Cognitive Impairment and Psychiatric Morbidity in Chinese Stroke Patients: Clinical and Imaging Characterization

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DECLARATION OF ORIGINALITY

The work contained in this thesis is original research carried out by the author in the Department of Psychiatry, Faculty of Medicine, the Chinese University of Hong Kong. No part of the thesis has been submitted to other universities or institutions for the purpose of being awarded a degree or diploma.

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LIST OF ABBREVIATIONS

AD	Alzheimer's disease
ANCOVA	analysis of co-variance
ASU	Acute Stroke Unit
CIND	cognitive impairment no dementia
CMBs	cerebral microbleeds
CT	computed tomography
CVD	cerebrovascular disease
DSMIV	Diagnostic and Statistical Manual, Fourth Edition
DWI	diffusion weighted imaging
FAB	Frontal Assessment Battery
FLA	frontal lobe atrophy
FLAIR	fluid attenuated inversion recovery
ICC	intraclass correlation coefficient
IQR	interquatile range
GDS	Geriatric Depression Scale
LAD	large artery disease
MMSE	Mini-mental State Examination
MRI	Magnetic Resonance Imaging
MTLA	medial temporal lobe atrophy
PFC	prefrontal cortex
DLPFC	dorsolateral prefrontal cortex

PSD	poststroke depression
PSDE	poststroke dementia
PWH	Prince of Wales Hospital
SIVD	subcortical ischemic vascular disease
SVD	small vessel disease
SPSS16.0	Statistical Package for the Social Sciences, version 16.0
VaD	vascular dementia
VBR	ventricle-to-brain ratio
VCI	vascular cognitive impairment
WHO	World Health Organization
WMLs	white matter lesions

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ABSTRACT

Abstract of thesis entitled

Cognitive impairment and psychiatric morbidity in Chinese stroke patients: clinical and imaging characterization

Submitted by CHEN Yangkun

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Poststroke cognitive impairment and psychiatric morbidity are common in stroke survivors, often leading to poor prognosis. Up-to-date data on and imaging analysis of poststroke cognitive impairment and psychiatric morbidity remain limited in Chinese populations.

A few longitudinal studies of cognitive impairment have employed imaging analysis, but they have not involved Chinese participants. The effects of white matter lesions (WMLs) and hippocampal atrophy on poststroke cognitive impairment and cognitive decline remain uncertain. The first study reported in this thesis involved 328 Chinese ischemic stroke patients who were administered a series of neuropsychological tests covering seven domains three months after stroke. Two hundred and fifty-six of these patients were followed-up for one year. Volumetry of the infarcts, WMLs, and hippocampus atrophy on magnetic resonance imaging (MRI) was conducted. The prevalence of cognitive impairment was 54.9% at baseline and 52.4% at the one-year follow-up, although most of the patients (85.5%) remained cognitively stable. The evolution of cognitive impairment no dementia (CIND) at the one-year follow-up was bidirectional, with 11.2% progressing to dementia and 21.0% reverting to cognitive intact. WMLs volume rather than hippocampal volume was a significant predictor of cognitive impairment, cognitive decline, and

delayed dementia. WMLs also had an independent effect on executive function, attention, visual memory, visuoconstruction, and visuomotor speed.

The prefrontal cortex (PFC) is involved in verbal fluency, and sex differences in verbal fluency have been reported in the healthy population. It is unknown whether PFC atrophy contributes to verbal fluency in stroke patients and whether there is any difference between the sexes. Thirty non-aphasic, elderly women with stroke and 30 age-matched male counterparts were included in this part of the study. MRI segmentation was employed to measure PFC volume and its subdivisions. After controlling for vascular risk factors, infarct features, and WMLs, left dorsolateral prefrontal cortex (DLPFC) volume was significantly associated with semantic verbal fluency performance in the women, but not in the men.

Poststroke depression (PSD) is the most common form of poststroke psychiatric morbidity. Small subcortical infarcts (SSIs) can result from small vessel disease (SVD) and large artery disease (LAD). No study has yet explored PSD in different etiological types of SSIs. To address this gap, 127 patients with SSIs resulting from LAD or SVD were examined. PSD was evaluated with the Geriatric Depression Scale (GDS) three months after stroke. The LAD group had a significantly higher frequency of PSD,

and LAD was found to be a significant independent risk factor for PSD. This study suggests that cerebral blood perfusion may play an important role in PSD.

Post-stroke emotional lability (PSEL) is a distressing and embarrassing complaint among stroke survivors. Lesions located in various cortical and subcortical areas are thought to be involved in the pathophysiology of PSEL.The clinical significance of microbleeds (MBs) in the development of psychiatric conditions following stroke is unknown. We carried out a study to examine the association between PSEL and MBs in 519 Chinese patients with acute ischemic stroke admitted consecutively. PSEL was evaluated three months after the index stroke, and the number and location of MBs were evaluated with MRI. According to Kim's criteria, 74 (14.3%) of the patients had PSEL. In comparison with the non-PSEL group, patients in the PSEL group were more likely to have MBs in the thalamus as a whole (16.2% versus 6.5%; $p = 0.004$) and in its anterior (6.9% versus 2.0%; $p = 0.02$) and paramedian territories (8.1% versus 3.1%; $p = 0.04$). MBs in the thalamus remained an independent predictor of PSEL in multivariate analysis, with an odds ratio (OR) of 4.7 ($p = 0.002$). Our results suggest that MBs in the thalamus may play a role in the

development of PSEL. The importance of MBs in PSEL and other psychiatric conditions in stroke survivors warrants further investigation.

Insomnia too is common in stroke survivors. We investigated the clinical and MRI correlates of insomnia symptoms in Chinese stroke survivors. Five hundred and eight ischemic stroke patients were recruited three months after stroke. Insomnia symptoms were evaluated with a standard questionnaire, and the location and size of infarcts were analyzed. One hundred and eighty-six of the patients (36.6%) had insomnia symptoms, and 64 (12.6%) had insomnia symptoms with daytime consequences. In addition to a high GDS score, frontal lobe infarction was a significant predictor of insomnia symptoms, and diabetes was predictive of such symptoms with daytime consequences. The results of this study indicate that insomnia symptoms have a multi-factorial origin in stroke.

Frontal lobe atrophy (FLA) is associated with late-life depression and cognitive impairment, although the pathogenesis of FLA in stroke is unclear. In an aim to ascertain whether FLA is affected by WMLs, we analyzed the MRIs of 471 Chinese ischemic stroke patients. Lobar atrophy was defined by a widely-used visual rating scale. WML severity was rated using the Fazekas scale. One hundred and seventy-four (36.9%) patients had FLA, and 30 (6.4%) had severe FLA. Age, previous stroke, and

periventricular hyperintensities (PVH) were found to be independent risk factors of FLA, and age and deep white matter hyperintensities (DWMH) independent risk factors of severe FLA. There was no correlation between PVH and DWMH and temporal and parietal atrophy. The results of this study suggest that FLA in ischemic stroke may be associated with SVD.

This thesis investigates the clinical and imaging characterization of cognitive impairment and psychiatric morbidity in Chinese stroke patients. The conclusions of the studies reported herein can be summarized as follows. (1) The prevalence of cognitive impairment is high among Chinese poststroke patients, but most remain cognitively stable at one year after stroke; WMLs rather than hippocampal atrophy predict cognitive impairment, longitudinal cognitive decline, and delayed dementia; (2) DLPFC atrophy is correlated with poor verbal fluency in elderly women with stroke, but not in their male counterparts; (3) LAD may be associated with PSD in patients with small subcortical infarcts; (4) MBs in the thalamus are associated with PSEL; (5) frontal lobe infarction and diabetes may be risk factors of insomnia symptoms in stroke patients; and (6) FLA in ischemic stroke may be associated with SVD.

