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Editor's Note

Linda Lam

Welcome to the Summer issue of HKPGA Newsletter. In this issue, you will find an inspiring article from Prof Gary Small, who gives us a comprehensive and updated review of the "Brain Imaging Surrogate Markers for Detection and Prevention of Cognitive Aging and Alzheimer's Disease". Meanwhile, Prof SF Xiao and Prof MY Zhang summarize the recent advances in one of the most important topics in old age psychiatry- Mild Cognitive Impairment. Both articles focus on early detection and intervention of memory problems and have significant implications to our practice. Besides, we are delighted to receive Ms Daphne Law's interesting report on the recent ADI Conference in New Zealand. Don't miss the abstracts of the award-winning projects of Drs Teresa Chan and WK Tang especially if you are interested in entering the HKPGA Research Awards Competition this year. Please enjoy these special articles in addition to the regular contributions from our members. Lastly, you are very much welcome to contribute to the Newsletter by passing your articles to hkpga@hongkong.com. Looking forward to hearing from you.

Brain Imaging Surrogate Markers for Detection and Prevention of Cognitive Aging and Alzheimer's Disease

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ABSTRACT

Recent evidence points to the importance of neuropathological and cognitive changes preceding Alzheimer's disease, and clinical trials have begun to focus on preventive treatments designed to slow age-related cognitive decline and delay the onset of Alzheimer's disease. Studying subjects with few deficits leads to diagnostic heterogeneity and a need for larger samples in order to detect active drug effects. In this report, I review results of recent studies designed to address such issues. Middle-aged and older adults with mild memory complaints were studied using brain imaging and measures of the major known genetic risk for Alzheimer's disease, the apolipoprotein E-4 (APOE-4) allele. In a study of positron emission tomography during mental rest, glucose metabolic rates were significantly lower in APOE-4 carriers in brain regions affected by Alzheimer's disease. Another study using functional magnetic resonance imaging showed increased brain activation during memory tasks in APOE-4 carriers in similar brain regions. Longitudinal follow-up after two years indicated the potential utility of such brain imaging measures, combined with genetic risk information, as surrogate markers in prevention treatment trials for cognitive aging and Alzheimer's disease. Current development focuses on novel technologies using positron emission tomography to directly image the neuritic plaques and neurofibrillary tangles of Alzheimer's disease in order to provide more specific measures of disease progression in future clinical trials.

KEY WORDS: Alzheimer's disease, apolipoprotein E, positron emission tomography, cerebral glucose metabolism

INTRODUCTION

In 1906, the German psychiatrist and neurologist Alois Alzheimer first described a middle-aged patient who had suffered from a progressive dementia affecting language, memory and behavior. After the patient's death at age 55 years, Alzheimer applied new staining techniques to the patient's brain tissue and demonstrated the presence of what is now termed neurofibrillary tangles and neuritic plaques in the neocortex and other brain regions. For years, Alzheimer's disease (AD) was considered a presenile dementia, partially because some plaques and tangles occurred in elderly persons without dementia and some elderly persons with dementia had few plaques and tangles. Such conflicts were resolved, however, in the late 1960s, when the degree of dementia was shown to correlate with the number of neuritic plaques in neocortical association areas. Moreover, causes of senile dementia other than Alzheimer's disease were recognized.

During the last decade, clinicians and investigators have focused greater attention on the transition between the normal age-related changes that developed in the brain and the neuropathological and clinical features of AD. Gradual progressive memory loss precedes clinically diagnosed AD. Findings of neuritic plaques (NPs) (Price and Morris, 1999) and neurofibrillary tangles (NFTs) (Braak and Braak, 1991), the neuropathological hallmarks of AD, in adults without dementia suggests that the neuronal deficits leading to AD begin years before any clinical changes. New and developing anti-dementia treatments focus on slowing disease progression rather than reversing neuronal death, emphasizing the importance of identifying early markers of future cognitive decline.

Studies searching for genetic risks for AD have identified an association between the apolipoprotein E-4 (APOE-4) allele on chromosome 19 and the common form of AD that begins after age 60 years (Saunders et al., 1993). APOE has three allelic variants (APOE-2, APOE-3, and APOE-4) and five common genotypes (2/3, 3/3, 2/4, 3/4, 4/4). The APOE-4 allele has a dose-related effect on increasing risk and lowering the age of onset of late-onset familial and sporadic AD (Saunders et al., 1993; Corder et al., 1993), while APOE-2 appears to confer protection (Corder et al., 1994). Although the APOE-4 allele may have a modest effect in predicting cognitive decline in older persons, APOE genotype alone is not considered a useful predictor in non-demented people (Relkin et al., 1996).

Several brain imaging techniques have been used to track brain changes through the course of AD, as well as various preclinical stages. Structural magnetic resonance imaging (MRI) in normal older persons may show medial temporal atrophy and predict future cognitive decline (Golomb et al., 1996); cerebral atrophy, however, is seen only after substantial cell death. Positron emission tomography (PET) studies of glucose metabolism during mental rest have identified parietal, temporal and prefrontal deficits in glucose metabolism in normal middle-aged APOE-4 carriers (Small et al., 1995; Reiman et al., 1996), who are not likely to develop the disease for decades.

In activation imaging, investigators compare brain activity while subjects perform a task relative to a control or resting state. This approach reveals more subtle

alterations in brain function, perhaps before the emergence of mild memory impairments. Activation PET studies, using cognitive and passive stimuli, have revealed more wide-spread brain activity among patients with AD compared with age-matched normal subjects (Grady et al., 1993; Mentis et al., 1996; Backman et al., 1999). Like PET, functional MRI provides measures of signal intensity associated with relative cerebral blood flow during memory or other cognitive tasks (Gabrieli et al., 1997), but has the advantages of high resolution in space and time and lack of radiation exposure. The MRI signal intensity associated with a particular task in comparison with the control condition reflects relative blood flow and consequently neural activity, though indirectly (Fox and Rachle, 1986; Ogawa et al., 1992; Kwong et al., 1992).

