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

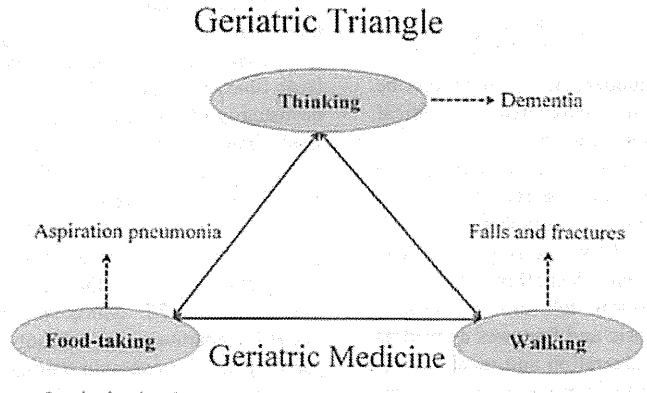

Fig. 1. Proposed concept of geriatric triangle.
At least three physical and mental functions are needed to support independence of life in elderly people. They are 1) Food-taking ability, 2) Standing and walking, and 3) Thinking and judgments. Loss of these basic functions alone or in combination will 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 ($A\beta$). $A\beta$ 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 $A\beta$ 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 $A\beta$ 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 $A\beta$-positive but tau-negative brains from cognitively normal elderly people in autopsy samples, suggesting that $A\beta$ deposition predates tau deposition (Arai et al. 1990). This time framework was further evidenced by the observation that $A\beta$-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 $A\beta$ (Citron et al. 1992). Other AD-causing mutations in PS-1 and PS-2 gene also enhance generation of amyloidogenic $A\beta$ by changing proteolytic processing of APP (Scheuner et al. 1996). Finally, a distinct $A\beta$ species ending at amino acid 42 ($A\beta42$) is highly amyloidogenic, and there was a uniform pattern of $A\beta42$ 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 $A\beta$ 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".

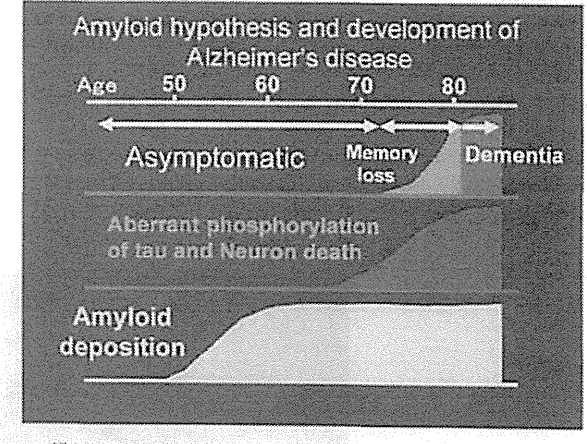

Fig. 2. Hypothetical scheme of progression of AD from amyloid deposition to development of dementia.
It is noteworthy that brain amyloid continues to be accumulating towards the onset of AD during which subjects are not aware of what changes are taking place in their brains. When subjects are first symptomatic, 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 $A\beta$ production and $A\beta$ clearance and this imbalance causes all existing events in the downstream of $A\beta$, 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-

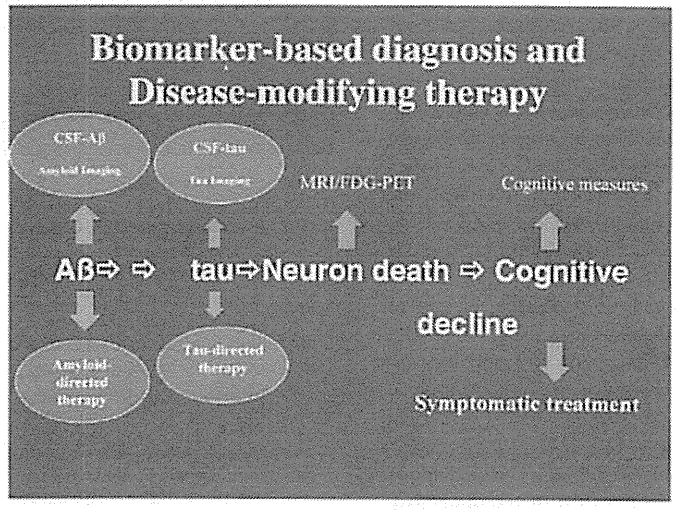

Fig. 3. Strategies for new diagnostic and therapeutic approaches for AD are presented based on amyloid hypothesis.
This figure illustrates a superimposition of the diagnostic and treatment framework in the context of the hypothetical amyloid cascade as described in Fig. 2. In the hypothesis, amyloid 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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LETTERS TO THE EDITOR

New dorsiflexion measure device: A simple method to assess fall risks in the elderly

Dear Editor,

Hip fracture is the third leading cause yielding bedridden status in Japan, and more than 80% of hip fractures are reported to be caused by falling. There are a variety of causes for falls in the elderly, and one of the significant causes is the inability to lift their toes when they walk. Here, we show a new device to measure dorsiflexion angle, an instrument that we developed to assess fall risks in the elderly.

Participants were requested to stand up straight and step back until the hip leaned on the wall (Fig. 1a). The fulcrum of the instrument was adjusted to the center of the external malleolus (Fig. 1b). The arm of the instrument was set to stay level, adjusting the branching thin arm placed on the ridge of the dorsum of the foot. Then, participants were asked to dorsiflex as much as possible. The mean time to measure bilateral dorsiflexion angles was within 5 min.