摘 要

腦卒中後認知與精神障礙在腦卒中存活者中十分常見，是導致預後不良的因素。到目前為止，在中國人群中，具有神經影像學分析的腦卒中後認知與精神障礙的研究仍然十分有限。本研究旨在探討中國腦卒中患者卒中後認知與精神障礙的臨床與影像學特征。

在腦卒中後認知功能障礙方面，至今只有少數的前瞻性研究采用了影像學分析，而在中國人群中仍然缺乏這樣的研究。腦白質病變和海馬萎縮對腦卒中後認知障礙的影響仍然未完全清楚。在腦卒中後 3 個月，我們納入了 328 例缺血性腦卒中患者，進行了多個認知域的神經心理學檢查。256 例患者完成了一年後的臨床與神經心理學隨訪。同時，我們對患者的腦部 MRI 進行定量測量，包括了腦白質病變和海馬體積等。結果顯示，在卒中後 3 個月，認知障礙的發生率為 54.9%，85.5%的患者在一年後認知功能保持穩定。在 3 個月時為非癡呆型認知功能障礙（CIND）的患者中，11.2% 1 年後進展為癡呆，21.0%好轉至正常水平，顯示了 CIND 的演變是雙向的。腦白質病變是腦卒中後認知障礙、認知功能惡化和遲發性癡呆的危險因素。同時，它對執行功能、注意力，视觉记忆，视空间构建和視運動速度等五個認知域有獨立的影響。

前額葉皮層對語言流暢性有重要作用，而語言流暢性的性別差異已有報道。前額葉皮層的萎縮對卒中後患者的語言流暢性是否有影響以及是否存在性別差

異，目前尚不清楚。我們納入了 30 位不伴失語的老年女性腦卒中患者和 30 位年齡配對的老年男性患者，采用 MRI 腦區分割的方法測量前額葉皮層及其下的幾個分區，與語言流暢性測驗進行比較。在平衡了血管危險因素、梗死體積和白質病變後，在女性病人中，左側背外側前額葉皮層的體積與其語義性語言流暢性結果仍然顯著相關。而這一結果並未在男性病人中發現。

抑鬱是腦卒中後最常見的精神障礙。皮層下小梗死有多種發病機制，可由大血管病變或小血管病變所導致。目前尚無研究探討在皮層下小梗死中不同發病機制與卒中後抑鬱的關系。我們納入了 127 例皮層下小梗死的患者，按照可能的發病機制分為大血管病組和小血管病組。結果顯示，大血管病組的卒中後抑鬱發生率明顯比小血管病組高，大血管病是卒中後抑鬱的獨立危險因素，提示了腦血流灌注情況可能在卒中後抑鬱的發生中有一定作用。

情感失控是腦卒中病人一種常見的情感障礙。大腦皮層和皮層下的病變均可導致情感失控。目前尚無研究探討大腦微出血對卒中後精神障礙的影響。我們在卒中後 3 個月時納入 519 例缺血性腦卒中患者進行情感失控的評估，並測量 MRI 中大腦微出血的分布和數目。結果顯示，74 例（14.3%）患者有情感失控，情感失控者丘腦微出血的比例明顯高於無情感失控者（16.2% vs 6.5%; p=0.004), 尤其以丘腦前部 (6.9% vs 2.0%, p=0.02) 和旁正中部明顯 (8.1% vs 3.1%; p=0.04)。Logistic 回歸顯示，丘腦微出血是腦卒中後情感失控的獨立危險因素 （OR=4.7，p=0.002)。研究結果提示了丘腦微出血可能與腦卒中後情感失控的發生有關，大腦微出血對卒中後精神障礙的影響有待進一步研究。

腦卒中患者常有失眠癥狀。我們研究了腦卒中患者失眠癥狀的臨床與影像學因素。我們納入了508例缺血性腦卒中患者進行睡眠狀況的評估。結果顯示，失眠癥狀的發生率為36.6%，失眠癥狀伴有日間功能障礙的發生率為12.6%。除抑鬱癥狀外，額葉梗死是失眠癥狀的危險因素，糖尿病是失眠癥狀伴有日間功能障礙的危險因素，提示了腦卒中患者失眠癥狀是受多因素影響的。

最後，我們研究了在腦卒中患者中，額葉萎縮是否受腦部小血管病變影響。我們分析了 471 例缺血性腦卒中患者的 MRI，使用目視評分量表來評估額葉、頂葉與顳葉的萎縮情況，使用 Fazekas 評分來評估白質病變嚴重性。Logistic 回歸顯示：年齡，既往卒中史和腦室旁白質病變評分是額葉萎縮的危險因素，年齡和深部白質病變評分是重度額葉萎縮的危險因素。此結果提示了額葉萎縮可能與腦部小血管病變有關。

本研究探討了中國人群中腦卒中認知與精神障礙的臨床與影像學特征。本研究的結論為：（1）中國人群中卒中患者認知功能障礙的發生率較高，但大部分患者在 15 個月內認知功能穩定。腦部白質病變，而非海馬萎縮，對認知功能障礙、認知功能障礙惡化和遲發性癡呆均有顯著影響；（2）左側背外側前額葉皮層萎縮影響老年女性腦卒中患者的語言流暢性；（3）大血管病變可能對卒中後抑鬱有影響；(4）丘腦微出血與腦卒中後情感失控的發生有關；（5）額葉梗死和糖尿病可能與腦卒中患者的失眠癥狀有關；（6）額葉萎縮可能與腦部小血管病變有關。

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CHAPTER 1 INTRODUCTION AND LITERATURE REVIEW

1.1. An overview of stroke

Stroke is the third leading cause of death in most countries of the world (Caplan, 2000), and the second leading cause in China (Ministry of Public Health of China, 2006) in both urban and rural areas. In 2005, there were 5.7 million fatal strokes worldwide, and more than 1.4 million of these occurred in China (Strong et al., 2007). The global stroke death toll is expected to reach 7.8 million in 25 years' time if the current trend continues (Strong et al., 2007). Annual stroke mortalities in Hong Kong consistently number above 3,000 (Ng, 2007).

An epidemiological study conducted in three large cities in mainland China from 1991-2000 indicated that the annual age-adjusted incidence of stroke was 76.1-150 per100,000 (Jiang et al., 2006). It is thus estimated that 1.5-2 million new strokes occur in China every year. Age-adjusted stroke prevalence in the country varies between 259.86 per 100,000 and 719 per 100,000 for all age groups (Liu et al., 2007). Although no comparable epidemiological study is available in Hong

Kong, statistics from the Hospital Authority show that annual stroke admissions to public hospitals have surged to 20,000 (Ng, 2007). With the aging of the population across China, society can no longer afford to ignore stroke.

Stroke has an enormous adverse impact on patients, their families, and society as a whole, and is the leading cause of long-term disability (Bonita et al., 1994). A study conducted in Hong Kong showed that more than 50% of stroke patients were unable to live independently one year after the index stroke (Lo et al., 2008). Stroke often precludes patients from returning to work or regaining their role within the family. It also represents a great burden to the family, especially if the patient is dependent on a family member as his or her caregiver. Both the stroke survivor's and the caregiver's quality of life is adversely affected (Visser-Meily et al., 2005).

Of the stroke subtypes among the Chinese, more than 80% are ischemic stroke (Liu et al., 2006), for which hypertension, diabetes mellitus, hyperlipidemia, smoking, and heart disease are the common risk factors. The development of neuroimaging techniques, especially magnetic resonance imaging (MRI), and angiography techniques has greatly helped clinicians to identify the accurate location of infarctions

and has shed light on the mechanisms of stroke. Measures aimed at the primary prevention of stroke, which focus on controlling the risk factors, have successfully reduced the incidence of stroke in a number of large clinical trials (Gilbert et al.,1996), and secondary prevention measures, e.g., antiplatelet therapy (Forbes, 1998) and statin treatment (Amarenco et al., 2006), have successfully reduced its recurrence. Advances in the treatment of acute-phase stroke, e.g., antiplatelet therapy (Dippel, 1998), thrombolysis using a recombinant tissue-type plasminogen activator (r-TPA) within three hours (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995; Albers et al., 2000, 2002), and the therapy employed in a stroke unit (Stroke Unit Trialists' Collaboration, 2007), have also led to reduced mortality in the acute phase of stroke and to reduced disability.

However, chronic complications following stroke, such as poststroke cognitive impairment and poststroke psychiatric morbidities, which are also important in rehabilitation, have received less attention from clinicians. Aside from their strong association with stroke severity, these complications can also occur in independent stroke survivors.

Depression is common among stroke patients, with its prevalence estimated to be between 30-35% and 60% (Lenzi et al., 2008).

Poststroke depression (PSD) is a predominant factor in poor quality of life (Carod-Artal et al., 2009) and is associated with poor prognosis, including greater long-term mortality (Morris et al., 1993). Whether antidepressant medication can help to prevent PSD and decrease poststroke mortality requires further study (Starkstein et al., 2008).

Cognitive impairment is also common in stroke. Up to 64% of stroke patients have some degree of cognitive impairment (Jin et al., 2006), with up to a third developing frank dementia (Barba et al., 2000; Pohjasvaara et al., 1997). Poststroke dementia also predicts poor long-term survival (Melkas et al., 2009), and stroke significantly deteriorates cognitive function in patients with Alzheimer's disease (AD) (Sheng et al., 2007). A huge increase in the prevalence and burden of poststroke dementia is likely to occur (Mackowiak-Cordoliani et al., 2005), given the decline in mortality following stroke (Rothwell et al., 2004) and the aging of populations. Unfortunately, few effective drugs for the treatment of vascular dementia (VaD) have yet been confirmed, although there is evidence to suggest the efficacy of controlling risk factors and adopting measures to prevent the recurrence of stroke (Birks and Flicker, 2007). The early detection of poststroke cognitive impairment is thus essential. In the past decade, increasing numbers of

healthcare professionals have become aware of the importance of cognitive and behavioral impairment in stroke patients. Early and appropriate intervention will benefit patients, their families and society.

1.2. Vascular cognitive impairment

1.2.1 Current concept of vascular cognitive impairment

Vascular cognitive impairment (VCI) comprises a range of cognitive disorders related to cerebrovascular disease (CVD). The term multi-infarct dementia was first used to discriminate dementia related to cerebral vascular disease from AD (Hachinski, 1974). VaD subsequently replaced it, as there were other etiologies apart from multiple infarcts, including single strategic infarction, leukoaraiosis, hypoperfusion, and hemorrhage (Bowler, 2007).

