

Dementia in Taiwan: Past, Present, and Future

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Abstract- The percentage of Taiwanese aged 65 years and older has been increasing over the past 27 years, from 4.1% in 1980 to 10.2% in 2007. Studies on the Taiwan population have shown that the prevalence of dementia is approximately 1.7 - 4.3% among aged people, and that the most common cause of dementia is Alzheimer's disease (AD). However, compared to Western countries, this is a low prevalence rate, which might be due to the simple lifestyle led by aged Taiwanese, a selective higher mortality rate in Taiwanese, and a low prevalence of the APOE4 allele in Taiwanese. The current evaluation of dementia in Taiwan derives from several reliable and valid cognitive and behavioral assessment tools originally developed in Western countries. These tools are not only useful for clinical evaluation, but also have offered a method for possible cross-cultural assessment. Behavioral and psychiatric symptoms of dementia in Taiwan have been shown to be similar to other ethnic groups, except for a relative high prevalence of apathy. Although three cholinesterase inhibitors and one glutamate NMDA receptor antagonist are available in Taiwan to treat dementia, their insurance reimbursement is strictly regulated and only a small proportion of patients with AD receive medical treatment. A local consensus of and guideline for diagnosis and treatment of dementia is needed in Taiwan.

Key Words: Alzheimer disease, Cross-cultural study, Dementia, Taiwan

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INTRODUCTION

The percentage of aged persons (≥ 65 years old) in the total population has risen continuously over the past 27 years from 4.1% in 1980 to 6.1% in 1990 to 8.6% in 2000 to 10.2% in 2007⁽¹⁾. The estimated average life expectancies in 2007 were 81 for women and 75 years for men. The declining birth rate and increasing life expectancy has resulted in an increasing burden on care

facilities and services for the aged in Taiwan. Therefore, dementia has become a major public health problem in Taiwan.

Looking back over the past 20 years, the knowledge learned from dementia studies in Taiwan is enormous. It is important to reflect on our past accomplishments as we work to create a better future in understanding dementia. In this article, we will review the past three decades of dementia studies in Taiwan, dis-

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Discuss the current status of dementia in the aged, and project future directions for dementia care in Taiwan.

EPIDEMIOLOGICAL STUDIES OF DEMENTIA IN TAIWAN

1. Prevalence and incidence

Several epidemiological studies have shown that the prevalence of dementia in Taiwan is between 1.7% and 4.3% in adults aged 65 or more years⁽²⁻⁷⁾ (Table). All of these studies have shown that the prevalence of dementia increases with age and is higher among women than among men. The prevalence of dementia in Taiwan has been shown to be quite similar to that reported in mainland China, which also demonstrates a range from 1.1% to 4.6%⁽⁸⁻¹¹⁾. However, the reported prevalence rates of dementia in Europe and the US are higher, ranging from 5% to 10%⁽¹²⁻¹⁶⁾.

The subjects of dementia and differences in dementia across ethnic groups have generated interest recently. Conclusions of ethnic differences in dementia are quite controversial, as it is difficult to compare findings across studies due to differences in methodology and diagnosis. However, if ethnic differences do exist, they may be due to racial genetic factors, shared cultural practices, or common environmental factors. The low prevalence of dementia in persons of Chinese descent might be due to underreporting of data, a selectively high mortality rate, or the low prevalence of the apolipoprotein E (ApoE) 4 allele in Chinese populations⁽¹⁷⁾.

The diagnostic criteria of DSM-IV⁽¹⁸⁾ require that the diagnosis of dementia fulfill the specific criterion of significant impairment in social or occupational functioning. However, because aged Chinese are frequently freed from household responsibilities, their family members