We measured dorsiflexion and Fall Risk Index (FRI),[1,2] including the history of falls within the past year, in 131 women (46–89 years, mean age 78.0 ± 7.1 years) and 88 men (46–93 years, mean age 76.2 ± 8.6 years) who visited the fall prevention clinic in Kyorin University Hospital. The occurrence of falls within the past year was 35.6%. Falls occurred 2.0 ± 0.1 times in fallers within 1 year, and women fell more frequently than men (42.7% *vs* 25.0%, $\chi^2 = 7.2$, $P \leq 0.01$). The average FRI score was 6.7 ± 3.4 in non-fallers and 10.6 ± 3.0 in fallers ($P < 0.0001$). Women showed a higher FRI score than men (8.8 ± 3.6 *vs* 7.0 ± 3.8, $P = 0.003$).

This new device appears promising in detecting the high-risk group of fallers, because the dorsiflexion angle was significantly smaller in fallers than non-fallers (right 9.6 ± 8.4 *vs* 13.7 ± 9.6 degrees, $P = 0.012$; left 10.0 ± 8.5 *vs* 14.2 ± 9.8 degrees, $P = 0.014$). Furthermore, the occurrence of falls was more frequent as the dorsiflexion angle decreased in women ($\chi^2 = 6.4$, $P = 0.042$; Fig. 1c), and half of the subjects, whose dorsiflexion angle was less than 10 degrees, experienced falls within a year.

Previously, it was reported that hip fractures occur more frequently in women than men, even though the incidence rate of falls was comparable until the age of 90 years. This is considered to be a result of the higher prevalence of osteoporosis in women.[3] In contrast, the present study found that women less than 90 years-of-age fell more frequently than men in the Japanese population of this age group. We also found that the FRI score was higher in women than men, as has been shown previously.[4] In addition, dorsiflexion angle was

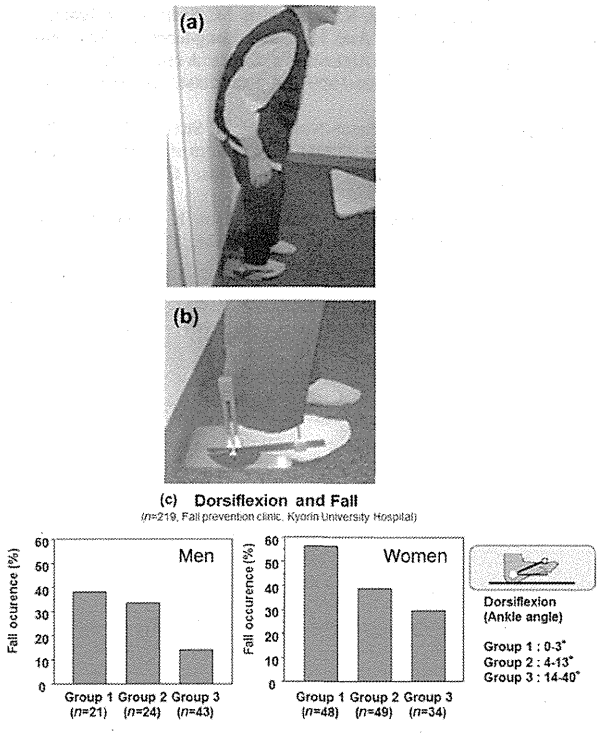

Figure 1 (a,b) How to measure dorsiflexion angle using a dorsiflexion measure device. (c) The relationship between dorsiflexion angle and the occurrence of falls within the past year. In men and women respectively, participants were grouped by tertile according to the dorsiflexion angle.

smaller in women than men (right 10.3 ± 8.4 *vs* 15.2 ± 10.1 degrees, $P = 0.0001$; left 11.0 ± 8.5 *vs* 15.2 ± 10.4 degrees, $P = 0.0013$), and a stepwise increase in the fall occurrence rate according to the level of dorsiflexion angle was evident in women (not significant in men). These results show that less ability to dorsiflex would partly explain the sex difference in the occurrence of falls and ensuing hip fracture.

The new dorsiflexion measure device we report here is easy and less time-consuming to use, and will be sure to help identify a high-risk group of fallers in the elderly.

Disclosure statement

This study was approved by the Ethics Committee of Kyorin University School of Medicine. Accordingly, written informed consent was obtained from all patients. All authors contributed significantly to this work and are

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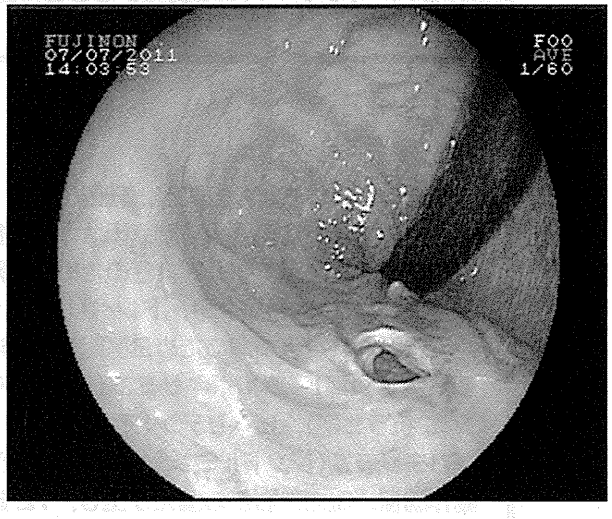
Rectal perforation as a result of self-administration of retrograde enema in an elderly dementia patient

Retrograde cleansing enemas are commonly used in the treatment of chronic constipation, especially in the elderly.[1] We report a case of colorectal perforation as a result of self-administered retrograde water enema in an elderly dementia patient.

