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The Epidemiology of Dementia in Taiwan

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The aged population in Taiwan has increased rapidly, form 7.03% in 1993 to 9.3% in 2004 and the increasing rate is only second to that of Japan. According to our previous study, we adjust with the current age structure. To determine the prevalence and subtypes of dementia in southern Taiwan, a two-phase study consisting of a phase-I screening survey using the Mini-Mental Status Examination (MMSE) and a phase-II diagnostic examination using the CERAD neuropsychological battery and the neurobehavioral examination was conducted in 1993. According to the household records, stratified random sampling by the degree of urbanization of the community was used, and 2915 inhabitants aged 65 and over participated in this study. The ICD-10NA criteria for dementia, NINCDS-ADRDA guidelines for Alzheimer's disease (AD), and NINDS-AIREN criteria for vascular dementia (VaD) were employed. Three hundred and ninety-eight persons who had MMSE scores below the cutoff values were recruited into the phase-II study, of whom 108 had dementia. The prevalence rate (PR) of dementia increased from 1.3% in people 65-69 y/o to 16.5% in people 85 y/o and older. According to current age structure in Taiwan, the age-standardized PR (ASPR) was 5.0%. AD (58 cases, 53.7%, PR=2.0%, ASPR=3.0%) was the most common cause of dementia, followed by VaD (25 cases, 23.1%, PR=0.9%, ASPR=1.0%), and mixed dementia (8 cases, 7.4%). After adjusting for age, sex and education using logistic regression analysis, aging was a significant risk factor for AD, VaD and total dementia. Female sex and illiteracy were significant risk factors for AD only. We concluded that the prevalence of dementia in Taiwan is lower than in the developed countries, which could be due to a relatively young elderly population and a high mortality from dementia in Taiwan. AD is the leading cause of dementia in Taiwan. Considering the high stroke prevalence, the relatively lower prevalence of VaD in Taiwan deserves further investigation.

In order to determine the incidence rate (IR) and subtypes of dementia in southern Taiwan, the abovementioned cohort was followed-up as prevalence study annually. 2507 and 2175 subjects participated in the first and second-year follow-up survey respectively. The annual IR for total dementia increased with age from 0.77% for 65-74 year olds, to 6.19% for persons aged 85 or older. According to current age structure in Taiwan, the age-standardized IR (ASIR) was 1.74% per year. AD (25 cases, 41.7%, IR=0.84%) was the most common cause of dementia, followed by VaD (19 cases, 31.7%, IR=0.41%) and mixed dementia (9 cases, 15.0%). After adjusting for sex, increasing age was significantly associated with total dementia and AD (p<0.01). Illiteracy was associated with a marginally increased risk for total dementia (aRR=1.59 p< 0.1) as was female sex for AD (aRR=1.92, p<0.1). The two-year mortality rate was high among the demented (48% in total dementia, 38% in AD, and 60% in VaD).

In conclusion, the age-specific incidence of dementia in Taiwan is approaching that of developed countries and the low prevalence of dementia (especially VaD) may be mainly due to the high mortality. Age was the major risk factor for total dementia and AD. Female sex was probably a risk factor for AD as was illiteracy for total dementia.

The significant high dementia incidence among the patients with mild cognitive impairment (MCI), about ten times of same aged population, has driven the study of MCI very much. Given to its heterogeneity and no uniform diagnostic criteria, definition of MCI determines, investigation related to prevalence of MCI is limited. To evaluate the prevalence of MCI in community of Taiwan, multiple-step stratified random sampling was applied to recruited 1666 people aged 65 and over from southern Taiwan. A two- phase cross-sectional study with a demographic questionnaire, Chinese-adapted version of Cognitive Ability Screening Instrument (CASI), Center for Epidemiologic Studies Depression Scale (CES-D), and questionnaire of activities of daily living were performed by trained interviewers. In the second phase, a comprehensive neuropsychological test, Clinical Dementia Rating Scale (CDR), physical, and

neurological examination were performed by the psychologists and senior neurologists. Modified MCI criteria is recognized as following: (a).impaired memory function more than 1.5 standard deviation (SD) related to age- and education-specific norms, accessed by the sub-test of recent memory in CASI, (b).preserved general cognitive function with a test performance of CASI more than 1SD related to age-and education-specific norms, (c).intact ability to perform activities of daily living, (d). absence of dementia accessed by DSM-IV criteria. The overall prevalence rate is 10.02% (95%CI, 8.67%-11.56%; n=166/N=1666), and the higher prevalent rate is noted in illiterate subjects:10.70% (95%CI, 8.79%-12.97%; n=90/ N=841) compared with the literate:9.33% (95%CI, 7.53%-11.51%; n=77/N=825). Prevalence rate was slightly increased with age as 8.47% (95%CI, 6.44%-11.05%; n=48/N=567) in aged65-69, 8.73% (95%CI, 6.67%-11.36%; n=49/N=561) in aged 70-74, and 13.01% (95%CI, 10.43%-16.12%; n=70/N=538) in aged>74. Higher prevalence was also found in illiterate subjects rather than literate (illiterate age65-69: 9.13% (95%CI, 6.05%-13.55%; n=21/N=230); literate age 65-69: 8.01% (95%CI, 5.56%-11.41%; n=27/N=337); illiterate age70-74: 9.25% (95%CI, 6.39%-13.21%; n=26/N=281); literate age70-74: 8.21% (95%CI, 5.54%-12.02%; n=23/N=280); illiterate age>74: 13.03% (95%CI, 9.82%-17.09%; n=43/N=330); literate age>74: 12.98% (95%CI, 9.08%-18.23%;n=27/N=208).

In conclusion, the prevalence of MCI was only slightly increased with age, and was quite different from that of dementia. Further study regarding the incidence of MCI and turn-oven rate of MCI to dementia is needed.

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Insight into Management of Dementias from Neuroimaging

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SUMMARY

Structural and functional neuroimagings are the most powerful tools for differential diagnosis and early diagnosis of dementia. Besides clinical use, they also contribute to neuroscience and to testing efficacy as surrogate measures in clinical trial. This paper, focusing on two different models beyond the therapeutic nihilism, discusses the roles of neuroimaging in relation to treatment of dementias; 1) treatable "incurable dementia" - Alzheimer's disease (AD) and 2) untreated "curable dementia" - idiopathic normal pressure hydrocephalus (INPH).

Key Words: Hydrocephalus, Dementia, Alzheimer's disease

Treatable "incurable dementia" - Alzheimer's disease

The progressive course of AD corresponds to ongoing neuronal loss, predominantly affecting the association areas of the neocortex and the limbic system. Given the prolonged course of progressive neuronal loss, strategies aimed at reducing the rates of neuronal loss and thus preserving function (i.e. neuroprotection or disease modification) are particularly important. Cholinesterase inhibitors (ChEIs), which are currently the most used for treating patients with AD, have been thought to treat only the symptoms caused by cholinergic imbalances in AD. This overly simplistic cholinergic hypothesis in AD is limited to symptomatic treatments and ignores the potential of cholinergic therapies as disease-modifying agents[1]. Evidence has now accumulated that ChEIs have a neuroprotective, disease-modifying property. Of particular interest are the signal transduction pathways mediated through cholinergic receptors that promote nonamyloidogenic amyloid precursor protein processing and decrease tau phosphorylation, and the role of the cholinergic system in the aggregation of beta-amyloid peptide. Clinical studies with "delaying end-point", "withdrawal", and "randomized start" designs, and functional brain imaging studies using regional cerebral blood flow and glucose metabolism suggested a possible neuroprotective effect of ChEIs. However, the clinical measures to evaluate the disease-modifying effect of an intervention are readily confounded by any symptomatic benefit of the intervention. Thus, when testing putative neuroprotective agents that are known to have symptomatic effects, it can be difficult to separate the two effects. Although it is relatively easy to study methods of neuroprotection in in-vitro models of cell damage and death and in animal models of neurodegenerative disease, the clinical measures that have been used to evaluate the effect of a possible neuroprotective drug on disease progression are readily confounded by any symptomatic benefit of the study intervention. This is an even greater problem when testing putative neuroprotective agents that are known to have symptomatic effects, as like ChEIs.