This report summarizes recent findings from PET and functional MRI in middle-aged and older adults with mild memory complaints. These studies show a pattern of brain activity that differs according to genetic risk that may be useful in future clinical trials of drugs designed to prevent age-related cognitive decline.

Cerebral Metabolic and Cognitive Decline in APOE-4 Carriers

To determine cognitive and metabolic decline patterns according to genetic risk, Small et al. (2000) investigated cerebral metabolic rates using positron emission tomography (PET) in middle-aged and older non-demented persons with normal memory performance. Subjects were right-handed and in the 50 to 84 year age range. Of the 54 subjects with mild memory complaints, 27 were APOE-4 carriers and 27 were non-carriers. A single copy of the APOE-4 allele was associated with lowered inferior parietal, lateral temporal, and posterior cingulate metabolism, which predicted cognitive decline after two years of longitudinal follow-up. For the 20 non-demented subjects followed longitudinally, memory performance scores did not decline significantly but cortical metabolic rates did. In APOE-4 carriers, a 4% left posterior cingulate metabolic decline was observed, and inferior parietal and lateral temporal regions demonstrated the greatest magnitude (5%) of metabolic decline after two years.

These results have practical implications for clinical trials of dementia prevention treatments. The right lateral temporal metabolism for APOE-4 carriers at baseline and two-year follow-up yielded an estimated power under the most conservative scenario (i.e., assuming that the points are connected exactly in reverse order) of 0.9 to detect a 1-unit decline from baseline to follow-up using a one-tailed test. A sample size of only 20 subjects, therefore, would be needed in each treatment arm (i.e., active drug or placebo) to detect a drug effect size of 0.8 (É— = 0.05, power = 0.8). Thus, a clinical trial of a novel intervention to prevent cerebral metabolic decline would require only 40 subjects over a two-year treatment period. Such findings are consistent with previous PET studies showing stable and replicable results (Andreasen et al., 1996) and suggest that combining PET and AD genetic risk measures will allow investigators to use relatively small sample sizes when testing anti-dementia treatments in preclinical AD stages. These results indicate that the combination of cerebral metabolic rates and genetic risk factors provides a means for preclinical AD detection that will assist in response monitoring during experimental treatments. Reiman and co-workers (2001) recently replicated these results in an independent sample.

Brain Activation During Memory Tasks in People at Genetic Risk

To determine the relationship between brain responses to memory tasks and genetic risk for Alzheimer's disease, Bookheimer et al. (2000) performed APOE genotyping and functional magnetic resonance imaging (MRI) while cognitively intact older persons performed memory tasks. The study included 30 subjects aged 47 to 82 years with mild memory complaints but normal memory performance, of whom 16 were APOE-4 carriers and 14 were not. The age and prior educational achievement in the two groups were similar. Brain activation patterns were determined from functional MRI scanning while subjects memorized and recalled unrelated word pairs. Memory performance was reassessed on 14 subjects two years later. The magnitude and spatial extent of brain activation during memory performance in regions affected by Alzheimer's disease, including left hippocampal, parietal, and prefrontal regions was greater in the subjects with APOE-4 alleles as compared with those with no APOE-4 alleles. During memory performance tasks, the APOE-4 carriers demonstrated a greater percent increase in hippocampal MRI signal intensity and a greater number of activated regions throughout the brain than did subjects without APOE-4. Longitudinal assessment after two years indicated that greater baseline brain activation correlated with verbal memory decline. These results indicate that brain activation patterns during memory tasks differ according to genetic risk for Alzheimer's disease and may provide information that eventually predicts future cognitive decline.

Preclinical Detection: Benefits and Strategies

Even though we have no cure for AD, preclinical disease detection has several potential benefits. If an early detection assessment is negative, the person with mild memory complaints can be reassured that their forgetfulness reflects a normal age-related change that probably will not progress. Many people also would like to know even a negative prognosis while they are still in a mildly impaired state in order to plan their futures while mental faculties remain. One of the most compelling arguments for preclinical detection strategies is to identify candidates for novel anti-dementia treatments before the dementing process causes extensive neuronal death since new anti-dementia treatments are more likely to delay the dementing process than to reverse neuronal death. Although current cholinergic treatments have been shown to result in symptomatic rather than disease altering or structural effects, it would certainly be of interest to initiate treatments very early when searching for a disease modifying effect. Moreover, both the expense and potential risks of treatment make it reasonable to reserve treatment only for those people who are at the greatest risk for developing the disease.

Several lines of research suggest that AD actually begins years before its clinical manifestations are obvious. The PET studies of glucose metabolism combined with genetic risk assessment show regional glucose abnormalities in middle-aged persons with the APOE-4 allele (Small et al., 1995, 2000; Reiman et al., 1996). Studies of structural images suggest that regional atrophy of hippocampus and other medial temporal regions may be an early predictor of future cognitive decline (Golomb et al., 1996). Brain autopsy studies of normal aging and older persons with mild cognitive impairment also indicate very early, preclinical accumulation of NPs and NFTs, the neuropathological hallmarks of AD, years before a clinical diagnosis can be confirmed (Price and Morris, 1999; Braak and Braak, 1991). Finally, findings from a study of 93 nuns also support the notion of subtle preclinical functional abnormalities. In that study (35), a systemic assessment of these nuns' early autobiographies (mean age = 22 years) and their later (age 75-95) cognitive performances found that low idea density and lack of grammatical complexity in early life predicted low cognitive test scores in late life (Snowdon et al., 1996).

