−1.5 SD could represent the best target for early detection of AD.

Finally, it is important to test for possible non-response bias for this kind of study, thus we have examined this issue elsewhere (Miyamoto *et al.*, 2009). This cross-sectional study of MCI was unable to evaluate positive predictive power for each subtype of MCI. Nevertheless, the present community-based study appears to provide useful information on MCI.

CONFLICT OF INTEREST

None known.

ACKNOWLEDGEMENTS

Funding for this research was obtained from the Ministry of Health, Labor and Welfare (Grant No. 2001-dementia and fracture-003).

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Invited Review for the 90th Anniversary

Geriatric Medicine, Japanese Alzheimer's Disease Neuroimaging Initiative and Biomarker Development

Hiroyuki Arai,[1] Nobuyuki Okamura,[2] Katsutoshi Furukawa[1] and Yukitsuka Kudo[3]

[1]Department of Geriatrics and Gerontology, Division of Brain Science, Institute of Development, Aging, and Cancer, Tohoku University, Sendai, Japan
[2]Department of Pharmacology, Tohoku University Graduate School of Medicine, Sendai, Japan
[3]Department of Neuroimaging Research, Innovation of New Biomedical Engineering Center, Tohoku University, Sendai, Japan

Due to a change in disease spectrum in aged countries, the primary role of geriatricians should be directed to an appropriate management and prevention of 1) cognitive decline and dementia, 2) swallowing and aspiration pneumonia and 3) falls and fractures. Management of dementia constitutes a central part in the practice of geriatric medicine in order to support independence of life in elderly people. The current paradigm of cognitive function-based testing for the diagnosis and treatment of Alzheimer's disease (AD) is going to drastically shift to a biomarker-based test approach, a shift that will correspond to the emergence of disease-modifying drugs. In addition, a new molecular imaging technique that visualizes neuronal protein deposits or pathological features has been developed in Japan and the U.S.A. Based on these achievements, the Alzheimer's Disease Neuroimaging Initiative (ADNI) was proposed and initiated in 2005. The ADNI is a long-term observational study being conducted in the U.S.A., Europe, Australia, and Japan using identical protocols. The objectives of ADNI are: 1) to establish methodology which will allow standard values related to long-term changes in imaging data, such as MRI and PET, in patients with AD and mild cognitive impairment and normal elderly persons; 2) to obtain clinical indices, psychological test data, and blood/cerebrospinal fluid biomarkers to demonstrate the validity of image-based surrogate markers; and 3) to establish optimum methods to monitor the therapeutic effects of disease-modifying drugs for AD. Patient enrollment in the Japanese ADNI has begun in July 2008. Imaging of AD pathology not only acts as a reliable biomarker with which to assay curative drug development by novel pharmaceutical companies, but it also helps health promotion toward AD prevention.

Keywords: geriatric medicine; Alzheimer's disease; Amyloid β-peptide; Biomarker; Amyloid imaging; ADNI
Tohoku J. Exp. Med., 2010, **221** (2), 87-95.

Geriatrician's role and proposal of "Geriatric Triangle"

Geriatric medicine is an independent internal medicine division that is specialized for management of medical problems of elderly people. Despite a fact that elderly people appear healthy, a variable latent organ dysfunction may be present due to a limited residual capacity. A condition referred to as geriatric syndrome is a complex and multi-organ disease especially suffered by elderly people. The geriatric syndrome consists of more than 50 medical conditions such as dementia, depression, delirium, pneumonia, urinary incontinence, osteoporosis and fractures as well as malnutrition, sarcopenia, skin ulceration and renal failure. Importantly, these clinical conditions often occur in combination rather than separately. As illustrated in Fig.1, most important functions which support independence of life in later years are: 1) Thinking and judgments; 2) Eating and swallowing; and 3) Standing and walking. Loss of these basic functions alone or in combination will directly lead to devastating health implications and reduced quality of life. Disturbance of cognitive ability manifests as dementia. Impairment of ordered oropharyngeal functions causes a disturbed swallowing or dysphasia followed by development of aspiration pneumonia. Failure of standing and walking results in repeated falls and fractures. — all being hardly present before the age of 65 but highly prevalent over the age of 75. Moreover, these problems not merely occur in separate occasions but they also are inter-related each other. For example, people with advanced dementia are likely to develop eating problems and aspiration (Nakagawa et al. 1997; Wada et al. 2001; Mitchell et al.

Received March 23, 2010; revision accepted for publication April 5, 2010. doi:10.1620/tjem.221.87
Correspondence: Prof. Hiroyuki Arai, Department of Geriatrics and Gerontology, Division of Brain Science, Institute of Development, Aging, and Cancer, Tohoku University, Sendai, Miyagi, 980-8575, Japan.
e-mail: harai@idac.tohoku.ac.jp

2009). Repeated episodes of pneumonia will develop disturbed nutrition and dehydration which leads to sarcopenia with an increased risk of falls and fractures (Lang et al. 2010). A long-term bedridden state due to hip or vertebral fractures will result in worsening of dementia (Muir et al. 2009). Conversely, demented patients who were treated by anti-psychotic drugs are associated with an increased risk of falls and fractures (Horikawa et al. 2005). A long-term bedridden state due to hip or vertebral fractures are prone to develop esophageal regurgitation and aspiration (Matsui et al. 2002). Drugs that up-regulate brain dopaminergic function are occasionally beneficial to prevent aspiration pneumonia in the elderly (Yamaya et al. 2001). Here, we propose to term such a closely-related condition as "geriatric triangle" as shown in Fig.1. Patients diagnosed as having geriatric triangle are likely to be placed on a long-term care facility due to reduced quality of life (Sasaki 2008). Therefore, the primary role of geriatricians should be directed to an appropriate management and prevention of geriatric triangle. Moreover, every single geriatrician should be capable of managing the geriatric triangle beyond a scope of each organ specialist (Sasaki 2008). Hence, primary targets of geriatric medicine may include assessment and treatment of 1) cognitive decline and dementia, 2) swallowing and aspiration pneumonia and 3) falls and fractures. On the other hand, it is unlikely as a primary role of geriatrician only to manage elderly people with diseases which are spanning entire stages of life. Such diseases, for example, hypertension and diabetes mellitus, can be taken care of by each organ specialist. Due to a change in disease spectrum in aged countries, it should be emphasized that geriatric medicine has become a separate and independent practice division from other organ-specialized fields of internal medicine.

Current scientific approach toward understanding of Alzheimer's disease (AD) pathogenesis

Alzheimer's disease (AD) deprives sufferers of variable life-supporting functions that are necessary for independence in the later years of life. Development of AD leads to parting from society. Care-taking families sacrifice their quality of life and their mental and physical burdens are immeasurable. Loss of personality due to alteration of brain function while physical appearance remains the same is horrible and miserable. As an essential domain of geriatric triangle as described in Fig. 1, prevalence of dementia (the number of people with the disease at any one time) doubles for every 5-year age group beyond the age 65. Briefly, dementia hardly develops prior to age 60. However, according to data from Ministry of Health, Labor and Welfare in Japan, the prevalence of dementia is estimated to be 1.5% for age 65-69, 3.6% for age 70-74, 7.1% for age 75-79, 14.6% for age 80-84, 27.3% beyond age 85 (http://www.mhlw.go.jp/english/index.html). The elderly population aged 65 or older is now approximately 22% of the whole population in Japan. Therefore, it is likely that dementia becomes quite common over the age of 65. According to recently conducted community survey, AD is a leading cause of dementia among elderly Japanese population (Yamada et al. 2001; Wada-Isoe et al. 2009). The rapid increase in the number of AD patients can be a consequence of a rapid increase in human life span. In Japan, an average life span in 1947 was 50.6 years for men and 53.9 years for women. Surprisingly, that was 79.3 years for men and 86.1 years for women in 2008. It is possible that AD is only encountered when the nation reaches a sufficiently aged society. Furthermore, AD is a major factor in increasing national medical expense. It is a universal desire to find a way to control AD. The U.S.A. calls the rapid increase in

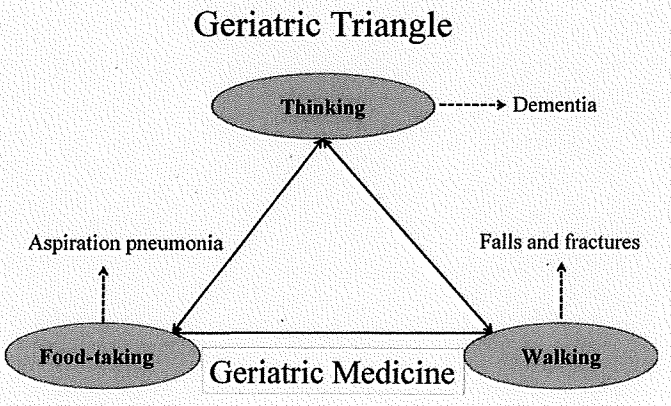

Fig. 1. Proposed concept of geriatric triangle.
At least three physical and mental functions are needed to support independence of life in elderly people. They are 1) Food-taking ability, 2) Standing and walking, and 3) Thinking and judgments. Loss of these basic functions alone or in combination will lead to devastating health implications and reduced quality of life through a vicious circle. Here, we propose to term such a vicious circle as "geriatric triangle". Geriatric triangle constitutes a major part of geriatric syndrome. Therefore, each geriatrician should be capable of managing the geriatric triangle beyond a scope of each organ specialist.