To obtain clinical evidence of a neuroprotective effect, end-points for clinical trials that are not confounded by symptomatic effects of the study intervention are mandatory. Neuropathological features of AD include the presence of neurofibrillary tangles and senile plaques, impaired synaptic function, and neuronal cell loss. These microscopic changes are accompanied by progressive brain atrophy, which is demonstrable and measurable in vivo by MRI[2]. Volumetric changes in the medial temporal lobe or in the whole brain detected by MRI are valid biomarkers of pathologic progression of AD, and are correlated with memory or other cognitive functions[2]. This method can track directly the neuroanatomical changes that underlie the clinical manifestation of the disease, and therefore provides empirical evidence that an index of pathological progression in patients with AD may be altered by a pharmacological treatment. Among the characteristic neuropathological changes in AD, the most prominent structural changes at the initial stage occur in the medial temporal lobe. MRI measurements of rates of whole brain or hippocampal atrophy can be used as outcome measures in several therapeutic trials in AD[3]. MRI measures serve as quantifiable surrogate markers for effects on disease progression, as opposed to just symptomatic effects, in instances in which a treatment effect was shown on the behavioral or cognitive measures[1]. The most convincing evidence of neuroprotective effects with donepezil treatment comes from MRI studies, where hippocampal volumes were compared between treated and untreated patients[4]. MRI volumetry is the only established and practical tool to track directly the neuroanatomic changes that underlie the clinical manifestation of the disease, and has been put into practice as a surrogate maker of disease progression in trials of possible disease-modifying compounds, which provide invaluable clues on the validation and limitation of the measure.

We investigated the potential disease-modifying effects of donepezil by comparing the rate of brain atrophy as revealed by MRI measures of the hippocampus taken at 1-year intervals. Patients treated with donepezil were compared with historical control subjects assessed identically prior to the availability of donepezil therapy[4]. There was a significant difference between two groups: the mean annual decline in the ADAS-cog score in the control group (3.6 points) was significantly larger than in the treated group (0.8 points), and the mean annual rate of hippocampal atrophy in the treated group (3.82%) was significantly lower than that in the historical control group (5.04%). The mean annual rate of hippocampal atrophy was significantly higher in patients with the APOE ε4 allele than in those without the APOE ε4 allele, replicating our previous observation that the APOE epsilon4 allele is specifically related to accelerated hippocampal pathology in AD[3]. No significant interaction was noted between donepezil treatment and the APOE genotype, suggesting that the effect of donepezil treatment did not appear to be affected by the APOE genotype. The use of historical control subjects (as opposed to a randomized double-blind control group) in the study requires that the findings be regarded as tentative; however, the results

indicate that donepezil has not only a symptomatic effect but also a neuroprotective effect. Krishnan et al.[5], in a prospective double-blind, placebo-controlled 6-month trial with parallel groups, also found a beneficial effect of donepezil on maintenance of hippocampal volume, supporting the neuroprotective effect of donepezil.

Although larger randomized trials with parallel groups would be necessary to fully confirm and determine the clinical significance of such potential neuroprotective effects of donepezil and other ChEIs, If donepezil really influence disease progression, we need to modify our treatment strategies; donepezil is not an optional but rather a mandatory treatment for AD and should be started in the prodromal or very early stage of the disease. ChEIs in AD provide a model beyond the therapeutic nihilism that dementia is certainly treatable.

Untreated "curable dementia" - idiopathic normal pressure hydrocephalus

INPH is a syndrome characterized by ventricular dilatation due to disturbed cerebrospinal fluid circulation, accompanied by gait disturbance, dementia and/or urinary incontinence without causative disorders. However, the diagnosis of INPH in the elderly remains a substantial issue, and the treatment is not always adequately provided[6]. Since Adams and Hakim introduced the concept of normal pressure hydrocephalus in 1965, iNPH had been widely recognized as a "treatable dementia". However, a gross exaggeration as a treatable dementia and overdiagnosis of INPH in the past caused so many unsuccessful and complicated results that lead negativism among clinicians including neurosurgeons. As a result, most patients with possibly curable INPH often are disregarded and misdiagnosed as having AD or vascular dementia. The criterion of "improvement after shunt surgery" in the original definition of INPH was certainly circular and useless in the decision making for surgery, likely causing loose diagnosis and uncritical expansion of shunt indication. The current situation seems to be a reaction against the past. In any event, disregarding the possibility of INPH before further diagnostic workup would be unfortunate, although it is certainly a curable dementia[1].

Problems in gait, cognition, and urinary function may commonly arise in elderly, and ventriculomegary may occur in association with brain atrophy either in aging or in degeneration (i.e., "hydrocephalus ex vacuo"). Detection of hydrocephalus on structural neuroimaging would be the most initial and critical step. The key neuroimaging feature is disproportionate ventriculomegary. We delineated the MRI features of INPH several years ago[7]. In patients with INPH, the CSF volume was increased in all parts of the ventricular system as compared with those with AD or vascular dementia, whereas the high convexity and interhemispheric subarachnoid CSF spaces were reduced. The CSF in the Sylvian fissure was greater in those patients with INPH than in those with AD. The CSF volume in the basal cisterns was also increased. All abnormalities of CSF distribution in INPH were corrected with shunt surgery, indicating that these changes are related to hydrocephalus. Although an enlarged ventricular system and decreased sulci are characteristic of communicating hydrocephalus, including INPH, the finding of an enlargement of the Sylvian fissure and the basal cistern is a previously unrecognized feature of INPH. This feature is not present in secondary NPH subsequent to subarachnoid hemorrhage, meningitis, and other causes, where the Sylvian fissure and basal cistern are tightly closed. Another unrecognized feature observed in patients with INPH is that a few sulci over the convexity or medial surface of the hemisphere were dilated in isolation. This isolated semi-ovoid sulcal dilatation appeared to be caused by the accumulation of CSF in the subarachnoid space in a specific sulcus. In other types of hydrocephalus, the pressure from the ventricular system does not occur uniformly over the brain surface, resulting in uneven dilatation of the sulci. Although atrophy may predominate in the parietotemporal association cortices in AD, and focal cortical destruction or atrophy may be present in vascular dementia, the combination of focal enlargement of sulci with an otherwise constricted subarachnoid space is unlikely under those conditions. Moreover, this semi-ovoid sulcal dilatation is morphologically distinctive from dilated sulci surrounded by atrophic gyri in AD and vascular dementia. The findings of enlarged basal cisterns and Sylvian fissures and of focally dilated sulci do not exclude, but rather support, the diagnosis of INPH when accompanied by large ventricles and tight suprasylvian subarachnoid spaces.

In Japan, once these MRI features were recognized as indicative of INPH, INPH is being reappraised. To facilitate the appropriate management, a clinical guidelines for INPH was published recently in Japan[8,9]. Furthermore, to validate the management scheme described in the guideline, a prospective study of INPH on Neurological Improvement (SINPHONI) was conducted[10]. This multi-center prospective cohort study evaluates the efficacy of shunt operation for idiopathic normal pressure hydrocephalus, and determines the

diagnostic value of noninvasive procedures commonly practiced in the clinic. Subjects are patients who had both at least one of the triad (gait disturbance, cognitive impairment, and urinary incontinence) and disproportionate ventriculomegary with tightened CSF space at high convexity on MRI. Ventriculoperitoneal shunting are made in all subjects by using Codman-Hakim programmable valve and the standardized shunt pressure setting scheme. The primary end point is >1 grade improvement in the modified Rankin scale at 1 year after surgery. In this protocol, the value of MRI, tap test, CT cisternography, and cerebral blood flow measurement with SPECT in the diagnosis will be determined, and the shunt pressure setting scheme for prevention of overdrainage problems will be also validated. The study will be completed in the end of 2006. INPH is an instructive model that a therapeutic enthusiasm is often counterproductive.

