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

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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

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. 2002).
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 paring 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

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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 21 coupled 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-
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 pre-onset 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 hippocampal volume is also shown in Fig. 3. In this figure, we can see the progression of AD from preclinical stage to clinical stage, with imaging biomarkers playing a crucial role in identifying and monitoring the disease.
c Campbell 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 et al. 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-[2-18F]fluoroethyl}(methyl)-2-naphthyl)ethylidene) malononitrile ([18F]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-[11C] 2-(4′-methylamino-phenyl)-6-hydroxybenzothiazol ([11C]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 [11C]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-
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.

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
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.

References


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