AD patients and concomitant pressure on federal budget a "National Crisis" which illustrates the seriousness of the problem (A National Alzheimer's Strategic Plan, 2009).

Understanding of pathogenesis of AD has markedly progressed in the last 3 decades. Pathological changes of AD occur gradually initially in cognitively normal people with dementia representing the end stage of many years of accumulation of amyloid β-peptide (Aβ). Aβ was first sequenced from meningeal blood vessels of AD brains (Glenner&Wang 1984). A year later, the same peptide was discovered as the primary components of senile plaques (Masters et al. 1985). Shortly after these earlier findings, cloning of the gene encoding amyloid β-peptide precursor protein (APP) and its localization to chromosome 21coupled with the recognition that Down's syndrome (trisomy 21) leads invariably to AD neuropathology set a initial hypothesis that Aβ is a primary driving force in the pathogenesis of AD. The other neuropathological features that are characteristic of AD include neurofibrillary changes and neuron death. Spatial distribution of senile plaques differs from that of neurofibrillary changes (Arriagada et al. 1992a; Arriagada et al. 1992b). A major building block of neurofibrillary changes was shown to be abnormally phosphorylated tau (Lee et al. 1991). According to the amyloid hypothesis, cortical Aβ accumulation causes all of the disease process associated with AD including microglial and astroglial activation, synaptic injury, oxidative injury followed by abnormal tau phosphorylation and eventually loss of neurons and dementia (Hardy and Selkoe 2002). The amyloid hypothesis also tells us that control of amyloid deposition would achieve success to control AD. There have been several conceptually important observations that strongly support the amyloid hypothesis. First, we occasionally see Aβ-positive but tau-negative brains from cognitively normal elderly people in autopsy samples, suggesting that Aβ deposition predates tau deposition (Arai et al. 1990). This time framework was further evidenced by the observation that Aβ-positive senile plaques occur at age 30's, whereas tau-positive neurofibrillary changes are seen only after the age of 40 in the brains afflicted with Down's syndrome (Mann et al. 1989). Thirdly, genetic mutations causing autosomal dominant familial AD were discovered in the APP gene clustering at or very near the sites that are normally cleaved by proteases called β or γ-secretases (Goate et al. 1991). These mutations enhance proteolytic processing of APP to generate amyloidogenic Aβ (Citron et al. 1992). Other AD-causing mutations in PS-1 and PS-2 gene also enhance generation of amyloidogenic Aβ by changing proteolytic processing of APP (Scheuner et al. 1996). Finally, a distinct Aβ species ending at amino acid 42 (Aβ42) is highly amyloidogenic, and there was a uniform pattern of Aβ42 deposition as an initial event of pathology either in non-demented, AD or Down's syndrome patients (Iwatsubo et al. 1994). As illustrated in Fig. 2, we can use a hypothetical assumption to think about the progression of AD. Namely, assuming that memory loss became noticeable at the age 70 followed by progression of multiple cognitive decline and behavioral problems at the age of 75. The patient was eventually diagnosed as suffering AD. In such an instance, we can assume that accumulation of cerebral Aβ may have started at around 50 years of age followed by intracellular accumulation of tau in the form of neurofibrillary changes as well as neuron death may have started at approximately 60-65 years of age. Therefore, it should be emphasized that there is an approximately 20-year time lag between the initiation of amyloid protein deposition and onset of the earliest clinical manifestations of dementia in AD. During this lag-period, individuals are cognitively normal but they are not aware of what changes are taking place in their brains. We assume that such individuals would ultimately develop AD if he or she lived long enough. Furthermore, a prodromal stage of AD often referred to as mild cognitive impairment (Petersen et al. 2009) is characterized by onset of mildest cognitive symptoms despite a massive neuron loss in vulnerable cortical areas (Gómez-Isla et al. 1997). Hence, there is an extremely high need for development of methods that simply and reliably detect amyloid and tau deposits. One such approach is a recently developed molecular imaging technique called "amyloid imaging".

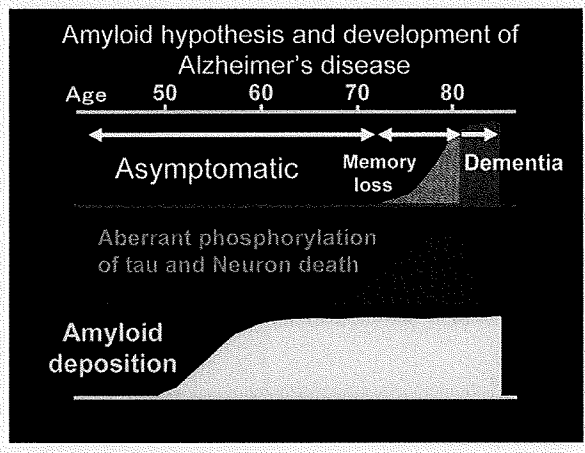

Fig. 2. Hypothetical scheme of progression of AD from amyloid deposition to development of dementia.
It is noteworthy that brain amyloid continues to be accumulating towards the onset of AD during which subjects are not aware of what changes are taking place in their brains. When subjects are first symptomatic, abundant neurofibrillary changes and a massive neuron death have already begun in vulnerable brain regions such as hippocampal or entorhinal cortex. Original description was made by Yasuo Ihara.

A paradigm shift in the diagnosis and treatment of AD

Fig. 3 illustrates a superimposition of the diagnostic and treatment framework in the context of the hypothetical amyloid cascade described above. AD has so far been diag-

nosed clinically only by demonstrating "cognitive decline" which has progressed to a stage that is sufficient enough to disturb independent social or occupational life. It is likely that cognitive decline is associated with a massive neuron death that exceeds so-called "cognitive reserve capacity" (Stern 2009). In addition to cognitive testing, two other diagnostic techniques including magnetic resonance imaging (MRI) and fluorodeoxyglucose (FDG)-PET are currently in common use to demonstrate a mass of dead nerve cells directly or indirectly. Symptomatic drugs such as donepezil hydrochloride and memantine hydrochloride are best considered at this point. However, a dramatic improvement of memory function cannot be expected since disturbance of episodic memory is based upon a massive loss of hippocampal and entorhinal cortical neurons. Accordingly, if we assume that AD represents chronic effects of a long-standing imbalance between Aβ production and Aβ clearance and this imbalance causes all existing events in the downstream of Aβ, a special attention should be directly paid to amyloid and tau depositions in the development of preventive strategies. If we are successful in developing diagnostic methodologies to detect amyloid or tau deposition before a massive neuron death occurs, such approaches will make a great contribution to developing a disease-modifying or curative treatment that directly targets amyloid and also tau. A paradigm of cognitive function-based testing for the diagnosis and treatment of AD is going to drastically shift to a biomarker-based test approach in accordance with the emergence of disease-modifying drugs. Hope for prevention of AD would be potentially carried out. As mentioned later, the Alzheimer's Disease Neuroimaging Initiatives (ADNI) will change paradigm of diagnostic and treatment of AD drastically with biomarkers as a bridging role in the paradigm shift.