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Subjective Memory Complaints are not Sine Qua Non as Diagnostic Criteria for MCI: the Tajiri Project

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SUMMARY

Background: To investigate whether subjective memory complaints are sine qua non as diagnostic criteria for mild cognitive impairment (MCI), a comprehensive approach is required. Information from a memory clinic and an epidemiologic field are required, and both are available in the Tajiri Project. Methods: We report two MCI cases, one of a patient complaining of memory decline, and the other of a patient without such complaints. Also, epidemiologic data were obtained from the healthy and MCI groups, and we analyzed the relationship between the Everyday Memory Checklist scores obtained from the participants and their families. Results: For both cases, MRI were compatible with Alzheimer's disease (AD), and the both actually progressed to clinical AD. Based on the epidemiologic survey, two patterns emerged regarding the relationship between subjective complaints and family observations: the "anosognosia" pattern associated with the memory questions, and the "self-recognition" pattern related to the questions on communication problems. Conclusions:

The case studies and the epidemiologic data suggest that subjective memory complaints have no significant meaning for distinguishing MCI patients from healthy subjects. Hence, we consider that subjective memory complaints are not sine qua non as diagnostic criteria for MCI.

Key Words: MCI, Memory complaints, Everyday Memory Checklist, Case study, Epidemiology

INTRODUCTION

The aging of the world population has led to an increase in the number of dementia, and early intervention and possible prevention of dementia[1] requires diagnosis at a pre-dementia stage. For the original criteria for mild cognitive impairment (MCI)[2], subjective memory complaints are understood to be the first criterion. However, patients with early Alzheimer's disease (AD) do not always recognize their memory impairments as due to brain disease, and sometimes misunderstand as normal changes[3]. Epidemiologic studies[4,5] show that subjective complaints are not always necessary for diagnosis of pre-dementia, and clinic-based and community-based studies often give different results. However, to provide appropriate medical care and welfare for elderly people with MCI or early dementia, a comprehensive approach including both information from a memory clinic and epidemiologic field data is required. Since 1988, we have been involved with and performed research in a stroke, dementia, and bed-confinement prevention program in Tajiri, Japan (Tajiri Project)[1,5-8]. We herein report two case studies and epidemiologic data, and conclude that subjective memory complaints should not be considered sine qua non as diagnostic criteria for MCI.

METHODS

We define MCI as follows: a Clinical Dementia Rating (CDR)[9] of 0.5 for the memory domain and 0 or 0.5 for other domains, normal daily activities, and lack of dementia. Neuropsychological test were not used as diagnostic criteria, because these data are affected by age and educational level[6]. Two MCI cases are presented: Case #1 originated from the Memory Clinic in Tajiri, and Case #2 arose from a community-based survey. We analyzed the relationship between the Everyday Memory Checklist[10] obtained from the MCI participants and those obtained from their families. A clinical team including medical doctors and public health nurses determined the CDR as described previously[5].

RESULTS

Case reports

Case #1: In September 2002, a 72-year-old woman came to the Memory Clinic due to memory complaints. She had a nervous temperament and was sensitive to the views of her husband, who often pointed out her memory difficulties. She complained about her memory problems and showed a depressive mood. Her Mini-Mental State exam (MMSE)[11] score was 26 and her CDR score was 0.5. Trazodone was administered and gradually her depressive mood improved. Her MMSE had decreased to 23. Importantly, her family's recognition of her memory problem had increased, compared with the earlier situation, and became greater than that of her own complaints. After her family forced the patient to give up driving her scooter, she developed a depressive mood again. After administration of Minacerin, her depressive mood improved, and her own complaints decreased. However, her MMSE score decreased to 20. In January 2005, she was diagnosed as probable AD (NINCDS-ADRDA).

Case #2: A 77-year-old man was assessed as MCI in the epidemiologic survey. He himself had no memory complaints; however, his wife had observed deterioration in his memory. He showed apathy and had no particular social interests. His MMSE score was 22 and his CDR score was 0.5. His wife took him to the Clinic in August 2002. Subsequently, he did not come to the clinic due to denial of his problems. In January 2005, he was diagnosed as probable AD. The MRI and SPECT images of both cases are typical of those of AD.

Epidemiologic study

The differences in subjective memory complaints and family observations between the healthy subjects and the MCI group are found. For the subscores, two patterns became apparent: "self-recognition" and the 'anosognosia' patterns. As for the relationship between subjective memory complaints and objective neuropsychological findings, we previously reported[5] that these were not related. In the current study, we examined this possible relationship using the Everyday Memory Checklist and Cognitive Abilities Screening Instrument (CASI)[12], and again we did not find a significant relationship.

DISCUSSION

In this study, we reported two MCI cases, one of a patient from the memory clinic who complained of memory decline, and the other of a patient identified in a community survey who did not complain of memory

decline. MRI/SPECT images in both cases were compatible with AD, and clinically both progressed to AD. Our epidemiologic data raise questions regarding the meaning of subjective memory complaints in the assessment of MCI.

Using the Checklist, two patterns emerged for the relationship between subjective complaints and family observations: the anosognosia pattern and the self-recognition pattern. The former was detected in the answers to questions associated with memory, and the latter occurred for questions related to communication problems. AD patients usually forget certain past episodes. However, such patients may have normal conversation, and may be aware that they are repeatedly pointing out their daily problems with their family. These characteristics may explain the anosognosia pattern for questions on memory and the self-recognition pattern for questions that dealt with immediate communication problems.

In conclusion, we return to the question of whether subjective complaints have any meaning in the assessment of MCI. Epidemiologic data suggest that subjective complaints have no significant meaning when attempting to distinguish MCI subjects. However, some residents spontaneously came to the Clinic with severe memory complaints. An MCI patient with severe memory complaints may have a depressive state, as illustrated by Case #1, but there may also be MCI cases with no remarkable complaints other than apathy, but in which the patient shows gradual cognitive deterioration, as illustrated by Case #2.

As a matter of course, caution should be used in examining the differences between community-based and clinic-based studies. However, to provide appropriate medical care and welfare for early dementia, it is of little value to simply emphasize the differences between these two kinds of studies. The comprehensive approach allows us to conclude that understanding of patients with MCI requires consideration of two different balances: between memory complaints and family observations; and between subjective complaints and neuropsychological findings. Hence, in conclusion, subjective memory complaints are not sine qua non as diagnostic criteria for MCI.

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The Neuropsychological Studies of Dementias in Taiwan: Focus on Way-finding Problems in Alzheimer's Patients

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SUMMARY

Human urban navigation depends on environmental cognition and the decision making to choose route. Impairment of these two components may result in way-finding problems, one of the most frequent symptoms in patients with AD. Chiu and her colleagues had studies getting lost behavior in AD patients and concluded that the getting lost behavior in such patients is in part accounted by their executive dysfunction. Pai and his colleagues, on the other hand, used experimentally designed tasks to test AD patients what they have called "the retrogenetic hypothesis of navigational ability". They have been focused on environmental cognition. Recently, they have begun to explore this issue by using electrophysiological tools and yielded some results.

Key Words: Neuropsychology, Dementias, Taiwan, Navigation, Cognition

Background

Over the past years, the studies of navigational ability or way finding problems in patients with AD, as one of the most frequent symptoms in such patients, are increasing in number. This is also true in Taiwan. Basically, human urban navigation depends on two major components, namely, environmental cognition and decision making to choose route. Impairment of these two components may result in way-finding problems.

Chiu's group, getting lost behaviors and executive functions

Chiu and her colleagues[1] had studies 116 community-dwelling participants, including normal subjects, patients with questionable dementia and patients with mild AD. They found that attention impairments, consisting of distractibility, impulsivity, and executive function problems, significantly predict getting lost behavior (GLB) in familiar and unfamiliar environments. Irritability and executive function problems are associated with mental difficulties in choosing a turn, whereas the use of way-finding strategies reduces GLB. They further used Everyday Spatial Questionnaire for Dementia-patient version (ESQD-P) to test this population[2]. The findings indicated that the ESQD-P is a reliable instrument for measuring GLB. Again, they showed that executive functions predict both global and analytic way finding strategies.

Pai's group

From the above studies, it seems that the GLB is related to executive function or attention; both are related to frontal lobe function. There is always something wrong encountered by a navigator before he or she is forced to make a decision to choose route. More often than not, it is a perceptual deficit of the landmarks and/or scenes, or an impairment of the spatial representations of the environments. This is the basis what Pai's group has been studied.