PET Imaging of Amyloid Senile Plaques and Neurofibrillary Tangles

Development of new small molecule probes to image the amyloid NPs and NFTs has been a research agenda for several centers during the past decade. Current methods for measuring brain amyloid, such as histochemical stains, require tissue fixation on post-mortem or biopsy material. Available in vivo methods for measuring NPs or NFTs are indirect (e.g., CSF measures) (Motter et al., 1995). Studies that may lead to direct in vivo human AÉ“Énimaging include various radiolabeled probes using small organic and organometallic molecules capable of detecting differences in amyloid fibril structure or amyloid protein sequences (Ashburn et al., 1996). Investigators also have used chrysamine-G, a carboxylic acid analogue of Congo red, an amyloid-staining histologic dye (Klunk et al., 1995), serum amyloid P component, a normal plasma glycoprotein that binds to amyloid deposit fibrils (Lovat et al., 1998), or monoclonal antibodies (Majocha et al., 1992). Methodological difficulties that hinder progress with these techniques include poor blood-brain barrier crossing and limited specificity and sensitivity. In addition, most approaches do not measure both NPs and NFTs. Recently, Barrio and colleagues (Barrio et al., 1999) reported using a hydrophobic radiofluorinated derivative of 1,1-dicyano-2-[6-(dimethylamino)naphthalen-2-yl]propene (FDDNP) (Jacobson et al., 1996) with PET to measure the cerebral localization and load of NFTs and NPs in AD patients. The probe showed visualization of NFTs, NPs and diffuse amyloid in AD brain specimens using in vitro fluorescence microscropy, which matched results using conventional stains (e.g., thioflavin S) in the same tissue specimens. Such approaches may ultimately aid in the early detection of AD and brain function monitoring during anti-dementia treatment trials, particularly those designed to interrupt accumulation of NPs and NFTs

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老年輕度認知功能損害的研究新進展 (Recent Advances in Mild Cognitive Impairment)

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Abstract

While life expectancy has been increasing steadily worldwide, an expanding elderly population has led to a rapid rise in the number of older adults suffering from dementia, a disease with a predilection for this age group. Early detection and treatment of cognitive impairment has therefore become one of the major foci in psychogeriatric research, especially with the introduction of anti-dementia medications in the past few years. However, there are controversies over the diagnosis of cognitive impairment that exceeds the changes associated with normal ageing, but does not fulfill the criteria of dementia. In this article, the authors review the evolution of the concepts of AAMI, AACD and MCI, and the diagnostic criteria, prevalence and etiologies of the latter. They also summarize the results of recent studies on pathological, neuroimaging, EEG, and neuropsychological findings related to MCI, and the treatment strategies currently under research.

隨著世界人口老齡化的加快和老年期癡呆的患病率增加，特別是近十年來治療癡呆的有效藥物的出現，使得老年輕度認知功能損害（mild cognitive impairment，MCI）越來越受到人們的重視。本文擬介紹 MCI 的概念演變和近年的研究進展。

1. 概念演變

輕度認知功能損害是 Reisberg 等[1](1988)在編制一個認知功能分級量表即總體衰退量表（GDS）時首次使用的，他們將認知功能和社會職業功能有輕度損害，但日常生活無明顯影響的老年人歸?MCI。文獻中對 MCI 的描述曾用過多個術語。

早在 1958 年[2]，Kral 提出了老年良性遺忘（benign senescent forgetfulness）的概念，其特點是在某一時刻回憶名字或往事困難，而在另一時刻又能回憶起來，有自知力，患者往往企圖彌補自己的記憶困難，記憶測驗的成績與沒有記憶困難主訴的人差不多，不會發展?癡呆。由於良性遺忘的定義不甚準確，良性與惡性的界限不清，爭議頗多。

美國國立精神衛生研究所於 1986 年提出了與年齡有關的記憶損害（age-associated memory impairment ， AAMI）並制定了研究用診斷標準[3]。AAMI 強調的是與年齡相符的記憶減退，其診斷標準中要求記憶測驗成績低於“年輕成年人”常模一個標準差，其他認知功能基本正常。因此，按常態分佈大致有 16% 的“年輕成年人”到老年後即便沒有記憶減退就可能符合 AAMI 診斷。

由於衰老不僅有記憶減退，其他認知功能也會受影響，故國際老年精神科協會（1994）提出了與衰老有關的認知功能下降（aging associated cognitive decline, AACD) [4]。AACD 與 AAMI 的區別是，不僅記憶受損，其他認知功能也受損，認知功能下降的原因可以是生理性的，也可以是病理性的。有些 AACD 是早期癡呆，而有些則與衰老有關。AACD 雖然希望改進 AAMI 的定義，但按 AACD 的定義，似乎異源性還是比較大。

鑒於上述原因，許多研究者建義制定與年齡不符的 MCI 診斷標準，認?這樣更有利於研究和交流。因此，在 ICD-10 中出現了輕度認知功能障礙（mild cognitive disorder, MCD）的診斷條目[5]，其定義是有認知功能損害，但不符合癡呆診斷標準；在 DSM-IV 中將輕度神經認知障礙（mild neurocognitive disorder, MND）作?需要進一步研究的問題提出[6]，被認?是由普通醫學疾病引起的神經認知功能損害，對社會生活功能有一定影響，但不符合癡呆診斷標準。ICD-10 和 DSM-IV 都強調 MCI 是一種病理性的認知功能損害，在診斷時需要有明確的器質性病因，這在實際使用時有一定困難。

