADNI研究メンバー間で統計学的解析を共同で推進することにより，統計学モデルや個別の知見を相互に確認し，言語や文化の相違により認知機能検査の基準の確立が困難な場合にも，脳に生じた客観的変化は一定であるかどうかを検証する機会が得られ，さらに解析上の問題点を共有することにより解決策の探索が可能になるということが強調され，日米のみならず世界で共通の方法を用いた縦断研究を行うことの重要性が議論された。

IV おわりに

本Worldwide-ADNI symposiumでは，US-ADNIの進捗が確認されるとともに，J-ADNIの順調なスタートが報告され，日米を基軸とする世界4極でのAD画像・バイオマーカー評価基準制定の流れが参加者に印象づけられた。アカデミック，製薬企業，米国アルツハイマー協会など多彩な顔ぶれからなる350名の参加者，24名の講演者の間でも，会議のみならず懇親会やexcursionを通じて交流が深められた。末筆ながら，本シンポジウムを支援いただいたNEDO，長寿科学振興財団，バイオテクノロジー開発技術研究組合，製薬企業各社に改めて厚く御礼を申し上げる。

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Relationship between white matter changes and cognition in healthy elders

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SUMMARY

Objectives Cerebral WMHs on T2-weighted magnetic resonance imaging (MRI) are common incidental findings in cognitively healthy elderly subjects. The relationship between such changes and cognitive function remains unclear.
Methods The present study evaluated the relationship between the degree of white matter changes and cognitive function using data from 172 cognitively healthy subjects who underwent MRI and a battery of neuropsychological tests. The degree of WMHs was rated using a four-point scale for images on a computer screen.
Results Regarding the frontal and parieto-occipital regions and basal ganglia region, compared with the group with no WMHs, the group with the most severe WMHs showed significantly lower performances for attention and disorientation to time, respectively.
Conclusions Our results suggest that even in cognitively healthy elderly individuals, presence of large WMHs affects performance on certain cognitive domains according to their localization.

KEY WORDS—White matter hyperintensity; magnetic resonance imaging; cognitive function; mini-mental state examination

INTRODUCTION

White matter hyperintensities (WMHs) are common findings on cerebral magnetic resonance imaging (MRI) among elderly people. Several studies have shown that the frequency of vascular lesions including WMHs on MRI is higher for Japanese than for Caucasians (Chalmers *et al.*, 2000). Although the presence of WMHs is reportedly associated with brain atrophy and reduced cerebral blood flow (Mirsen *et al.*, 1991; De Reuck *et al.*, 1992), the pathogenesis of WMHs has not been fully elucidated.

Some studies have found associations between WMHs and dementia among elderly people (Breteler *et al.*, 1994; Barber *et al.*, 1999). Even in cognitively healthy elderly individuals, WMHs reportedly affect cognitive function, including speed of cognitive processes and executive function (Junque *et al.*, 1990; Schmidt *et al.*, 1993), though some studies have shown conflicting results (Barber *et al.*, 1999). Such discrepancies may be attributable to differences in assessment methods for measurement of WMHs and cognitive function, as well as bias in sample selection. Regarding assessment methods, some studies have rated WMHs of the whole brain, whereas others have only examined certain regions of interest (ROIs) in the brain. In addition, similar previous studies have evaluated cognitive function using only a simple screening test.

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To the best of our knowledge, no Japanese studies have investigated the relationship between WMHs and cognitive function among cognitively healthy elderly individuals. As a part of community studies for the elderly, our participants underwent cranial MRI and a battery of neuropsychological tests assessing five cognitive domains. Cognitive status of each subject was determined using data including results of the test battery, and WMHs of the whole brain and in four brain regions were rated. Among subjects judged to have been cognitively healthy, the relationship between WMHs and cognitive function was examined.

METHODS

Subjects

This study was part of a project aimed at preventing dementia in the community of Tone town, Ibaraki, Japan. The protocol for this study was approved by the ethics committee of the University of Tsukuba.

At the baseline for this project, cognitive function of inhabitants was examined between December 2001 and April 2002. Cognitive function was assessed using a battery of neuropsychological tests: category-cued recall for memory (Grober *et al.*, 1988); set-dependency activity for alternating attention (Sohlberg and Mateer, 1986); category verbal fluency for language ability (Monsch *et al.*, 1992); clock-drawing test for visuospatial function (Mendez, 2000); and Wechsler Adult Intelligence Scale Revised (WAIS-R) similarities for abstract reasoning (Wechsler, 1981).

After assessment, our team reviewed the functional, medical, neurological, psychiatric, and neuropsychological data and reached a consensus regarding the presence or absence of dementia by diagnosis according to Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria. Only those individuals who were not diagnosed as having dementia were considered as candidate participants for the present MRI study. Test scores for candidates were required to be within normal limits (score $>$ 1 SD below the demographically corrected mean) for all five cognitive domains (i.e., memory, attention, language, visuospatial, and reasoning) (Miyamoto *et al.*, 2009). At the end of the baseline examination period, 1888 of the 2698 candidate inhabitants (70%) were enrolled.

We randomly selected MRI study subjects with normal cognitive function from among baseline participants and invited them to participate in the study. As a result, 172 subjects (77 men, 95 women; mean age 73.0 ± 4.3 years; mean years of education 10.9 ± 2.7 years; mean mini-mental state examination (MMSE) score, 28.2 ± 2.1) participated in this study, which started in October 2002. All participants provided written informed consent.

Data acquisitions

First, study subjects underwent the MMSE (Folstein *et al.*, 1975). Cranial MRI was then performed using a 1.5-T Magnetom Symphony system (Siemens, Erlangen, Germany). Conventional axial T2-weighted turbo spin echo images was performed using the following settings: repetition time (TR), 4000 ms; echo time (TE), 96 ms; echo train length, 11; slice thickness, 5 mm; intersection gap, 1.5 mm; matrix, 512×256; field of view, 230×230 mm; number of signals acquired, 2; scan time was 3 min. In addition to T2-weighted imaging, high spatial resolution, three-dimensional (3D) T1-weighted imaging was also used for study. Scans for 3D T1-weighted imaging were made in the sagittal plane using the following settings: TR, 2800 ms; TE, 3.93 ms; flip angle, 12°; effective section thickness, 1.20 mm; slab thickness, 173 mm; matrix, 512×512; field of view, 280×280 mm; number of signals acquired, 1. This yielded 144 contiguous slices through the head.