Clinical observation Pai and his colleagues have published three papers of non AD patients with TD, in which the loci of the damage are right parahippocamus [3,4], right parietal lobe[3], and right thalamus[5]. For the last case, the patient manifested transient TD for only four minutes, and his SPECT examination showed hypoperfusion in the right thalamus. These cases support that the role of certain cerebral structures in human navigation[6].

By interview, they studied the incipient symptoms of 155 AD patients in southern Taiwan and found that 7% of the patients had TD as one of the first symptoms[7]. They further explored the prevalence of TD in 112 community residing patients, and found that as high as 55% of the patients had a current TD. More importantly, 18% of them had ever been escorted by policepersons or others after having been lost[8]. In order to understand the context in which a patient may be lost, they further studies the first ever GL in 19 patients, and found that 17 of them had their first ever GL in the places they were familiar to and on the way to a definite destination, rather than aimless wandering[9].

Neuropsychological studies Pai and Hsiao[10] designed experiments to test what they called "retrogenetic hypothesis of navigational ability", which is based on the Braak and Braak pathological staging of AD[11], Piaget's developmental psychology[12], Reisberg's retrogenesis[13] and the neural correlates for topographical orientation[6]. In the hypothesis, they predicted patients with AD, along with the progression of the disease, would lose cognitive map or internal spatial representation of the environments first, followed by the ability to follow routes egocentrically, and finally the recognition of familiar landmarks. The tasks included novel landmark learning and recognition, egocentric route learning, and internal spatial representation. The participants were 21 normal controls, 22 amnesic mild cognitive impairment (MCI)

and 38 mild AD patients. In brief, the AD group performed poorer than normal and MCI group in novel landmark recognition, while no difference appeared between MCI and normal controls. Regarding the nature of the landmarks used in this experiment novel to participants, they designed another experiments by using personally familiar landmarks near their residence. This time, there showed no difference among groups[14]. This is compatible with the hypothesis. As for the egocentric route learning task, it showed difference between normal and MCI, and MCI and mild AD. In the allocentric spatial representation, however, the MCI behaved as well as normal controls did in the task pointing to the starting point in a journey of a long trip, while AD was poor in this task. Finally, MCI and normal were less often to choose the map representing the real route least like. In this study, MCI group performed as well as normal controls did in tasks supposed to be a hippocampal function.

Physiological studies From case study, AD patients may feel familiar in a place in fact strange to them, or the opposite. This feeling provokes negative or bad emotional response to the patients, which we suspect may produce confusion and uncertainty and lead patients lost. By using evoke-related potentials (ERP), Pai and his colleagues tested 11 couples of spouse who had been living in the current residence for more than five years. Behaviorally, the AD patients recognized familiar landmarks as well as their spouses did. These patients, however, responded to the stimulus slower than their counterpart, as measured by latency of the wave specific to familiar landmark recognition[15]. Now, a study combining skin conductance recording and ERP has been undergoing to demonstrate a possible discrepancy between cognition and emotion.

DISCUSSION

Although executive function is related with GLB, the causality remains a question to be tested. On the other hand, human navigation in modern environments is quite different from animals moving in wild world where landmarks are rare or not salient. Adequate perception to environments, especially the landmarks, plays an even more important role. Regarding this, AD patients may complain that they could identify a scene or landmarks, but they had a strange feeling whether it is exactly the one or ones they had recognized. This feeling would provoke an uncertainty and urge the navigator to make a decision to choose a route or a turn.

The strange feeling may come from a failure to identify the landmark from its background or context, or to identify the scene as a whole, rather than the landmark itself. Under certain condition, although rare, patients may be unable to recognize familiar scenes in spite of being able to recognize individual landmark in it. It seems that there is a specific mechanism making sense these already recognized landmarks, especially for those isolate and prominent buildings. To recognize a landmark can be fulfilled by right lingual gyrus, when damaged there may result in landmark agnosia[6], while to perceive the scene or context as a whole is the hallmark function of hippocampus. Damage to hippocampus may dampen the ability to sense the meaning of context while keeping isolated landmark recognition normal. Applying this, it is plausible the early AD patient may successfully recognize an isolate landmark, but their ability to make sense of it or retrieve its value in route guidance is impaired.

Another possibility is that the patient loses the sense of direction. The lesion in posterior cingulum or retrosplenial cortex may lead to head disorientation[6]. In addition to entorhinal, hippocampus and related structures, the patients with very early AD have lesions in posterior cingulum or retrosplenial cortex as well[11], which may explain why such patients may lose their sense of direction although they can identify isolated landmark or scene at crossroads.

In conclusion, more studies on way finding behaviors in early AD patients are needed. In addition, the cognitive map at this stage is perhaps not important[16], and the role of hippocampus in human navigation remains unsolved.

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The Genetic Studies of Dementias in Taiwan

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SUMMARY

In Taiwan, Alzheimer's disease (AD) followed by vascular dementia (VsD) is the most common cause of dementia among Taiwanese (ethnic Chinese). Several studies have documented the increase of risk for AD among the apolipoprotein E gene allele 4 (*ApoE4*) carriers in Taiwanese. It is a consensus that *ApoE4* is the most important risk factor for AD at present. The researchers also found that *ApoE4* allele frequency is lower in Taiwanese, around 7%, than it in the most Caucasian populations. This phenomenon raises the hypothesis that low *ApoE4* allele frequency contributes to low prevalence of AD in Taiwanese. Besides, many genetic studies were involved in genetic impacts on modulation or regulation of the manifestation, progression, and treatment response of AD. But, these genetic studies are still inconclusive. Few familial AD attributed to PS1 gene mutation has been identified. The genetic studies of VsD are just beginning and NOTCH3 gene mutation has been detected in Taiwanese cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy (CADASIL) families. Since there is a large proportion of non- *ApoE4*-associated AD in Taiwanese, it remains more researches to look for novel genetic factors in Taiwanese. Based on the Japanese experience of studies, the association between the polymorphisms of ApoE and familial AD, sporadic early-onset AD respectively warrants further investigation.

Key Words: Genetic, Alzheimer's disease, Chinese, Taiwanese, Dementias

BACKGROUND

Dementia is a group of diseases characterized by a decline of cognitive function. In Taiwan, AD followed by VsD is the most common cause of dementias[1]. Based on compelling evidence, genetic background is involved in the occurrence of dementias. Variations of genetic background might also cause huge impact on the presentation, response of treatment and prognosis of dementias. Molecular genetic studies not only can help on clinical diagnosis, understanding the pathophysiology but also might provide relevance for prediction of treatment outcome. Herein, we review the status of the molecular genetic researches of dementias in Taiwan.

Alzheimer disease (AD)

The characterized pathological changes of AD include extracellular senile plaques, intraneuronal

neurofibrillary tangles, neuronal and synaptic loss, and neurotransmitter deficits in the brain. The pathogenesis of AD is complex and might involving both environmental and genetic factors. Although most of the patients are sporadic, with an obscure etiology, some patients of AD are inherited and few genes have been found to be involved in familial AD. Three genes are linked to early onset, familial forms of AD. They are amyloid precursor protein gene (*APP*), presenilin-1 (*PS-1*) and presenilin-2 (*PS-2*). On the other hand, inheritance of the ε4 allele of apolipoprotein E gene (*ApoE4*) is conferred a genetic risk for developing late-onset, sporadic AD. Besides, some genes also were with association of modulating and regulating the manifestations, progression, and treatment responses of AD.