對 MCI 的概念一直存在著爭議，爭議的焦點是：MCI 到底是生理性的還是病理性的？如何鑒別生理性和病理性 MCI？儘管爭論還將繼續，但目前大多數學者比較一致的觀點是， MCI 是介於正常衰老和癡呆之間的一種認知功能損害狀態，大部分屬病理性 MCI 將發展?癡呆， MCI 是老年期癡呆特別是阿爾茨海默病（Alzheimer's disease, AD）的臨床早期表現。

2. 診斷標準

目前尚無一致認可的 MCI 診斷標準，各種標準寬嚴不一，不少研究者還自定了一些標準。以下介紹近年發展的幾個標準。

MCD 診斷標準[5]：1.自訴或可靠的知情人認?有認知功能障礙，持續時間至少 2 周；2.認知障礙表現?至少以下之一：記憶（尤其是回憶）或學習新知識、注意、思維（如問題解決或抽象思維）、語言（如理解、找詞）、視覺空間功能；3.定量認知功能評價有異常和下降（如神經心理測驗）；4.上述認知功能障礙的程度還不足以診斷?癡呆、器質性遺忘綜合征、腦振蕩綜合征或精神活性物質引起的認知損害。

MND 研究用診斷標準[6]：A.存在下述認知功能損害至少 2 項，持續至少 2 周，期間大部分時間有症狀（自訴或可靠的知情者報告）：1.記憶損害，表現?學習或回憶能力下降；2.執行功能紊亂如計劃、組織、抽象推理；3.注意或資訊處理速度異常；4.感知運動能力損害；5.語言能力損害（如理解、找詞）。B.體檢或實驗室檢查（包括神經影像學檢查）有客觀證據表明，神經系統或普通軀體病與認知功能障礙在病因學上相關。C.神經心理測驗或定量認知評價有異常或成績下降的證據。D.認知缺損導致明顯的痛苦或引起社會、職業或其他重要功能的損害，表現?比以前的功能水平下降。E.認知障礙不符合譫妄、癡呆或遺忘障礙的診斷標準，也不能用其他精神障礙來解釋（如抑鬱障礙、與精神活性物質有關的精神障礙）。

美國羅切斯特大學醫學院的 Mayo 研究組將 MCI 定義?介於正常衰老與 AD 之間的過渡階段，並提出 MCI 的 Mayo 診斷標準（1997) [7]，具體?：1.病人自覺有記憶減退，或家屬、醫生認?病人有記憶障礙；2.總體認知功能正常；3.客觀檢查有記憶損害或有一項其他認知功能受損，記憶或認知功能受損評分低於同年齡均數 1.5 ～ 2 個標準差；4.臨床癡呆評定量表評分?0.5；5.日常生活功能正常；6.不符合癡呆診斷標準；上述定義和診斷標準比較準確，操作性較好，故使用比較多。

上海市精神衛生中心老年精神科在 1996 年制定了 MCI 診斷標準[8]， 1998 年經過修訂後如下：1.年齡 55 ～ 85 歲；2.主觀和客觀檢查有認知功能損害；3.韋氏記憶測驗的記憶商（WMS, MQ）在 60 ～ 79 分之間；4.MMSE 得分(26 分， GDS 評定?2 ～ 3 級；5.生活及社會功能有降低：日常生活能力量表（ADL）得分(18 分；6.Hachinski 缺血指數<4 分；7.認知功能損害病程大於 3 個月；8.不符合癡呆診斷標準；9.排除特殊原因引起的認知功能損害。

有些研究者提出了對 MCI 進行分型的想法。Zaudig 曾將 MCI 分?三型[9]：第一型只表現有近記憶和遠記憶障礙；第二型表現?記憶損害加上至少一項其他皮質功能缺陷，但日常生活功能無明顯影響；第三型?有第一、二型的表現，但日常生活功能有明顯影響，?癡呆早期。我們認?，根據 MCI 的轉歸可以分?四型即 AD 型、血管性癡呆型（VD 型）、正常衰老型和其他型（少見原因所致）。

3. 流行病學

將 MCI 作?一個臨床診斷實體來研究的歷史並不長，故流行病學資料比較少。而且，到目前?止還沒有一個公認的 MCI 診斷標準，所以文獻報道的 MCI 患病率有較大的差異，從 2.8%-80% 不等。多數學者認?Graham 等報道的約 17% 的患病率比較接近實際[10]。那些按 AAMI 和 AACD 診斷標準的研究得出的患病率比較高，幾乎是其他類似研究的 2 倍。 MCI 的患病率隨著年齡增加而增高， 60-70 歲的患病率約?18% ， 71-80 歲約?27% ，80 歲以上約?30% 。