However, the increasing body of neuropathological and neuropsychological evidence produced by the end of the past century led to criticisms of the VaD definition. First, biopsy evidence has shown most dementias to have both neurodegenerative and vascular characteristics (Neuropathology Group, 2001; Riekse et al., 2004;

Petrovitch et al., 2005) that may act synergistically (Snowdon et al., 1997; Lim et al., 1999; Hachinski, 2007). Second, the current VaD criteria were based on the AD paradigm, which is unable to demonstrate precisely the neuropsychological characteristics of dementia that are related to CVD. Commonly used criteria, such as the Diagnostic and Statistical Manual of Mental Disorders (4th edition) (DSM-IV) (American Psychiatric Association, 1994) and the International Classification of Diseases (10th Revision) (ICD-10) (WHO, 1992), necessarily require the impairment of memory dysfunction, in addition to the progression and irreversibility of cognitive decline. These criteria work well for indentifying patients with AD, but may result in misdiagnosis for those with predominant executive dysfunction but preserved memory of vascular origins (Erkinjuntti et al., 1997). Third, it is difficult to determine the extent of vascular lesions on neuroimaging that leads to cognitive impairment or dementia, according to current evidence. Thus, the imaging definition of VaD in the current criteria (e.g., NINDS-AIREN) (Román et al., 1993) is somewhat arbitrary (Bowler, 2007). Finally, the VaD criteria are able only to detect the late stage of CVD-related cognitive impairment, which provides little room for prevention and treatment (Moorhouse and Rockwood, 2008). It is

essential that clinicians recognize early cognitive impairment that is insufficiently severe to meet the criteria for dementia.

Based on these concerns, Hachinski and Bowler (1993) suggested VCI to refer to any cognitive impairment related to CVD. VCI encompasses all levels of cognitive decline, from the earliest stage to more severe global decline, related to all causes of CVD. The Canadian Health Study group proposed "cognitive impairment no dementia" (CIND) to describe those with mild VCI (Ebly et al., 1995). The VCI definition thus encompasses V-CIND, VaD, and mixed dementia (AD plus CVD). This concept has been widely accepted in recent years, and data on VCI are growing, although an operational clinical VCI criterion remains unavailable to date (Hachinski et al., 2006).

Poststroke dementia (PSDE) is also used to define dementia in the stroke cohort. The PSDE substrate is variant, as its origins may lie elsewhere than in VaD (Leys et al., 2005). Previous studies have indicated that 7-16% of those exhibiting PSDE had prestroke dementia, which may be related to AD pathology (Henon et al., 1997; Pohjasvaara et al.,1999; Tang et al., 2004). The term is thus useful for patients who are followed-up after stroke before their dementia can be diagnosed as VaD, AD, or mixed dementia.

The concept and definition of VCI are still evolving, but have resulted in greater attention being paid to the early prevention and intervention of CVD-related cognitive impairment and the coexistence of AD and CVD.

1.2.2. Epidemiology, pathogenesis, and subtypes of VCI

The prevalence and incidence of VaD variances depend on the criteria or tools being applied. Evaluation of 11 pooled European population-based studies of subjects over the age of 65 revealed an age-standardized prevalence rate of 6.4% for all types of dementia, 4.4% for AD, and 2.6% for VaD (Lobo et al., 2000); VaD accounted for 15.8% of all dementia cases. In Canadian studies of those above 65, 12.1% had VaD and 12.8% mixed AD/VaD (Rockwood et al., 2000). The incidence of VaD in Canadians varies between six and 15 cases/year/1,000 persons aged 70 and older, and increases with advancing age (Hebert et al., 2000). An epidemiological study among the Chinese revealed that the incidence of VaD (with the ICD-10 criteria) is 16 cases/year/1,000 person aged over 60 (Yan et al., 2002). In Chinese people older than 60, VaD prevalence varies from 0.49% to

1.06%, whereas AD prevalence ranges from 0.95% to 4.43% (Fan et al., 2000; Tang et al., 2002).

Epidemiological data on VCI and V-CIND are accumulating. Rockwood et al. (2000), for example, reported VCI prevalence among Canadians to be about 5% in people over the age of 65, with V-CIND the most prevalent form among those aged 65 to 84 years. A Japanese community-based study found that 8.5% of people older than 65 had V-CIND (Ishii et al., 2007). In stroke survivors, VCI prevalence ranges from 37.5% to 64% (Zhou et al., 2005; Jin et al., 2006).

VCI comprises a wide range of cognitive disorders related to CVD. Its pathogenesis can be categorized into VaD due to cortical infarction, VaD due to strategic infarct (e.g., infarcts in the thalamus, angular gyrus, caudate nucleus, basal forebrain or hippocampus), and VCI due to subcortical ischemic vascular disease (SIVD) (Moorhouse and Rockwood, 2008).

Cortical VaD (also termed MID and poststroke VaD) is considered to be related to large vessel disease and cardioembolic stroke (Erkinjuntti and Gauthier, 2009). It is characterized by predominant cortical and cortical-subcortical arterial territorial and watershed infarcts. Patients with VaD present with some degree of memory impairment and

heteromodal cortical symptom(s) such as aphasia, apraxia, agnosia, visuospatial difficulty, or executive dysfunction (Erkinjuntti and Gauthier, 2009). Different degrees of motor, sensory, and visual deficit are also common.

Stroke patients with only a tiny infarct in the thalamus, angular gyrus, basal forebrain, caudate nucleus, or hippocampus may also have apparent cognitive impairment (Auchus et al., 2002). These strategic areas have important cognitive functions or are compositions of an important cortical-subcortical circuit (e.g., the thalamus) (Szirma et al., 2002), and thus the devastation and interruption of these structures may lead to severe impairment in certain cognitive domains.

Subcortical VCI is the most common VCI subtype, accounting for 40% of cases (Bowler, 2007). SIVD is a characteristic, with multiple lacunar infarcts or white matter lesions (WMLs) on MRI (also termed leukoaraiosis) (Pohjasvaara et al., 2003; Jokinen et al., 2009). WMLs are visible in more than 90% of the elderly (de Leeuw et al., 2001), are associated with vascular risk factors (Inzitari et al., 1987; Lindgren et al., 1994; Henon et al., 1996), and are common in both VaD and AD (Erkinjuntti et al., 1994). WMLs may result from the incomplete occlusion of microvessels or deep cerebral hypoperfusion (Brun and

Englund, 1986; Wiszniewska et al., 2000), impairment of the blood-brain barrier (Hanyu et al., 2002; Topakian et al., 2009), and non-vascular mechanisms (Barber et al., 1999). WMLs increase the risk of recurrent stroke in stroke survivors (Fu et al., 2005). In population-based studies, WMLs are associated with late-life depression (Firbank et al., 2004; Dalby et al., 2009), disability (Pantoni et al., 2005a), and cognitive impairment (DeCarli et al., 1995; Wen et al., 2004). Lacunar infarction is another feature of SIVD, and is commonly seen in the coronary radiata, centrums semi-ovale, internal capsule, basal ganglia, thalamus, or pons (Roman et al., 2002). The Cardiovascular Health Study Group has found MRI-defined lacunar infarcts to occur in nearly one-fifth of the elderly (Longstreth et al., 1998). The specific cognitive profiles of subcortical VCI have not been fully established, but current evidence suggests that executive dysfunction rather than memory impairment is prominent in this condition (Jokinen et al., 2006). Nimodipine has been shown to have some benefit in SIVD (Pantoni et al., 2005b).

1.2.3. Neuropsychological profiles of VCI

VCI has no specific neuropsychological pattern, as it is a combination of cognitive disorders with different etiologies. Previous studies have revealed that neuropsychological assessment can discriminate AD from pure VaD (Lafosse et al., 1997), but not from mixed dementia (Bowler, 2007). As the harmonization standards developed by the National Institute for Neurological Disorders and Stroke (NINDS) and Canadian Stroke Network (CSN) harmonization of VCI pointed out, there is no specific cognitive domain in VCI, and neuropsychological tests should thus cover multiple cognitive domains (Hachinski et al., 2006).