Biomarkers with a bridging role in the paradigm shift

In general, biomarkers of AD are defined as indicators of specific features that characterize AD in vivo. Either biochemical or imaging biomarkers are expected to provide potentially diverse purposes as summarized elsewhere (The Ronald and Nancy Reagan Research Institute of the Alzheimer's Association & NIAWG 1998; Frank et al. 2003; Shaw et al. 2009). First, biomarkers will support preonset diagnosis. As demonstrated in Fig. 2 and 3, AD pathology has already started with abundant amyloid pathology even though individuals are otherwise normal and are still independent in their daily living activities,. This stage can be an ideal therapeutic time point in which disease-modifying or curative drugs should be indicated before neurodegenerative cascade is triggered. Such biomarkers will enable us to move from disease modification to prevention of AD. Second purpose is evaluation of disease severity. Currently, severity or clinical stage of AD is evaluated by neuropsychological testing. However, neuropsychological test results are likely to vary due to the patient's physical condition on the day of the test and experience of the examiners. In a study involving 192 AD patients performed by Jack et al., the annual change in ADAS-Cog score in mild to moderate AD was 4.25 ± 7.2 (mean ± S.D.) points, while the yearly change in hippocampal volume on MRI in the same patients was −234 ± 144 (mean ± S.D.) mm^3 (Jack et al. 2003; Petersen et al. 2005). The SD, representing variation of the values, of the hippo-

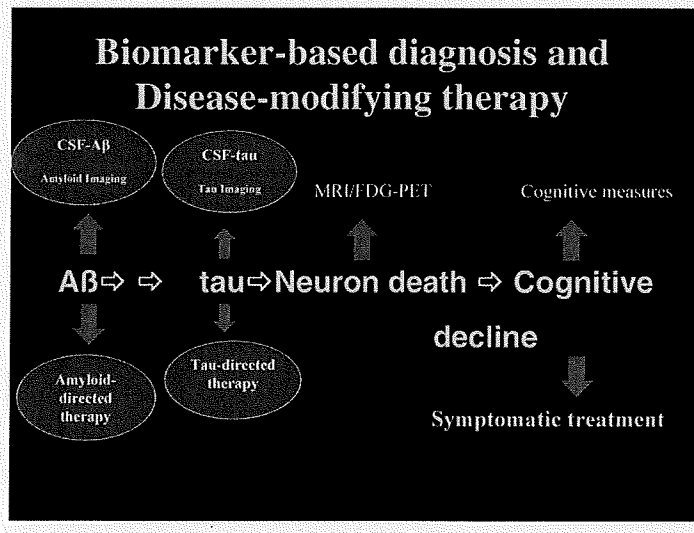

Fig. 3. Strategies for new diagnostic and therapeutic approaches for AD are presented based on amyloid hypothesis.
This figure illustrates a superimposition of the diagnostic and treatment framework in the context of the hypothetical amyloid cascade as described in Fig. 2. In the hypothesis, amyloid is located upstream probably due to a causative agent of AD. Therefore, amyloid imaging is quite attracting because this technology will facilitate both detection and intervention that targets amyloid. If tau imaging would also be possible, tau-targeting therapy might be considered.

campal index was only 0.6 times the mean, while that of ADAS-Cog was 1.7 times. Since image processing is a uniform mechanical task, variation of the imaging biomarker should be small. Sensitive biomarkers which reliably and objectively reflect changes in lesions, even though the effect size is small, are expected to be used analogously to commonly used laboratory test indices for evaluation of the disease severity in clinical practice such as C-reactive protein in inflammatory diseases, serum transaminase levels in liver diseases as well as serum creatinine kinase levels in muscular diseases. Thirdly, we need biomarkers that support evaluation of therapeutic effects. Several classes of amyloid-reducing drugs such as γ-secretase inhibitors (De Strooper et al. 2010) and amyloid immunization therapy (Tabira 2010) might become available in the near future. For the development of these therapeutic drugs, development of methodology to objectively access "decrease or removal of amyloid" is necessary. For example, when the brain amyloid level is reduced by a novel treatment, the biomarker levels are expected to return closer to normal range. Ideal biomarkers may also provide important information regarding the timing of treatment initiation, discontinuation and changing of drug treatment. However, it may be unlikely that a single biomarker meets all conditions described above, and it may be more realistic to prepare a combination or panel of several different biomarkers.

Since therapy is likely to be most effective at or before symptom onset, early or pre-symptomatic detection of AD is highly desirable before neurodegeneration becomes obvious. Thus, there is a great need for blood and CSF biomarkers that substantially aid tracking disease progression of AD and eventually promoting prevention strategy. As reviewed elsewhere (The Ronald and Nancy Reagan Research Institute of the Alzheimer's Association & NIAWG 1998; Frank et al. 2003), ideal AD biomarkers should detect a fundamental feature of AD neuropathology, be validated in autopsy confirmed cases, have a diagnostic sensitivity > 80% for detecting AD and a specificity of > 80% for distinguishing AD from other dementias. Moreover, assays using AD biomarkers should be reliable, reproducible, non-invasive, simple to perform and inexpensive. Further, validation of AD biomarkers requires confirmation by at least 2 independent studies from qualified investigators published in peer-reviewed journals. Tau and Aβ are major components of the two neuropathological hallmarks of AD (tangles and plaques respectively), and they are the most intensively studied candidate AD biomarkers where they are best studied in cerebrospinal fluid (CSF) using extensively characterized ELISAs (Arai et al. 1995; Arai et al. 1997; Arai et al. 1998; Tomita et al. 2007). A recent examination of > 100 subjects with autopsy-confirmed diagnoses reached a conclusion that elevated CSF tau levels are associated with the presence of AD pathology and CSF Aβ42 levels are decreased in AD (Clark et al. 2003). Currently, it is widely accepted that biomarkers of brain amyloid burden are reductions in CSF Aβ42 and increased amyloid PET tracer retention (Fagan et al. 2006; Jack et al. 2010). As shown in Fig. 2, after a lag period, which varies from patient to patient, neuronal dysfunction and neurodegeneration become the dominant pathological processes. Biomarkers of neuronal injury and neurodegeneration are increased CSF tau and structural MRI measures of cerebral atrophy (Arai et al. 1995). Neurodegeneration is accompanied by synaptic dysfunction, which is indicated by decreased FDG-PET (Jack et al. 2010).

Development and clinical applications of amyloid imaging

Amyloid imaging is currently considered to be the most promising candidate biomarker since it meets many possible conditions of an ideal biomarker as described above. The most difficult hurdle for clinical application of this technology is to find a probe with following excellent characteristics: 1) it should selectively bind to Aβ aggregates with β-sheet-structure; 2) it should readily penetrate the blood-brain barrier (BBB) while being rapidly cleared off from the brain in the absence of the target; 3) the labeled form should not lose the characteristics of the mother compound. In our experience, enhancing one of several necessary characteristics causes loss in another, requiring extensive adjustment.

Although brain Aβ deposits are still well beyond the resolution of conventional neuroimaging techniques such as MRI, the density of these deposits in the brain tissue can be visualized through specific radiotracer and positron emission tomography (PET). The first compound to emerge as an amyloid-imaging agent was Chrysamine-G (Klunk et al. 1995). This compound shows similar binding characteristics to Congo-red, but unfortunately, due to its limited BBB permeability, there was no use as a clinical PET tracer. A marked progression in the development of amyloid-imaging tracers was made by the development of 2-(1-{6-[(2-[^{18}F]fluoroethyl)(methyl) amino]-2-naphthyl}ethylidene) malononitrile ([^{18}F]FDDNP) (Agdeppa et al. 2001). This compound is highly lipophilic and can easily cross BBB, and has been used in human PET studies (Shoghi-Jadid et al. 2002; Small et al. 2006; Barrio et al. 2008). However, this agent has some limitations in its practical use due to its low signal-to-background ratio (Tolboom et al. 2009). Currently, the most successful amyloid-binding agent is a thioflavin-T derivative, N-methyl-[^{11}C] 2-(4′-methylaminophenyl)-6-hydroxybenzothiazol ([^{11}C]PIB) which has been shown to possess a high affinity for Aβ fibrils (Klunk et al. 2003; Mathis et al. 2003; Klunk et al. 2004). An autoradiographic study using AD brain sections revealed that [^{11}C]PIB, in addition to binding to the classical fibrillar Aβ plaques, also binds to a range of Aβ containing lesions including diffuse plaques and cerebrovascular amyloid angiopathy (Lockhart et al. 2007). In vitro binding studies indicated that PIB preferentially binds to Aβ1-42 fibrils with high affinity (Klunk et al. 2003) with a negligible binding to α-synuclein and tau (Lockhart et al. 2007; Fodero-

Tavoletti et al. 2007). The [^{11}C]PIB retention in the neocortical areas is correlated with the Aβ plaque load (Bacskai et al. 2007; Ikonomovic et al. 2008) with an inverse relation to CSF Aβ42 levels (Fagan et al. 2006). The frequency of cognitively normal individuals with positive PIB binding rose in an age-dependent manner from 0% at ages 45-49 years to 30.3% at ages 80-89 years. (Rowe et al. 2007; Morris et al. 2010). Further, CSF tau and phospho-tau$_{181}$ increased with cortical PIB binding in cognitively normal individuals (Fagan et al. 2009). However, there is currently no evidence of how frequently PIB-positive normal individuals will convert to develop dementia or how long is the interval between the detection of significant Aβ burdens and the onset of dementia. Longitudinal amyloid imaging studies are needed to demonstrate the reality of amyloid hypothesis via looking at relation between amyloid deposition and temporal AD progression.