Data post-processing

The degree of white matter changes was rated using a four-point scale for images on a computer screen. White matter changes on MRI were defined as ill-defined hyperintensities $\geq$5 mm in diameter on T2-weighted images. Lacunae were defined as well-defined areas $>$2 mm with signal isointensity to cerebrospinal fluid. Lesions with these characteristics $\leq$2 mm were considered as perivascular spaces. Changes in the basal ganglia were rated in the same manner and considered as white matter lesions even if located in gray matter nuclei, as these contain small amounts of white matter. The scoring system was 0, no lesion; 1, focal lesions; 2, beginning confluence of lesions for white matter lesions and $>$1 focal lesion for basal ganglia lesions; 3, diffuse involvement of the entire region for white matter lesions and confluent lesions for basal ganglia lesions (Figure 1) (Wahlund *et al.*, 2001). The previous study rated the WMH using proton density weighted image (PD) or fluid attenuated inversion recovery (FLAIR) in addition to T2WI, but we rated only on T2WI. In this point, the rating scale was modified. These WMH scores were

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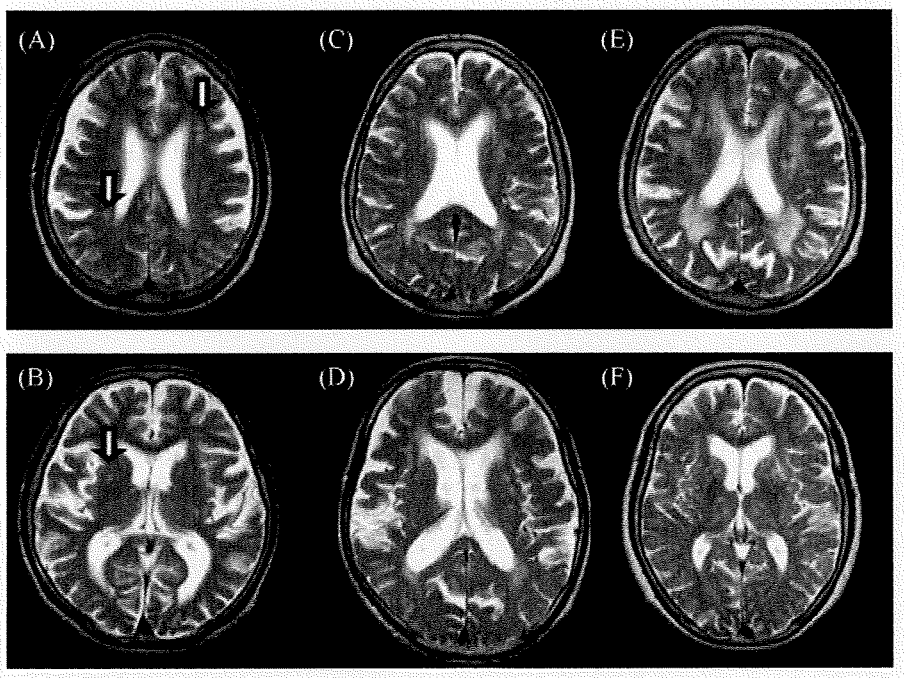

Figure 1. (a–f) Examples of rating scores 1, 2, and 3 on cerebral T2-weighted imaging. For a rating score of 1, a single lesion is clearly seen in a and b. There are two lesions in the left frontal white matter and on lesion in the right parietal white matter on a (arrow). There is one right putaminal lesion on b (arrow). Additional lesions lead to a score of 2, as exemplified in c and d. Rating score 3 is shown in e and f. Subcortical WMHs are shown in a, c, and e and basal ganglial WMHs are shown in b, d, and f. Definitions of rating scores: 0, no lesion; 1, focal lesions; 2, beginning confluence of lesions for white matter lesions and >1 focal lesion for basal ganglia lesions; 3, diffuse involvement of entire region for white matter lesions and confluent lesions for basal ganglia lesions.

rated in four brain subregions: (1) the frontal area corresponding to the frontal lobe anterior to the central sulcus; (2) the parieto-occipital area, consisting of both parietal and occipital lobes; (3) the temporal area, corresponding to the temporal lobe (the border between the parieto-occipital and temporal lobes was approximated as a line drawn from the posterior part of the Sylvian fissure to the trigone areas of the lateral ventricles); and (4) the basal ganglia region, including the striatum, globus pallidus, thalamus, internal and external capsules and insula. Some previous studies have evaluated the degree of whole-brain lesions without considering the localization of them, while we rated the degree of WMHs in the subcortical white matter of areas (1), (2), and (3) and substituted the results as whole-brain lesions. Two trained operators rated the scale, and reproducibility was calibrated. Intra-class correlation coefficients (ICCs) for these measurements were 0.91 in subcortical WMHs and 0.94 in basal ganglia WMHs, respectively. ICC values >0.9 are regarded as excellent, so this rating scale was considered reliable (Fleiss, 1987). The demographics of each four groups were summarized in Table 1.

Statistical analysis

Statistical analyses were performed using SPSS for Windows 11.0.1J software (SPSS Japan, Tokyo, Japan). To compare the score of each detailed neuropsychological tests for picking up the cognitively normal candidates, it is necessary to correct the individual scores for age, years of education, and sex (Miyamoto *et al.*, 2009). So we did not dealt with the detailed neuropsychological tests but use the subdivisions of MMSE as score of cognitive function. Differences in scores for each item of the MMSE among WMH staging (0–3) groups for the four brain subregions were evaluated using the Kruskal–Wallis test (Table 2). Non-parametric tests were applied to post hoc analyses. Values of $p < 0.05/(6 \times$ number of items demonstrated to be statistically significant in the Kruskal–Wallis test) were considered as statistically significant to avoid type 1 errors in the multiplicity of statistical analysis.

As a similar previous study indicated the influence of age and years of education on cognitive performance (de Groot *et al.*, 2000), Pearson's correlation method was used to further evaluate correlations between both

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Table 1. The demographics of the four groups