Executive dysfunction is characterized by difficulty in organizing behavioral responses to solve complex problems, such as learning new information, copying complex figures, or systematically searching the memory (Chow and Cummings, 1999). Executive function involves the ability to initiate, plan, sequence, and monitor behavior. The measurement of executive function appears to be highly predictive of functional status in terms of the higher activities of daily living (Boone et al., 1992). Studies examining patients with VaD indicate that attention, processing speed, and executive function are the most frequently and most severely impaired aspects of cognition (Mendez et

al., 1991; Padovani et al., 1995; Lafosse et al., 1997), whereas memory has been reported to be relatively preserved (Sachdev et al., 2004). Executive dysfunction is also prominent in non-demented patients (Stephens et al., 2004; Sachdev et al., 2004), although the results have been inconsistent due to the variance in stroke etiologies. The SIVD subtype characterized by extensive WMLs and lacunar infarcts may have a more homogeneous impaired cognitive profile. Jokinen et al. (2006) recruited 323 consecutive patients with ischemic stroke, and found executive deficits to be the most prominent cognitive characteristic associated with MRI-defined SIVD. The mechanism of executive dysfunction is considered to be the result of pre-existing small vessel disease (SVD) (WMLs and lacunar infarcts) disrupting the frontal-subcortical pathways (Cohen et al., 2002; Burton et al., 2003; Vataja et al., 2003). The commonly used neuropsychological tools for the assessment of executive function include the verbal fluency test, Stroop test (Golden, 1978), Go-No Go test, Wisconsin Card Sorting Test (WCST) (Heaton et al., 1993), and the Trail-making test (Reitan and Wolfson, 1985), among others. Integrated batteries include the Mattis Dementia Rating Scale-Initiation/Perseveration (MDRS-I/P) (Mattis, 1988) and Frontal Assessment Battery (FAB) (Dubois, 2000).

Memory dysfunction is, by definition, a requirement for the diagnosis of dementia. In a systematic review of five longitudinal studies, the prevalence of memory dysfunction in non-demented stroke patients varied from 23-50% three months poststroke, but declined from 11-31% one year poststroke (Snaphaan et al., 2007). Despite stroke rarely involving the brain structure critical for memory encoding and retrieval (the medial temporal lobe), the relatively high prevalence of VaD (or PSD) indicates that prestroke changes in the brain (such as WMLs, silent infarcts, or hippocampal atrophy) may play a role in the development of memory dysfunction. The assessment of memory function should include the assessment of working, episodic (verbal memory and visual memory), and semantic memory. The pattern of memory dysfunction may differ between VaD and AD patients. Previous studies have shown that patients with VaD exhibit superior performance in certain tests of working memory relative to AD patients (Kontiola et al., 1990; Padovani et al., 1995). VaD patients may also be more capable of drawing on semantic clues in the retrieval phase than AD patients.

The slowing of psychomotor speed (also known as mental processing speed or visuomotor speed) is also often observed in stroke

patients (Ballard et al., 2003; Jokinen et al., 2005). In the Helsinki Stroke Aging Memory Study of 323 stroke survivors, mental processing speed was found to be one of the most affected cognitive domains (Jokinen et al., 2005). Patients with frontal lobe infarction are reported to be significantly slower than those without such infarction in time-limited tasks measuring mental processing speed (Leskela et al., 1999). In the Leukoaraiosis and Disability (LADIS) study, patients with SIVD also had dominant impairment in psychomotor speed compared to the controls (Jokinen et al., 2009).

Impairment in other cognitive domains, such as attention (Stephens et al., 2004) and visual spatial function, has also been reported in non-demented stroke patients. The variation in results may be partly due to differences between participants and tools.

To date, there is no standardized neuropsychological battery for diagnosing VCI or V-CIND (Hachinski et al., 2006), with most studies employing their own neuropsychological tests. Most of these studies do agree, however, that VCI should be defined as impairment in at least one cognitive domain (although not specific to any one domain), regardless of whether the criteria for dementia are fulfilled (Tham et al., 2002; Sachdev et al., 2006; Serrano et al., 2007). The harmonization

standards developed by the NINDS and CSN recommend different neuropsychological tests for different purposes, including the 5- and 30-minute test and the 1-hour test (Hachinski et al., 2006). As an integrated screening tool, the Mini Mental Status Examination (MMSE) (Folstein et al., 1975), which is widely used in the screening of AD, is considered less sensitive in detecting VCI. As an alternative, the Montreal Cognitive Assessment (MoCA) (www.mocatest.org), which is being used more frequently, has had more success in recognizing subjects with mild cognitive impairment (MCI). The Cambridge Cognitive Examination (CAMCOG) (Roth et al., 1999) is also an acceptable tool for detecting CIND.

1.2.4. Longitudinal studies on cognitive impairment in the stroke cohort

Data on VCI (including CIND and MCI) have accumulated over the past decade. In the stroke cohort, many studies have aimed to illustrate the prevalence, clinical, and imaging predictors of poststroke cognitive impairment, although longitudinal studies of such impairment following stroke are limited. According to the literature, the prevalence of

cognitive deficits after stroke ranges widely, from 10% to 82%, depending primarily on the criteria used to define cognitive impairment, the time interval since stroke onset, and the patient population selected (Bowler, 2007). The evolution of CIND following stroke is bidirectional (Tham et al., 2002; Rasquin et al., 2004), with 5-12.5% of stroke survivors developing dementia in the first year after the index stroke (Tham et al., 2002; Ballard et al., 2003; Srikanth et al., 2004) and almost half developing it within five years (Wentzel et al., 2001). However, there are also reports that CIND (or MCI) does not increase over time within the two years following the index stroke (Rasquin et al., 2007).

The wide use of imaging techniques, particularly MRI, in clinical stroke practice has facilitated the detection of lesions other than the index infarcts. Moreover, MRI more easily and accurately identifies the volumetry of WMLs and the hippocampus *in vivo*. MRI has also been helpful in allowing insight into the biological substrates of cognitive impairment in stroke. It thus appears essential that MRI variables be included in studies aimed at finding the predictors of cognitive decline following stroke.

Longitudinal studies of cognitive impairment (meeting the current concept of VCI) in stroke patients with MRI/computed tomography (CT) variables analyzed are limited, with only eight identified in a literature review. Of these, four included MRI analysis (Mungas et al., 2002; Firbank et al., 2006; Williamson et al., 2008; Dufouil et al., 2009) and four only CT analysis in the same stroke cohort (Rasquin et al., 2004a, 2004b, 2005, 2007). Very few studies have included integrated radiological analysis. In terms of the measurement of infarcts, WMLs, hippocampal size, and global atrophy, most of these studies have employed qualitative methods (e.g., the visual rating method). Only two studies (Mungas et al., 2002; Firbank et al., 2006) quantified WML volume and hippocampal size (the former using the visual rating method and the latter the volumetric method). None has included cerebral microbleeds (CMBs) in analysis. The sample size for baseline assessment in these studies has been relatively small, ranging from 31-226 (median 95). To obtain a stronger prediction of cognitive decline following stroke, it is important that studies combine the clinical and integrated imaging parameters into their analysis.

Tham et al. (2002) conducted the first longitudinal studies of VCI in Singaporean Chinese (83% of their subjects were Chinese) stroke

survivors. They concluded that 11.0% of patients with V-CIND at baseline progressed to dementia within one year. However, they collected no imaging variables.

1.2.5. Clinical and imaging predictors of cognitive impairment and cognitive decline following stroke

It is critical that patients at high risk of cognitive impairment be identified. Prediction of those who will progress to dementia is even more important. Numerous cross-sectional studies have investigated the correlates of cognitive impairment in the stroke cohort. An older age, lower education level, prior stroke, and stroke severity are widely accepted as risk factors of cognitive impairment following stroke. However, findings on the association of vascular risk factors, such as hypertension, diabetes, hyperlipidemia, and smoking, have been inconsistent (Tatemichi et al., 1992; Sachdev et al., 2006). Other possible risk factors include low education level, daily alcohol consumption (Zhou et al., 2005), and the APOE4 genotype (Ballard et al., 2005). Some cross-sectional studies have measured the role of imaging variables in cognitive impairment following stroke. Infarct

location (e.g., the left internal carotid artery [ICA] territory) (Rasquin et al., 2004; Zhou et al., 2005; Nys et al., 2007), infarct volume (Sachdev et al., 2006), WMLs severity (Mov et al., 2005; Sachdev et al., 2006), global atrophy (Fein et al., 2000), and regional atrophy (e.g., atrophy of the hippocampus, thalamus, amygdala) (Fein et al., 2000; Sachdev et al., 2007a, 2007b; Grau-Olivares et al., 2007; Stebbins et al., 2008) have all been reported to be linked to cognitive impairment. However, the results of these studies have not always been consistent due to differences in study samples, methodology, and prestroke lesion load.

Data are accumulating for the prediction of cognitive decline following stroke, with most studies indicating that the cognitive function of stroke patients without dementia at baseline remains stable in the first one to two years (Sachdev et al., 2004; del Ser et al., 2005; Rasquin et al., 2007). An older age (Rasquin et al., 2004; del Ser et al., 2005), lower education level (Rasquin et al., 2004), prestroke cognitive decline (del Ser et al., 2005), and diagnosis of CIND at baseline (Serrano et al., 2007; Sachdev et al., 2009) have all been found predictive of delayed dementia or cognitive decline.

Only a few longitudinal studies have assessed imaging variables. Altieri et al. (2004) followed-up 191 non-demented stroke patients for

four years and found cortical atrophy (visual rating, Hazard ratio = 3.4, p = 0.004) and multiple lesions (Hazard ratio = 3.4, p = 0.009) to be predictors of delayed dementia. A volumetric MRI study also confirmed the role of cortical atrophy in predicting dementia in SIVD (Fein et al., 2000). Global atrophy, however, results from aging, as well as from vascular risk factors or ischemic vascular lesions, and the strong correlation between global atrophy and age may blur the clinical implications of this study.