Benzoxazole derivatives are also promising alternatives as amyloid-imaging probes (Okamura et al. 2004). A PET study using the ^{11}C-labeled benzoxazole derivative 2-(2-[2-dimethylaminothiazol-5-yl]ethenyl)-6-(2-[fluoro]ethoxy) benzoxazole (BF-227) demonstrated significantly higher retention of this tracer in cerebral cortices of AD patients compared to the majority of healthy elderly subjects (Kudo et al. 2007). The retention of this tracer in cerebral cortices of mild cognitive impairment patients was intermediate between AD and healthy normal subjects (Waragai et al. 2009; Furukawa et al. 2010). A voxel-by-voxel analysis demonstrated a higher retention of [^{11}C]BF-227 in the posterior association cortex of AD patients. The pattern of this distribution corresponds well with the distribution of neuritic plaques in postmortem AD brains (Okamura et al. 2009). These findings suggest [^{11}C]BF-227 may be distinct from [^{11}C]PIB in detecting different populations of amyloid deposits. In addition, glucose metabolism demonstrated by FDG-PET was negatively correlated with that of BF-227, suggesting that extracellular amyloid surrounds synapses and impairs neuronal function (Furukawa et al. 2010). In my personal view, a highly expected value of amyloid imaging may be its capability to monitor treatment effects in PIB or BF-227 positive normal individuals who have received amyloid-reducing therapies (Rinne et al. 2010). The [^{11}C]-labeled form has a short half-life (20.4 minutes) and its synthesis requires a facility capable of radioisotope synthesis using a cyclotron, whereas the [^{18}F] -labeled form has a longer half-life (109.7 minutes), which may be amenable for delivery to various sites. Therefore, the [^{18}F]-labeled compounds, for example, [^{18}F]AV-45 will probably be a standardized agent for future clinical uses (Personal communication from Skovronsky D).

Future prospects of the Japanese ADNI

Development of curative molecular targeting therapy for AD has rapidly progressed centering mainly in work done by U.S. pharmaceutical companies. Clinical trials of symptomatic treatments currently on the market could be completed within about 6 months, but planned disease-modifying drugs to delay progression of AD may require trial durations of at least one year or longer to confirm sufficient drug effect. Development of a surrogate biomarker which reflects the pathology of the disease and monitors its progression may be desperately needed for conducting long-term clinical trials. Based on this consideration, an observational clinical study called "The Alzheimer's Disease Neuroimaging Initiative (ADNI)", was proposed and initiated in the U.S.A. in 2005 (Mueller et al. 2005; http://www.adni-info.org/ ; http://www.loni.ucla.edu/ADNI/). ADNI is a non-randomized long-term observational study undertaken in the U.S.A., Europe, Australia, and Japan using an identical protocol in each participant nation. Japanese ADNI (J-ADNI) is planning to follow 300 patients with MCI for 3 years, 150 patients with early AD for 2 years, and the other 150 normal subjects for 3 years in a cooperative study of a total of 38 facilities nationwide with sufficient experience in the management of dementia (http://www.j-adni.org/). The principle investigator is Professor Takeshi Iwatsubo at University of Tokyo. The study objectives are: 1) to establish methodology that will determine standard values related to long-term changes in image data, such as MRI and PET, in AD and MCI patients and normal elderly persons; 2) to simultaneously collect clinical indices, psychological tests, and blood/cerebrospinal fluid biomarkers to demonstrate the validity of image surrogate markers, and 3) to establish the optimum method to monitor therapeutic effects of curative drugs (disease-modifying drugs) for AD, for which analyses of the following observation items are prioritized: 1) Rate of conversion from MCI to AD, 2) rates of whole brain and hippocampus volume changes via MRI, 3) rates of change in blood and cerebrospinal fluid biomarkers, and 4) rate of change in glucose metabolism on FDG-PET. In addition, baseline amyloid PET scans are given to subjects who agreed it in J-ADNI. We hope that J-ADNI project promotes long-delayed improvements of Japanese infrastructure of medical care system for dementia. It is inadvisable for Japanese medical society to ignore that in the U.S.A. a paradigm shift in AD from 'cognitive measures-based to biomarker-based' has begun after deliberation and discussion on subjects such as clinical trial efficiency and cost reduction. Many different curative drugs are under development by pharmaceutical manufacturers, and global clinical trials of these new drugs are ongoing.

In J-ADNI, firstly, several of Japanese version of the cognitive test batteries were revised by Sugishita M. et al. to normalize the relative difficulty and to enhance maximum compatibility of the test with World Wide ADNI and later for global clinical trials of new drugs. The first patient was successfully enrolled at the National Center of Neurology and Psychiatry in July 2008. More than 330 patients have already been enrolled as of March 10, 2010. The consent rate to FDG-PET, amyloid PET, and sampling of cerebrospinal fluid was obtained from 80, 44, and 40% of the participants, respectively. We will attempt to increase the

number of patients enrolled and the rate of consent to biomarker sampling, aiming at a great success of J-ADNI and World Wide ADNI together.

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European Journal of Neurology 2010, 17: 823–829 doi:10.1111/j.1468-1331.2009.02940.x

Clinical features of non-hypertensive lobar intracerebral hemorrhage related to cerebral amyloid angiopathy

M. Hirohata[a], M. Yoshita[a], C. Ishida[a,b], S. I. Ikeda[c,d], A. Tamaoka[c,e], S. Kuzuhara[c,f], M. Shoji[c,g], Y. Ando[c,h], T. Tokuda[c,i] and M. Yamada[a,c]

[a]*Department of Neurology and Neurobiology of Aging, Kanazawa University Graduate School of Medical Science, Kanazawa;* [b]*Department of Neurology, National Hospital Organization Iou Hospital, Kanazawa;* [c]*The Brain Amyloidosis Subcommittee, the Amyloidosis Research Committee from the Ministry of Health, Labour, and Welfare;* [d]*Department of Medicine (Neurology and Rheumatology), Shinshu University School of Medicine, Matsumoto;* [e]*Department of Neurology, Institute of Clinical Medicine, University of Tsukuba, Tsukuba;* [f]*Department of Neurology, Mie University Graduate School of Medicine, School of Medicine, and Mie University Hospital, Tsu;* [g]*Department of Neurology, Institute of Brain Science, Hirosaki University School of Medicine, Hirosaki;* [h]*Department of Neurology, Graduate School of Medical Sciences, Kumamoto University, Kumamoto; and* [i]*Department of Neurology, Kyoto Prefectural University of Medicine, Kyoto, Japan*

Keywords:
cerebral amyloid angiopathy, Japanese, lobar intracerebral hemorrhage, neuroimaging, non-hypertensive

Received 16 September 2009
Accepted 2 December 2009

Background and purpose: The present study aims to clarify the clinical features of non-hypertensive cerebral amyloid angiopathy-related lobar intracerebral hemorrhage (CAA-L-ICH).

Methods: We investigated clinical, laboratory, and neuroimaging findings in 41 patients (30, women; 11, men) with pathologically supported CAA-L-ICH from 303 non-hypertensive Japanese patients aged ≥55, identified via a nationwide survey as symptomatic CAA-L-ICH.

Results: The mean age of patients at onset of CAA-L-ICH was 73.2 ± 7.4 years; the number of patients increased with age. The corrected female-to-male ratio for the population was 2.2, with significant female predominance. At onset, 7.3% of patients received anti-platelet therapy. In brain imaging studies, the actual frequency of CAA-L-ICHs was higher in the frontal and parietal lobes; however, after correcting for the estimated cortical volume, the parietal lobe was found to be the most frequently affected. CAA-L-ICH recurred in 31.7% of patients during the average 35.3-month follow-up period. The mean interval between intracerebral hemorrhages (ICHs) was 11.3 months. The case fatality rate was 12.2% at 1 month and 19.5% at 12 months after initial ICH. In 97.1% of patients, neurosurgical procedures were performed without uncontrollable intraoperative or post-operative hemorrhage.

Conclusions: Our study revealed the clinical features of non-hypertensive CAA-L-ICH, including its parietal predilection, which will require further study with a larger number of patients with different ethnic backgrounds.

Introduction

Cerebral amyloid angiopathy (CAA), a condition characterized by cerebrovascular amyloid deposition, causes intracerebral hemorrhage (ICH) and other cerebrovascular disorders [1,2]. Sporadic amyloid β-protein (Aβ)-type CAA, the most common form of CAA, is frequently found in the elderly and in patients with Alzheimer's disease (AD) [3].

There have been many reports of hospital-based studies on CAA-related ICH (CAA-ICH) [1,4–13]. From the viewpoint of lobar ICH (L-ICH), our previous pathological study on elderly Japanese patients indicated that hypertension was the most frequent cause of L-ICH, and CAA, the second-most [11]. Although hypertension may coexist with CAA and contribute to the development of L-ICH [6,11,12,14], clinical details of non-hypertensive cases of L-ICH related to CAA (CAA-L-ICH) must be clarified. In this study, we characterized the clinical features of patients with

Correspondence: Prof Masahito Yamada, MD, PhD, Department of Neurology and Neurobiology of Aging, Kanazawa University Graduate School of Medical Science, Kanazawa 920-8640, Japan (tel.: +81 76 265 2290; fax: +81 76 234 4253; e-mail: m-yamada@med.kanazawa-u.ac.jp).

non-hypertensive CAA-L-ICH identified by a nationwide study in Japan.