Frontal	WMH score	Age	Education period
	0 ($N=110$)	71.9 ± 3.9	10.9 ± 2.8
	1 ($N=34$)	74.6 ± 4.6*	11.2 ± 2.6
	2 ($N=21$)	75.4 ± 4.2*	10.2 ± 2.5
	3 ($N=7$)	75.3 ± 3.5	11.4 ± 3.5
Temporal			
	0 ($N=143$)	72.4 ± 4.1	10.9 ± 2.8
	1 ($N=24$)	76.2 ± 4.2*	10.6 ± 2.2
	2 ($N=3$)	75.7 ± 0.5	11.7 ± 2.1
	3 ($N=2$)	71.0 ± 2.8	12.0 ± 4.2
Parieto-occipital			
	0 ($N=114$)	72.1 ± 4.0	10.8 ± 2.8
	1 ($N=23$)	73.4 ± 4.6	11.1 ± 2.4
	2 ($N=23$)	75.6 ± 4.4*	10.5 ± 2.6
	3 ($N=12$)	76.1 ± 3.1*	11.5 ± 2.8
Subcortical white matter			
	0 ($N=105$)	71.9 ± 4.0	10.9 ± 2.8
	1 ($N=24$)	73.1 ± 4.5	10.8 ± 2.7
	2 ($N=30$)	75.3 ± 4.3*	10.7 ± 2.6
	3 ($N=13$)	75.9 ± 3.1*	11.2 ± 2.9
Basal			
	0 ($N=140$)	72.4 ± 4.1	11.0 ± 2.8
	1 ($N=8$)	77.5 ± 3.2*	9.4 ± 2.6
	2 ($N=6$)	72.8 ± 4.5	10.7 ± 3.1
	3 ($N=18$)	75.7 ± 4.0*	10.7 ± 2.4

*Significant difference was detected compared to score = 0 ($p < 0.05$ after Bonferroni correction).

age and years of education and cognitive performances that were demonstrated to be statistically significant.

RESULTS

Table 2 shows the relationships between cognitive score and WMH stage in each of five ROIs. No significant differences were found for total MMSE score among groups divided according to WMH stage in each ROI. However, WMHs in frontal and parieto-occipital areas were associated with significant differences in "attention and calculation". As for WMHs in basal ganglia, significant differences were found for "orientation to time". Post hoc testing revealed significant differences between groups with scores of 0 and 3 in frontal, parieto-occipital, and basal ganglia regions. Concerning "attention and calculation", the cross-interaction of WMH grades for frontal and parieto-occipital areas were evaluated using two-way analysis of variance (ANOVA), showing no significant interaction of frontal × parieto-occipital ($p = 0.76$).

We evaluated correlations between both age and educational period and "attention and calculation" and "orientation to time" using Pearson's correlation method. For correlation analysis, values of $p < 0.025$ ($= 0.05/2$) were considered significant. As a result, a significant correlation was only seen between years of education and "attention and calculation" (correlation coefficient $= 0.271$; $p < 0.001$). However, no significant differences in years of education were seen between score 0 and score 3 groups for the frontal and parieto-occipital areas (score 0, 10.9 ± 2.8; score 3, 11.4 ± 3.5, $p = 0.79$ in frontal and score 0, 10.8 ± 2.8; score 3, 11.5 ± 2.8, $p = 0.43$ in parieto-occipital).

Significant differences in "attention and calculation" were also noted among groups for WMHs in the whole subcortical white matter (Table 2). Post hoc testing revealed significant differences between groups with scores 0 and 3, scores 1 and 3, and scores 2 and 3. We evaluated differences among groups according to age and education period using one-way ANOVA. No difference in years of education were seen among groups, and significant differences in age were only seen between groups with scores 0 and 2 and scores 0 and 3. No age differences were found between groups with scores 1 and 3 or scores 2 and 3 (mean age: score 0, 71.9 ± 4.0; score 1, 73.1 ± 4.5; score 2, 75.3 ± 4.3; score 3, 75.9 ± 3.1).

DISCUSSION

A characteristic of this study was the use of subdivided MMSE to evaluate cognitive function. No correlation was seen between the grade of WMH and total MMSE score in subjects. That is, individuals judged as being cognitively healthy in our evaluation displayed favorable MMSE scores regardless of the grade of WMH.

However, associations between some types of cognitive function (subitems of MMSE) and the grade of WMH were shown in these subjects. Moreover, the type of cognitive function impairment was shown to differ according to the injured region of brain.

Prevalence of cerebrovascular disorders is reportedly higher among Japanese than among Caucasians (Chalmers *et al.*, 2000). Approximately 25% of subjects in this study displayed a high WMH score of 2 or 3 (Table 2). Wahlund *et al.* (2001) conducted a study in Caucasian subjects that used methods similar to ours. All subjects in that study displayed normal cognitive function, as individuals with impaired cognitive function were excluded. The results of that study and the present investigation showed similar proportions of subjects with WMH scores of 2 or 3. These findings indicate that WMHs generally are not

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Table 2 C. ognitive scores for each group rated into four grades of WMHs in the four brain subregions and whole subcortical white matter (median (lower–upper quartile))

Frontal	0 ($n=110$)	1 ($n=34$)	2 ($n=21$)	3 ($n=7$)	Temporal	0 ($n=143$)	1 ($n=24$)	2 ($n=3$)	3 ($n=2$)
Orientation to time	5 (5–5)	5 (5–5)	5 (5–5)	5 (5–5)	—	5 (5–5)	5 (5–5)	5 (4.5–5)	5 (5–5)
Orientation to place	5 (5–5)	5 (5–5)	5 (5–5)	5 (5–5)	—	5 (5–5)	5 (5–5)	5 (4.5–5)	5 (5–5)
Repeat three objects	3 (3–3)	3 (3–3)	3 (3–3)	3 (3–3)	—	3 (3–3)	3 (3–3)	3 (3–3)	3 (3–3)
Attention and calculation	5 (3.5–5)	5 (4.25–5)	5 (2–5)	2 (2–3)*	—	5 (3–5)	5 (2.75–5)	5 (3–5)	2 (2–2)
Recall	3 (2–3)	2 (2–3)	2 (2–3)	3 (2.5–3)	—	3 (2–3)	2 (1.75–3)	3 (2.5–3)	3 (3–3)
Recognize objects	2 (2–2)	2 (2–2)	2 (2–2)	2 (2–2)	—	2 (2–2)	2 (2–2)	2 (2–2)	2 (2–2)
Recognize idiom	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)	—	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)
Close eyes	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)	—	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)
Copy a design	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)	—	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)
Write sentence	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)	—	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)
Three-step command	3 (3–3)	3 (3–3)	3 (3–3)	3 (3–3)	—	3 (3–3)	3 (3–3)	3 (3–3)	3 (3–3)
MMSE	29 (27–30)	29 (27.25–30)	29 (25–30)	27 (26.5–27.5)	—	29 (27–30)	28 (26–29.25)	30 (26.5–30)	27 (27–27)