WMLs, also termed leukoaraiosis, are focal or confluent on Proton Density/T2 or FLAIR MRI. Longstreth et al. (1996) observed WMLs in 96% of community volunteers over 65 years of age. WMLs are generally considered to be features of cerebral SVD. Occlusive venous and arterial disease, disruption of the blood brain barrier and edema, are regarded as pathomechanism of WMLs (Black et al., 2009). WMLs have also been linked to cognitive impairment and cognitive decline (Paul et al., 2005; Mosley et al., 2005) in healthy subjects, as well as in patients with AD (Burns et al., 2005; Bracco et al., 2005). A few studies using visual rating methods have found that WMLs also contribute to longitudinal cognitive decline in the stroke cohort (Henon et al., 2001; Cordoliani-Mackowiak et al., 2003; Dufouil et al., 2009). Dufouil et al.

(2009) conducted a four-year follow-up study and found a severe WMLs load (OR = 7.7, $p < 0.005$) to be a strong predictor of dementia and cognitive decline in patients with a CVD history. However, other studies (Sachdev et al., 2004; Altieri et al., 2004; Rasquin et al., 2005; Firbank et al., 2007) have questioned their conclusions including three studies employing MRI volumetry to assess WMLs (Mungas et al., 2002; Sachdev et al., 2004; Firbank et al., 2007). Further MRI volumetric studies are required to confirm whether WMLs predict cognitive decline in stroke patients.

Hippocampal atrophy, which is commonly regarded as a feature of AD, is also present in subjects with SIVD (Fein et al., 2000; Bastos-Leite et al., 2007), and the severity of hippocampal atrophy can also differentiate AD from VCI (Burton et al., 2009). Cross-sectional studies have found a significant association between medial temporal lobe atrophy (MTLA) or hippocampal atrophy and cognitive impairment in stroke (Bastos-Leite et al., 2007; Grau-Olivares et al., 2007), although Sachdev et al. (2007) questioned these findings. Firbank et al. (2007) recruited 79 non-demented stroke survivors aged > 75 years (mean age 80) and followed them up for two years. They found MTLA (visual rating) rather than WML volume to predict cognitive decline two years

after the index stroke. The only longitudinal study employing volumetry of the hippocampus included 50 patients with lacunar stroke (including seven with clinical dementia rating [CDR] = 1.0 at baseline) and reported that hippocampal atrophy did not predict cognitive decline in these patients (Mungas et al., 2002). In the study carried out by Firbank et al. (2007), the sample included only elderly stroke patients, who may have had more underlying AD pathological changes than a consecutive stroke cohort. In that carried out by Mungas et al. (2002), the interval from stroke to neuropsychological assessment was not constant, which may have affected the cognitive changes following stroke. Thus, the role played by hippocampal atrophy in cognitive decline following stroke remains unconfirmed.

CMBs are focal deposits of hemosiderin that indicate prior micro-hemorrhages and are visible in gradient echo images on MRI (Vernooij et al., 2008). CMBs are related to cerebral amyloid angiopathy and to SVD. Recent evidence also suggests that CMBs may be an important cause of cognitive impairment in subcortical VaD (Won et al., 2007), in which they are associated with cognitive dysfunction, particularly executive dysfunction (Werring et al., 2004). To date, no study has attempted to assess the role of CMBs in cognitive decline in stroke.

1.3. Psychiatric morbidity following stroke

1.3.1. Poststroke depression

PSD is the most common psychiatric disorder following stroke, experienced by between 11% and 50% of stroke survivors (Eastwood et al., 1989; Desmond et al., 2003). This wide range in PSD estimates is due to differences in research methods and samples. Longitudinal studies have suggested the prevalence of PSD increases within two to three years after stroke (Astrom et al., 1993), but data on PSD in Chinese populations are limited. Tang et al. (2005) investigated 189 consecutive Chinese patients from an acute hospital and found 16.4% of them to experience some type of depression (DSM-IV criteria) at three months after the index stroke. PSD is associated with the impaired recovery of cognitive function (Robinson et al., 1986; House et al., 1991; Spalletta and Caltagirone, 2003) and the activities of daily living (Pohjasvaara et al., 2001). Patients with diagnoses of major or minor depression after stroke are 3.4 times more likely to die within 10 years of a stroke than are non-depressed patients (Morris et al., 1993).

Diagnosing depression according to the DSM criteria (e.g., DSM-III and IV) is the most common approach (Sanjit et al., 2004), although the severity of depressive symptoms can also be assessed with the Hamilton Depression Rating Scale (HDRS), Zung Self Report Depression Questionnaire, Geriatric Depression Scale (GDS), and Beck Depression Inventory (BDI) (Sanjit et al., 2004; Tang et al., 2004).

It is important to identify those at risk of PSD. Its risk factors have been found to include functional and cognitive impairment, a previous history of depression and stroke, being female, an older age, hypercortisolism, and poor social support (Terroni et al., 2003). Many studies have attempted to find the neuroanatomic correlates of PSD. Despite extensive research, however, the role of infarct location in PSD pathogenesis remains uncertain (Astrom et al., 1993; Herrmann et al., 1995; Vataja et al., 2004). In meta-analysis of 34 primary studies (Carson et al., 2000), no association was found between lesion location and PSD. Differences in depression measurement, study design, and presentation of the results may have contributed to the heterogeneity of the findings (Sanjit et al., 2004), although some studies have suggested that lesions involving the structures of the frontal-subcortical circuits (FSC) (Vataja et al., 2004; Tang et al., 2005; Hama et al., 2007) may be

more likely to produce PSD. Evidence obtained using the Xenon inhalation method also indicates that regional cerebral hypoperfusion may be a possible mechanism (Yamaguchi et al., 1992).

PSD treatment has been examined in several placebo-controlled, randomized clinical trials with nortriptyline, citalopram, and sertraline and shown their efficacy (Lipsey et al., 1984; Lazarus et al., 1994; Andersen et al., 1994; Rasmussen et al., 2003). The progression of recovery following stroke can be altered by treating depression, and such treatment has also been shown to improve recovery in activities of daily living and cognitive impairment and to decrease mortality (Jorge et al., 2003).

1.3.2. Poststroke emotional lability

Emotional lability (EL) is a condition defined by uncontrollable episodes of laughing, crying, or both (Parvizi et al., 2006). Uncontrollable laughter or crying may be triggered in poststroke patients by even a mild emotional stimulus, although, less commonly, poststroke EL (PSEL) may occur for no apparent reason. PSEL is sometimes referred to in the literature as poststroke emotional

incontinence (Kim, 1997), pathological laughing and crying (Robinson et al., 1993), and poststroke emotionalism (Langhorne et al., 2000). The burst of laughter or crying usually lasts from several seconds to several minutes, and it frequently recurs, sometimes dozens of times per day. PSEL usually begins within weeks of a stroke, lasts for one week to a few years (Ceccaldi et al., 1993; Kim, 1997), and takes a fluctuating clinical course (Dark, 1996). Although PSEL often coexists with PSD, it is considered to be an emotional disorder independent of it (Kim and Choi-Kwon, 2000). PSEL is distressing and embarrassing for sufferers. It is socially disabling and may interfere with stroke rehabilitation (Andersen et al., 1993). To date, however, healthcare professionals have paid scant attention to the condition.

According to reports in the literature, PSEL prevalence ranges from 11-52% (Schiffer and Pope, 2005) in stroke survivors in the first three to six months after the index stroke. The condition is also relatively common in Chinese stroke survivors. A hospital-based, cross-sectional study of 127 Chinese patients in Hong Kong found 17.9% of them to suffer from PSEL at three months post-index stroke using Kim's criteria and 6.3% of them to do so using those of House et al. (Tang et al., 2004).

Only a few studies have explored the clinical correlates of PSEL. For example, female stroke patients have been reported to be at greater risk of PSEL (Kim and Choi-Kwon, 2000). PSEL patients tend to have greater stroke severity (Kim and Choi-Kwon, 2000), and stroke patients with concurrent depression or a history of depression appear more likely to suffer from PSEL (Langhorne et al., 2000; Tang et al., 2004). Cognitive impairment is also a possible correlate of PSEL (Asfora et al., 1989).

The neuropathological underpinnings of PSEL have yet to be determined, although patients with cortical infarcts appear to be at greater risk (Tang et al., 2004). More detailed observations have revealed that EL in neurological diseases may be induced by anterior cortical (Kim and Choi-Kwon, 2000) and frontal infarction (Feinstein et al., 1999). Subcortical strokes, particularly those in the basal ganglia (lenticulocapsular area) (Kim and Choi-Kwon, 2000; Kim, 2002) have also been linked to PSEL. However, studies with large sample sizes and sophisticated brain imaging analysis are limited. Recent evidence does not support the supposition that a specific lesion produces PSEL, except for the structures along the FSC (Cummings, 1993). The FSC originate in the frontal cortex, project to the striatum (caudate, putamen, and

ventral striatum), connect to the globus pallidus and substantia nigra, and from there to the thalamus. They are known to modulate emotion and affective behavior. In a study of PSEL among the Chinese (Tang et al., 2005), PSEL subjects were found to have significantly more infarcts in the frontal lobe or basal ganglia. A significant correlation between PSEL severity and frontal infarcts was also detected. Interruption of the other circuits that connect the prefrontal cortex (PFC) and limbic system may also play a role in the development of PSEL (Moller et al.,2007). Neurochemical studies have shown the condition to be predominantly related to serotonergic system dysfunction (Andersen et al., 1993).