Apolipoprotein E polymorphisms in Alzheimer disease

Apolipoprotein E (ApoE) is a protein constituent of plasma lipoproteins. It transports cholesterol and other lipids to the liver by interaction with the low-density lipoprotein receptor on the cell surface of hepatocytes. There are three isoforms of ApoE, in terms of E2, E3, and E4 coded by three different alleles, *Apoε2*, ε3, and ε4 respectively. The allele frequency of the *Apoε4* increased in AD patients by comparison with it in healthy controls among many ethnic populations, whereas *Apoε2* allele, in a few studies, was involved in potential protection against AD[2]. Hong et al., in 1996, first reported the allele frequencies of *Apoε4* in Taiwanese (ethnic Chinese) with late-onset sporadic AD and their results supported the association between *Apoε4* and AD[3]. Later, several studies also confirmed this important finding[4,5,6]. It's interesting that several studies all find a lower prevalence of AD among the Taiwanese or Chinese in comparison with Caucasian populations[1]. The *Apoε4* allele frequency in Taiwanese ranges from 4.9 to 11.0%, but it is usually higher than 9.0% among Caucasian populations in the most studies[7]. Liu HC first raised the possibility that this phenomenon can be in part attributed to low *Apoε4* allele frequency in Taiwanese. On the other hand, this also enhanced the causal-relationship of ApoE in AD. The results of Japanese studies are similar to that of Taiwanese[8]. Lung et al found that inheritance of an ε2 allele significantly lowers the risk of containing an ε4 allele for AD[2].

Many studies have investigated the association between *ApoE4* allele and behavior psychiatric symptoms of dementia (BPSD) in patients with AD, but this issue remains inconclusive. Chang et al. found that AD patients with *ApoE4* allele may be associated with an increased frequency of psychotic symptoms, such as delusions and hallucinations[9]. However, Liu et al. found that no association between depression and *ApoE4* or *ApoE2* allele in AD. Few studies explored the phenotype of accelerated reduction of cholinergic activity among *ApoE4* allele carriers. Wang et al. identified a synergistic effect of the estrogen-metabolizing gene, *COMT*, and *ApoE4* on occurrence of AD. It is possible that a high metabolism rate of estrogen by COMT enzyme results in carriers of COMT HH genotype having less protective effect of estrogen in AD[10]. In Japan, *ApoE4* allele has been found to be associated with both early-onset AD and late-onset AD. In addition, *ApoE4* allele seems to play a more important role in the early-onset AD. In familial AD (FAD), the role of *ApoE4* allele has also been demonstrated.

Genetic risk factors other than ApoE in Alzheimer disease

Cheng CY et al documented the association of *ACE* gene polymorphisms in Taiwanese AD patients. There are drugs of cholinesterase inhibitors widely used for mild to moderate AD. Acetylcholine is degraded by two enzymes, acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). No synergistic effect was found between the *BuCHE-K* variant and *ApoE4* in their study[11]. Liu et al. tested the allelic variant (C267A) of the cholinergic receptor muscarinic 1 (*CHRM1*) and they suggest that the *CHRM1 C267A* polymorphism is not conferred in susceptibility to AD. Liou et al. found that the genetic polymorphism of partially duplicated alpha7 nAChR contributes no major effect on AD. Tsai et al. found that the 267C allele of one of the serotonin receptor genes, the *5-HT6* gene, is a risk factor for AD. Wang et al. studied the tryptophen hydrolase gene (TPH) polymorphism in AD, but the results were negative. The N-methyl-D-aspartate (NMDA) receptor 2b subunit (*NR2b*) was studies by Tsai et al. They demonstrated no statistically significant association between the *NR2b* C2664T polymorphism and AD. Liu et al. found no significant difference in adenosine A2a receptor (*A2aAR*) genotype distribution or allelic frequency by comparison of AD patients and normal controls. Hong et al. studied the relationship between the polymorphisms of the alpha1a- and the alpha2a-adrenoceptor genes and AD. The results demonstrated that none of the alpha1a/2a-adrenoceptor polymorphisms were associated with increased susceptibility to AD. Wang et al. conducted an association study of *ACT* polymorphisms and Taiwanese AD patients. Their results indicated that the *ACT* polymorphisms had no effect on the development of AD either alone or in combination with the *ApoE4* allele. Alpha-2 macroglobulin (A2M) encoded by the gene A2M, is a serum panprotease inhibitor. A2M binds tightly to

Amyloid-beta (A-beta) peptide and attenuates fibrillogenesis and neurotoxicity of A-beta. The association between *A2M-2* (a polymorphism of *A2M* gene) and AD was disproved[5,12]. Presenilin-1 (*PS-1*) gene is one of three genetic loci linked to early onset familial AD. Two studies conducted to evaluate the relationship between intronic polymorphism of the *PS-1* gene and late-onset AD showed no association between the polymorphism of the *PS-1* gene and AD[4,5]. Liou et al. conducted a study to examine the role of the polymorphisms of neuronal NOS (*nNOS*) gene in AD and found no association between AD and *nNOS* polymorphism. The deposition of A-beta plays a crucial role in the pathogenesis of AD. Beta-site APP cleaving enzyme (BACE) is the rate-limiting enzyme in the A-beta formation. Liu et al. studies all the exons of BACE by single strand conformation polymorphism (SSCP) and found a novel polymorphism in this gene, but the polymorphism showed no significant association with the occurrence of AD[13]. The *IL-1A* C (-889)T polymorphism has been analyzed in Taiwanese population by at least two groups. The results were both negative. In summary, the only one consensus of genetic risk for AD is *ApoE4* allele. The genetic studies of AD other than *ApoE4* in Taiwan are still inconclusive. Few familial AD resulting from PS1 gene mutation were identified.

Vascular dementia

VsD is the second leading cause of dementia in Taiwan[1]. The genetic factors have been found, such as familial vascular encephalopathies, in terms of cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy (CADASIL), and possibly *ApoE4*. Tang et al. first reported the *NOTCH3*, Arg332Cys mutation at exon 6 in Asia patients and they emphasized the importance of genetic analysis of *NOTCH3* for Asians with a phenotype consistent with CADASIL[14]. A few reports have documented levels of plasma lipoproteins as risk factors in cerebral arteriosclerosis. The association between the allele frequency of *ApoE4* and VaD is also controversial. In Taiwan, several studies have been conducted to clarify whether the *ApoE4* is associated with VaD but these studies conclude that *ApoE4* plays no significant role in the development of VaD[6]. *ApoE 2* has a protective effect with regard to the development of intracranial vascular diseases (ICVD) and VaD for young Taiwanese aged below 65[15]. No difference in allele frequencies of C-889T polymorphism on *IL-1a* between the VsD and non-VsD controls. In summary, the genetic studies of VsD are just beginning in Taiwan. Only *NOTCH3* gene mutation has been identifies in CADASIL families.

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The Studies of Behavioral and Psychological Symptoms of Dementia in Taiwan

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SUMMARY

The behavioral and psychological symptoms of dementia (BPSD) are common serious problems that affect the quality of life for both the patients with such symptoms as well as their caregivers. BPSD present a major challenge in the medical management of patients and are the major cause of institutionalization. Alzheimer's Disease (AD) is the most common type of dementia in Taiwan. I performed a systematic literature review on BPSD studies and found that Taiwanese patients with AD exhibit many of the BPSD. Studies showed that between 30% and 63% of Taiwan's AD patients experienced delusion. Hallucination occurred less frequently, which ranged from 21% to 26%. Anxiety occurred in 35-76% of patients and depression 22-50%, sleep abnormalities 26-61% and 39-46%. The differences in the prevalence of BPSD might result from the different clinical settings and evaluation instruments. The prevalence and clinical manifestations of BPSD in Taiwan are similar to Western reports and it suggests that most of BPSD are neurobiologically determined. Based on differing cultural backgrounds, the interpretation of agitation and apathy might differ, so, the development of cross-cultural applicable criteria and rating scales for the assessment and treatment of BPSD are important for future studies.

We performed a systemic review of published medical literature between January 1990 and November 2005 through the PubMed and Chinese Electronic Periodicals Service databases with the terms: "psychosis", "behavioral", "delusion", "hallucination", "agitation", "depression", "BPSD", "Alzheimer's disease", "dementia" and "Taiwan". Manual cross-referencing of bibliographies from all papers and reviews was also done. Since most of the studies were conducted in patients with Alzheimer's disease (AD) and AD is the most common type of dementia in Taiwan, only the studies reporting data on BPSD in patients with AD were selected. Using these methods, we identified 23 articles and retrieved the full text of these publications and reviewed each article in detail. The following table summarizes the prevalence of common BPSD in the published literature from Taiwan.