A 76-year-old chronically constipated man was admitted to Turkiye Yuksek Ihtisas Hospital Gastroenterology Department in Ankara, Turkey, with a 1-week history of rectal pain. His medical history showed he had the diagnosis of dementia. Clinical examination at that time showed normal vital signs, on examination of the abdomen there was no defense or rebound, digital examination was normal, and respiratory and circulatory system examinations were normal. All laboratory investigations including full blood count, serum amylase, liver function tests, urea and electrolytes were within normal limits. There was no abnormality in abdominal X-ray and abdominal ultrasonography. He was started on a retrograde enema by his family practitioner 7 days earlier for constipation. He described that the pain was precipitated by the first self-administration of the retrograde irrigation enema and the patient denied subsequent use. A preplanned colonoscopy was carried out, and on retroflexion a rectal perforation was detected (Fig. 1). An abdominal computed tomography scan showed perirectal air. Conservative management with intestinal rest and intravenous antibiotics was carried out. The clinical course of the patient was favorable without sepsis or generalized peritonitis. He was discharged home after a 7-day inpatient stay.



Perforation of the rectum and sigmoid colon caused by cleansing enemas, used by chronically constipated patients, has rarely been reported. In the largest series, Paran *et al.* reported that three of 13 patients with rectal perforation as a result of retrograde enema died because of late diagnosis.[2] Gayer *et al.* reported 14 elderly patients (average age 80 years) with rectal perforation as a result of cleansing enema. Surgery was carried out in 10 of 14 patients, and nine of the 14 patients died. Interestingly, in all of these cases the enema was given by paramedic personnel.[3] It is perhaps not so well known that the rectal wall, even in the absence of disease, can be perforated by the tip of a rubber catheter introduced for the purpose of administering a simple cleansing enema.[4] Because of the possible risk of morbidity and mortality, especially in elderly patients in whom the process can be more catastrophic, rectal perforation risk should be kept in mind and administration of rectal cleansing enemas should be carried out gently and carefully by paramedic personnel. Also, the position of the body when inserting the enema tip is important. An enema should be carried out, in principle, with the patient in the left lateral decubitus position.[5]

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高齢者の安全な薬物療法　第27回

監修：秋下　雅弘，葛谷　雅文

薬剤起因性歩行障害

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高齢者は複数の慢性疾患を抱え，訴えも多いため服用薬剤数が多くなりやすい．不用意な鎮静催眠薬，抗うつ薬，抗精神病薬の使用は転倒を誘発すること，また，消化管運動調整薬の長期連用はパーキンソニズムを誘発することに留意すべきである．もし，めまい，ふらつき，歩行障害，易転倒性のある患者をみた場合，「お薬手帳」で投薬内容を確認し，薬剤による副作用を念頭に置くべきである．

症例呈示

73歳/女性

主訴：ふらつき，歩行障害，転倒．

生活歴：夫と2人暮らしで家事は本人が行う．

現病歴：高血圧，脂質異常症のためA医院でベザフィブラート(ベザトール®SR)，オルメサルタン(オルメテック®)，ドンペリドン(ナウゼリン®)，酸化マグネシウム，また，69歳時に診断されたうつ病のためB医院(精神科クリニック)にてアモキサピン(アモキサン®：三環系抗うつ薬)，フルボキサミン(デプロメール®：抗うつ薬(SSRI))，トラゾドン(レスリン®：抗うつ薬)，ビペリデン(アキネトン®：抗コリン薬)，エチゾラム(デパス®：抗不安薬)，ブロチゾラム(レンドルミン®：睡眠薬)の処方を受けていた．特に，抗うつ薬の服用開始後，動作緩慢，脱力，右手の震えが生じ，72歳のときからふらつき，前傾歩行，突進歩行，転倒するようになった．これに対してB医院でアモキサピンの増量を行ったところ，ふらつきが増悪したため，娘に付き添われて当院外来を受診した．

身体所見：異常所見として寡動，仮面用顔貌，口唇の不随意運動，右上肢の振戦を認めた．

検査所見：肝，腎，甲状腺機能を含めて血液検査所見上特記すべき異常なし．頭部CT異常なし．

臨床経過：抗うつ薬，抗不安薬によるふらつき，歩行障害とドンペリドンによる薬剤性パーキンソニズムと考え，順次薬剤を減量・中止した(図1)．これにより，ふらつき，歩行障害は顕著に改善し，また，パーキンソン徴候(寡動，仮面用顔貌，不随意運動)もほぼ消失，意欲の向上がみられ，初診から7カ月後に終診とし，かかりつけ医(A医院)のみに通院することになった．

解説

本症例では，SSRI以外の抗うつ薬であるアモキサピン，トラゾドン，ならびに抗不安薬エチゾラムを減量・中止し，また薬剤性パーキンソニズムの原因になっていると考えられるドン