Parieto-occipital	0 ($n=114$)	1 ($n=23$)	2 ($n=23$)	3 ($n=12$)	Subcortical white matter	0 ($n=105$)	1 ($n=24$)	2 ($n=30$)	3 ($n=13$)
Orientation to time	5 (5–5)	5 (5–5)	5 (5–5)	5 (5–5)	—	5 (5–5)	5 (5–5)	5 (5–5)	5 (5–5)
Orientation to place	5 (5–5)	5 (5–5)	5 (5–5)	5 (5–5)	—	5 (5–5)	5 (5–5)	5 (5–5)	5 (5–5)
Repeat three objects	3 (3–3)	3 (3–3)	3 (3–3)	3 (3–3)	—	3 (3–3)	3 (3–3)	3 (3–3)	3 (3–3)
Attention and calculation	5 (3–5)	5 (5–5)	5 (3.5–5)	2.5 (2–4.25)*	—	5 (3–5)	5 (3–5)	5 (4–5)	2 (2–4)**
Recall	3 (2–3)	2 (2–3)	2 (2–3)	2.5 (2–3)	—	3 (2–3)	2 (2–3)	2 (2–3)	3 (2–3)
Recognize objects	2 (2–2)	2 (2–2)	2 (2–2)	2 (2–2)	—	2 (2–2)	2 (2–2)	2 (2–2)	2 (2–2)
Recognize idiom	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)	—	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)
Close eyes	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)	—	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)
Copy a design	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)	—	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)
Write sentence	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)	—	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)
Three-step command	3 (3–3)	3 (3–3)	3 (3–3)	3 (3–3)	—	3 (3–3)	3 (3–3)	3 (3–3)	3 (3–3)
MMSE	29 (27–30)	29 (28.5–30)	29 (26.5–29.5)	27 (25–28.5)	—	29 (27–30)	29 (28–30)	29 (27–29.75)	27 (25–28)

Basal	0 ($n=140$)	1 ($n=8$)	2 ($n=6$)	3 ($n=18$)
Orientation to time	5 (5–5)	5 (5–5)	5 (5–5)	5 (5–5)*
Orientation to place	5 (5–5)	5 (5–5)	5 (5–5)	5 (5–5)
Repeat three objects	3 (3–3)	3 (3–3)	3 (3–3)	3 (3–3)
Attention and calculation	5 (3–5)	5 (4.25–5)	5 (3–5)	4 (2–5)
Recall	3 (2–3)	2 (2–2.25)	1.5 (1–2)	3 (2–3)
Recognize objects	2 (2–2)	2 (2–2)	2 (2–2)	2 (2–2)
Recognize idiom	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)
Close eyes	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)
Copy a design	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)
Write sentence	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)
Three-step command	3 (3–3)	3 (3–3)	3 (3–3)	3 (3–3)
MMSE	29 (27–30)	29 (28–29.25)	28 (27.25–28.25)	28 (25.25–29.75)

*Significant difference detected compared to score = 0 ($p < 0.05$ after Bonferroni correction).
**Significant difference detected compared to score = 0, 1, and 2 ($p < 0.05$ after Bonferroni correction).

particularly serious even in Japanese, as long as no impairment of cognitive function is present.

Previous studies have reported not only a correlation between WMH volume in each subdivided region and WMH volume for the brain as a whole, but also between WMH volume in other subdivided regions (DeCarli *et al.*, 2005). Meanwhile, studies have also shown that the cognitive dysfunction seen differs according to where WMHs are present (de Groot *et al.*, 2000; O'Brien *et al.*, 2002).

In our study, the grade of WMH in each subdivided region correlated with the grade of WMH in the brain as a whole and with the grade of WMH in other subdivided regions (data not shown). However, the

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grades of WMH varied in the different cerebral lobes, with correlations seen between cognitive function test results and the grade of WMH in the frontal and parieto-occipital lobes, respectively. These results indicate that WMH volume must be considered separately for each region. Moreover, among subjects in this study, cognitive dysfunction was present only in the group with a large WMH score. Van Straaten *et al.* examined the validity of quantitative measurement of WMH volume and qualitative evaluation by visual assessment. Although the results demonstrated the validity of visual assessment, the regression equation obtained using this method was not linear, but rather approximately exponential. That is, WMH volume of the group with the greatest severity in visual assessment was clearly much greater than WMH volumes of the other groups (van Straaten *et al.*, 2006). In other words, clear impairment of cognitive function can be inferred when the WMH score is 3 and indicative of a severe condition.

"Attention and calculation" refers to "serial sevens", or the task of repeatedly subtracting 7 from 100. The two elements of attention and calculation are naturally involved in this task. The frontal and parietal lobes are clearly involved in calculation (Stanescu-Cosson *et al.*, 2000), and a relationship has also been identified between the frontal lobe and attention (Au *et al.*, 2006). These results we obtained follow logically from such findings. Moreover, the results showed a clear relationship between extent of WMHs in the brain as a whole and attention and calculation. This is probably because degeneration of white matter is milder in the temporal lobe than in the frontal and parietal lobes, meaning that nearly all white matter degeneration in the brain is accounted for by WMH volume in the frontal and parietal lobes (DeCarli *et al.*, 2005).

We also identified an association between time disorientation and the region of the basal ganglia. Impaired orientation is generally recognized as involving whole-brain function rather than localized function. Impaired orientation is also thought to be caused by impairment of brain structures that integrate multiple neural pathways, such as the thalamus (Spiegel *et al.*, 1955; Kumral *et al.*, 2007). Our results therefore also likely mean that time disorientation was caused not by localized impairment of the basal ganglia, but rather by impairment resulting from damage to the basal ganglia that extended to multiple systems.

Unlike previous studies, this study found no significant correlations between age and either attention or time orientation. This may be attributable to the narrow age range of subjects, whose mean age was 73.0 ± 4.3 years.

KEY POINTS

- Regarding the frontal and parieto-occipital regions and basal ganglia region, the group with the most severe WMHs showed low performances for attention and disorientation to time, respectively.
- Our results suggest that presence of large WMHs affects performance on certain cognitive domains according to their localization.

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Prevalence of four subtypes of mild cognitive impairment and APOE in a Japanese community

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SUMMARY

Background The results of previous reports estimating the prevalence of mild cognitive impairment (MCI) have varied widely according to the criteria used to define MCI.

Methods We assessed the cognitive function of Japanese community-dwelling individuals ≥65 years old and attempted to estimate the prevalence of four MCI subtypes (amnestic single, amnestic multiple, nonamnestic single, and nonamnestic multiple) using two cutoffs (1 and 1.5 SD) below normative standard. Presence of apolipoprotein E4 allele (APOE4), which is known as a strong risk factor for AD, is reportedly associated with high risk of conversion from MCI to AD. We therefore calculated the frequency of APOE4 carriers for each MCI subtype.

