スクリーニング脱落時の手順

研究参加施設

1. スクリーニング脱落

J-ADNI 研究管理システムの被験者個人ページから『スクリーニング脱落』をクリックする。

2. 来院データの入力

収集した全データを入力する。最低限、下記フォームを入力する。

- 被験者登録
- 適格性の確認（被験者が不適格であることを示し、理由を記載する）
- 被験者背景情報
- 登録追跡

3. 資料の保存

他の資料、心理検査用紙およびその他原文書を被験者バインダーに保管する。

注意：入力画面が脱落モードに入ると、データが部分的にしか入力できなくなるため、スクリーニング脱落例のデータを入力する際には十分注意すること。

J-ADNI データセンター

1.スクリーニング脱落のデータをチェックし、研究参加施設へ疑義事項への回答または修正を依頼する。

ベースラインから最終来院までの手順

研究参加施設

1. 検査用紙の印刷

CRF、心理検査および CDR 検査用紙を含む検査用紙一式を研究管理システムの被験者個人ページから印刷する。(J-ADNI 研究管理システム操作マニュアル参照)。

2. 来院データの入力

各来院後 7 日以内に来院データを全て研究管理システムに入力する。検査用紙は全て専用スキャナで読み取り PDF 化してアップロードする。MRI 画像データは MRI 検査後 24 時間以内にアップロードすること。

3. 問い合わせへの回答および修正

J-ADNI データセンターからの問い合わせおよび修正に関する依頼に対応する。修正事項は必ず原資料にも反映させる。

4. 原資料の保存

原資料および検査用紙は全て被験者バインダーに保存すること。

J-ADNI データセンター

1. J-ADNI データセンターが来院データをチェックし、研究参加施設へ疑義事項への回答または修正を依頼する。

2. 画像 QC 結果を MRI QC チームおよび PET QC コアが入力する。結果は研究管理システム上の被験者個人ページで参照可能である。

注意：ベースライン来院のデータ入力後、その後の来院全てについての来院規定日が被験者個人ページで参照できる。来院および画像検査はこの規定範囲内で設定すること。

再スクリーニング手順

研究参加施設	J-ADNI データセンター
1. J-ADNI 研究管理システムから新規被験者の登録を行う。診断カテゴリーが正しいかどうかを確認する。 2. 『被験者登録』の『再登録ですか？』という質問項目に『はい』と回答し、前回のスクリーニング時のJ-ADNI被験者IDを入力する。再スクリーニングが 2 回以上の場合、初回のIDを入力する。 3. 前回スクリーニング時に生化学検査および*ApoE 遺伝子型決定が行われていなければ、通常のスクリーニング手順に従って検査を行う。 4. 前回スクリーニング時の生化学検査結果を用いる場合、SRL に連絡（連絡先は 56 ページ参照）し、新旧 ID を伝えて ID の更新を行ってもらう。新 ID での検査結果が再度送付される。 * 同意者のみ	通常のスクリーニング手順に従う（既述事項を参照のこと）。

スクリーニングの診断カテゴリー変更手順

研究参加施設	J-ADNI データセンター
1. 「スクリーニング脱落時の手順」に従うこと（前ページ参照）。 2. 新たな診断カテゴリーについて、被験者が選択/除外基準に合致するかを確認する。施設代表医師か施設協力医師が、被験者が選択基準に合致すると判断した場合、臨床判定委員会からメールで承認を得て、新カテゴリー下で被験者を再スクリーニングすること。 3. 再スクリーニング手順に従う（上述）。	通常のスクリーニング手順に従う（既述事項を参照のこと）。

スクリーニング後の診断カテゴリーの変更はいずれも、『診断サマリー』および『診断サマリー ベースラインからの変化』用紙への記入により報告すること。

来院スケジュールに関する規則

スクリーニング来院は、適格性を病歴や診療録でチェックした結果、研究に参加できる可能性が高く、研究への参加期間（満 2 年ないし 3 年）その地域に居住することが想定される者に対してのみ実施すること。ベースライン後の来院日は、ベースラインの来院日を基準に算出する。各被験者のベースライン以降の規定来院日は J-ADNI 研究管理システムから確認できる。

来院および画像検査はできる限り規定日に近い日に実施するよう努めること。

画像検査日および来院日の規定		
来院	スケジュールに関する規則	例外について
スクリーニング MRI（1.5 テスラ MRI のみ）	スクリーニング来院後 14 日以内に検査を予定する。	J-ADNI データセンターに問い合わせる。
ベースライン来院	必ず 1.5 テスラ MRI の最終承認後に実施すること。スクリーニング来院後 28 日以内。	J-ADNI 研究管理システムで例外申請する。
ベーススキャン（3 テスラ MRI もしくは FDG-PET、アミロイド PET）	1.5 テスラ MRI の最終承認後に実施する。**ベースライン来院±14 日以内。**	研究管理システムにプロトコル逸脱の理由を入力する。
6 ヶ月後～最終来院	規定日±14 日以内に完了する。	研究管理システムにプロトコル逸脱の理由を入力する。
ベースライン後の全ての画像検査	規定日±14 日以内に完了する。	研究管理システムにプロトコル逸脱の理由を入力する。
ベースラインおよび 12 ヶ月後来院	腰椎穿刺は常に MRI または PET 検査**後**に実施すること。不可能な場合は、検査を腰椎穿刺の 72 時間以上後に設定する。	研究管理システムにプロトコル逸脱の理由を入力する。