may not identify any decline until the condition is severe; therefore, the prevalence of dementia might be underreported. Ross et al.⁽¹⁹⁾ found that more than 60% of their Asian participants identified as having dementia via a survey either were not recognized by their family informants to have a memory concern or were not medically evaluated for this concern. As these study participants were Japanese-American and as Japanese culture is known for its respect for the aged, Ross et al.⁽¹⁹⁾ hypothesized that family members of demented participants denied mild cognitive deficits out of respect for this cultural tradition. Similar to the Japanese culture, the Chinese culture is also known for respecting its aged and thus the Taiwanese may fail to recognize or report mild cognitive deficiencies in their aged. Additionally, traditional Asian populations have low expectations of their aged and subsequently treat memory decline as a normal part of the aging process. Thus, when epidemiological surveys rely mostly on informants' report, they might underestimate the prevalence of dementia. Two studies using extensive cognitive testing in Chinese populations have reported high dementia rates^(7,10); however, it cannot be ruled out that these high rates may have been due to high false-positive rates in populations with low education.

Two population-based studies in Taiwan reported mortality rates ranging from 32% to 48% in patients with dementia^(5,20). One hospital-based study showed a mean survival time for AD patients at 4.48 years (SD = 0.1 years) from time of enrollment⁽²¹⁾. These rates are higher than most Western reports⁽²²⁾. Since prevalence rates are a function of disease incidence and disease survival, selectively high mortality rates found in Taiwanese dementia patients might have produced low prevalence rates.

Table. Prevalence of dementia among persons ≥ 65 years in studies conducted in Taiwan

Authors, Year	Site	Sample size	Prevalence of dementia (%)	Predominant type of dementia
Rin H, 1987 ⁽²⁾	Rural	1586	1.7%	Vascular dementia
Liu HC, 1988 ⁽⁶⁾	Rural/Urban	1469	2.0%	Alzheimer's disease
Yip PK, 1991 ⁽³⁾	Urban	1038	1.9%	Not available
Liu HC, 1993 ⁽⁵⁾	Rural	1764	2.6%	Alzheimer's disease
Liu CK, 1993 ⁽⁷⁾	Urban	1016	4.3%	Alzheimer's disease

Because incidence rates better reflect true rates of disease occurrence, comparing incidence rates among different populations might provide more accurate information regarding differential risk factors. The annual incidence of dementia among those aged 65 or more years in Taiwan is 1.3%, with incidence risk increasing with age from 0.77% for those aged 65 to 74 years to 6.19% for those aged 85 or more years⁽²⁰⁾. The incidence of dementia in Taiwan is similar to that in mainland China (1.2%)⁽²³⁾, but lies on the lower end of the range reported in Western countries (1.3-2.5%)⁽²⁴⁻²⁸⁾. Interestingly two additional incidence studies from Asia, one from Japan⁽²⁹⁾ and one from India⁽³⁰⁾ also report low rates of dementia. This implies that a difference in the incidence of dementia might exist between the East and West. APOE genotype is a strong and consistent risk factor for non-familial Alzheimer's disease (AD)⁽³¹⁻³⁵⁾. Genotypes containing the $\epsilon 4$ allele are associated with an increased risk of AD in many ethnic groups, including Chinese⁽¹⁷⁾. Two studies conducted in Taiwan demonstrated an association between the $\epsilon 4$ allele and AD, but not between the $\epsilon 4$ allele and vascular dementia (VaD)^(36,37). The frequency of the $\epsilon 4$ allele was lower among Chinese populations (4.8-11.0%)⁽³⁸⁻⁴⁰⁾ than among Western populations (9.0% to 16.5%)⁽³²⁻³⁵⁾. The lower frequency of the $\epsilon 4$ allele might be one factor contributing to the low prevalence of dementia in Taiwan.

2. Type of dementia

With the exception of a single study in Beijing⁽⁸⁾, AD was the most common cause of dementia in community-based studies of Chinese populations⁽⁵⁻⁷⁾, as is true in Western populations. Two hospital-based studies found higher frequencies of VaD than AD in Taiwanese patients^(41,42). One community study demonstrated a predominance of woman with AD, and a predominance of men with VaD⁽⁷⁾. Some authors have attributed this gender discrepancy to the likelihood that stroke patients are more likely to be brought to hospitals. Thus, at present it is not certain whether AD is the leading cause of dementia in Taiwan^(41,42). Since neuroimaging plays a critical role in the diagnosis of VaD, the low ratio of VaD found in the community study might be due to lack of brain

imaging data. The higher mortality rate of patients with VaD compared to patients with AD might also partly contribute to low prevalence data for VaD⁽²⁰⁾.