CONCLUSIONS

BPSD is common in patients with AD in Taiwan. Except for agitation or apathy, the frequencies of other BPSD are similar to those of in Western studies. Development of cross-culturally applicable methods for assessment and treatment protocols for BPSD evaluation and study are both needed and important.

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Table.

Symptom	Author, year	Case no	Method	Prevalence (%)
Depression	Liu, 1999 (1)	141	SCID	Major depression 5%, Dsythymia 8%, Depressive disorder NOS 4%
	Liu, 1999 (2)	103	BEHAVE-AD	22%
	Fuh, 1999 (3)	76	RMBPC	50%
	Fuh, 2001 (4)	95	NPI	38%
	Chow, 2002 (5)	230	NPI	44%-49%
	Fuh, 2005 (6)	320	NPI	47%
Anxiety	Liu, 1999 (2)	103	BEHAVE-AD	35%
	Fuh, 1999 (3)	76	RMBPC	76%
	Fuh, 2001 (4)	95	NPI	54%
	Chow, 2002 (5)	230	NPI	38%-39%
	Fuh, 2005 (6)	320	NPI	37%
Delusions	Hwang, 1996 (7)	54	BEHAVE-AD	63%
	Liu, 1999 (2)	103	BEHAVE-AD	30%
	Fuh, 2001 (4)	95	NPI	47%
	Chow, 2002 (5)	230	NPI	31%-40%
	Fuh, 2005 (6)	320	NPI	31%
Hallucination	Hwang, 1996 (7)	54	BEHAVE-AD	26%
	Liu, 1999 (2)	103	BEHAVE-AD	26%
	Fuh, 2001 (4)	95	NPI	21%
	Chow, 2002 (5)	230	NPI	19%-25%
	Fuh, 2005 (6)	320	NPI	24%
Sleep disturbance	Hwang, 1997 (8)	75	BEHAVE-AD	61%
	Liu, 1999 (2)	103	BEHAVE-AD	26%
	Fuh, 2001 (4)	95	NPI	36%
	Chow, 2002 (5)	230	NPI	35%-36%
	Fuh, 2005 (6)	320	NPI	42%
Aggression/agitation	Tsai, 1996 (9)	47	BEHAVE-AD	57% (physical)
	Hwang, 1997 (8)	75	BEHAVE-AD	55% (physical)
	Liu, 1999 (2)	103	BEHAVE-AD	Verbal: 21%, physical: 10%
	Fuh, 1999 (3)	76	RMBPC	Verbal: 35%
	Fuh, 2001 (4)	95	NPI	46%
	Chow, 2002 (5)	230	NPI	40%-46%
	Fuh, 2005 (6)	320	NPI	39%
Apathy	Fuh, 2001 (4)	95	NPI	44%
	Chow, 2002 (5)	230	NPI	39%-47%
	Fuh, 2005 (6)	320	NPI	42%

Interventional Studies with the Aim of Reducing the Burden of Care Through Drug Therapy of BPSD

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Key Words: BPSD, Caregiver burden, Alzheimer's disease, Dementia with Lewy bodies, Frontotemporal lobar degeneration

INTRODUCTION

Behavioral and psychological symptoms of dementia (BPSD) are highly prevalent in patients with dementia and are a major source of difficulty and distress for caregivers. BPSD are one of the main reasons for hospital or nursing home placement of patients, and thus contribute greatly to the cost of caring for dementia patients. While a number of intervention studies have aimed to reduce the burden of caring for patients with dementia through family support and counseling of caregivers, few studies have focused on using drug therapy to alleviate BPSD and reduce the care burden.

Patients with dementia of different etiologies show the different patterns of BPSD. For example, patients with Alzheimer's disease (AD) have higher rates of delusions and wandering than vascular dementia patients. In dementia with Lewy bodies (DLB), visual hallucinations are prominent, whereas in frontotemporal lobar degeneration (FTLD) inappropriate eating behavior and aggression are more pronounced.

BPSD arise from complex changes in central neurotransmitter levels, with particular categories of symptoms linked to certain neurotransmitter abnormalities. Aggression is associated with raised levels of norepinephrine and reduced levels of serotonin, psychosis with low acetylcholine and elevated dopamine, and stereotypy with low serotonin. Thus, the choice of treatment should be based on the neurochemical target for each BPSD in each dementia etiology.

Treatment of BPSD in AD

In comparison with vascular dementia, more productive (positive) symptoms such as delusions and aberrant motor behavior were found in AD[1]. Conventional neuroleptics such as haloperidol have been commonly used to treat AD patients who exhibit these productive symptoms. However, these conventional antipsychotics are, at best, modestly efficacious for treating these symptoms with high incidence of extrapyramidal adverse reactions and other unwanted side effects. Low-dose atypical neuroleptics such as risperidone and olanzapine are efficacious and well tolerated in AD patients with BPSD[2,3]. Delusions of theft are one of the most frequently observed neuropsychiatric manifestation of the BPSD in patients with AD[4]. In addition, the delusions and ensuing aggression and anxiety are major factors that increase the burden of caregivers. Delusions of theft in patients with AD were eliminated or reduced with risperidone[5]. This significantly reduced the burden of care overall for caregivers, evaluated using the Zarit Caregiver Burden Interview.

Treatment of BPSD in DLB

After AD, DLB is recognized as the next most common neurodegenerative cause of dementia. BPSD, such as visual hallucinations and misidentification delusions, are prominent clinical features of DLB. Symptomatic treatment of these psychotic BPSD may be required, but can be extremely difficult. In particular, approximately half of all DLB patients who receive neuroleptics experience life-threatening adverse effects, termed neuroleptic sensitivity[6]. Given the complications associated with the use of neuroleptic drugs in DLB, interest in alternative treatment strategies has increased. As patients with DLB are reported to have a marked cholinergic deficit, cholinomimetic drugs may be beneficial in reducing BPSD and ameliorating cognitive impairment. Results of recent reports using cholinesterase inhibitors such as donepezil, rivastigmine and galantamine in DLB showed improvements in BPSD without deterioration in motor functions[7]. In our preliminary study, treatment of BPSD with donepezil therapy reduced the burden of caring for patients with DLB and is, therefore, of great importance to the provision of satisfactory home care for these patients[8].

Treatment of BPSD in FTLD

Distinctive clinical features in frontotemporal lobar degeneration (FTLD) include behavioral symptoms, affective symptoms, and cognitive symptoms. In particular, unusual behaviors of FTLD, such as disinhibition, loss of social awareness, overeating, perseverative and stereotyped behavior, and impulsivity, are serious obstacles to managing and caring for patients with FTLD[9]. These behavioral symptoms found in FTLD have been associated with serotonin abnormalities, and serotonin selective reuptake inhibitors (SSRIs) may be beneficial in reducing these symptoms[10]. The behavioral symptoms, especially stereotyped behaviors of FTLD, significantly improved after treatment with

fluvoxamine[11]. Trazodone is an atypical serotonergic agent with the original characteristics of moderate serotonin reuptake inhibition and a serotonergic antagonist effect. The behavioral symptoms, especially eating disorders, agitation, irritability, and depression/dysphoria of FTD, significantly improved after treatment with Trazodone[12]. SSRIs and trazodone might reduce the BPSD severity and improve quality of life of FTLD patients and their caregivers.

COMMENTS

BPSD are responsible for increased numbers of hospitalizations and emergency room visits, and cause excess disability in patients with dementia, leading to a decline in functioning beyond that due to cognitive deficits alone. Together, these effects of BPSD substantially increase the cost of care. Furthermore, BPSD markedly diminishes the quality of life of both patients and caregivers. These findings underline the paramount importance of appropriately managing and treating BPSD.