来院または画像検査が実施されなかった場合、スケジュールを再設定すること。被験者が来院しなかった、または画像検査に来なかった場合で再来院・再検査が設定できない場合、J-ADNI データセンターに直ちに連絡すること。来院および画像検査が実施されなかった理由を J-ADNI 研究管理システムから入力すること。

来院時に必要なデータを**全て**得ることが不可能だった場合、J-ADNI データセンターに直ちに連絡すること。各来院時に必要なデータを全て得ることは非常に重要であるため、データが欠けていた場合、全データを収集するため直ちに被験者を再来院させるよう努めること。

重要な注意：来院スケジュールを設定する前に、必ず来院時の資材（採血用チューブなど）が十分あることを確認すること。

研究参加期間中の施設変更不可

J-ADNI で解析に用いられる MRI または PET 機器は同一のものを用いることが重要であるため、被験者が研究参加施設を変更して J-ADNI を継続することは認められない。被験者が半年間別の地域で生活するなどの場合、研究参加施設は登録の前に当該被験者がその後のスケジュールに来院できるかどうかを良く確認すること。

研究の早期中止

被験者が研究手順のうちいずれの手順の中止を希望する場合でも、バイオマーカー用の試料採取および心理評価を継続する意思がある場合には、研究を継続する。

部分的中止（腰椎穿刺、3 テスラ MRI または PET の中止）は J-ADNI 研究管理システム上で、早期中止および早期脱落フォームに入力すること。被験者がベースライン来院前に、腰椎穿刺の同意を撤回した場合、研究参加施設は下記を実施すること。

1. 早期中止および早期脱落フォームに入力。
2. 『スクリーニング来院』の腰椎穿刺のチェックをはずし、『選択基準』フォームを更新する。

もし被験者が 1.5 テスラ MRI を中止するが追跡調査には同意する場合、研究参加施設は、J-ADNI データセンター(center@j-adni.org)へメールを送り、主任研究者（東大　岩坪威）および臨床判定委員会から追跡調査の許可を得ること。上記は個別に決定する。

スケジュール外来院

6 ヶ月後の来院を完了した被験者で、研究の早期中止を希望し、その後来院する意思がない場合は最終的なデータを得るためスケジュール外の来院を検討すること。

スケジュール外来院は、J-ADNI 研究管理システムの被験者個人ページから要請すること。研究参加施設は、完全な（被験者に割り当てられた全手順）、または部分的な来院のいずれを要するのかを入力する。主任研究者がスケジュール外来院の実施が研究全体に有用か否かを判断し、要請を承認または否認する。

スケジュール外来院が承認された場合、研究中止理由を記録する。実際の来院が不可能な場合、研究参加施設スタッフが電話でスケジュール外来院の内容をできる限り完了させること。

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Alzheimer's & Dementia

Perspectives

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

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

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Keywords: ■■■

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

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

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

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

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

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

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

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

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

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

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

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

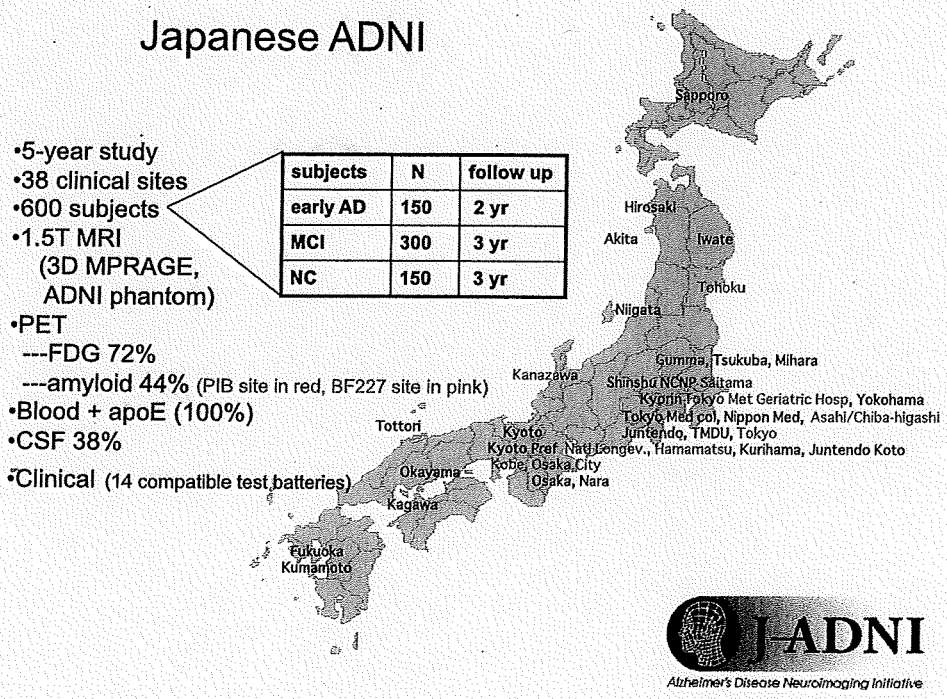

Fig. 1. Overview of J-ADNI.