有些學者對 MCI 的轉歸和危險因素等進行了研究[1 ， 7]。 Reisberg 將 GDS 評?3 級的老人稱?MCI ，平均隨訪 3.5 年， 16.7% 發展?癡呆。而 GDS1 ～ 2 級的人只有 5.5% 發展?癡呆，與普通老年人群癡呆的發病率差不多。按 Mayo 標準入組的 MCI ，平均每年約有 10%-15% 發展?癡呆。 Bowen 等的研究表明， 50%-80% 的 MCI 在 5-7 年內發展?癡呆。芬蘭的 Kivipelto 等對一隨機樣本的老年人群進行了 21 年的隨訪研究[11]，結果 1449 例 65 ～ 79 歲的老人中，符合 Mayo 標準的患病率?6.1% ，中年時血漿膽固醇升高(?6.5mmol/L）是 MCI 的重要危險因素，同時收縮壓升高也具有重要作用。瑞典的 Anaiz 等用 PET 和神經心理測驗的方法研究 MCI 轉化?AD 的預測因素[12]，發現左顳頂葉局部葡萄糖代謝降低和積木測驗成績差兩項指標預測的正確率達 90% ，單指標預測的正確率分別?75% 和 65% 。作者認?顳頂葉代謝和視覺空間功能可預測 MCI 是否會轉化?AD 。 Morris 等對一群社區的 MCI 老人進行了 9.5 年的隨訪[13]，生存分析顯示第 5 年時有 60.5% 進展?AD ， 9.5 年 100% 進展?AD 。對 25 例 MCI 進行了病理檢查，結果 24 例具有癡呆的神經病理改變，其中 21 例?AD 病變（84% ）。作者認?，總體而言， MCI 基本上就是早期 AD 。少數研究還發現， MCI 的門診次數、急診次數、住院時間和藥品使用明顯增加，其年均醫療費用要比認知正常的老人高得多。

4. 遺傳、生化、病理

Traykor 等將 MCI 分?有和無血管性疾病兩種類型[14]，分析這兩型 MCI 的載脂蛋白（APOE）等位元基因型，結果顯示 APOE ε 4 等位元基因是非血管型 MCI 的危險因素（OR=7.0) ，與 AD 相似（OR=8.8) 。血管性癡呆和血管性 MCI 的 APOE ε 4 基因頻率與對照人群無顯著差異。有人研究攜帶 APP 基因和早老素 1 基因突變基因者，結果這些攜帶者在發展?AD 的 10 年以前就開始有認知功能下降。

Mufson 等研究 MCI 鼻內側皮質中的澱粉樣蛋白（A β）沈積[15]，結果 12 例 MCI 中有 10 例， 20 例正常對照組（NC）中有 12 例和全部 12 例 AD 病人可見 A β 沈積。A β 沈積有二種類型，即位於皮質 3-4 層的新月狀帶和位於 2-3 層或 5-6 層的雙層染色。AD 的 A β 沈積最嚴重（4.55），顯著高於 NC 組（1.32）。MCI 組的 A β 沈積居中（2.60），與 AD 和 NC 組無統計學差異。但個別 NC 的 A β 沈積比 AD 和 MCI 還要嚴重，說明 A β 沈積可能不是 AD 或認知損害的唯一病理原因。 Arai 等檢測 20 例 MCI 患者（最後都發展?AD）和 7 例有記憶減退主訴但無客觀記憶損害的對照者的腦脊液（CSF）tau 蛋白， 20 例 MCI 中有 13 例（65% ）的 CSF tau 蛋白增高，而 7 例對照者的 tau 蛋白水平都降低[16]。 Andreasen 等測量 16 例在隨訪期間發展?AD 的 MCI 患者的 CSF tau 蛋白和 A β 42?，並且與 15 例年齡匹配的對照者比較。基線測量時， 88% 的 CSF tau 蛋白升高和 / 或 A β 42 降低，說明 AD 在出現明顯臨床症狀前 CSF tau 蛋白和 A β 42 就有異常，對預測 MCI 是否發展?AD 可能有幫助[17]。另外，有研究顯示 MCI 患者的血漿中神經生長因數水平與認知功能相關，還有人發現 MCI 的腦脊液中 APOE 升高。

最近的研究認?，AD 的大腦中基底神經核神經元（nucleus basalis neurons）含酪氨酸激?A 受體（trkA）的神經元顯著減少。Mufson 等[18]對 30 例老年人進行屍體解剖，平均年齡?84.7 歲，這些老人在死亡前的 12 月內都進行過認知功能檢查，平均 MMSE 得分?24.2 分，其中 9 例診斷?AD ， 12 例?MCI ， 9 例認知功能正常。屍解顯示， AD 和 MCI 含 trkA 的神經元數都比認知功能正常的老人顯著減少， MCI 減少 46% ， AD 減少 56% ，而且 MCI 與 AD 間無顯著差異。含 trkA 的神經元數與波斯頓命名測驗和總體認知功能評價得分顯著相關，說明 MCI 有與 AD 相似的含 trkA 的神經元改變，提示 MCI 是 AD 的早期。 Gilmor 等研究 MCI 、 AD 和 NC 的 Meynert 基底神經核（nbM）中含膽鹼乙?基轉移?(ChAT）和囊泡乙?膽鹼轉運體

（VAChT）的神經元數[19]，結果 AD 組的膽鹼能神經元減少 15%，膽鹼能神經元數與認知損害程度顯著相關，不過三組間無顯著差異。另有屍解顯示，大部分 MCI 已有 AD 的大腦病理改變（神經元減少、老年斑和神經元纖維纏結），主要集中在海馬結構如 CA1 區、鼻內側皮質。