Results Initially 1888 (70%) of 2698 baseline samples participated, and 1433 (53%) subjects who had complete clinical data including APOE typing remained for the final analysis. The prevalence of MCI subtypes varied within the range of 1.7–16.6%, depending on the criteria applied. Prevalence of MCI was higher using a cutoff at −1.0 SD than at −1.5 SD, and prevalence of amnestic MCI single at −1.5 SD was lowest among all subtypes of MCI. Frequency of APOE4 was higher for amnestic MCI than for non-amnestic MCI or the cognitively normal group.

Conclusion The prevalence of MCI was highly dependent on the diagnostic criteria applied. A higher frequency of APOE4 in participants with amnestic MCI subtype suggested a greater risk of future AD. For future interventions to delay the onset of dementia, targeting individuals with amnestic MCI multiple at −1 SD might be desirable.

KEY WORDS—MCI; pre-dementia; community; prevalence; APOE

INTRODUCTION

Mild cognitive impairment (MCI) has been used to describe a distinct state of abnormal cognition that does not amount to dementia, but is distinguishable from normal cognitive decline associated with aging (Petersen, 1995). Although the MCI defined by Petersen (amnestic MCI single) is assumed to represent a core subtype of MCI and prodromal of dementia, evidence against this has been raised by community studies. For example, prevalence in community-based cohort was very low compared to the established incidence rate of Alzheimer disease (AD) (Jungwirth *et al.*, 2005). Indeed, prevalence rates varied widely in more than 20 reported community-based epidemiological studies of MCI and similar conditions have been reported, related in part to the different diagnostic criteria applied (Panza *et al.*, 2005). A more complete definition of MCI has recently been proposed, including the consideration of multiple types of cognitive impairment in addition to

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the memory impairment that characterizes amnestic MCI. This approach distinguishes four clinical subtypes: amnestic MCI single; amnestic MCI multiple; non-amnestic MCI single; and non-amnestic MCI multiple (Petersen *et al.*, 2004). To the best of our knowledge, only two epidemiological studies employing this newclassification of MCI have been published (Jungwirth *et al.*, 2005; Busse *et al.*, 2006).

The significance of the entity of MCI depends on a high specificity and sensitivity for conversion to dementia, including AD. In other words, the significance depends on predictive validity. However, there is currently no consensus with respect to specific thresholds for cognitive performance defining the diagnosis of MCI. For cognitive domains including memory, both performance worse than 1.0 and 1.5 standard deviation (SD) below the mean for those of similar age and education have been applied in previous studies (Busse *et al.*, 2003; Jungwirth *et al.*, 2005).

It is likely that several clinical and etiological heterogeneities exist between subtypes of MCI (Petersen *et al.*, 2004). However, amnestic MCI appears most closely linked with AD, sharing clinical and pathological features (Petersen *et al.*, 2006), including increased plasma levels of amyloid beta-protein Aβ42 (Assini *et al.*, 2004) which is the major pathogenic event of AD and the association between plasma Aβ40 concentration and extent of white matter hyperintensity on MRI (Gurol, 2006). In addition, some clinic-based researches have shown a relationship between possession of APOE4 and risk of conversion from MCI to AD (Petersen *et al.*, 1995; Devanand *et al.*, 2005). Data on APOE4 frequency for each subtype of MCI could therefore provide some information about risk of AD conversion and associated clinical characteristics.

We attempted to estimate the prevalence of MCI subtypes using two thresholds (1.0 and 1.5 SD below age-, sex- and education-matched means) and to determine the cross-sectional frequency of APOE4 for each MCI subtype among a Japanese population of elderly individuals.

METHODS

The present research was conducted in Tone town, which consists of 22 districts. On May 1, 2001, a total of 3083 inhabitants $\geq$65 years old lived in the town. These 3083 inhabitants were considered as the pool of potential candidates.

This research was conducted by seven psychiatrists and eight psychologists trained for this study by the authors, along with public health nurses. All study protocols were approved by the ethics committee of the University of Tsukuba (Miyamoto *et al.*, 2009).

First phase

The general design of the project is shown in Figure 1. This was a cross-sectional study. The first phase was conducted between December 2001 and April 2002. Before baseline examination, a letter was sent to each potential candidate explaining the objectives of the project. Individuals with whom a local welfare commissioner could not meet or contact despite three telephone calls were excluded as uncontactable.

Each of the 22 districts was visited once a week to conduct group screenings (1 in the morning, 1 in the afternoon). In addition to group screenings at the 22 districts, we visited 44 individuals who were institutionalized in a long-term care facility and performed examinations using the methods described below.

Assessment procedures. Eligible subjects provided informed written consent to participate in the study. After providing informed consent, all participants underwent a screening interview.

Demographics and medical and psychiatric issuesc. The interview consisted of a structured questionnaire assessing age, sex, education and medical and psychiatric condition. Subjects were also asked to provide blood samples for routine testing and genotyping of APOE (Corder *et al.*, 1993).

Mood status. This interview was followed by the 15-item short version of the Geriatric Depression Scale (Brink *et al.*, 1982) for mood assessment. Subjects scoring $\geq$6 were considered to display depressive symptoms.

Perceived memory difficulty. Subjects were asked whether they had memory difficulties using the 19 items of the Deterioration de Cognitive Observe (DECO), which was originally developed to objectively assess memory difficulty (Ritchie *et al.*, 1992). Memory difficulties were considered present if the subject indicated problems on $\geq$1 item.

Assessment of activities of daily living. Basic abilities in activities of daily living (ADL) were measured using Nishimura's Activities of Daily Living (N-ADL) (1993), which determines the level of independence in five activities: walking/transferring; going outside;