To complicate matters, PSEL has also been observed in patients without acute lesions, which suggests that prestroke cerebral abnormalities (e.g., silent lacunar infarcts, CMBs, and brain atrophy) may also contribute to, or at least increase the likelihood of, PSEL development.

It is imperative that PSEI be treated as early as possible to avoid negative effects on patients' social relations and quality of life. Antidepressants may be an effective treatment option (Robinson et al., 1993; Andersen et al., 1993), with pooled analysis of four studies that evaluated nortriptyline, citalopram, sertraline, and fluoxetine treatment

showing response rates of 96% for active medication and 27.5% for a placebo (Robinson, 2006).

1.3.3. Insomnia symptoms

Insomnia, which involves difficulties in initiating or maintaining sleep or early awakening with the inability to fall asleep again (Estivill et al., 2003), is a common complaint among stroke survivors (Palomaki et al., 2003). As insomnia may affect their prognosis and quality of life, it should be taken into consideration in the treatment and rehabilitation of stroke survivors.

Data on insomnia or insomnia symptoms in stroke, however, are limited. A Finnish study (Leppavuori et al., 2002) found insomnia complaints in 56.7% of stroke patients, with 38.6% meeting DSM-IV criteria A-C for insomnia diagnosis. Another study conducted in Finland revealed that insomnia complaints occurred in 49% of patients at 18 months after stroke (Palomaki et al., 2003). Insomnia has been associated with the severity of disability, anxiety, dementia, and the use of psychotropic drugs (Leppavuori et al., 2002), thus suggesting that its development is multi-factorial. Depression and anxiety affect 16-40% of

stroke patients (Chemerinski and Robinson, 2000; Pohjasvaara et al., 1998; Tang et al., 2005) and may partly account for insomnia symptoms.

Regulation of the sleep/wake cycle requires the anatomical and functional integrity of the neuronal networks in cortical and subcortical structures (Nofzinger, 2004). Leppavuori et al. (2002) examined the neuroradiological correlates of stroke-related insomnia and found the major dominant stroke to be associated with new-onset insomnia in 277 ischemic stroke patients. However, the relationship between brain lesions and insomnia is still poorly understood (Autret et al., 2001).

Li Pi Shan and Ashworth (2004) conducted a randomized, crossover, double-blinded trial comparing the effects of lorazepam and zopiclone on insomnia in patients with stroke and brain injury and found both drugs equally effective in the treatment of insomnia.

CHAPTER 2 OBJECTIVES

Poststroke cognitive impairment and psychiatric morbidity are common in stroke survivors, interfering with recovery and leading to poor prognosis. The imaging correlates of longitudinal poststroke cognitive decline are understudied, and data on poststroke cognitive impairment and psychiatric morbidity in Chinese populations are limited. The purpose of the studies reported in this thesis was to investigate the clinical and imaging characterization of cognitive impairment and psychiatric morbidity in Chinese stroke patients. Their specific objectives were as follows.

(1) To investigate the prevalence and clinical and imaging predictors of poststroke cognitive impairment and cognitive decline; to demonstrate the evolution of vascular CIND in a longitudinal study; and to explore the role of WMLs and hippocampal atrophy in poststroke cognitive impairment and cognitive decline and their effects on cognitive domains. We hypothesized that WMLs, rather than hippocampal atrophy, are important predictors of poststroke cognitive

impairment and cognitive decline, and affect multiple cognitive domains.

(2) To explore the effect of PFC atrophy and its subdivisions on verbal fluency in poststroke patients. We hypothesized that PFC, or its subdivisions, is associated with verbal fluency performance and that there is a sex difference in the impairment of such fluency.

(3) To assess the relationship between large artery disease (LAD) and PSD. We postulated that the frequency of PSD is higher in patients with small subcortical infarcts (SSIs) resulting from LAD than from SVD.

(4) To examine the role of microbleeds (MBs) in PSEL. We hypothesized that MBs play a role in the development of PSEL.

(5) To investigate the prevalence and clinical and imaging predictors of insomnia symptoms in stroke patients. We hypothesized that the location of the infarction contributes to poststroke insomnia symptoms.

(6) To explore the correlates of lobar atrophy in stroke patients. We hypothesized that frontal lobe atrophy (FLA) is associated with cerebral SVD in stroke patients.

CHAPTER 3 RECRUITMENT OF THE STUDY PARTICIPANTS

The study participants were all recruited from the Acute Stroke Unit (ASU) of the Prince of Wales Hospital (PWH), a university-affiliated general hospital serving a population of 800,000 in Hong Kong. All had been admitted to the ASU because of acute first-ever or recurrent ischemic stroke. They were screened for participation in a psychiatric (or cognitive) interview at three months after stroke.

Patients were invited to participate in the psychiatric (or cognitive) interview if they (1) were aged ≥ 40 years; (2) had acute first or recurrent ischemic stroke; (3) were of Chinese descent and fluent in the Cantonese dialect; and (4) were willing and able to give informed consent. Patients were excluded if they (1) had a central nervous system disease other than stroke; (2) did not have an MRI scan; (3) had significant aphasia or dysarthria (a National Institutes of Health Stroke Scale [NIHSS] best language score ≥2 or dysarthria score ≥ 2) to the extent of precluding meaningful communication; (4) had a recurrent stroke within three months of the index stroke; (5) were too fragile or had had prolonged hospitalization; or (6) had a severe co-morbid

disease (e.g., malignant tumors, schizophrenia, decompensatory chronic heart failure, or chronic respiratory failure).

The recruitment period can be divided into two stages. Subjects involved in the poststroke psychiatric studies (Chapters 6-8) were recruited from December 2004 to June 2007, and those involved in the poststroke cognitive study (Chapters 4 and 5) were recruited between June 2006 and July 2008. The participants in the final study (Chapter 9) constituted a consecutive sample of ischemic stroke patients with an MRI examination who were recruited from May 2005 to May 2007. They were not restricted to those attending the aforementioned interviews.

Flow charts illustrating the recruitment periods and sample numbers of the various studies reported herein are presented in Figures 3-1 and 3-2.