3. Risk factors of dementia

In addition to the $\epsilon 4$ allele of the APOE gene, age and low education are two confirmed risk factors of dementia in Taiwan⁽⁶⁾. The older one is, the greater is the probability of dementia. Two hypotheses for the putative underlying mechanisms of the association between low education and high risk of dementia have been put forth. The first hypothesis states that people with low levels of education are more likely to lead unhealthier lifestyles, suggesting that both factors may concurrently contribute to dementia or AD. The second hypothesis states that highly educated people are likely to have a greater cognitive reserve, thus postponing negative effects of dementia. Two (99m)Tc-hexamethylpropyleneamine oxime brain SPECT studies have demonstrated an influence of education on regional cerebral blood flow (rCBF) in AD patients; however, the disparate results revealed different directions of that influence^(43,44). One study reported that patients with more years of formal schooling demonstrated lower cerebral perfusion but higher cognitive test scores among the patients with less years of schooling but similar degree of dementia⁽⁴³⁾. The second study reported that patients with higher educational levels demonstrated relatively higher basal rCBF in specific brain areas than did the patients with lower educational levels⁽⁴⁴⁾. Both studies used the brain reserve hypothesis to explain their results. The first study⁽⁴³⁾ supported a negative cognitive reserve view, suggesting that the increased rCBF represented the brain actively attempting to cope with, or compensate for, pathology and the second study⁽⁴⁴⁾ supported a neural reserve view, suggesting that preexisting brain networks that are more efficient, or have greater capacity, may be less susceptible to disruption. Further research is still needed to clarify the potential underlying mechanisms contributing to the education/dementia association.

Two additional studies suggested other factors increasing risk for dementia; one study conducted in Taiwan found that light smoking demonstrated a

decreased risk for AD (AD: 2.0%, controls: 21.4%, odds ratio = 0.10, $p = 0.003$), whereas daily smoking demonstrated a trend toward increased risk for AD (AD: 45.9%, controls: 26.5%, odds ratio = 1.73, $p = 0.08$)⁽⁴⁵⁾. A recent case-control study demonstrated a J-shaped relationship between body mass index (BMI) at midlife and dementia⁽⁴⁶⁾.

4. Neuropsychological measurements of dementia in Taiwan

Most of the instruments used for screening Chinese populations are adapted from the original versions developed in the West. One of the major challenges to studying dementia in Chinese communities is to select a screening instrument for dementia that is translated into the local dialect, is culturally appropriate, and is suitable for testing in both illiterate and literate individuals. It has been suggested that questions from the dementia assessment tools should be modified to culturally appropriate circumstances and that scoring methods should be maintained as in the original version⁽⁴⁷⁾. Since many aged persons in Taiwan are illiterate, the assessment of dementia has to consider illiteracy as a factor influencing dementia scores, in addition to language and cultural factors. In this review, we introduce the commonly used neuropsychological measurement for dementia in Taiwan, the Mini-Mental State Examination (MMSE).

(1) The MMSE

The MMSE is the most widely used screening instrument for detecting dementia⁽⁴⁸⁾ and as such many versions are available in various languages. The MMSE is currently the most popular screening instrument for dementia in Taiwan. Several Chinese versions of the MMSE have been developed and validated⁽⁴⁹⁻⁵¹⁾. Although most versions preserve the original structure, some differences exist in terms of neuropsychological and procedural aspects of the test. As examples, in one of the Taiwanese versions, a novel 7-character Chinese phrase was used in place of the original 5-word repetition phrase “no ifs, ands, or buts,” and “hand it back to me” was used instead of “put it on the floor” for the last part of the three-step command⁽⁵⁰⁾. In the Chinese version

of the MMSE in China, two items were modified⁽⁴⁹⁾: the repeated phrase “no ifs, ands, or buts” was substituted with a famous Chinese alliteration “44 stone lions” and “say a sentence” was substituted for “write a sentence.”