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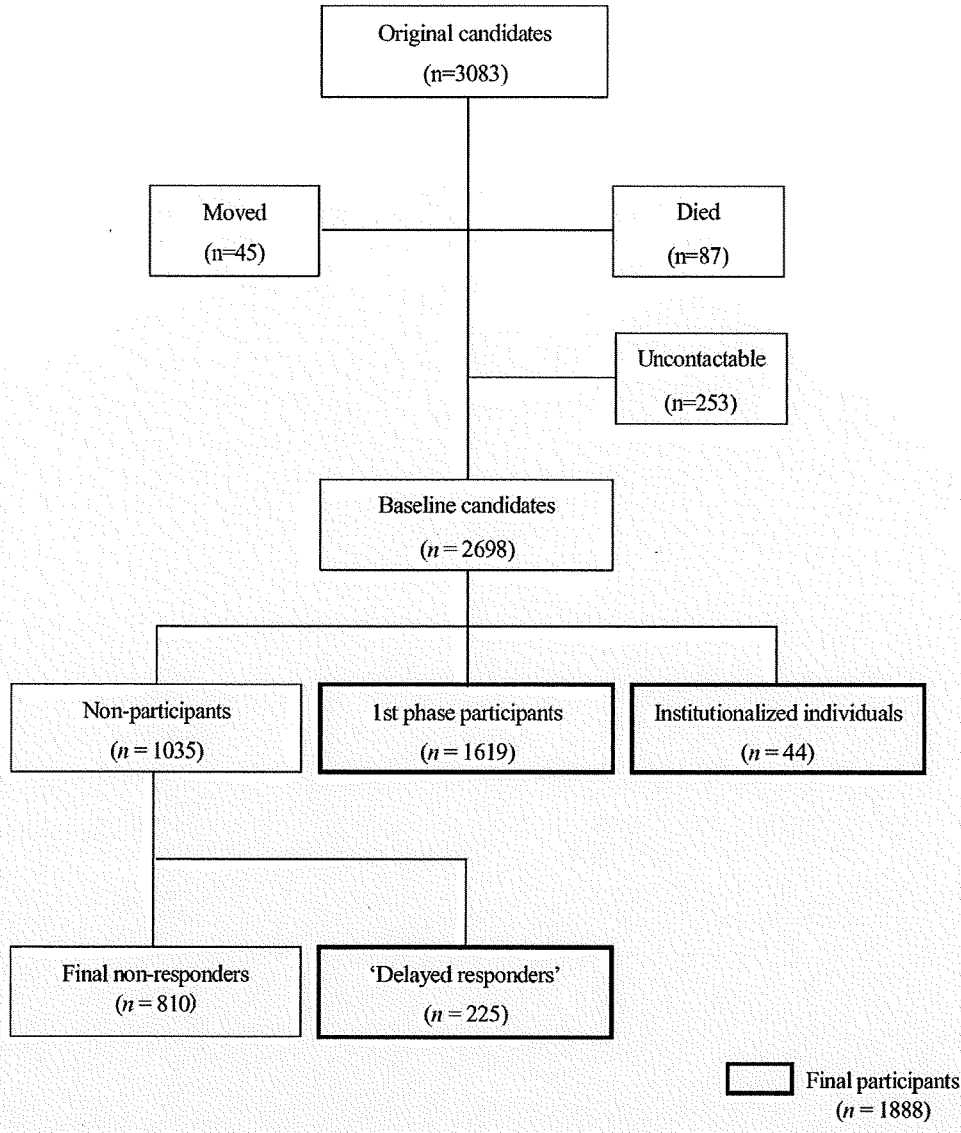

Figure 1. Flow chart indicating sources of identification for prevalent cases of MCI.

dressing/bathing; feeding; and toileting. Responders were considered functionally intact if no difficulties were reported on any of the 5 items of the NADL.

Neuropsychological battery. All participants underwent a group assessment that used a set of 5 tests measuring the following cognitive domains: attention; memory; visuospatial function; language; and reasoning. This set of tests was named the 5-Cog.

Attention was evaluated using a Japanese version of the set dependency activity (Sohlberg and Mateer, 1986), which assesses alternating attention. A Category Cued Recall test (Grober *et al.*, 1988) was used to assess memory ability. The Clock Drawing test, which requires subjects to draw the hands of a clock to depict the time at 'ten after eleven' (Freedman *et al.*, 1994), was used to assess visuospatial function. Language ability was examined using a category fluency test (Soloman and Pendlebury, 1998). The similarity subset of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981) was employed to assess abstract reasoning ability.

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This cognitive assessment was conducted in a group setting (maximum, 50 participants) by an examiner with the use of a projector. All participants were asked to record their answers on an answer sheet. Mean duration of the 5-Cog examination was 35 min. For participants who had difficulty understanding the tasks or impaired hearing or vision, the examination was conducted using an individual version of the 5-Cog in a face-to-face setting.

During the interview, subjects who could not respond to our instructions and/or some of the scales due to obvious cognitive impairment were also identified.

Consensus diagnosis. After each assessment, our team reviewed the functional, medical, neurological, psychiatric and neuropsychological data and reached a consensus regarding the presence or absence of dementia by diagnosis according to DSM-IV (American Psychiatric Association, 1994) criteria. Only subjects who were not diagnosed with dementia were considered for a diagnosis of MCI.

MCI diagnostic criteria

Criteria for MCI were retrospectively applied among non-demented individuals after the consensus conference. Consistent with the standard criteria, for all subtypes of MCI described below, subjects considered for MCI were required to have: (1) objective impairment in $\geq$1 cognitive domain based on the average of scores on neuropsychological measures within that domain and 1 SD and 1.5 SD cutoffs using normative corrections for age, years of education, and sex; (2) essentially preserved ADL(defined above); (3) presence of memory complaints (defined above); and (4) no diagnosis of dementia at the consensus diagnosis.

First, for our subtype of amnestic MCI single, memory impairment was defined as a score less than 1 or 1.5 SD below the demographically corrected mean on the category cued recall test, and performance on scores from all other cognitive domains (i.e. attention, language, visuospatial and reasoning) was required to fall within normal limits (more than 1 or 1.5 SD below the demographically corrected mean). Second, amnestic MCI multiple was diagnosed in the presence of memory impairment and impairment in one or more cognitive domains. Third, diagnosis of non-amnestic MCI single required cognitive impairment in a single non-memory domain and performance on scores in all other cognitive domains falling within normal limits. Finally, non-amnestic MCI multiple was diagnosed if impairment was seen in $\geq$2 of the four non-memory domains, and if the memory domain score was within normal limits. We thus estimated the prevalence of eight forms (2 cutoffs $\times$ 4 subtypes) of MCI.

Second phase (investigation of delayed-responders)

At the completion of the first phase, we had identified a total of 1035 non-participants who were contacted but had refused to participate, excluding the above-defined uncontactable individuals. As we desired to make this study representative, a door-to-door survey of non-participants was attempted to enroll as many participants as possible.

This portion of the phase was conducted with the aid of general practitioners and local welfare commissioners (persons vested with promoting social welfare in each local area), in the hope that their invitations would encourage participation of newcomers from among non-participants. They contacted and explained our project to individuals appearing on the non-participants list, with 225 non-participants subsequently agreeing to participate. These subjects were considered as 'delayed responders'. Our team visited the home of each delayed responder and conducted the same interview and tests that had been used in the first phase. The individual version of the 5-Cog was used for cognitive assessment. After each assessment, the case was discussed on the basis of the consensus diagnosis described above.

We did not ask the 'delayed responders' and 44 institutionalized individuals enrolled in the first phase to provide blood samples for genotyping of APOE because of the difficulty in collection and delivery of blood samples for laboratory examination.