五. 腦影像

腦影像學檢查是評價腦組織的形態結構和功能變化的重要手段。Jack 等用 MRI 測量 80 例 MCI 的海馬體積[20]，並隨訪 32.6 月， 27 例在隨訪期間發展?AD 。 MCI 期海馬萎縮與 MCI 發展?AD 顯著相關，相對危險度?0.69 。作者認?，海馬體積測量是預測 MCI 是否轉化?AD 的敏感指標。最近，Jack 等又用 MRI 研究 AD 、 MCI 和 NC 的海馬隨時間的萎縮程度[21]，平均隨訪 3 年。海馬體積的年萎縮率?：AD 最嚴重，達 3.5%；MCI 組中，認知功能穩定者?2.55%，認知功能下降者?3.69%；正常組中，認知功能穩定者?1.73%，而認知功能下降者?2.81%。從海馬的萎縮程度看， NC 、 MCI 和 AD 似乎是一個連續發展的過程。正常老人海馬萎縮與年齡顯著相關， MCI 和 AD 則與年齡相關不顯著。 Xu 等用 MRI 三維測量法比較 AD 、 MCI 和 NC 三組的海馬和鼻內側皮質體積，結果三組間有極顯著差異，但 MCI 與 NC 之間無顯著差異。 Convit 等隨訪 26 例 MCI 和 20 例 NC3. 2 年[22]，其中 12 例 MCI ， 2 例 NC 發展?AD 。根據隨訪時的 MRI 三維測量結果進行 Logistic 回歸分析，海馬、海馬旁回和全腦萎縮指數預測 MCI 發展?AD 的準確率?80.4%；如果加入基線測量的邊緣顳枕葉和顳葉中、下回結果進行分析，則預測的準確率達 95.6%，敏感性?92.8%。其他變數的預測敏感性都不超過 71%。

Okamura 用 SPECT 研究 MCI 的局部腦血流，顯示後扣帶回的血流灌注顯著降低，區分 MCI 與 NC 的特異性?80%，敏感性?80.5%。 De Santi 等以 MRI 三維測量和 PET 相結合研究 AD 、 MCI 和 NC 的大腦結構與腦代謝的關係[23]，發現鼻內側皮質的糖代謝水平和海馬體積這兩個指標區分 MCI 和 NC 最準確，而顳葉皮質的代謝水平和體積改變是區分 AD 和 MCI 的最好指標。 AD 的異常指標最多，最易與 NC 區分。分組比較表明，局部糖代謝測量比體積測量的診斷價值大， AD 和 MCI 的代謝降低程度遠超過腦體積縮小的程度。研究結果還顯示， MCI 在沒有明顯的皮質改變之前，已有海馬結構的改變。 Kantarci 等比較 AD 、 MCI 和 NC 的 1H- 磁共振光譜（MRS）變化[24]，結果顯示在左外側顳葉和後扣帶回 AD 的 N- 乙?門冬氨酸與肌酐的比例比 MCI 和 NC 顯著降低。 AD 和 MCI 的後扣帶回的肌醇與肌酐的比例比 NC 顯著升高。 AD 的後扣帶回的膽鹼與肌酐的比例顯著高於 MCI 和 NC 組。結果提示， AD 的病理發展過程是先有肌醇與肌酐的比例增高，進而出現 N- 乙?門冬氨酸與肌酐的比例降低，後期出現膽鹼與肌酐的比例增高。

我們曾對 MCI 進行三維 MRI 、 SPECT 和 PET 研究[25 ， 26]，與 NC 比較，MCI 的灰質體積顯著縮小，側腦室體積顯著擴大，額葉、顳葉和頂葉血流灌注降低，顳葉和額葉葡萄糖代謝下降。

6. 腦電生理、神經心理

Huang 等研究 MCI 、 AD 和 NC 的腦電圖變化[27]，結果 AD 的 α 、 β 功率降低， δ 和 θ 功率增加，與 NC 和 MCI 有顯著差異，但 MCI 與 NC 無顯著性差異。隨訪 MCI 組 25 個月，認知功能有進行性下降者 EEG 顯示 α 功率顯著降低，局?性的 θ 、 β 和 α 波增加。Jelic 等隨訪 27 例 MCI 患者 21 個月，其中 14 例發展?AD （52%） ， 13 例認知功能相對穩定[28]。兩組的基礎定量腦電圖沒有顯著差異，但隨訪時顯示，發展?AD 的 MCI 患者在顳葉和顳頂區的 θ 相對功率顯著增高， β 功率和頻率都顯著降低。Logistic 分析表明，左顳頂區的 α 和 θ 相對功率及頻率是 MCI 發展?AD 的重要預測因素。我們對 MCI 進行多項腦誘發電位研究發現， MCI 的聽覺腦幹反應波 V 絕對波幅和 P300 的 P3 靶波幅比 NC 顯著降低，關聯性負變的反應時間明顯延長[29]。

神經心理測驗簡便易行，是採用比較多研究方法之一。大部分研究表明，MCI 的認知損害特點與早期 AD 的認知損害特點相似，但程度較輕，其認知功能衰退比 NC 快，但比 AD 慢[30]。我們用成套神經心理測驗研究顯示， MCI 的認知功能損害主要表現在辭彙記憶、執行功能和視覺空間功能障礙，其他認知功能損害相對較輕。神經心理測驗能比較靈敏地區分 MCI 和 NC ，判別的正確率達 83.9%。 MCI 的認知障礙可能與邊緣顳葉、前額葉、和顳 - 頂 - 枕聯絡皮質的損害有關[8 ， 31 ， 32]。

7. 治療

MCI 是癡呆的高危人群，具有可治療的認知功能和社會生活功能障礙。積極治療有可能防止或減緩 MCI 發展?AD ，從而提高 MCI 者的生活質量。MCI 的治療可分?非藥物治療和藥物治療。非藥物治療包括諮詢指導、記憶訓練、認知訓練、社會生活功能訓練等。有研究表明，記憶訓練對 MCI 有幫助，可改善記憶困難，但這種改善如不加強和鞏固，最終會消失。Cornmissaris 等對 MCI 患者進行綜合性的認知功能訓練[33]，重復神經心理測驗表明，患者的多種神經心理測驗得分顯著提高。世界各地用促智藥改善老年人的記憶幾乎是常規的治療方法，但真正令人信服的雙盲隨機研究甚少。現在一些作者推薦的治療 MCI 的藥物都是依據阿爾茨海默病的臨床治療研究，包括膽鹼脂?抑制劑、腦複康、尼莫地平、維生素 E 、單胺氧化?β 抑制劑、環氧化?-2 抑制劑、雌激素等[34]。目前國際上有 6 項用膽鹼酯?抑制劑、維生素 E 和腦複康治療 MCI 的多中心隨機雙盲對照研究正在進行中。總體而言，對 MCI 的干預治療還只是在近幾年才受到重視，治療的經驗還不多。