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The MCI Study in Taiwan

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SUMMARY

Veterans General Hospital started study for mild cognitive impairment (MCI) since 1996. We used clinical dementia rating (CDR) of 0.5 to define our questionable dementia (QD) subjects. These QD subjects received annual neuropsychological assessment in 5-year follow-up period. Annual conversion rate, apolipoprotein E (ApoE) genotype and neuropsychological risk factors for QD were investigated. We found a 19.9% person-year conversion rate for these QD subjects. Both of the poor cognitive performance and ApoE ε4 allele were risk

factors for progressing to dementia. Based on the results of this study and the progress in the concept of MCI, we added more complex verbal and visual memory tests as well as MRI-based volumetry measurement in our subsequent research. Peterson's amnestic MCI criteria were used to diagnose our MCI subjects. In the 3-year follow-up period, the conversional rate was 18.2% person-year for MCI subjects, similar to our previous finding in QD. We found hippocampal volume was positively associated with cognitive performance. ApoE genotype had effect on hippocampal volume. Subjects with lower cognitive performance and smaller hippocampi had higher risk converting to AD. With rapidly expanding research on dementia and MCI worldwide, we are looking forward to seeing the integration in neurobiology, neuroimaging, and neurobehavior fields to establish a multidisciplinary approach to MCI and dementia.

Key Words: MCI, Dementia, Alzheimer's disease

Alzheimer's disease (AD) is characterized by a slowly progressing degenerative process of cognitive decline. Some research has focused on the transitional stage between normal cognition and AD and the predictors for conversion to AD. Several terms for this transitional stage have been used, such as questionable dementia (QD)[1], mild cognitive impairment (MCI)[2], cognitive impairment not dementia[3], and preclinical phase of AD[4].

Individuals within this transition cognitive stage are at high risk for developing dementia[5]. Patients with mild cognitive impairment develop Alzheimer's disease (AD) at a rate of 10-15% per year, whereas the rate for healthy control subjects is 1-2% annually[2]. Therefore, the identification of people at potential risk of dementia with a view to early therapeutic intervention is important.

From 1996 to 2000, we recruited 168 questionable dementia (QD) subjects with clinical dementia rating (CDR) scale of 0.5. All participants were assessed about once a year. If there was indication of memory deterioration before the annual assessment, the subjects would be evaluated earlier. The diagnosis of QD was according to the criteria of Hughes et al[6]. Among the 168 QD subjects, 124 were included for this analysis with the following criteria: (1) subjective memory complaints, (2) aged 65 years and older, and (3) at least two full evaluations during the study period.

The mean duration of follow-up for the 124 QD subjects was 20.4 ± 12.4 months. During that period, 42 QD subjects developed dementia, and all were diagnosed to have probable AD according to the NINCDS-ADRDA criteria[7]. The annual conversion rate to AD for the 124 QD subjects was 19.9%. Compared to those remained QD, the individuals converted to AD at baseline had significantly poorer performance in total the Cognitive Ability Screening Instrument (CASI)[8] score, short-term memory, orientation, category fluency, and higher frequency of (apolipoprotein E) ApoE ε4 allele. To examine predictors for conversion of QD to AD, the Cox regression model using the following as independent variables: CASI total score, age, sex, education, Hamilton Anxiety Rating Sclal (HARS) scores, Hamilton Depression Rating Scale (HDRS) scores and ApoE ε4 allele frequency, was applied. The converters had lower CASI (odds ratio [OR] =0.93, 95% CI: 0.89-0.92, p=0.001) and HARS scores (OR=0.91, 95% CI: 0.84-0.98, p=0.017) and higher frequency of ApoE ε4 allele (OR=3.30, 95% CI: 1.61-6.79, p=0.001) at the baseline.

In recent years, the concepts and definition of MCI is getting lucid, especially in amnestic MCI. A decline in memory function is typically a benchmark of amnestic MCI and early AD. As the medial temporal lobe is important for memory integrity, medial temporal structures are the earliest and most extensively involved brain areas identified in postmortem AD pathology studies[9]. MRI imaging is useful for longitudinally measuring atrophy of medial temporal structures throughout the lifetime of the diseases[10].

From August 1999 to July 2003, we conducted a prospective study to evaluate the correlations of ApoE genotype, cognitive performance, medial temporal structure volumes, and clinical outcome in MCI[11]. All MCI patients fulfilled Petersen's criteria of amnesic MCI 2:1) memory complaint, preferably corroborated by an informant; 2) objective memory impairment; 3) normal general cognitive function; 4) intact daily living activities; and, 5) did not meet dementia criteria. Furthermore, each MCI patient had a CDR score of 0.5.

In total, 20 normal control, 58 MCI and 20 mild probable AD patients were recruited during the study period. Patients with MCI had intermediate cognitive performance and hippocampal volumes between those in normal and AD groups. The frequency of ε4 carrier (E4+) was highest in the AD group (50%), followed by the MCI (26.4%) and the normal control group (20%). Combined data from the control, MCI, and AD patients demonstrated good correlation between hippocampal volumes and cognitive performance. Bilateral hippocampal volume was predictive of scores on memory and global cognitive tests (CASI and MMSE).

Fifty-eight MCI patients underwent annual clinical follow-up evaluations. The end-point of follow-up was the

occurrence of dementia. Average follow-up period was 21.9 months (range, 10.7-34.8 months; median, 24.3 months). Nineteen MCI patients (32.7%) converted to AD at a rate of 18.2% per person-year. The MCI converter (MCI-C) group was slightly older than the MCI stable (MCI-S) group (77.6 ± 4.6 vs. 75.6 ± 3.6, p=0.084). The MCI-C patients were more impaired in the total recall in the Selective Reminding test (SRT), immediate and delayed recall in the Complex Figure Test (CFT), and CASI. The hippocampal volumes were significantly smaller in the MCI-C group compared with those in the MCI-S group (p=0.023, for bilateral hippocampi). The (4 carrier frequency was 33.3% in the MCI-C group and 22.9% in the MCI-S group (X^2=0.671, p=0.413). Both cognitive performance and hippocampal volume were predictive for progression to AD. However, stepwise Cox regression model integrating both neuropsychological and radiological variables showed that global cognitive performance was the only significant predictor for AD. A poor global cognitive score may be more crucial than a small hippocampal volume in the prediction of AD.

With rapidly expanding research on MCI and dementia worldwide, we are looking forward to seeing the integration in neurobiology, neuroimaging, and neurobehavior fields to establish a multidisciplinary approach to MCI and dementia. This also is the goal of our future research.

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Neurobiological Studies of Dementia - Biological Markers and Neuroprotective Strategies for Alzheimer Disease

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ABSTRACT

Tau protein and amyloid s (Aβ), two major components of neuropathology in Alzheimer disease (AD), have been applied for establishment of more useful biomarkers and therapeutic approaches. Total tau protein in CSF is a biomarker for AD, however increased levels of total tau in CSF were also observed in other neurological disease with dementia. Phosphorylation is an important feature of tau protein and phosphorylated tau in CSF is useful to distinguish AD from other disease. Aβ has toxic effects on neuronal cells, and its mechanisms are complicated. One of mechanism of Aβ-cytotoxicity is a down-regulation of XIAP, and this effect

is observed in the low concentration of Aβ. XIAP might be a therapeutic target employing compounds that increase expression of XIAP in neuronal cells.

Key Words: Dementia, Alzheimer's disease, Biomarker, Tau protein

INTRODUCTION

Senile plaques (SP) and neurofibrillary tangles (NFT) are neuropathological hallmarks of Alzheimer disease (AD), and amyloid β (Aβ) and abnormally hyperphosphorylated tau protein are major protein components of SP and NFT, respectively. In this review, neurodegenerative processes in AD are focused and the approaches in establishment of biomarkers for AD, and therapeutic treatment for it are described.