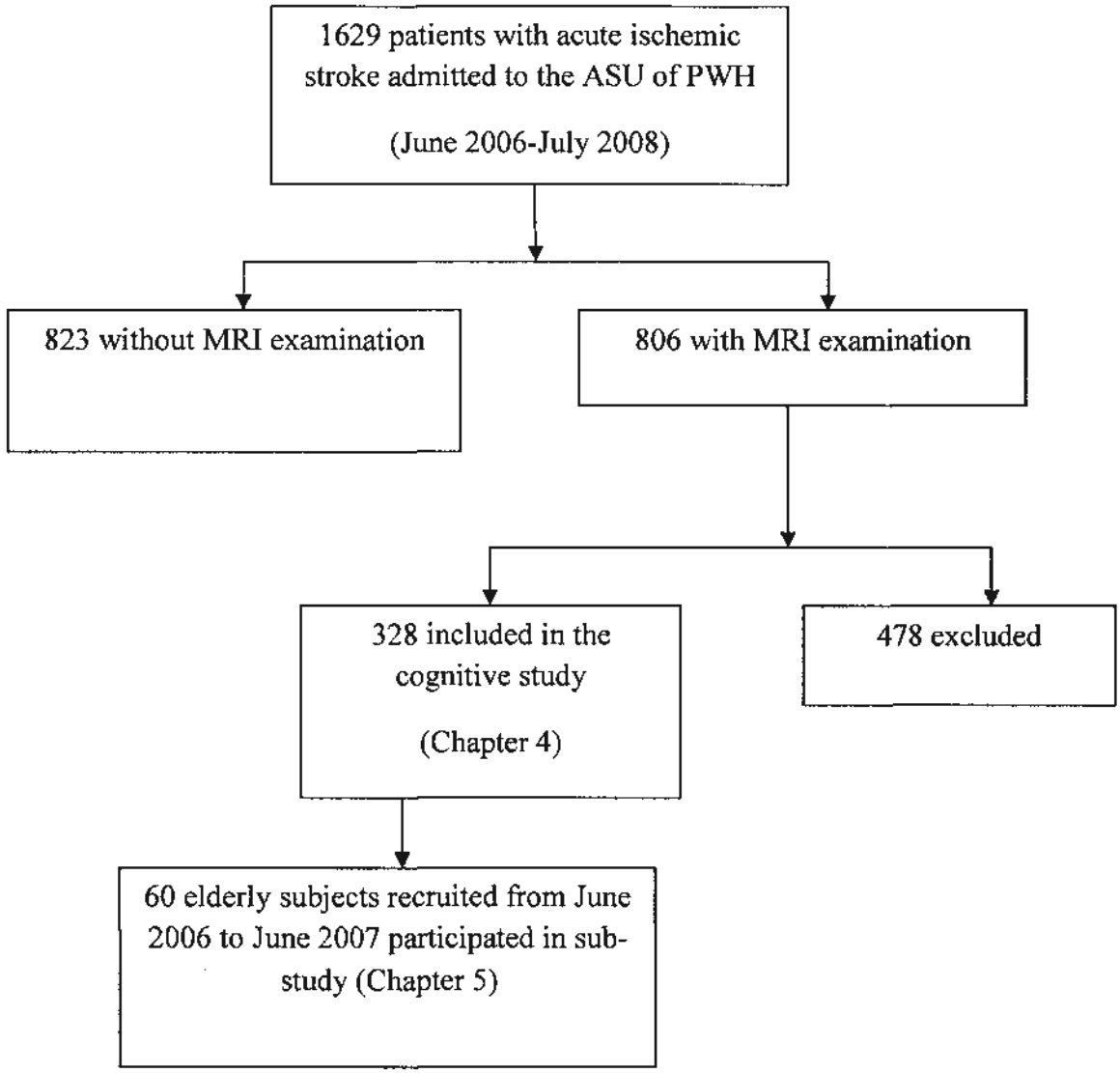


Figure 3-1. Flow chart of participant recruitment for poststroke cognitive study (Chapters 4 and 5).

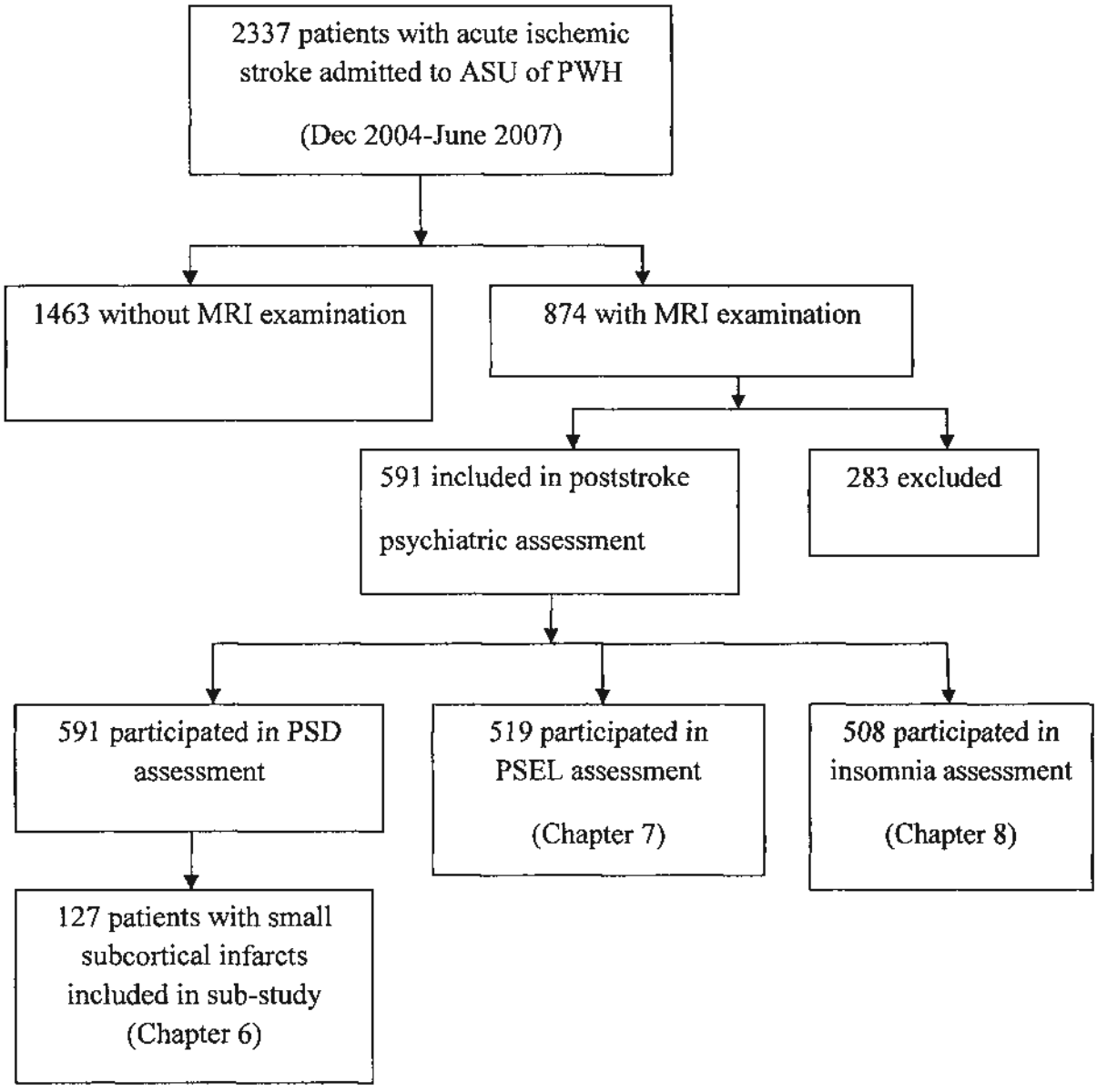


Figure 3-2. Flow chart of participant recruitment in PSD, PSEL, and poststroke insomnia studies (Chapters 6-8).

CHAPTER 4 COGNITIVE IMPAIRMENT IN CHINESE STROKE PATIENTS: A ONE-YEAR FOLLOW-UP STUDY

4.1. Background and objectives

Cognitive impairment is common in poststroke patients, with up to 64% of them displaying some degree of such impairment (Jin et al., 2006) and up to a third developing frank dementia (Pohjasvaara et al., 1997; Barba et al., 2000). As previously noted, Hachinski and Bowler (1993) coined VCI to refer to any CVD-related cognitive impairment, and thus it encompasses all levels of cognitive decline, from the earliest stage to severe global decline, related to all causes of CVD. CIND is used to describe a cognitive state that is characterized by mild impairment but does not meet the criteria for dementia (Ebly et al., 1995).

Data on cognitive impairment in stroke have accumulated over the past 10 years, with many studies attempting to illustrate the prevalence and clinical and imaging predictors of poststroke cognitive impairment. Longitudinal studies of such impairment, however, are limited. The evolution of CIND following a stroke is bilateral (Tham et al., 2002;

Rasquin et al., 2004), with 5-12.5% of stroke survivors (Tham et al., 2002; Ballard et al., 2003; Srikanth et al., 2004) developing dementia in the first year after the index stroke and almost half developing it within five years (Wentzel et al., 2001) .

The wide use of imaging techniques, particularly MRI, in clinical stroke practice has facilitated the detection of many important lesions apart from infarctions. Moreover, MRI allows the easier and more accurate in vivo assessment of WML volumetry and hippocampal size, which is helpful in providing insight into the biological substrates of cognitive impairment in stroke.

To date, only a few longitudinal studies have included imaging variables. Of these studies, only four included MRI analysis (Mungas et al., 2002; Firbank et al., 2006; Williamson et al., 2008; Dufouil et al., 2009). With regard to the measurement of infarcts, WMLs, hippocampal size, and global atrophy, most of these studies employed only qualitative methods (e.g., the visual rating method). WML volume was quantified in only two studies (Mungas et al., 2002; Firbank et al., 2006). These studies were also the only two to measure hippocampal size, one with the visual rating method (Mungas et al., 2002) and the other with the volumetric method (Firbank et al., 2006). No study to date has

analyzed CMBs. In addition, the sample sizes in these studies are relatively small, and no longitudinal study of poststroke cognitive impairment in a Chinese population that includes imaging data is available.

The role played by WMLs and hippocampal atrophy in stroke remains uncertain. WMLs have been linked to cognitive impairment and cognitive decline (Paul et al., 2005; Mosley et al., 2005) in healthy subjects, as well as in those with AD (Burns et al., 2005; Bracco et al., 2005). In cross-sectional studies in stroke cohorts, WMLs have been reported to be associated with VCI or VaD (Pohjasvaara et al., 2000; Burton et al., 2004; Sachdev et al., 2007). However, follow-up studies have failed to confirm the relationship between WMLs and poststroke cognitive decline due to conflicting results (Altieri et al., 2004; Firbank et al., 2006; Dufouil et al., 2009). Hippocampal atrophy, another critical structural change associated with cognition, has rarely been investigated in stroke subjects (Firbank et al., 2006). A longitudinal study investigating the volumetry of both WMLs and the hippocampus is thus needed to confirm their contribution to poststroke cognitive decline.