Statistical analysis. For normative data, we excluded data from participants who did not complete the series of interview and examinations or had been diagnosed with dementia. Test–retest reliability of the 5-Cog was confirmed (Miyamoto *et al.*, 2009).

The characteristics and cognitive status of participants were analyzed using a t-test and χ^2 test for continuous and categorical variables, respectively. We show the frequency of each MCI subtype as percent prevalence. The significance level was set at $p < 0.05$. Data were analyzed using SPSS 15.0J software (SPSS, Chicago, IL, USA).

RESULTS

Study sample

Of the 3083 potential candidates, 132 were excluded (Figure 1). Specifically, 87 had died and 45 had moved

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before initial examination. An additional 253 residents were 'uncontactable individuals'. The remaining 2698 residents were considered as candidates at the baseline. Of the 1035 residents who initially refused to participate (non-participants), 225 became 'delayed responders'. As a result, 1888 (1619 first study and 225 'delayed responders' and 44 institutionalized individuals) (70%) of the 2698 baseline candidates were enrolled.

Prevalence of MCI

As a result of consensus diagnosis, we estimated a prevalence of 4.5% for any type of dementia combined among the 1888 participants. We excluded 186 subjects of the first phase participants who had been diagnosed with dementia and/or refused APOE typing. As described, 225 'delayed responders' and 44 institutionalized individuals did not provide blood samples for APOE typing.

Consequently, 1433 (53%) of the 2698 candidate subjects remained for the final analysis. The final subjects had complete data including APOE typing and were not demented. Basic data for the subjects are shown in Table 1, and prevalence of the eight subtypes of MCI among subjects are shown in Table 2.

The main findings were as follows: (1) prevalence of MCIs ranged from 1.7% to 16.6%, depending on the diagnostic criteria applied, with the lowest prevalence for the original MCI (amnestic MCI single −1.5 SD); (2) when cutoffs of −1.0 SD and −1.5 SD were used, 18.9% and 38.9% of study participants were operationally diagnosed with some subtype of MCI, respectively; (3) prevalence of MCI using a cutoff of −1.0 SD was 1.5–3.5 times higher than for using −1.5 SD for the four MCIs; (4) the prevalence of amnestic MCI multiple was higher than the prevalence of amnestic MCI single, and MCI multiple at −1.0 SD displayed the highest prevalence (11.0%).

Frequency of APOE4

APOE genotyping revealed that 19.9% of the 1433 participants were APOE4 carriers (2/4, 3/4 or 4/4). Frequencies of APOE4 for each subtype of MCI are shown in Table 3. Frequency was higher for the combined group of any type of MCI than for the cognitively normal group.

We first employed the analysis of multiple comparison among all four MCI subtypes and non-MCI, however the analysis showed no significant difference. Then, frequency was compared among normal, amnestic MCI (single and multiple) and non-amnestic MCI (single and multiple) groups using χ^2 analyses with Ryan's multiple comparison procedure as a post hoc analysis. As a whole, the highest frequency was found in the amnestic MCI group (single and multiple) (Figure 2)

For the amnestic MCI group, the highest frequency of APOE4 (39.5%) was found in the multiple −1.5 SD subtype, whereas the lowest frequency (25.0%) was found in the single −1.0 SD subtype. The frequency for Petersen's original MCI (single −1.5 SD) was 32.0%. Frequency was higher for a cutoff of −1.5 SD than for −1.0 SD for all MCIs other than non-amnestic MCI multiple.

DISCUSSION

General

The sample size in the present study seems comparable to the largest studies among previously

Table 1. Demographic characteristics

Characteristic	Overall group	APOE ε4 non-carrier	APOE ε4 carrier	*P*
	(*n* = 1433)	(*n* = 1148)	(*n* = 285)	
Age, years	73.6 ± 5.8	73.6 ± 5.7	73.6 ± 5.8	0.882
Female, *n* (%)	844 (58.9)	670 (58.4)	174 (61.1)	0.409
Years of education	10.0 ± 2.6	10.0 ± 2.6	10.0 ± 2.7	0.792
GDS score	2.9 ± 2.6	2.9 ± 2.6	2.7 ± 2.6	0.190
N-ADL score	49.7 ± 1.3	49.7 ± 1.3	49.7 ± 1.2	0.805
IADL score	5.2 ± 1.6	5.1 ± 1.6	5.2 ± 1.6	0.872
BMI	22.8 ± 3.2	22.9 ± 3.3	22.7 ± 3.0	0.368
Alcohol consumption, *n* (%)	493 (34.4)	396 (34.5)	97 (34.0%)	0.876
Smoking, n (%)	501 (35.0)	405 (35.3)	96 (33.7%)	0.600

Values represent mean ± SD.
BMI = body-mass index; GDS = Geriatric Depression Scale; IADL = instrumental activities of daily living; N-ADL = Nishimura's activities of daily living.

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Table 2. Baseline prevalence of 4 types of MCI

MCI subtype	Severity level of MCI SD‡	Baseline prevalence	
		n	%
Amnestic type			
single	1.0	44	3.1%
	1.5	25	1.7%
multiple	1.0	157	11.0%
	1.5	38	2.7%
Non-amnestic type			
single	1.0	238	16.6%
	1.5	164	11.4%
multiple	1.0	118	8.2%
	1.5	44	3.1%
All subtypes of MCI			
	1.0	557	38.9%
	1.5	271	18.9%
Non-MCI (no impairment in cognitive domains)			
	1.0	876	61.1%
	1.5	1162	81.1%

‡Different MCI subtypes were determined according to different severity levels: cognitive performance 1.0 SD and 1.5 SD below the means of age-, education- and sex-matched control subjects.

reported population-based prevalence studies of pre-dementia syndromes including MCI from Western countries (Panza *et al.*, 2005). About half of these studies used amnestic MCI single as the diagnostic criteria, and most showed prevalence rates <6%. Our prevalence rates of 3.1% and 1.7% (−1 SD, −1.5 SD) for amnestic MCI single appears lower in comparison with previous results. However, we stand by the validity of our results on the following grounds. Age, educational level and gender have been reported as related to the prevalence of pre-dementia, but some of the previous studies estimating prevalence did not control for such factors (Panza *et al.*, 2005). Controlling for these factors might have contributed to the lower values. To the best of our knowledge, only two previous studies have identified MCI subtypes using similar methods to the present (Busse *et al.*, 2003; Jungwirth *et al.*, 2005). General findings of the current study resembled those of the two studies. Our estimated prevalence of MCIs, including amnestic MCI single, thus appear plausible.