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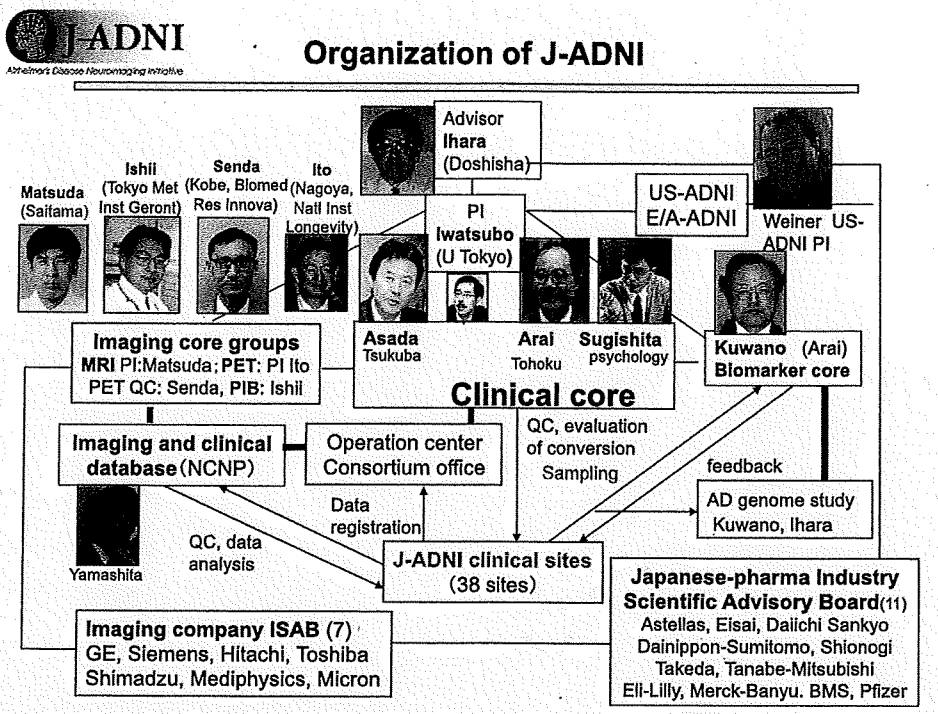

Fig. 2. Organization of J-ADNI.

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

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

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

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Invited Review for the 90th Anniversary

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
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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.

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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

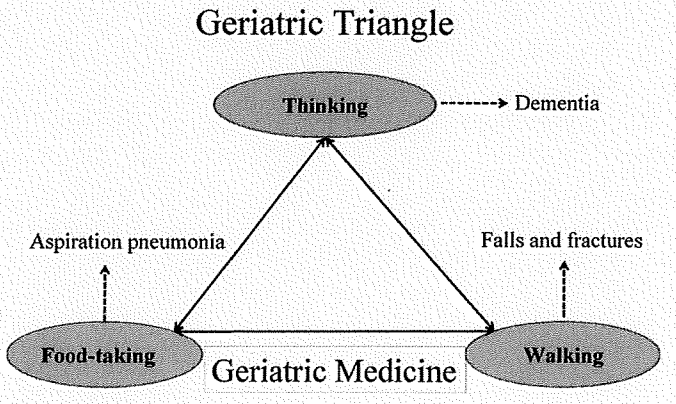

Fig. 1. Proposed concept of geriatric triangle.
At least three physical and mental functions are needed to support independence of life in elderly people. They are 1) Food-taking ability, 2) Standing and walking, and 3) Thinking and judgments. Loss of these basic functions alone or in combination will 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".

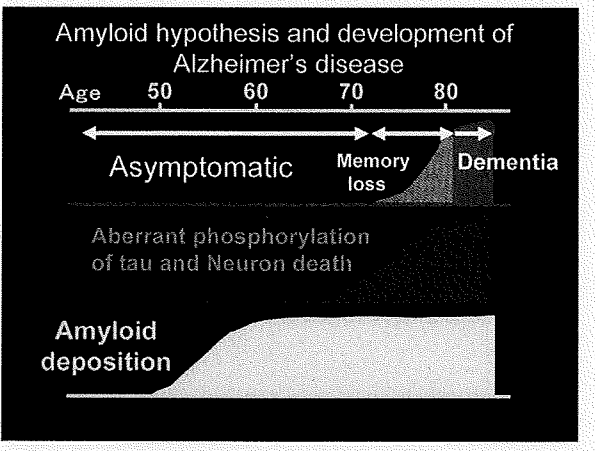

Fig. 2. Hypothetical scheme of progression of AD from amyloid deposition to development of dementia.
It is noteworthy that brain amyloid continues to be accumulating towards the onset of AD during which subjects are not aware of what changes are taking place in their brains. When subjects are first symptomatic, 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-