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Council News

Wai-chi Chan

The Council would like to invite members to enter the HKPGA Research Awards Competition this year. Details of the Awards are as follows:

2002 HKPGA Research Awards

Sing-yuen Li

The Awards

The **Hong Kong Psychogeriatric Association (HKPGA) Research Awards** were established with an annual donation from the Pfizer Corporation to encourage and reward fine research projects in psychogeriatrics. There are three awards, which will be given annually to the best-submitted projects that have attained a good scientific standard as decided by the selection board. The **HKPGA Postgraduate Research Award**, of value **HK$10,000**, will be awarded to the best-submitted postgraduate research project. The **HKPGA Postgraduate Research Award**, of value **HK$5,000**, will be awarded to the second best-submitted postgraduate research project. The **HKPGA Undergraduate Research Award**, of value **HK$5,000**, will be awarded to the best-submitted undergraduate report. The submitted reports for postgraduate awards have to be either unpublished research reports or research reports that have been published within one year dating back from the closing date of submission. The submitted reports for the undergraduate award have to be research reports, projects or review articles relevant to the local setting. The postgraduate awards will be awarded to postgraduates of any discipline. Only members of the HKPGA will be eligible for the postgraduate prizes.

The prizes will be presented at the Annual Scientific Meeting of the HKPGA. Abstracts of the winning projects will be published in the HKPGA Newsletter.

Call for Submissions

Submissions of research reports are invited for the 2002 HKPGA Research Awards. Research reports should reach the Association not later than 31 August 2002.

Requirements

* Papers must be written in English with author-date citations of references in text. APA style (per Publication Manual of the American Psychological Association, 4th ed.) is preferred.

* References must include complete titles, all author names, and journal names spelled out in full. References to works written in another language must include both the original title and its English translation.

* Papers must be double-spaced on one side of A4-size white bond paper with margins on all four sides. When a paper has been written on a computer, a floppy disk containing a copy of the paper should be sent, if possible. Be sure the disk is labeled with the name of the word processing program used and the correct file name under which the paper is saved.

* An abstract of no more than 250 words must precede the text.

* The paper should have no more than 30 pages of text, plus literature citations, tables and figures. The latter should not exceed 12 pages.

* The title page should include the following information: title of paper, author (s) name(s), degrees, and affiliations; complete mailing address and telephone, fax and e-mail for the corresponding author, and at the top, the phrase "**Submission for 2002 HKPGA Research Awards**".

* A page stating only the title of the paper also must be included. This page, which is needed for the blind-review process, must immediately follow the complete title page.

* If art is included, only original black-and-white drawings or glossy prints may be submitted.

* Four copies of the paper must be submitted. Submissions should be forwarded to:

Selection Board of HKPGA Research Awards
Hong Kong Psychogeriatric Association
c/o Community Psychogeriatric Team
Castle Peak Hospital
Tuen Mun, NT
HONG KONG

News from Sponsorship Committee

Wah-fat Chan

IPA European and Mediterranean Regional Meeting on 1 - 4 April 2002 in Rome, Italy. 2 sponsorships offered by Pfizer to psychogeriatricians. Sponsorships were granted to Dr Ting Sik-chuen and Prof Helen Chiu.

The 4th Asia Pacific Psychopharmacology Workshop on 10 -11 May 2002 in Dalian, China. 2 sponsorships offered by Janssen to members who work with Hospital Authority. No application was received.

The Committee has extended invitation to all members to apply for the sponsorships offered by HKPGA to join the IPA Asia Pacific Regional Meeting on 23 - 26 October 2002. 100 sponsorships are open to application. Please email to the Honorary Secretary at hkpga@hongkong.com if you need extra application forms. Looking forward to seeing you at the Meeting.

Due to administrative reasons, the study tour to Japan will be postponed until further notice. The Council apologizes for any inconvenience caused.

Psychiatric morbidity in first-ever stroke patients in Hong Kong: A pilot study in a rehabilitation unit

WK Tang, Chinese University of Hong Kong

Objectives: There is a paucity of data on poststroke psychiatric morbidity in Chinese populations. We examined the frequency of post-stroke psychiatric morbidity in Chinese first-ever stroke patients, including depressive and anxiety disorders, mania, and psychosis.

Methods: One hundred and fifty-seven patients with first-ever stroke, who were consecutively admitted to a rehabilitation unit, participated in this prospective, cross-sectional study. All subjects were interviewed by a qualified psychiatrist using the SCID-DSM-III-R. Subjects' cognitive function, neurological status, and level of functioning were also measured. Twenty-five (92.6%) of the subjects with the diagnosis of depression were followed up 6.0+ 3.9 months after the initial assessment.

Results: The frequency of all depressive disorders was 17.2%. Major depressive episodes, adjustment disorder with depressed mood, dysthymia, and generalized anxiety disorder were diagnosed in 7.6%, 8.2%, 1.3% and 0.6% of the subjects, respectively. No cases of other anxiety disorders, mania or psychosis were found. The majority of depressed subjects were in remission at the follow-up assessment.

Conclusions: The low morbidity of affective disorders and their relatively favourable short-term outcome in Chinese first-ever stroke patients warrants further investigation.