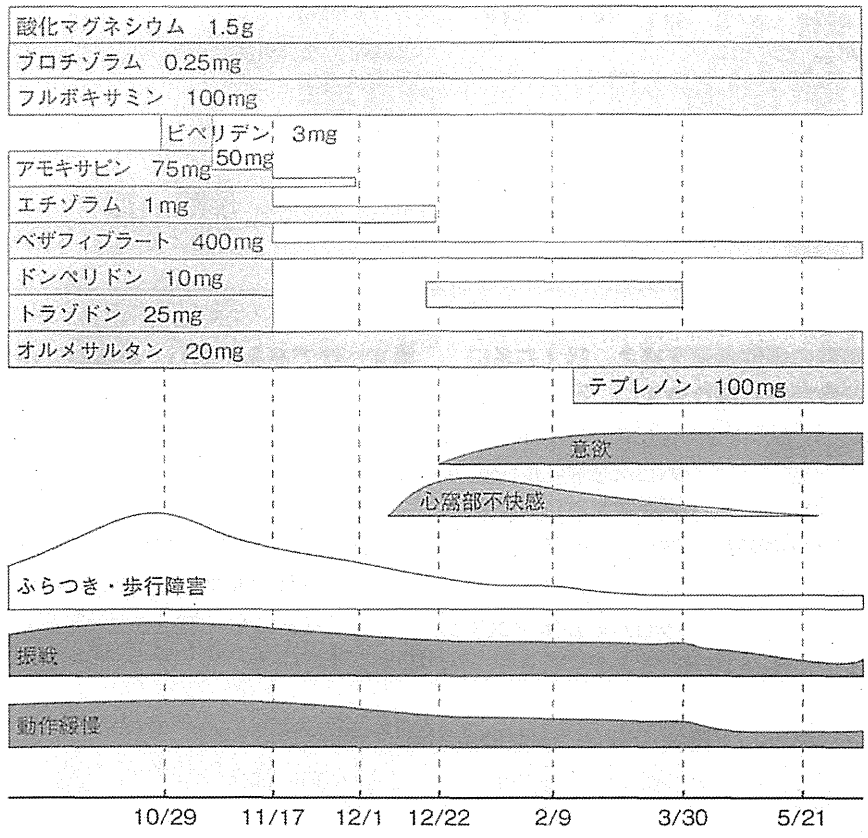

図1 症例の経過

ペリドンを中止したことが効を奏したと考えられる．なお，薬剤の減量・中止は症状の推移をみながら慎重に行うべきであり，患者ならびに家族に対してくれぐれも自己判断で中止しないよう説明する必要がある．

薬剤によるふらつき，転倒

転倒を起こしやすい主な薬剤を表1に示す．これらの薬剤が転倒を起こすのは，鎮静作用，眠気，注意力低下，筋弛緩作用，起立性低血圧，錐体外路症状などが関係している．眠気，ふらつき，注意力の低下など意識や平衡覚を低下させる薬剤として，ベンゾジアゼピン系および非ベンゾジアゼピン系の鎮静睡眠薬が代表的である．加えて，これらの薬剤は筋弛緩作用をもつものが多く，下肢の脱力とともに転倒を誘発する危険がある．また，鎮静睡眠薬，抗うつ薬，抗パーキンソン薬，β遮断薬，H_2ブロッカーはせん妄を起こすことによって転倒を誘発する危険がある．起立性低血圧は自律神経による血圧調節がうまくいかないために起こり，高齢者に多く認められる．降圧薬は一般に低血圧を起こす危険があるが，特にα遮断薬と利尿薬(脱水を起こしやすいため)の使用の際には注意が必要である．

高齢者は不眠を訴えることが多く，睡眠薬を使用する機会が多いが，夜間トイレに行く際に覚醒不良のため転倒する危険がある．これを防ぐために，服用前にトイレを済ませておくこと，トイレへの動線を明るくすること，つっかけ式のスリッパを使わないことなど具体的な生活指導を行う必要がある．使用薬剤としては半減期が短く，筋弛緩作用の弱いゾピクロン(アモバ

表1　転倒を起こしやすい薬物

系統	代表的薬剤(商品名)
鎮静催眠薬	
ベンゾジアゼピン系	トリアゾラム(ハルシオン®)，ブロチゾラム(レンドルミン®)，エスタゾラム(ユーロジン®)，ニトラゼパム(ベンザリン®)，ジアゼパム(セルシン®)，ロラゼパム(ワイパックス®)，エチゾラム(デパス®)
非ベンゾジアゼピン系	ペントバルビタール(ラボナ®)，バルビタール(バルビタール)，合剤(ベゲタミン®)
抗うつ薬	
三環系	アミトリプチン(トリプタノール)，イミプラミン(トフラニール®)，クロミプラミン(アナフラニール®)
そのほか	マプロチリン(ルジオミール®)
抗精神病薬	
フェノチアジン系	クロルプロマジン(コントミン®，ウィンタミン®)
ブチロフェノン系	ハロペリドール(セレネース®，リントン®)
ベンズアミド系	スルピリド(ドグマチール®，アビリット®)
利尿薬，そのほかの降圧薬	フロセミド(ラシックス®)，ドキサゾシン(カルデナリン®)
抗ヒスタミン薬	ジフェンヒドラミン(レスタミン)，d-クロルフェニラミン(ポララミン®)
抗てんかん薬	クロバザム(マイスタン®)，フェノバルビタール(フェノバール®)