Methods

This two-stage study was conducted by the Brain Amyloidosis Subcommittee, a subgroup of the Amyloidosis Research Committee funded by the Ministry of Health, Labour, and Welfare, Japan. We identified non-hypertensive patients aged ≥55 with CAA-L-ICH of different diagnostic reliabilities, including pathologically supported and clinically suspected cases. All patients had multiple or single L-ICH, with or without support of CAA pathology. We did not focus on microbleeds, because gradient-recalled echo T2*-weighted magnetic resonance imaging (MRI) studies were not performed in all patients. Patients with hypertension were defined as those with systolic pressure ≥160 mmHg or diastolic pressure ≥95 mmHg, or those on anti-hypertensive medication. We excluded those with other causes of L-ICH, including excessive warfarin (international normalized ratio >3.0), antecedent head trauma or ischaemic stroke, central nervous system tumor, vascular malformation or vasculitis, and blood dyscrasia or coagulopathy as in the Boston criteria for the diagnosis of CAA-ICH [15].

In the first stage of the survey, we mailed letters of inquiry, including the above criteria, to the chiefs of 625 neurology departments registered as teaching hospitals by the Japanese Society of Neurology, 378 neurosurgery departments registered as teaching hospitals by the Japanese Society of Neurosurgery, and 375 pathology departments registered as teaching hospitals by the Japanese Society of Pathology. It is highly likely that almost all cases of CAA-L-ICH in Japan were diagnosed in these institutions. The inquiry letter requested information regarding the number of pathologically supported or clinically suspected patients with CAA-L-ICH identified between October 1998 and September 2003.

In the second stage of the survey, we collected data on clinical features, brain imaging, laboratory tests, and pathological examinations. No data were duplicated. Clinical data included the age at onset, gender, past medical history, use of anti-platelet or anti-coagulation agents, family history, mode of onset, manifestations, number of CAA-L-ICH episodes, CAA-L-ICH lesions identified by brain imaging [via computed tomography (CT), MRI, or both], laboratory and pathological findings, and treatments. We defined the CAA-L-ICH centers within the cerebral lobes on the basis of their locations, in accordance with previously published criteria [16].

We obtained formalin-fixed and paraffin-embedded sections of brain tissues harvested from CAA-L-ICH patients, together with supporting pathology data. We stained the sections with hematoxylin–eosin and Congo red. To characterize the vascular amyloid protein, immunohistochemical analysis was performed using antibodies against Aβ (4G8, 1:2000; Chemicon, Temecula, CA, USA), cystatin C (Cys-C, 1:4000; Dako, Glostrup, Denmark), transthyretin (TTR, 1:300; Behringwerke AG, Marburg, Germany), and prion protein [PrP (3F4), 1:500; Signet Laboratories Inc., Dedham, MA, USA] [2].

Data on treatment modalities included surgical procedures such as craniotomy with hematoma evacuation, stereotactic CT-guided and simple aspiration, and ventricular external drainage. We considered any difficulty in controlling abnormal intraoperative bleeding in intraoperative hemorrhage. We defined post-operative hemorrhage as any new ICH confirmed by post-operative CT/MRI scan within 48 h of a neurosurgical procedure.

The study protocols conformed to the *Ethical Guidelines for Epidemiologic Studies* by the Ministry of Health, Labour, and Welfare, Japan, and were approved by the Medical Ethics Committee of Kanazawa University.

We corrected the female-to-male ratio (F/M) in each age group to account for the female predominance in the Japanese population aged ≥55 in 2000 [age, 55–64 years (F/M = 1.05); age, 65–74 years (F/M = 1.16); age, 75–84 years (F/M = 1.66); age, 85–94 years (F/M = 2.36); and age, ≥95 years (F/M = 3.83)] [17]. We analyzed the F/M value using a binomial test and approximated to a normal distribution. We calculated case fatality rates at 1 and 12 months after initial L-ICH and the overall fatality rate by dividing the number of patients who died during their clinical course by the total number of patients. We calculated the ratio of the crude number of L-ICH lesions (%) to the estimated cortical volume (%) of each lobe and statistically analyzed for the null hypothesis that L-ICHs were uniformly distributed according to the expected cortical volumes [13]. We used a binomial test to analyze the hemisphere laterality of the lesions. We used standard deviation (SD) to define dispersion. Statistical significance was defined as $P < 0.05$. Statistical analyses were performed using Microsoft Excel 2004 for Macintosh (Microsoft Corporation, Redmond, WA, USA).

Results

In the first stage of the survey, we obtained 486 responses from 418 institutions and identified 794 patients with CAA-L-ICH. In the second stage, we

requested data on the 794 patients from institutions where CAA-L-ICH cases had been identified; data were available on 340 patients. We collected complete data for 303 patients, including those with 'pathologically supported CAA-L-ICH' (n = 41) and those with 'clinically suspected CAA-L-ICH without CAA pathology' (n = 262). The former included cases supported by autopsy (n = 9) and biopsy (n = 32), and the latter included cases of multiple (n = 95) and single L-ICH (n = 167). Tissues from 23 patients from the pathology-supported group were available for immunohistochemical analysis. In all patients, CAA was strongly positive for Aβ, but negative for TTR and PrP. There were weak immunoreactivities to Cys-C in some vessels with CAA as reported previously [18].

The following results are based on data from the pathologically supported CAA-L-ICH group because diagnoses were highly reliable in these cases.

The mean age at onset was 73.2 ± 7.4 years [range, 55–85 years; men, 73.7 ± 9.3 years (55–85 years); women, 72.9 ± 6.7 years (56–85 years)] for pathologically supported CAA-L-ICH. The age distribution at onset is shown in Table 1. The number of cases increased with age. After correcting for the populations in the corresponding decades of age, we found significant female predominance (corrected F/M = 2.2), particularly in the 65–74-year age group (F/M = 3.7, $P < 0.05$; Table 1).

No patient had an obvious family history of CAA-L-ICH or mutations in the amyloid precursor protein gene, although some family members had experienced a cerebral infarction (2.4%) or unclassified stroke (9.8%). One patient (2.4%) had AD at the onset of CAA-L-ICH. Some patients (7.3%) had undergone anti-platelet therapy, including ticlopidine hydrochloride, aspirin, or ibudilast. No patients were treated with anti-coagulation therapy. There were no cases of Down syndrome.

Table 1 Age distribution at onset and female-to-male ratio for 41 non-hypertensive patients with pathologically supported cerebral amyloid angiopathy-related lobar intracerebral hemorrhage

Age at onset	Number of patients	F/M	Corrected F/M for the population[a]
55–64	5	3/2	1.4
65–74	16	13/3	3.7[b]
75–84	20	14/6	1.4
85–94	0	–	–
95≤	0	–	–
Unknown	0	–	–
Total	41	30/11	2.2[b]

CAA-ICH, cerebral amyloid angiopathy-related intracerebral hemorrhage; F/M, female-to-male ratio; [a]2000 Population Census of Japan [17]; [b]$P < 0.05$, binomial test approximating a normal distribution.

The clinical characteristics of CAA-L-ICH are summarized in Table 2. After ICH, the patients were followed up for periods ranging from 1 day to 84 months (average, 35.3 months). We observed ICH recurrence in 31.7% of the patients during the follow-up period (mean interval, 11.3 months). Common manifestations included motor paresis, disturbance of consciousness, abnormalities in higher brain functions (e.g., aphasia and apraxia), visual loss and headache at the acute stage, and dementia and seizure at the chronic stage.

The distribution and characteristics of symptomatic CAA-L-ICHs are shown in Tables 3 and 4. The actual frequency of CAA-L-ICHs was higher in the frontal and parietal lobes; however, after correcting for estimated cortical volume, we found the parietal lobe to be the most frequently affected lobe (Table 3). ICHs communicated with subarachnoid space in 19.0% (Table 4).

Table 2 Clinical characteristics of 41 non-hypertensive patients with pathologically supported cerebral amyloid angiopathy-related lobar intracerebral hemorrhage

Mode of onset for the last ICH, n of patients (%)	n = 41
Acute	37 (90.2)
Subacute	–
Chronic	–
Unknown	4 (9.8)
Manifestations at the acute stage, n of episodes (%)	n = 54[a]
Motor paresis	44 (81.5)
Disturbance of consciousness	42 (77.8)
Abnormalities in higher brain functions	23 (42.6)
Visual loss	18 (33.3)
Headache	9 (22.0)
Meningeal signs	5 (9.3)
Seizures	3 (5.6)
Others[b]	6 (11.1)
Neurological deficit at the chronic stage, n of patients (%)	n = 41
Dementia	6 (14.6)[c]
Seizures/epilepsy	7 (17.1)
Parkinsonism	3 (7.3)
Others	Not available
Episode of CAA-L-ICH, n of patients (%)	n = 41[d]
Single	28 (68.3)
Recurrent	13 (31.7)
Unknown	0 (0)

CAA-L-ICH, cerebral amyloid angiopathy-related lobar intracerebral hemorrhage; CT, computed tomography; ICH, intracerebral hemorrhage; n, number; [a]There were 64 CAA-ICH episodes in the pathologically supported CAA-L-ICH category. Data on the clinical manifestations at the acute stage were available for 54 episodes; [b]Included vomiting, respiratory failure, conjugate deviation, speech disturbance, sensory disturbance, or ataxia; [c]Two (22.2%) of the nine autopsied patients with pathologically supported CAA-L-ICH had a pathological diagnosis of Alzheimer's disease; [d]Average months of follow-up: 35.3.