(2) The Informant Questionnaire on Cognitive Decline in the Elderly

The IQCODE is a 26-item questionnaire that asks the informant about cognitive changes that may have occurred in everyday cognitive functions over the previous 10 years^(51,52). In our previous study, the IQCODE was found to perform better than the MMSE as a screening test for dementia in a population with a large variation in educational background⁽⁵²⁾. Nevertheless, the outcome of both tests was no different in illiterate individuals. Therefore, the IQCODE and MMSE perform similarly among participants with similar educational backgrounds, but the IQCODE outperforms the MMSE among participants of varied educational backgrounds, like in most Asian countries⁽⁵²⁾. However, a major concern of the IQCODE was that the validity of this questionnaire assumes objectiveness and honesty on the part of the informant; variations from this assumed integrity can bias the results.

(3) Alzheimer’s Disease Assessment Scale (ADAS-Cog)

Since its publication in 1984, the ADAS-Cog has become the instrument most widely used in the follow-up of AD, including the efficacy of dementia medications in drug trials⁽⁵³⁾. ADAS-Cog contains 12 subtests: word recall; naming (objects and fingers); following commands; constructions (drawing); ideational praxis; orientation; word recognition; recall of test instructions; spoken language ability; word-finding difficulty and comprehension of spoken language; assessing memory; praxis and language. The Chinese version of ADAS-Cog was developed in 2002 with one adaptation: a picture recall test replaced the word recall test of the original version⁽⁵⁴⁾. The Chinese ADAS-Cog has demonstrated high internal consistency (Cronbach’s alpha = 0.87), very high interrater reliability (intraclass correlation coefficient, or ICC, = 0.99) and high test-retest reliability.

ty (ICC= 0.96). Scores from the Chinese ADAS-Cog have demonstrated high correlations with scores from the Clinical Dementia Rating Scale ($r= 0.85$), with scores from the Cognitive Abilities Screening Instrument (CASI) ($r= -0.88$), and with cognitive abilities screening instrument CASI-estimated scores on the MMSE ($r= -0.85$).

(4) Cognitive Abilities Screening Instrument CASI

The CASI is a cross-culturally validated neuropsychological test that consists of nine domains: long-term memory; short-term memory; attention; concentration and mental manipulation; orientation; visual construction; abstraction and judgment; list-generation fluency; and language^(55,56). Scores from the MMSE, the Modified MMSE, and the Hasegawa Dementia Screening Scale can be estimated from various subsets of the nine CASI domains. The scores of CASI range from 0 to 100. Typical administration time is 15 to 20 minutes. The cut-off scores for the diagnosis of dementia using the CASI are chosen according to different educational levels. (educational years = 0: 49/50 (sensitivity = 0.83; specificity = 0.85); educational years = 1-5: 67/68 (sensitivity = 0.83; specificity = 0.91), and educational years ≥ 6 : 79/80 (sensitivity = 0.89; specificity = 0.90))⁽⁵⁷⁾. Some investigators have proposed a new scoring system for CASI to improve dementia screening ability⁽⁵⁸⁾. It has been found that short-term memory and orientation were the two most relevant domains and that their combined score is more effective than the total score in screening dementia.

5. Behavioral and psychological symptoms of dementia (BPSD)

In addition to cognitive disturbances, behavioral and psychiatric symptoms of dementia (BPSD) are very common. Hwang et al.⁽⁵⁹⁾ reported a higher frequency of BPSD in psychiatric inpatients with AD in Taiwan compared with western countries. However, most studies in Taiwan do not support this result^(60,61). It is very difficult to perform comparative assessments of BPSD since studies are conducted in different clinical settings. Psychiatric inpatients might have a higher frequency of

behavioral disturbance than outpatients, especially in neurological clinic samples. Besides this, the definition of BPSD was different among studies. Since behavioral disturbances are related to cognitive impairment^(59,62), the levels of cognitive impairment of the recruited patients in studies influence the prevalence of BPSD.