表2　パーキンソン徴候を起こす可能性のある薬物

系統	代表的薬剤(商品名)
定型抗精神病薬	
フェノチアジン系	レボメプロマジン(ヒルナミン®，レボトミン®)，クロルプロマジン(コントミン®，ウィンタミン®)など
ブチロフェノン系	ハロペリドール(セレネース®，リントン®)，チミペロン(トロペロン®)，ブロムペリドール(インプロメン®)など
ベンズアミド系	スルピリド(ドグマチール®，アビリット®)，チアプリド(グラマリール®)，スルトプリド(バルネチール®)
消化管運動調整薬	
ドパミン受容体拮抗薬	メトクロプラミド(プリンペラン®)，ドンペリドン(ナウゼリン®)，スルピリド(ドグマチール®，アビリット®)

ン®)，ゾルピデム(マイスリー®)，リルマザホン(リスミー®)，クアゼパム(ドラール®)，ブロチゾラム(レンドルミン®)などが使いやすいようである．

薬剤性パーキンソニズム

一部の薬剤でパーキンソン徴候(動作緩慢，仮面様顔貌，振戦，ふらつき，小刻み歩行，すくみ足)が出現することがあり，特にふらつきや小刻み歩行，すくみ足を起こすために転倒しやすくなる．誘発頻度の高い薬剤を表2に示す．多くの定型抗精神病薬は抗ドパミン作用があるため，パーキンソン徴候を起こす可能性がある．このような場合，非定型抗精神病薬であるリスペリドン，クエチアピン，オランザピンなどのセロトニン・ドパミンアンタゴニストへの変更を検討すべきである．そのほか，定型抗精神病薬は遅発性ジスキネジア(口唇や舌の不随意運動や四肢の粗大な振戦)，アカシジア(静座不

薬剤起因性歩行障害のポイント

- 転倒を起こしやすい薬剤に関する知識をもっておく必要がある.
- パーキンソニズムを起こしやすい薬剤を知っておく必要がある.
- 「お薬手帳」をみて,多院からの投薬内容を含めて薬剤の服用状況を確認する.
- めまい,ふらつき,歩行障害,易転倒性がみられたら,薬剤による副作用の可能性を念頭に置く.

能)などの錐体外路徴候を起こすこともある.薬剤によるパーキンソン徴候は一般に薬剤を中止することで消失するが,気づかずに,もしくはやむを得ないとの判断で長期連用すると,薬剤を中止しても症状が完全には消失しないこともあるので注意が必要である.

おわりに

高齢者は複数の慢性疾患を抱え,愁訴も多いため服用薬剤数が多くなりやすい.しかも,肝,腎機能が低下しているため薬物有害事象が生じやすい[1].特に,鎮静催眠薬,抗うつ薬,抗精神病薬の使用は転倒を誘発しやすいこと,消化管運動調整薬は長期連用によりパーキンソン徴候を誘発しやすいことに留意すべきである.「お薬手帳」をみて他院からの投薬内容も確認し,投薬の重複がないよう注意すべきである.もし,めまい,ふらつき,歩行障害,易転倒性が生じた場合,まず薬剤による副作用を念頭に置く必要がある.

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Geriat. Med. 49(9) : 971～975, 2011

特集　骨粗鬆症診療の最近の進歩

総説

3．骨粗鬆症と高齢者の虚弱

神﨑　恒一

KEY WORD

- 骨折
- ADL
- サルコペニア
- 転倒スコア
- 虚弱

SUMMARY

骨粗鬆症は虚弱の重要な一因であり，椎体骨折，関節の変形とあいまって姿勢変化を生み，歩行障害を来す．さらに転倒を起こしやすく，これによって高齢者のQOL，ADLは低下する．骨粗鬆症以外にもサルコペニアなど虚弱には多くの要因が関わるため，原因を求め，介入することは難しい．しかしながら，そういった中で骨粗鬆症は数少ない介入可能な因子であり，したがってエビデンスに基づく評価・介入を実践することが重要である．

骨粗鬆症に伴うADLの低下

骨粗鬆症とは骨量の減少と骨質の低下(海綿骨，皮質骨の減少よる骨微細構造の劣化)を特徴とし，その結果，骨の脆弱性が増し骨折しやすくなった全身性骨疾患である．ここに転倒などの外力が加わると，軽微な力であっても骨折が生ずる．骨粗鬆症に伴って起こりやすい骨折部位は大腿骨頸部，橈骨遠位端，上腕骨，脊椎(圧迫骨折)である．骨折すると痛みのため，生活の質(QOL)や日常生活活動度(ADL)が低下する(図1)．また，転倒は再発率が高いこともあり，再転倒することへの不安から，外出や生活そのものに対する意欲が損なわれ，これによってもQOLやADLが低下する．この状態が長く続くと，やがて要介護状態に至る危険が高い．