Regarding APOE4 frequency for Japanese, a little less than half of AD patients are known to have at least one APOE4 allele and frequency is about three-fold that in normal controls (Ueki *et al.*, 1993; Asada *et al.*,

Table 3. Prevalence of APOE ε4 alleles

APOE ε4 alleles	Amnestic type		Non-amnestic type		All subtypes of MCI	Non-MCI†
	Single	Multiple	Single	Multiple		
MCI subtypes, 1.0 SD below mean‡						
ε4−	33 (75.0)	113 (72.0)	192 (80.7)	96 (81.4)	434 (77.9)	714 (81.5)
ε4+	11 (25.0)	44 (28.0)	46 (19.3)	22 (18.6)	123 (22.1)	162 (18.5)
MCI subtypes, 1.5 SD below mean‡						
ε4−	17 (68.0)	23 (60.5)	124 (75.6)	37 (84.1)	201 (74.2)	947 (81.5)
ε4+	8 (32.0)	15 (39.5)	40 (24.4)	7 (15.9)	70 (25.8)	215 (18.5)

Values represent number (percentage).
†No impairment in cognitive domains.
‡Different MCI subtypes were determined according to different severity levels: cognitive performance 1.0 SD and 1.5 SD below means of age-, education- and sex-matched control subjects.

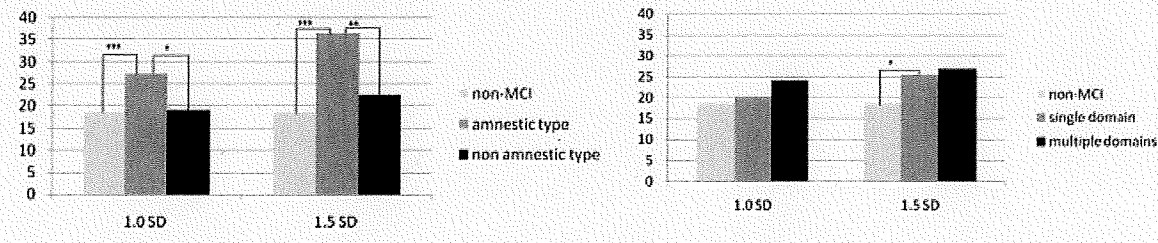

Figure 2. Proportion with APOE ε4 alleles between non-MCI, MCI-amnestic type and MCI-non amnestic type groups and between non-MCI, MCI-single domain impaired and MCI-multiple domains impaired groups $*p < 0.05$; $**p < 0.01$; $***p < 0.001$.

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1996). A frequency of 18.5% APOE4 for non-MCI participants thus appears similar to that for healthy Japanese elderly individuals, and the 39.5% for amnestic MCI multiple −1.5 SD subjects seems a little less than the frequency for Japanese AD patients. As described below, individuals with amnestic MCI are assumed to be likely to convert to AD, so a value of 39.5% appears plausible. To the best of our knowledge, the only community-based study of MCI estimating frequency of APOE4 carriers found an association between APOE4 and original amnestic MCI (Lopez *et al.*, 2003). In that study, APOE4 frequencies for amnestic MCI and healthy participants were 33% (12/40) and 20% (101/552), respectively. These results closely resemble our own and support the validity of results from the APOE study.

Amnestic vs non-amnestic MCI

According to the consensus of the Key Conference on MCI, amnestic MCI single is presumably caused by prodromal AD, and amnestic MCI multiple by AD or vascular dementia (VD) (Winblad *et al.*, 2004). In fact, two community-based longitudinal studies have shown that amnestic MCI is likely to convert to AD (Busse *et al.*, 2006; Fischer *et al.*, 2007). However, neither of these two studies reported APOE4 frequency. Conversely, non-amnestic MCI single is presumably caused by dementia with Lewy bodies (DLB) or VD, and non-amnestic MCI multiple by DLB or frontotemporal dementia. However, the course of non-amnestic MCI shown in the two studies was contradictory (Busse *et al.*, 2006; Fischer *et al.*, 2007).

Many clinic-based studies that have examined the utility of APOE4 in predicting AD conversion among amnestic MCI patients have shown affirmative results (Mosconi *et al.*, 2004; Devanand *et al.*, 2005). In the present study, comparison between the APOE4 frequency in combined amnestic-MCIs and the combined non-amnestic MCIs showed a statistically significant difference, however the analysis of multiple comparisons among all four MCI subtypes and non-MCI did not. The discrepancy appears to be attributable to small number of individuals with MCIs especially amnestic MCI single, however it may indicate the homogeneity of the amnestic MCI group (single plus multiple) and the non-amnestic group (single plus multiple). In any case, frequency of APOE4 was higher for the amnestic MCI group than for the non-amnestic group and normal elderly individuals, with similar frequencies for the latter two groups. Taking these findings together, amnestic- and non-amnestic MCI may differ in future course with respect to conversion to AD.

Clinical significance of amnestic MCIs

Among 4 subtypes of amnestic MCI, the highest prevalence ($n = 157$, 11.0%) was found for amnestic MCI multiple −1.0 SD, and this group showed relatively high APOE4 frequency (28.0%). Theoretically, the estimated number of individuals who will develop AD in future may be considerably larger for this subtype than for other MCI subtypes. Conversely, amnestic MCI multiple −1.5 SD ($n = 38$, 2.7%) showed the highest APOE4 frequency of 39.5%, not markedly different from that present in Japanese AD patients. On the basis of our experience, clearly distinguishing operationally diagnosed amnestic MCI multiple −1.5 SD from clinically diagnosed early dementia using DSM-IV criteria is difficult. Some individuals with our operational diagnosis of amnestic MCI multiple −1.5 SD could thus instead represent patients at the very early stages of AD.

Needless to say, cognitive impairment is milder for amnestic MCI multiple −1.0 SD than for amnestic MCI multiple −1.5 SD. For future community studies, providing a preventive intervention for amnestic MCI multiple −1.0 SD individuals might be desirable, while individuals with amnestic MCI multiple

KEY POINTS

- Prevalence of MCIs ranged from 1.7% to 16.6%, depending on the diagnostic criteria applied, with the lowest prevalence for the original MCI (amnestic MCI single −1.5 SD).
- Among normal, amnestic MCI (single and multiple) and non-amnestic MCI (single and multiple) groups, the highest frequency was found in the amnestic MCI group (single and multiple).
- The results of APOE4 frequency suggest that amnestic- and non-amnestic MCI may differ in future course with respect to conversion to AD.
- For future community studies, providing a preventive intervention for amnestic MCI multiple −1 SD individuals might be desirable, while individuals with amnestic MCI multiple −1.5 SD could represent the best target for early detection of AD.

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