Although it was hypothesized that Chinese participants would exhibit more severe symptoms of dementia at time of diagnosis due to the perceived delay in seeking medical care (only after noting behavioral changes), this hypothesis has not been supported⁽⁶⁰⁾. In terms of neuropsychiatric symptoms, a transcultural study showed that Chinese caregivers reported anxiety and delusions as the major symptoms exhibited in their dementia patients more frequently than whites, and whites reported appetite changes and apathy more frequently as the major symptoms exhibited in their dementia patients than the Chinese sample⁽⁶⁰⁾. Since the same procedural methods were used for assessment of the dementia patients, genetic or sociocultural factors might play a role in these differences expressed by caregivers. In addition, different prevalence rates of BPSD might exist across different ethnic groups. Finally, cultural or genetic factors might also influence the other neuropsychiatric manifestations that are exhibited in agitated patients with dementia. We studied three culturally diverse ethnic groups of dementia patients, Taiwanese, Italians, and Americans, and found that all three groups of dementia patients demonstrated a high rate of agitation⁽⁶³⁾. However, agitation was significantly associated with hallucinations in Taiwanese patients and was significantly associated with apathy in Italian patients. These findings imply that an underlying neurobiological change is important in the manifestation of agitation in dementia patients since the high rate of agitation was found uniformly across the different ethnic groups studied. Nevertheless, a sociocultural factor might be superimposed on the underlying neurobiological change since the manifestation of agitation did differ across the various ethnicities of dementia patients studied.

In our study, we found a lower prevalence rate (44%) of apathy in Taiwanese patients with dementia than in those previously reported in white populations

(72%)^(64,65). Chinese culture does not evaluate passive behavior in an aged person as being negative. The interpretation of behavioral change is culturally dependent, and caregivers might report apathy less frequently in Chinese dementia patients than in other ethnic groups. Nevertheless, euphoria was the least frequently recorded behavior among the three ethnic groups studied, suggesting that some behaviors might have a common underlying neuropathy, while others might be related to cultural or environmental factors.

6. Treatment of dementia in Taiwan

Currently, three kinds of acetylcholinesterase inhibitors (AChEI), donepezil, rivastigmine and galantamine, are approved for treatment of mild to moderate AD in Taiwan. One kind of glutamate NMDA receptor antagonist, memantine, is licensed for treatment of moderate to severe AD in Taiwan. Pharmacological therapy for dementia with AChEIs and NMDA receptor antagonists has been covered by insurance from the Bureau of National Health Insurance (BNHI) since 2000. Nevertheless, strict payment regulations, including mandatory prior authorization for all new cases and a reauthorization every 6 months for all continuing cases, are in force. Only neurologists and psychiatrists have the privilege of prescribing these medications, and patients must be followed with updated MMSE or Clinical Dementia Rating (CDR) assessments. Treatment is to be discontinued if, when compared to baseline, a decrease in MMSE score of two or more points or an increase in CDR score of one or more points is noted. According to a 2000-2002 survey only 66.5% to 72.6% of prior authorization cases were approved⁽⁶⁶⁾. Although an appeals system through the Dispute Mediation Committee (DMC) is available to argue denials of prior authorization by the BNHI, the majority of the appeals (111 [89.5%]) thus far have upheld the BNHI denial decision⁽⁶⁶⁾. The majority of the appeals have been denied due to lack of appropriate exclusionary data of other possible causes of dementia. Another survey has shown that the average duration for AChEI therapy is approximately 14 months and that only 9.6% of patients have maintained stable cognition assessments resulting in continued drug

refills for more than three years⁽⁶⁷⁾. The results from these surveys demonstrate that only a small proportion of AD patients in Taiwan receive licensed medical treatment, suggesting that knowledge of drug treatment efficacy and validity of diagnosis are still lacking in Taiwan.

CONCLUSION

The impact and burden of dementia in Taiwan will worsen, and the need for long-term care will increase as the population continues to age and the island continues to industrialize. A consensus must be reached to balance health economics and clinical practice. The development of culturally appropriate evaluation tools is a necessity, as is the establishment of a guideline for the diagnosis and treatment of AD.

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