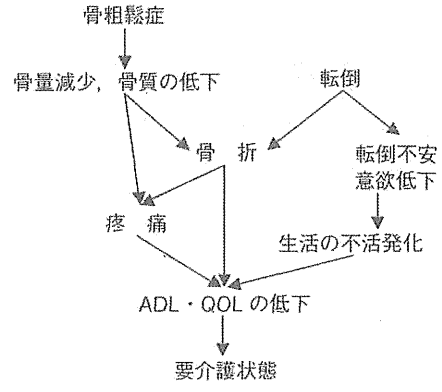
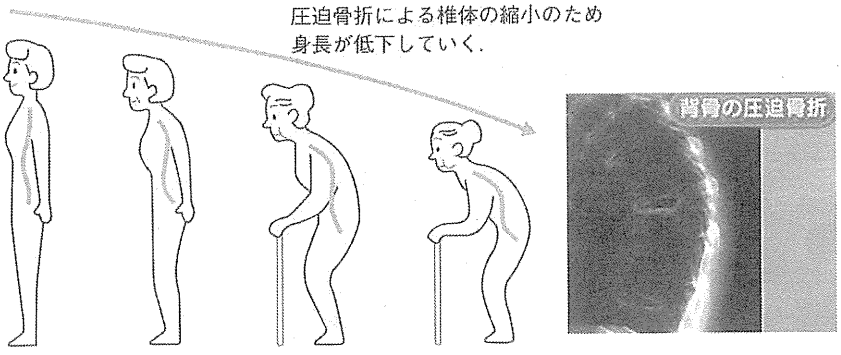


図1　骨粗鬆症と転倒によるADL，QOLの低下

骨粗鬆症，椎体骨折に伴う姿勢の変化

骨粗鬆症による椎体の変形に圧迫骨折を伴うと後彎が進み，身長が短縮する(図2)．脊椎が後彎すると，立位で重心が後方に移動するため，これを補正しようとして膝が前方に偏位する．このような姿勢の変化は歩行に支障を来し，これがもとで運動量が低下し，骨の粗鬆症化が進行する．このような悪循環が進むことで，高齢者の機能障害が進むと考えられる(図3)．われわれは，杏林大学医学部付属病院に通院する高齢患者を対象に，脊椎の後彎角度と転倒の既往との関係について解析した結果，後彎角度が大きいほど，また独自の計測機器を用いて，つま先が上がらない人ほど転倒率が高いことを見出

こうざき　こういち(杏林大学医学部高齢医学)



森井浩世：やさしい骨粗鬆症の自己管理，p6，医療ジャーナル社，大阪，2000 より一部改変引用

図2　椎体圧迫骨折による姿勢の変化

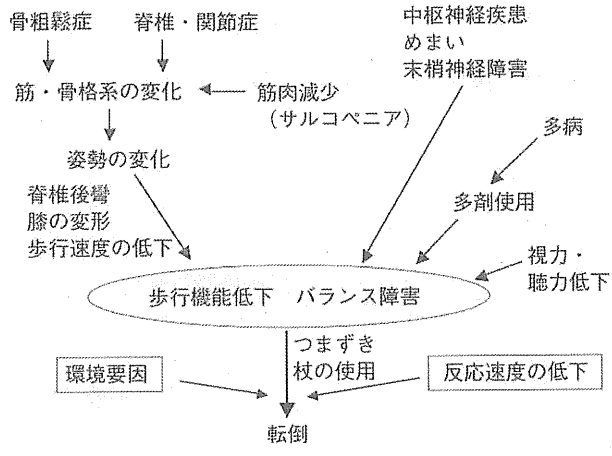


図4

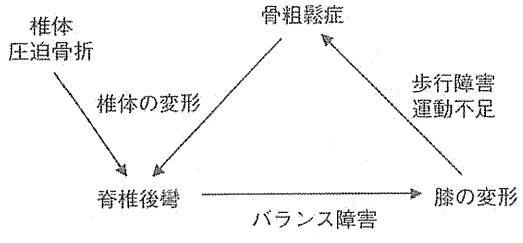


図3　骨粗鬆症に伴う姿勢変化の悪循環

している（未発表データ）．

多要因による歩行障害と転倒

高齢者の QOL，ADL を障害する歩行障害や転倒には，骨粗鬆症以外に多くの要因が関わる．姿勢の変化をもたらす骨・関節系の変化以外に，①高齢期に多くみられる筋肉減少症（サルコペニア），バランス保持能や深部感覚の低下，視力，聴力障害，運動速度や姿勢反射の低下などいわゆる加齢に伴う身体の虚弱化，②循環器系要因（起立性低血圧など），神経系要因（パーキンソン病，認知症などの中枢神経疾患，末梢神経障害，眩暈症など），脳血管障害後遺症などの身体疾患，③薬物（ベンゾジアゼピン系および非ベンゾジアゼピン系の鎮静睡眠薬，抗うつ薬，抗パーキンソン病薬，降圧薬，定型・非定型抗精神病薬など），④屋内の段差や障害物，手すりの有無，履物など環境要因など，要因は多岐に