Phosphorylated and other modified tau as a biomarker

Tau protein is abundant in NFT-bearing neurons in AD brain. This pathological observation has been applied for establishment of biomarker for AD. Assays of total tau in CSF have been first reported by Vandermeeren et al, and total tau in CSF is increased in AD[1]. However, increased levels of total tau in CSF were also observed in other neurological disease with dementia; corticobasal degeneration, frontotemporal dementia, Creutsfeldt-Jacob disease, and normal pressure hydrocephalus[2-5]. To overcome this situation, modified types of tau protein have been employed as diagnostic markers. As mentioned above, phosphorylation is a characteristic modification of tau in AD brain. Employing specific antibodies against phosphor-epitopes of tau protein, AT270 (against phoshorylated Thr181), CP9 (against phoshorylated Thr231), anti-PS199 (against phoshorylated Ser199), and PHF-1 (against
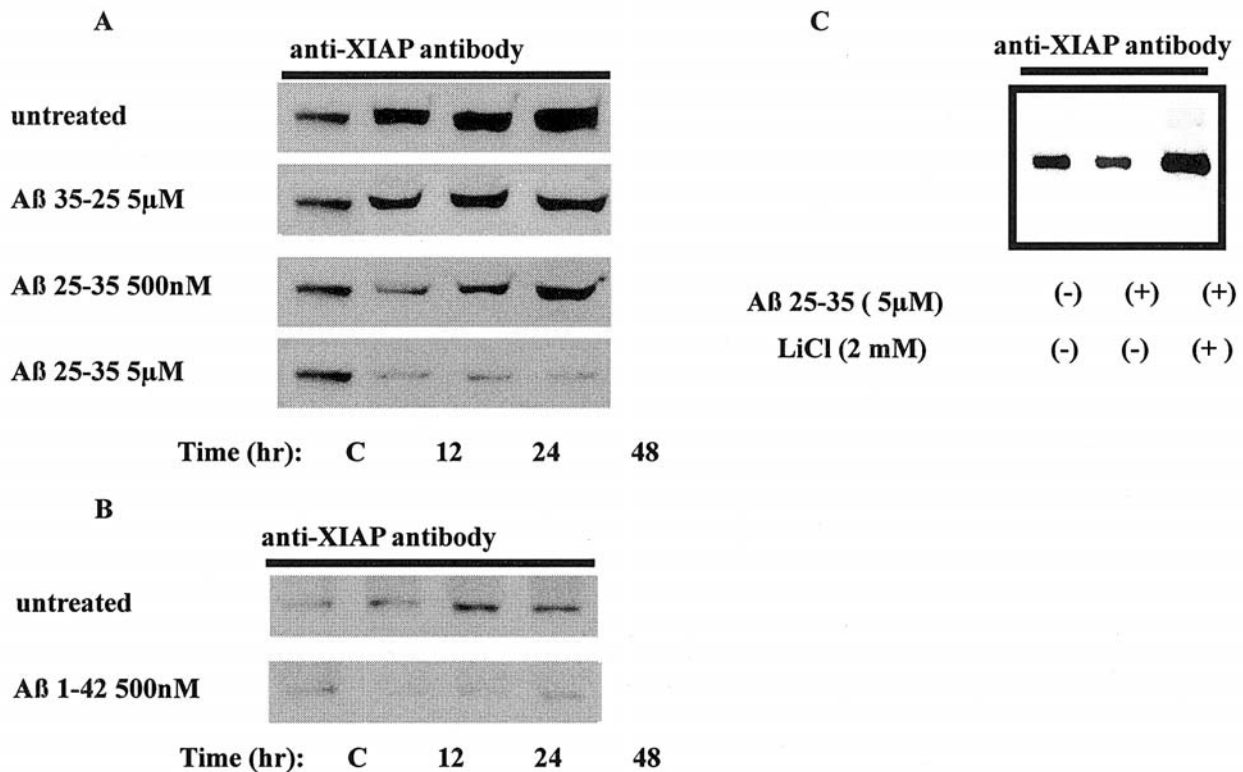
Figure. Effects on expression of XIAP by Amyloid β (Aβ) and lithium (A) SH-SY5Y cells were treated with 500nM and 5μM of Aβ25-35 and 5μM of Aβ35-25 (reverse peptide as control) for the indicated number of hours. Decreased expression of XIAP was observed in cells treated with 500nM and 5μM of Aβ25-35. (B) SH-SY5Y cells were treated with 500nM fibrillar Aβ1-42 for the indicated number of hours. Decreased expression of XIAP was observed in cells treated with fibrillar Aβ1-42. (C) SH-SY5Y cells were cultured in the presence of 5μM of amyloid β25-35 or in the presence of combination of 5μM of amyloid β25-35 and 2 mM lithium chloride. Decreased expression of XIAP was observed in cells treated with amyloid β25-35, however this effect was converted by lithium chloride.

phoshorylated Ser396/404), phosphorylated tau in CSF has been assayed by Blennow et al[6], Hampel et al[7], Ishiguro et al[8,9], Wang et al[10], respsctively. These assays have been shown to have higher specificities and sensitivities, compared to the total CSF-tau assay, probably because the phosphorylation, is based on neurodegenerative process of AD. Probably many other biomarkers for AD will appear in future and hopefully those biomarkers will be employed for early detection of AD and specific diagnosis of AD. Mild cognitive impairment (MCI) is one of recent clinical topics in AD research, and converters of MCI to AD might be distinguished by those useful biomarkers in future.

Amyloid toxicity and therapeutic approach

Several hypothesized mechanisms have been shown to explain the amyloid toxicity, and reactive oxygen species are thought to be one of mediators of apoptosis. In experimental cultures of neurons exposed to Aβ, dying cells display the characteristics of apoptosis. However, the Aβ concentration that leads to apoptosis is much higher (10~25 μM) than the physiological concentration (nM order). Apoptosis is regulated by several gene products which include the members of the caspase family, Apaf-1, the Bcl-2 family, and the inhibitor of apoptosis (IAP) family. Members of the IAP family are intrinsic cellular suppressors of apoptosis and are represented by highly conserved members found in a wide range of locations, from insect viruses to mammals. The most potent human IAP is the X-linked inhibitor of apoptosis (XIAP). Previously it was found that subtoxic, high physiological concentrations of Aβ increases vulnerability to oxidative stress, at least in part through an increase in the expression ratio of Bax/Bcl-2[11], therefore the effects of subtoxic concentrations of Aβ on the expression of XIAP were investigated[12]. SH-SY5Y human neuroblastoma cells were exposed to Aβ and there was no significant difference in cell death in cells treated with Aβ25-35 (500 nM ~ 5 μM), Aβ35-25 (reverse peptide) (500 nM ~ 5 μM), fibrillar Aβ1-42 (500 nM), Aβ42-1 (500 nM), and untreated cells up to 48 hours. To determine whether XIAP expression is involved in the Aβ-induced neurotoxic mechanism, the expression level of XIAP protein in SH-SY5Y cells exposed to Aβ was investigated by western blotting. Treatment cells with Aβ25-35 (500 nM), Aβ25-35 (5 μM), fibrillar Aβ1-42 (500 nM) reduced XIAP protein levels compared to cells treated with reverse peptide and untreated cells (Fig.1 A, B). Further study revealed that XIAP expression is involved in the mechanism of this Aβ-induced increase in vulnerability to oxidative stress. Briefly, increased numbers of cell death were observed in cells pretreated

with Aβ25-35 (5 μM) and fibrillar Aβ1-42 (500 nM) for 48hr and then submitted to low oxidative stress levels, using 0.5 μM H_2O_2. In contrast, the cells treated with the control peptide Aβ35-25 (5 μM) do not show increased sensitivity to such low levels of oxidative stress. Then the feature of decreased expression of XIAP was applied as a target of therapeutics. SH-SY5Y cells were cultured in the presence of Aβ25-35 (5 μM) or in the presence of combination of Aβ25-35 (5 μM) and lithium chloride (2 mM). Decreased expression of XIAP was observed in cells treated with Aβ25-35, however this effect was converted by lithium chloride (2 mM) (Fig. 1C). This result suggests that drugs that increase expression of XIAP might be useful therapeutics for attenuation of Aβ-induced cytotoxicity or vulnerabiliry.

CONCLUSION

Tau protein and Aβ are two major components of neuropathology in AD. Phosphorylation and other protein-modifications are important features of tau protein and CSF tau has been applied for biological marker for AD. In future these modified tau protein will be employed as a common diagnostic marker for AD, and in more earlier stages including MCI these markers will be helpful for prediction of conversion to real AD. Aβ has toxic effects on neuronal cells, and its mechanisms are complicated. One of the mechanisms of Aβ-cytotoxicity is a down-regulation of XIAP. This effect might be applied for therapeutics employing compounds that increase expression of XIAP in neuronal cells. In summary, based on the neurodegenerative mechanisms of AD, establishments of more useful biomarkers and more therapeutic compounds are required.

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