Table 3 Distribution of non-hypertensive cerebral amyloid angiopathy-related lobar intracerebral hemorrhage[a] identified by brain imaging

Number of actual ICH lesions, *n* (%)	*n* = 69[a]
Frontal	18 (26.1)
Parietal	20 (29.0)
Temporal	14 (20.3)
Occipital	14 (20.3)
Cerebellum	1 (1.4)
Deep central grey matter	2 (2.9)
Number of actual ICH lesions (%)/ estimated cortical volume (%) in each lobe[b]	
Frontal	0.64[c]
Parietal	1.50[d]
Temporal	0.91
Occipital	1.11

ICH, intracerebral hemorrhage; *n*, number; [a]Locations were identified for 69 (83.1%) of the 83 ICHs; these ICHs were detected by computed tomography (CT) alone in 61.0% of patients, by CT and magnetic resonance imaging (MRI) in 31.7%, and by CT or MRI (unclassified) in 7.3%. There was no ICH in the brainstem or thalamus; [b]Estimated cortical volumes (%) were 41.0% in the frontal, 19.3% in the parietal, 22.3% in the temporal, and 18.3% in the occipital lobes [13]; [c]$P < 0.001$ for the null hypothesis that hemorrhages are uniformly distributed according to cortical volume; [d]$P < 0.05$ for the null hypothesis that hemorrhages are uniformly distributed according to cortical volume.

Table 4 Characteristics of non-hypertensive cerebral amyloid angiopathy-related lobar intracerebral hemorrhage identified by brain imaging

Number of patients, *n* (%)	*n* = 41
With single ICH	26 (63.4)
With multiple ICHs	15 (36.6)
With simultaneous multiple ICHs	6 (14.6)
Unknown	–
Number of ICHs, *n*	
Total	83[a]
Average	2.0
Median	1
Range	1–16
Number of ICHs in each hemisphere, *n* (%)	*n* = 64[b]
Right	37 (57.8)
Left	27 (42.2)
Number of ICHs communicated, *n* (%)	*n* = 63[c,d]
With subarachnoid space	12 (19.0)
With ventricles	10 (15.9)

ICH, intracerebral hemorrhage; *n*, number; [a]These ICHs were detected by computed tomography (CT) alone in 61.0% of patients, by CT and magnetic resonance imaging (MRI) in 31.7%, and by CT or MRI (unclassified) in 7.3%. Gradient-recalled echo T2*-weighted MRI studies were available in 7.3% of patients; [b]Data were obtained from 64 of 83 ICHs; [c]Data were obtained from 63 of 83 ICHs; [d]When the analysis was limited to the 14 autopsied patients, the ICHs communicated with the subarachnoid space in three (21.4%) patients and with the ventricles in three (35.7%).

Among the 41 patients, 35 (85.4%) were treated with neurosurgical procedures (Table 5). Thirty patients underwent craniotomy with hematoma evacuation; three, stereotactic CT-guided aspiration; and two, ventricular external drainage. No patient had two or more neurosurgeries. Among the 35 surgically treated patients, none had uncontrollable intraoperative hemorrhage, but one (2.9%) had post-operative hemorrhage within 48 h after ventricular external drainage; this patient had not been treated with anti-platelet or anti-coagulation therapy. Of the 35 patients, seven (20.0%) had an ICH recurrence >48 h after a surgical procedure. Among the six autopsied patients who had not undergone a neurosurgical procedure, two (33.3%) sustained a recurrence of CAA-L-ICH during the 81-month follow-up or during the 4-month follow-up period until death.

Table 5 Outcome of 41 non-hypertensive patients with pathologically supported cerebral amyloid angiopathy-related lobar intracerebral hemorrhage

Outcome	Number of patients (%)
Operated cases	*n* = 35[a]
Intraoperative hemorrhage	0 (0)
Post-operative hemorrhage within 48 h	1 (2.9)
Recurrence of ICH >48 h after surgical procedures	7 (20.0)
Non-operated cases	*n* = 6[b]
Recurrence of ICH	2 (33.3)
Case fatality	*n* = 41[c]
1 month	5 (12.2)
12 months	8 (19.5)
Overall	13 (31.7)

ICH, intracerebral hemorrhage; *n*, number; [a]Average months of follow-up: 38.6 (range: 1 day–82 months); [b]Average months of follow-up: 16.5 (range: 1 day–81 months); [c]Average months of follow-up: 35.3.

Discussion

This study revealed the clinical characteristics of 41 non-hypertensive Japanese patients with pathologically supported CAA-L-ICH. We first described the significant female predominance and age-associated increase of CAA-L-ICH. The frequency of symptomatic CAA-L-ICHs was higher in the frontal and parietal lobes; however, after correcting for lobar volume, we found the parietal lobe to be more frequently affected. In 97.1% of patients, neurosurgical procedures were performed without uncontrollable intraoperative or post-operative hemorrhage.

The pathologically supported CAA-L-ICH cases showed significant female predominance. Non-significant female predominance has been reported in some previously studied smaller patient series [6,9,11,12,19–22]. Gender-related hormonal factors may be associated with both parenchymal and vascular Aβ deposition. CAA-L-ICH, as well as CAA [23], could

be predominated in women as in AD. Our finding of female predominance in CAA-L-ICH is in sharp contrast with that of hypertensive ICH, in which male predominance has been reported [24]. The F/M ratio obtained from the crude numbers in the hypertensive ICH registry (F/M = 0.83–0.90; age, ≥50 years) [24] was significantly different from that of our pathologically supported CAA-L-ICH cases ($P < 0.001$).

Our study is the first to show that the number of CAA-L-ICH patients increases with age, although data were not available for the oldest age group. This finding is consistent with the increased prevalence of CAA with aging, as determined in previous studies [19,23,25,26]. The mean age at onset was in the early 70s, which is similar to that reported earlier [4–12,20–23,27–29].

Our results indicated that non-hypertensive CAA-L-ICHs commonly occur in subjects without dementia/AD at the time of onset. During the clinical course of non-hypertensive CAA-L-ICH, the frequency of dementia (e.g., AD, vascular dementia) [2] generally increased until death, although 10.0–71.4% of the patients with CAA-ICH were reported to have AD at onset [7,8,21,29]. Anti-platelet or anti-coagulation agents were used by 5–33.3% of the CAA-ICH patients in previous studies [12,30]. These drugs were used by a relatively small percentage (7%) of our patients.

Most of our patients showed an acute onset of L-ICH, and some of them showed an unknown onset; previous studies indicated chronic or insidious onset in approximately 6% of the patients [4,12]. Among the manifestations at the acute stage, headache/meningeal signs and seizures were less frequent than in previous reports [4–10]. Headache/meningeal signs may be caused by a rupture of the ICH to the subarachnoid space (i.e., secondary subarachnoid hemorrhage) [11]. Only some of our patients had accompanying secondary subarachnoid hemorrhage, as revealed by neuroimaging or pathological studies. The overall recurrence rate among our patients (31.7% for an average follow-up of 35.3 months, with an average interval of 11.3 months between ICHs) was higher than that reported among Asian patients with hypertensive ICH (10.8% for an average follow-up of 67 months, with an average interval of 50.9 months) [31].

The frequency of symptomatic CAA-L-ICHs was higher in the frontal and parietal lobes; however, after correcting for lobar volume, the parietal lobe was found to be the more frequently affected lobe (Table 3). Most studies have reported a posterior predilection for CAA (occipital and temporal, occipital and parietal, or occipital) [19,25,26]. A recent amyloid positron emission tomography study of CAA patients also suggested a predominant occipital pattern of amyloid accumulation [32]. Nevertheless, in some CAA-ICH studies, the frontal lobe or the frontal and parietal lobes have been reported to be the most frequently affected locations [8,9,11,28,29]. When microbleeds were observed on $T2^*$-weighted MRI, CAA-ICHs were reported to have a posterior predisposition, particularly in the occipital and temporal lobes [13], although a parietal predilection was also reported [33]. The predilection of symptomatic non-hypertensive CAA-L-ICHs may not be simply explained on the basis of CAA distribution.