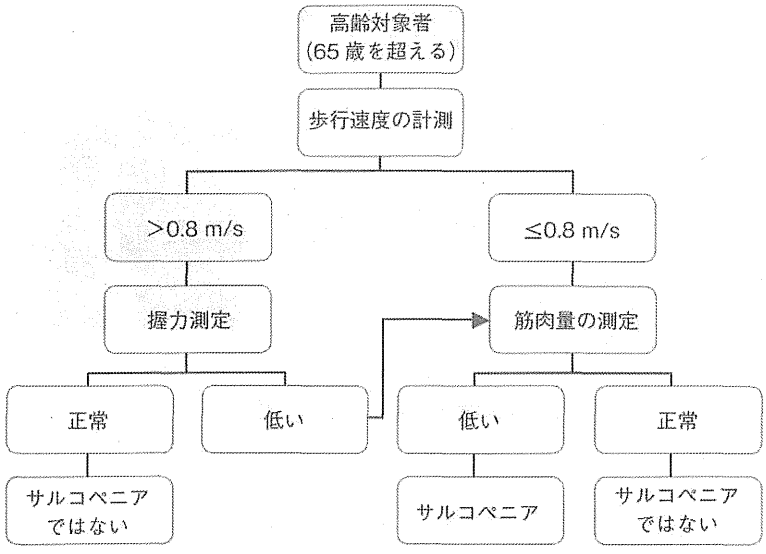


図5　高齢者におけるサルコペニアの発見のためのアルゴリズム

わたる(図4)．しかも，これらは複合して関わるため，1つひとつを区別して要因を分析することが難しい．

加齢性筋肉減少症(サルコペニア)

サルコペニアとは高齢者が虚弱(心身の機能低下)過程で全身，特に四肢の筋肉が量的，質的に低下することを指し，その結果，歩行機能をはじめとする身体機能が低下する．サルコペニアの原因や対策は世界的に注目されており，2010年にBritish Geriatrics Societyからサルコペニアの定義に関するコンセンサスレポート[1]が発表された．この中で，筋肉量の低下のみの場合“前サルコペニア(サルコペニアの前段階)”，筋肉量の低下に加えて筋力の低下もしくは身体機能の低下が認められる場合“サルコペニア”，筋肉量の低下，筋力の低下，身体機能の低下が3つとも認められる場合“重度のサルコペニア”と定義している．さらに，同コンセンサスレポートでは筋肉量をDXA法もしくは生体インピーダンス法で，筋力を握力で，身体機能を歩行速度，バランス，Up & Goテストの組み合わせで評価し，これを組み合わせて図5のような流れで判断するよう勧めている．また，サルコペニアの結果生じる事象として，日常生活自立度(基本的ADL，手段的ADL)，生活の質(QOL)，代謝・生化学・炎症マーカー，転倒，介護施設や病院への入所・入院，社会的支援，死亡率などに注目するよう勧めている．

転倒の評価方法

上記のコンセンサスレポートを加味して，われわれの施設では表1に示すような検査を行い，高齢者の易転倒性を評価している．もちろん，これらの検査は転倒リスクの評価に有用であるが，機器や人手，時間を要するなどマススクリーニングに向かない面もある．そこで，転倒のハイリスク者をより簡易な方法でスクリーニングするために考案したのが転倒スコアである．転倒スコアは自己記入式の調査票であり，身体機能に関する8項目，疾患もしくは老年症候群に関する8項目，環境要因に関する5項目の計21項目と，過去1年間での転倒歴を問う全22項目から成っている(表2)．“はい”，“いいえ”で答える二者択一形式になっており，転倒しやすい方の答えが多いほど転倒リスクが高い．地域在住高齢者を対象とした横断調査の結果，「つまずくことがある」，「信号が青の間に横断

表1　転倒評価のための検査

問診(転倒歴，ADL，環境要因，基礎疾患，服用薬剤)
診察(身長，体重，体脂肪率，血圧，下腿最大周囲径)
視力
下肢筋力
体組成測定
握力
片足立ち時間(開眼，閉眼)
継ぎ足歩行
手伸ばし試験
Up & Go テスト
重心動揺検査
脊椎X線
骨量測定
起立性血圧
頭部MRI
聴力・内耳機能

表2　転倒スコア

過去1年に転んだことがありますか？	(はい　いいえ)	
「はい」の場合，転倒回数(　回/年)		
1．つまずくことがありますか	(はい　いいえ)	身体機能
2．手すりを使わないと階段昇降ができませんか	(はい　いいえ)	
3．歩く速度が遅くなってきましたか	(はい　いいえ)	
4．横断歩道を青のうちに渡りきれますか	(はい　いいえ)	
5．1kmくらい続けて歩けますか	(はい　いいえ)	
6．片足で5秒くらい立つことができますか	(はい　いいえ)	
7．杖を使ってますか	(はい　いいえ)	
8．タオルは固く絞れますか	(はい　いいえ)	
9．めまい・ふらつきがありますか	(はい　いいえ)	疾患 老年症候群
10．背中が丸くなってきましたか	(はい　いいえ)	
11．膝が痛みますか	(はい　いいえ)	
12．目が見えにくいですか	(はい　いいえ)	
13．耳が聞こえにくいですか	(はい　いいえ)	
14．もの忘れが気になりますか	(はい　いいえ)	
15．転ばないかと不安になりますか	(はい　いいえ)	
16．毎日，お薬を5種類以上飲んでいますか	(はい　いいえ)	
17．家の中が暗く感じますか	(はい　いいえ)	環境要因
18．家の中によけて通るものがありますか	(はい　いいえ)	
19．家の中に段差がありますか	(はい　いいえ)	
20．階段を使わなくてはなりませんか	(はい　いいえ)	
21．生活上，急な坂道を歩きますか	(はい　いいえ)	