Highlights of the 17th Alzheimer's Disease International Conference

Siu-tuen Law
Occupational Therapist
Shatin Hospital

The 17th Alzheimer's Disease International Conference was held in Christchurch, New Zealand from 25th to 27th October 2001. I had the opportunity to meet with over 1000 participants from 47 countries around the world. This conference provided a unique opportunity for the participants, including professional staff, carers and dementia patients, to share and learn from one another.

The theme of the conference was " Partnerships with Dementia Care". Dementia is a global challenge and in this conference meaningful strategies catering for the needs of the 18 million people worldwide who had dementia and those who cared for them were presented. The conference covered a board range of information namely successful dementia care, research and policymaking and the strategies to build a bridge between people with dementia and their carers. Developing effective partnerships between people and among cultures will help all of us to meet the growing challenge of dementia.

Professor Helen Chiu was one of the keynote speakers in the conference. She gave a speech on the diversity of the problems related to dementia, dementia care in various countries as well as the partnership in dementia care among different cultures. She reviewed differences in the epidemiology of dementia in various parts of the world, challenges in dementia assessment arising from cultural factors and different cultural perspectives on dementia care.

Christine Boden, who has dementia, gave a presentation at the conference about her life, from being a victim to a survivor of dementia. She stressed that her psychic resource, e.g. personality and spirituality, laid the foundation for her journey through dementia. For detailed description of her experience, please refer to her book "Who will I be when I die?"

In the pre-conference site-visit, I visited a dementia-specific day care center, Harakeke Club. This purpose-built, dementia-specific day care center was opened in 1995 in Christchurch. The principles of normalization were foremost in the planning of this center. It united holistic care with a social club model, which facilitated the active participation of club members.

Apart from the informative presentation in the convention center, the beautiful gardens in the city of Christchurch was a memorable experience for me especially the Forget-me-not flower, which was the recognizable emblem of Alzheimer New Zealand.

Contact Information

Dementia Advocacy Support Newwork www.dasninternational.org

Dementia Care Australia www.dementiacareaustralia.com

Book recommended

Christine Boden, 1997, Who will I be when I die? Harper Collins

Validity of the Chinese version of the Community Screening Instrument for Dementia (CSI-D)

Teresa SF Chan, Tai Po Hospital
Linda CW Lam & Helen FK Chiu,
Chinese University of Hong Kong

Objective: To validate a Chinese version of the Community Screening Instrument for Dementia (CSI-D), which combines cognitive assessment of subject and informant interview into a single algorithm, as an education-fair screening test for dementia in Hong Kong.

Study design: CSI-D was translated and back translated and modified to adapt to our culture. The Chinese versions were applied in 120 subjects recruited from psychiatric centers and elderly community centers, with 30 matched for age in each of the four groups of mild to moderately demented, depressed, low education and high education normal control by independent raters blind to the group status. Internal consistency and inter-rater reliability were measured by split half and intraclass correlation respectively. Correlation between CSI-D and ten-word list learning task (TWLL), a test sensitive for early dementia, was evaluation for concurrent validity. The mean scores of CSI-D of the four groups were compared. Test performance of CSI-D was examined by ROC analysis.

Result: The split half correlation was >0.7. The intraclass correlation was >0.9. The correlation between CSI-D and TWLL were >0.6 ($p<0.01$). CSI-D distinguished dementia from the other 3 groups ($p<0.001$), but not the high from low education normal control ($p>0.05$). The AUC of the ROC curve for CSI-D was >0.9.

Conclusion: The Chinese version of CSI-D is a valid, reliable and education-fair screening instrument of dementia sensitive in detecting early stage of the disease.

Events Calendar

Wai-chi Chan

24-26 Sept 2002 Rehabaid Centre Hong Kong	**Rehabaid Workshop** **Psychological Approaches to Dementia Care** Speaker: Prof Bob Woods Target audience: Health Care Professionals Objectives: the nature of "personhood"; psychological approaches to working with people with dementia; psychological factors and interventions for challenging behaviour in dementia; psychological aspects of care-giving	Workshop fee: Rehabaid Society subscriber/ HA staff: $2500 Others: $3000 For more information contact: Ms Maisie Lau Tel: 2364 2345
22 October 2002 Hong Kong	**Joint Scientific Meeting of HKPGA and KAGP (Korean Association for Geriatric Psychiatry)** We are really honoured to hold a joint meeting with the KAGP, a professional body established in 1994 dedicating to the promotion of mental health among older adults in Korea. HKPGA members are cordially invited to participate in this important meeting. We will have the **HKPGA Annual General Meeting** after the joint meeting.	Details of the meeting will be announced shortly
23-26 October 2002 Gold Coast Hotel Hong Kong	**International Psychogeriatric Association** **Asia-Pacific Regional Meeting** *"Dementia, Depression & Suicide in the Elderly: Clinical & Cultural Aspects"* The Asia-Pacific Regional Meeting is fast approaching. It is difficult to go through the brochure and not charmed by its rich scientific programs and its distinguished speakers. Professors Tom Arie, Alistair Burns, Eric Caine, Maeng-Je Cho, Yeates Cornwell, Jeffrey Cummings, Akira Homma, Joel Sadavoy, Zhang Ming Yuan, and Helen Chiu will share with us their views and experience at this important regional meeting. The participants will also be able to meet and exchange ideas with delegates from neighbouring countries. Save the dates in your diary! Looking forward to seeing you in October.	For more information contact: IPA Secretariat 550 Frontage Rd., Ste 2820 Northfield, IL 60093 USA E-mail: ipa@ipa-online.org Web: http://www.ipa-online.org

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