Cerebral amyloid angiopathy-related lobar intracerebral hemorrhage has been reported to be associated with CAA-associated vascular changes, particularly aneurysmal dilatation with fibrinoid necrosis of the cortical or subarachnoid vessels [11,27,34,35]. Because our results indicated that relatively small percentages of the patients with CAA-L-ICH showed communications between CAA-L-ICHs and the subarachnoid space, it is unlikely that in most cases, CAA-L-ICHs originate from the rupture of subarachnoid vessels [35].

Neurosurgical procedures could be performed safely in most patients (97.1%). Previous studies reported significant post-operative hemorrhages in 0–12.5% of the patients after CAA-ICH evacuations, shunting procedures, or brain biopsies [20,22,28,36]. The recurrence rate >48 h after surgical procedures was 20.0% in our patients, during the average 38.6-month follow-up; that rate in previous studies was 0–37.5% (follow-up range, 3 days–93 months) [20,22,28,36]. In our non-operated patients, the recurrence rate was 33.3% during the average 16.5-month follow-up; that rate in previous studies was 20.0–50.0% (follow-up range, 1 day–83 months) [8,9,20,28]. Neurosurgical intervention does not appear to be associated with a higher CAA-L-ICH recurrence rate.

The case fatality rates (12.2% at 1 month and 19.5% at 12 months) were similar to those reported for L-ICHs of any cause (~10% at 1 month and 15% at 12 months) [24], but may have been lower than those for hypertensive putaminal hemorrhage (37.5% during a 42-day follow-up) [37].

There are several limitations in this study. We identified pathologically supported or clinically suspected cases of non-hypertensive CAA-L-ICH via a nationwide survey, so the patient population might be biased by the survey method and responses from the institutions that were queried. Because 35 of the 41 patients (85.4%) underwent neurosurgical procedures, including brain biopsies (58.4%), the enrolled patients might present more severe cases of CAA-L-ICH than average ones. Because we focused on sporadic Aβ-type CAA in the elderly, we did not include younger patients with ICH (≤54 years) in our study. Although hypertension may coexist with CAA, we excluded patients with hypertension to clarify the details of non-hypertensive

CAA-L-ICH. Non-CAA-related L-ICH patients had a higher prevalence of ICH risk factors, including hypertension or the intake of warfarin or anti-platelet agents [15]. The results of our previous study indicated that hypertension was the most frequent cause of L-ICH in elderly Japanese patients [11]; therefore, in this study, we excluded patients with a history of hypertension in addition to those excluded on account of other causes of L-ICH. Although the coexistence of CAA with hypertension is probably common in elderly people [6,11,12], a study on such hypertensive patients was out of the scope of the current study. Furthermore, we did not focus on the microbleed, a diagnostic marker for CAA [38], because sensitive $T2^*$-weighted MRI was not necessarily available in the institutions involved. Finally, we did not have well-defined controls such as hypertensive L-ICH patients that strengthen the unique features of non-hypertensive CAA-L-ICH patients.

In conclusion, our study revealed the clinical features of Japanese patients with non-hypertensive CAA-L-ICH, indicating female predominance, increase associated with age, and parietal predilection. Further study is necessary with a larger number of patients with different ethnic backgrounds.

Acknowledgements

We gratefully acknowledge the assistance of doctors at various institutions throughout Japan who participated in this study. We thank Prof Yosikazu Nakamura (Jichi Medical University, Japan) for his valuable suggestions regarding statistical analysis and Dr Kenjiro Ono (Kanazawa University, Japan) for data collecting. This study was partially supported by a grant from the Amyloidosis Research Committee, funded by the Ministry of Health, Labour, and Welfare; it was also supported by a grant-in-aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan (M.Y.).

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Neuroradiology (2010) 52:381–386
DOI 10.1007/s00234-009-0610-z

DIAGNOSTIC NEURORADIOLOGY

Detection of changes in cerebrospinal fluid space in idiopathic normal pressure hydrocephalus using voxel-based morphometry

Fumio Yamashita · Makoto Sasaki · Satoshi Takahashi · Hiroshi Matsuda · Kohsuke Kudo · Shinsuke Narumi · Yasuo Terayama · Takashi Asada

Received: 12 July 2009 / Accepted: 5 October 2009 / Published online: 22 October 2009

Abstract
Introduction We attempted to detect alterations in the cerebrospinal fluid (CSF) space in patients with idiopathic normal pressure hydrocephalus (iNPH) using voxel-based morphometry (VBM).
Methods We obtained sagittal volume images of the entire head by three-dimensional T1-weighted magnetic resonance imaging and compared the regional distribution of CSF in 12 patients with iNPH, 14 patients with Alzheimer's disease (AD), and 17 healthy individuals using VBM with automatically extracted CSF objects.
Results VBM demonstrated significant widening at the lateral ventricles and Sylvian fissures and narrowing of the CSF space at the high convexity/midline areas in iNPH patients, compared to the AD patients and healthy controls ($p<0.05$, after correction with a false-discovery rate). In addition, the ratio of the CSF volume in the lateral ventricle/Sylvian fissure area to that in the high convexity/midline area in iNPH patients (3.9±1.2) was remarkably greater than that in AD patients (1.2±0.3) and controls (0.9±0.3; one-way ANOVA, $p<0.001$; post hoc Tukey's test, $p<0.001$); we could discriminate iNPH patients from those in the other two groups without any overlap, when using a cutoff level of 1.9.
Conclusion VBM using CSF objects can be used to delineate the characteristic alteration of the CSF space in iNPH patients, which has been evaluated by visual interpretation.

Keywords Idiopathic normal pressure hydrocephalus · Cerebrospinal fluid space · Voxel-based morphometry · Magnetic resonance imaging

F. Yamashita (✉) · T. Asada
Clinical Neuroscience, Medical Sciences for Control of Pathological Process, Graduate School of Comprehensive Human Sciences, University of Tsukuba,
1-1-1 Tenno-dai,
Tsukuba-shi, Ibaraki-ken 305-8577, Japan
e-mail: fumio@ncnp.go.jp

M. Sasaki · K. Kudo
Advanced Medical Research Center, Iwate Medical University,
Morioka, Japan

S. Takahashi · S. Narumi · Y. Terayama
Department of Neurology, Iwate Medical University,
Morioka, Japan

H. Matsuda
Department of Nuclear Medicine,
Saitama Medical University International Medical Center,
Saitama, Japan

Introduction

Idiopathic normal pressure hydrocephalus (iNPH) is a relatively rare cryptogenic disorder with marked ventricular dilatation that occurs in the elderly population (>60 years). iNPH causes dementia, gait disturbances, urinary incontinence, or combinations thereof; the placement of a shunt can relieve these symptoms [1], but other neurological disorders must be excluded before surgery. In iNPH patients, magnetic resonance imaging (MRI) reveals dilation of the lateral ventricle (Evans' index ≥0.3), Sylvian fissure, and basal cistern [1, 2]. In addition, it has been reported that a narrowing of the cerebrospinal fluid (CSF) space at the high convexity/midline areas is characteristic of iNPH [2, 3]; nonetheless, visual interpretations of these changes are generally difficult, because the findings are relatively nonspecific and generally subtle, particularly in routine axial images [4].

Voxel-based morphometry (VBM) is one of the most common methods used to automatically detect structural changes in the brain, as wrought by neurodegenerative diseases and other disorders [5]. This technique helps in identifying regional volume loss—even in the early stages of Alzheimer's disease (AD) and other related disorders—and to characterize structural differences in brain tissue among patients and healthy subjects [6–10]. VBM may be able to detect structural changes of the CSF space; hence, iNPH can be one of the targets of VBM, although few reports have focused on altered CSF space. In this study, we aimed to establish a VBM method for automatically detecting abnormalities in the CSF space in iNPH patients and to examine whether this method can discriminate iNPH patients from AD patients and healthy individuals.

Methods

Subjects

We prospectively examined 12 consecutive patients with possible iNPH (six men and six women; age range, 56–83 years; mean age, 73.0 years) in accordance with the clinical guidelines for idiopathic normal pressure hydrocephalus of the Japanese Society for Normal Pressure Hydrocephalus, which includes ventricular dilatation with Evans' index of more than 0.3 as a mandatory criterion as well as narrowing of the CSF space at the high-convexity area and dilatation of the Sylvian fissure as non-mandatory criteria [2]. Among the 12 patients, 10 were subsequently diagnosed with probable iNPH (five men and five women; age range, 56–82 years; mean age, 72.6 years) because of an effective CSF tap test; two were diagnosed with definite iNPH (one man and one woman, 74 and 83 years old, respectively; mean age, 78.5 years) because they responded to a shunt surgery after a successful tap test.