歩道を渡れない」，「杖の使用」，「タオルを固く絞れない」，「めまい・ふらつきがある」，「膝が痛む」，「屋内の障害物」の7項目が，調査以前の転倒歴と関連すること[2]，「過去(調査以前)の転倒歴」，「歩行速度が遅くなった」，「杖の使用」，「背中が丸くなった」，「5種類以上の服薬」の5項目が，調査後の転倒発生と関連すること[3]が報告されている．転倒スコアは，簡便かつ包括的な転倒評価方法ということができる．

骨粗鬆症と虚弱

“虚弱”は高齢者が抱える普遍的な問題であり，要介護状態を生む大きな原因である．虚弱

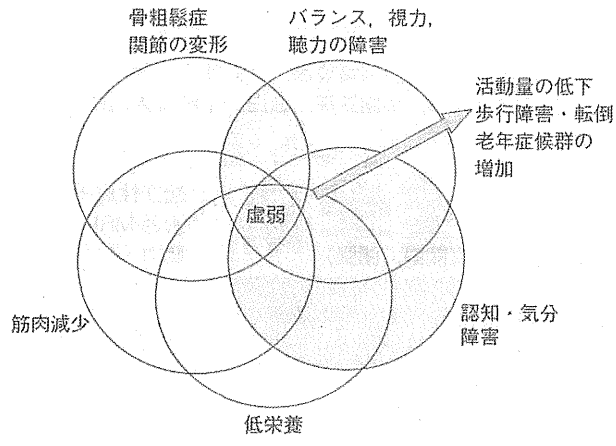


図6

とは加齢に伴って生ずる心身の脆弱な状態であり，複数の臓器・器官の機能低下に起因する．骨粗鬆症やサルコペニアはその主な要因であり，ほかに摂食・嚥下障害と関連する低栄養状態や認知・気分障害(意欲低下，うつなど)など様々な要因が関わる(図6)．虚弱は，活動量の低下，歩行障害・転倒，痩せ，そのほか老年症候群の集積をもたらす．虚弱はその多因子性ゆえ，原因を求め介入することが容易ではないが，骨粗鬆症はその中で数少ない介入可能な要因である．後述されるSeminarを基に，エビデンスに基づく評価・介入を行うことが大切である．

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CGAと包括的ケア

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高齢者の特徴とCGA

高齢になると種々の臓器、器官の機能が低下し、種々の疾患の発生、ストレス応答の低下、日常生活を阻害するさまざまな症候（老年症候群）が増加する（図1）。したがって、高齢者をみるうえでは病気を診るだけでなく、心身の機能を多面的に評価し、日常生活の様子を知る必要がある。たとえば、糖尿病のある独居高齢者で認知機能とADLに問題があり、食事や服薬に問題がある場合、いくら熱心に食事指導を行い、効果の高い糖尿病薬を使用しても血糖管理はうまくいかない。このように患者の生活環境、ADL、認知機能などを把握したうえで疾患の管理を行うことが必要である。

そのために役に立つのが高齢者総合的機能評価（CGA）である。CGAでは手段的ADL（独居生活の自立度）、基本的ADL（屋内生活の自立度）、生活環境、うつ（GDS15）、生活意欲（vitality index）、認知機能（MMSE、HDS-R）、その他を評価する（表1）。詳細は杏林大学医学部高齢医学教室のホームページ< http://www.kyorin-u.ac.jp/univ/user/medicine/geriatrics/medicine04.html >を参照されたい。なお、ADLとvitality indexは観察型評価なので、患者からの情報に問題があると考えられる場合、生活を共にする家族から情報を得る必要がある。一方、MMSE、HDS-R、GDS15は検者を必要とする質問式評価である。

CGA 7によるスクリーニング

上記の機能評価をすべて行うには時間がかかるので、これらの検査のうち代表的な7項目についてチェックする高齢者総合的機能簡易評価法（CGA7：表2）がある。5分以内で実施可能であり、スクリーニングに適している。表3に示すように、各項目はそれぞれ意欲、認知機能、手段的ADL、認知機能、基本的ADL、基本的ADL、うつについての質問項目であり、問題ありと判断したら、“次へのステップ”に示されるCGAを実施する。

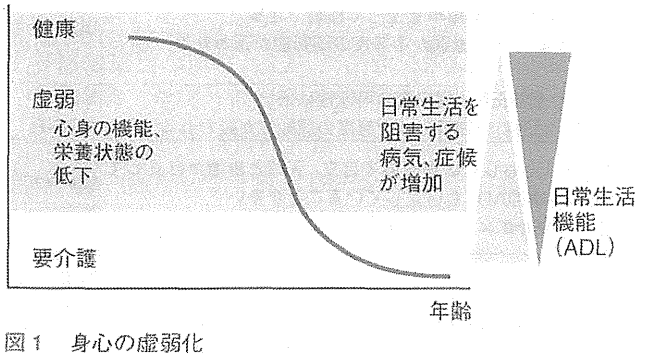

図1　身心の虚弱化

表1　認知症高齢者を診る上で知っておきたいこと
（高齢者総合的機能評価）

- 手段的ADL、基本的ADL
- 生活環境：住居、同居者とその人間関係、日中の過ごし方、外出状況、介護状況など
- うつの状態 → GDS15
- 生活意欲 → vitality index（リハビリ、活動への積極性）
- 認知機能 → MMSE, HDS-R
- 合併疾患は？ 服用薬は？
- 老年症候群