We also examined 14 age-matched patients with probable AD, diagnosed according to the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria [11] (six men and eight women; age range, 60–85 years; mean age, 74.2 years), who had a Mini-Mental State Examination score of 16–28 (median, 22.5; interquartile range, 19.8–25.5), as well as 17 age-matched healthy volunteers without iNPH or neurological symptoms (11 men and six women; age range, 62–82 years; mean age, 72.5 years).

No statistically significant difference was found among the three patient groups with regard to age or gender. Examinations were conducted following approval from the institutional review board, and written informed consent was obtained from all the subjects.

MRI data acquisition

We performed MRI using a 1.5-T scanner (Signa MR/i; GE Healthcare, Milwaukee, WI, USA). In the iNPH patients, the scan was performed before the CSF tap test. The pulse sequence used was sagittal T1-weighted three-dimensional fast RF-spoiled gradient echo (3D-FSPGR) with the following parameters: a repetition time (TR), 10.3 ms; echo time (TE), 2.2 ms; flip angle, 15°; field of view (FOV), 220 mm; matrix size, 256×256 (pixel size, 0.86×0.86); 128 sections with 1.5-mm slice thickness that covered the entire head; one averaged; and an acquisition time, 5.5 min. The horizontal lines of the sagittal sections were carefully set parallel to the anterior commissure–posterior commissure line. We also obtained axial dual-echo fast spin-echo images (TR, 3,000 ms; effective TEs, 10 and 100 ms; FOV, 220 mm; matrix, 256×256; and slice thickness, 5 mm with 1-mm intersection gaps) in order to exclude other CNS abnormalities.

Image analysis

For VBM analysis, we used the Statistical Parametric Mapping 5 (SPM 5) software (Wellcome Trust Centre for Neuroimaging, University College London, UK) running under MATLAB version 7.4 (MathWorks Inc., Natick, MA, USA). Objects of the CSF space were automatically segmented from the source data using the Montreal Neurological Institute template and were normalized by employing Diffeomorphic Anatomical Registration through an Exponentiated Lie Algebra, a suite of tools for achieving accurate intersubject registration of brain images [12].

After smoothing with an isotropic Gaussian kernel of 8-mm full-width at half-maximum, multiple comparisons were corrected using a false-discovery rate (FDR) [13], and the regional volume of the normalized CSF objects was compared for every combination among the three groups using a two-tailed t test with a cutoff value of $p<0.05$. We then generated color maps indicating clusters exceeding a voxel size of 100.

In addition, we defined regions of interest (ROIs) in the lateral ventricle/Sylvian fissure area and in the high convexity/midline area by automatically combining the largest clusters that showed significant changes between the iNPH and AD or control groups by using the Marseille Boite A Regions D'interet (MarsBar) ROI analysis tool [14]. The CSF volumes in these ROIs and the ratio of CSF volumes in the lateral ventricle/Sylvian fissure ROI to those in the high convexity/midline ROI were calculated using MarsBar.

The CSF volume in the lateral ventricle/Sylvian fissure ROI, the CSF volume in the high convexity/midline ROI, and the ratio of these ROIs were compared among the three groups by using a one-way analysis of variance (ANOVA) and a post hoc Tukey's test. The alpha level used was 0.05.

Results

In the patient and control groups, appropriate sagittal 3D-FSPGR images without apparent motion artifacts were successfully obtained and analyzed using VBM.

Comparison of CSF objects among the iNPH, AD, and control groups by using VBM

The VBM analyses of CSF objects using the two-tailed *t* test ($p<0.05$, FDR-corrected) revealed a large cluster with increased density in the lateral ventricle/Sylvian fissure area and another with decreased CSF density in the bilateral high convexity/midline area in the iNPH patients as compared with the AD patients (Fig. 1a–c). A comparison between the iNPH patients and healthy controls also revealed a similar pattern of altered CSF distribution in iNPH, i.e., increased CSF space in the lateral ventricle/ Sylvian fissure area and decreased CSF space in the high convexity/midline area (Fig. 1d–f). In contrast, a comparison of AD patients and healthy controls revealed clusters with increased CSF space in the lateral ventricle/Sylvian fissure area in the AD patients but no clusters with decreased CSF space (Fig. 1g–i).

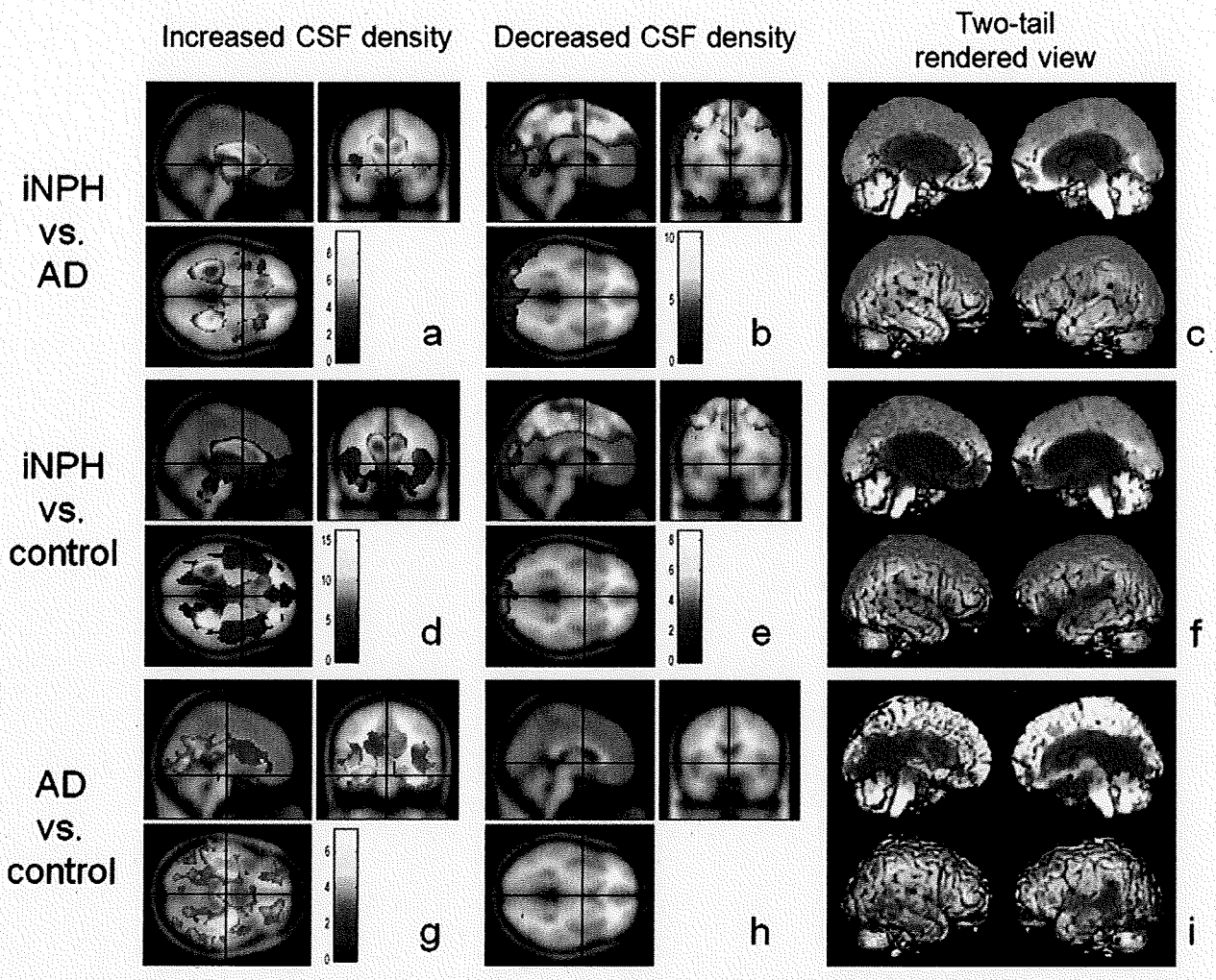

Fig. 1 Difference in CSF densities among iNPH patients, AD patients, and healthy controls, by VBM analyses. **a–c** iNPH patients vs. AD patients, **d–f** iNPH patients vs. controls; **g–i** AD patients vs. controls; **a**, **d**, **g** areas with increased CSF density with $p<0.05$ (false-discovery rate (FDR)-corrected); **b**, **e**, **h** areas with decreased CSF density with $p<0.05$ (FDR-corrected); **c**, **f**, **i** volume-rendered images for increased (*red*) and decreased (*green*) CSF density areas. In the iNPH patients, increased CSF density in the lateral ventricle and/or periSylvian area and decreased CSF density in the high convexity/ midline area are simultaneously observed when compared to the AD patients or healthy controls (**a–c**, **d–f**). In contrast, AD patients showed only an increased CSF density in the lateral ventricle and periSylvian areas, as compared to the healthy controls (**g–i**)