The effects of WMLs and hippocampal atrophy on different cognitive domains have been investigated in a stroke cohort. Most

studies have reported WMLs to be related to executive dysfunction (Vataja et al., 2003; Wen et al., 2004; Jonkinen et al., 2005), but their relationship with other cognitive domains has not been confirmed. Few studies have assessed a wide range of cognitive domains and employed a volumetric method to assess WMLs (Burton et al., 2003, 2004), and the effect of hippocampal atrophy on these domains has rarely been assessed (Sachdev et al., 2007).

This gap in the research motivated us to conduct a longitudinal study on poststroke cognitive decline in Chinese stroke patients, employing integrated and volumetric MRI analysis and a relatively large sample size. Our aim was to assess the role of WMLs and hippocampal atrophy on cognitive impairment and cognitive decline and on performance in individual cognitive domains.

4.2. Methods

4.2.1. Participants

All ischemic stroke patients consecutively admitted to the ASU of PWH between June 2006 and July 2008 were screened for neuropsychological assessment. The definition of ischemic stroke was according to the World Health Organization (WHO) criteria (WHO, 1988). Patients were invited to participate if they (1) were aged ≥ 40 years; (2) had an acute first or recurrent ischemic stroke; (3) were of Chinese descent and fluent in the Cantonese dialect; and (4) were willing and able to give informed consent. Patients were excluded if they (1) had a central nervous system disease other than stroke; (2) did not have an MRI scan; (3) had significant aphasia or dysarthria (NIHSS best language score ≥ 2 or dysarthria score ≥ 2) to the extent of precluding meaningful communication; (4) had a recurrent stroke within three months after the index stroke; (5) were too fragile to attend the interview; (6) had had prolonged hospitalization; (7) had a severe psychiatric disorder (e.g., schizophrenia); or (8) had a severe co-morbid disease (e.g., malignant tumors, decompensatory chronic heart failure, or chronic respiratory failure) that could affect the follow-up.

Patients with acute stroke did not receive an MRI examination if they had a magnetic foreign body within the eye or orbit, or cardiac pacemakers, magnetic intracranial aneurysm clips, and cochlear

implants, or had claustrophobia, or were medically-unstable. In PWH, stroke patients with cardioembolism were often excluded from MRI examination.

Basic socio-demographic and clinical data, including age, sex, education level, hypertension, diabetes mellitus, ischemic heart disease, hyperlipidemia, prior stroke, and NIHSS score on admission, were retrieved from the ASU stroke registry. Hypertension was defined as repeated blood pressure measures of $\geq$ 140/90 mm Hg or the need for chronic antihypertensive medication; diabetes mellitus was defined as fasting blood glucose $\geq$ 7.0 mmol/l, postprandial blood glucose $\geq$ 11.1 mmol/l, or current diabetes mellitus treatment; hyperlipidemia was defined as a total cholesterol level of at least 220 mg/dl, a low-density lipoprotein (LDL) cholesterol level of at least 140 mg/dl, or a triglyceride level of at least 150 mg/dl; and ischemic heart disease was defined as the presence of myocardial infarction, angina pectoris, or other ischemic heart disease.

Ethical approval was obtained from the Chinese University of Hong Kong, and all of the participants or their relatives signed a consent form.

4.2.2. Neuropsychological assessment

The stroke subjects had a baseline assessment at a research clinic three months following their stroke. The thesis author and a research assistant administered a number of neuropsychological and psychiatric tests, including the modified Vascular Dementia Battery (VDB; Tham et al., 2002), which comprises seven cognitive domains (Table 4-1): executive function (FAB; Dubois et al., 2000; Mok et al., 2004); attention (Forward and Backward Digit Span [Wechsler, 1997a] and an auditory detection test [Tham et al., 2002]); language (the modified Boston Naming Test [Cheung et al., 2004] and a verbal fluency [animal and food] test [Chui et al., 1997]); verbal memory (delayed word list recognition and immediate word list, delayed word list, immediate story, and delayed story recall [Wechsler, 1997b]); visual memory (immediate and delayed picture recall and delayed picture recognition [Wechsler, 1997b], and Visual Reproduction I and II from the Wechsler Memory Scale III [WMS-III; Wechsler, 1997b]); visuoconstruction (the Clock Drawing Test [Sunderland et al.,1989] and Wechsler Adult Intelligence Scale III [WAIS-III] Block Design [Wechsler, 1997a]) and visual reproduction (copy) (WMS-III [Wechsler, 1997b]); and visuomotor speed (Symbol Digit Modalities Test [Smith, 1991], Digit Cancellation

Test [Lewis and Rennick, 1979], and Maze Task [Tham et al., 2002]). A subject was judged to have impairment in an individual cognitive domain if his or her performance in at least 50% of the tests for that domain was impaired. The cut-offs for all of the neuropsychological tests were based on local data adjusted by age and/or education level. When normative data were applicable, test performance was judged to be "impaired" if it fell below the fifth percentile for persons of a similar age and educational background (Williamson et al., 2008). Global cognitive function was also assessed, using the Chinese Cantonese version of the MMSE (CC-MMSE) (Chui et al., 1994). A 15-item Chinese version of the GDS (GDS-15) (Lim et al., 2000) was employed to assess depressive symptoms. Prestroke cognitive function was evaluated with the Chinese version of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (Fuh et al., 1995) if the subject's relatives were available. If the prestroke IQCODE was ≥ 4.0 (average score), then he or she was considered to have prestroke dementia.

Table 4-1. Neuropsychological tests.

Domains	Neuropsychological Tests
Executive function	Frontal Assessment Battery (FAB)
Attention	Digit Span Forward
	Digit Span Backward
	Visual Memory Span Forward
	Visual Memory Span Backward
	Auditory Detection Test
Language	Modified Boston Naming
	Verbal Fluency: Animal
	Verbal Fluency: Food
Verbal memory	Word List Recall:
	Immediate Recall
	Delayed Recall
	Delayed Recognition
	Story Recall:
	Immediate Recall
	Delayed Recall
Visual memory	Picture Recall:
	Immediate Recall
	Delayed Recall
	Delayed Recognition
	WMS-III Visual Reproduction (VR):

	Immediate Recall (VR I)
	Delayed Recall (VR II)
	Delayed Recognition
Visuoconstruction	WMS-III Visual Reproduction (Copy)
	Clock Drawing Test
	WAIS-III Block Design
Visuomotor speed	Digit Cancellation Task
	Symbol Digit Modalities Test
	Maze Task

4.2.3. Follow-up

The aforementioned neuropsychological assessments were repeated in non-demented subjects one year after the baseline assessment (15 months after stroke) at the same research clinic. The recurrence of stroke and death during the three- and 15-month intervals were also recorded. The stroke patients were also followed-up by their physicians and received therapy and/or drugs at public and private outpatient clinics.

4.2.4. Definition of cognitive impairment and dementia

Cognitive impairment was defined as impairment in at least one cognitive domain (Ebly et al., 1995). Dementia was diagnosed according to DSMIV criteria (American Psychiatric Association, 1994) by a psychiatrist (WKT) and the thesis author separately. At baseline assessment, a diagnosis of dementia or not was determined by WKT in 266 (81.1%) patients and the rest (18.9%) was determined by the thesis author. At follow-up, 95 (33.2%) were determined by WKT and 161 (66.8%) by the thesis author.The agreement of a dementia diagnosis was

tested in 45 subjects which were rated by the above two researchers separately.The kappa value for the agreement was 0.656. Delayed dementia was referred to dementia at follow-up (Altieri et al.,2004). CIND was defined as "cognitive impairment, not meeting the criteria of dementia", according to the method of Ebly and colleagues in the Canadian Study of Health and Aging (Ebly et al.,1995) by the above two researchers. Cognitive decline was confirmed if the cognitive status changed from cognitive intact to CIND or from CIND to dementia (Tham et al., 2002). The etiologies of dementia were classified as VaD or "dementia due to multiple etiologies," according to the DSM-IV criteria (see Appendix 1 and II for the DSM-IV criteria for dementia and VaD).

4.2.5. MRI measurement

MRI, including diffusion-weighted imaging (DWI), T1 weighted imaging, T2 weighted imaging, Fluid Attenuation Inversion Recovery (FLAIR), $T2^*$ weighted gradient echo, and T1 weighted 3-dimensional multiplanar reconstruction (3D-MPR), was performed on each

participant with a 1.5 T system (Sonata, Siemens Medical, Erlangen, Germany) within seven days of admission.

DWI spin echo and echo planar imaging (EPI)(TR/TE/excitation = 180/122/4, matrix = 1286128, field of vision [FOV] = 230 mm, slice thickness/gap = 5 mm/1 mm, EPI factor = 90, acquisition time = 55 s) with three orthogonally applied gradients was employed with b values of 1000 and 500. Axial gradient echo images were acquired as the second sequence, with imaging parameters of TR/TE/excitation = 350/30/2, flip angle = 30 u, slice thickness/gap = 5 mm/0.5 mm, FOV = 230 mm, matrix = 256 × 256, and acquisition time = 5 min 4 s. Axial SE T1 (TR/TE/excitation = 425/14/2, FOV = 230 mm, slice thickness/gap = 5 mm/0.5 mm, matrix = 256 × 256, acquisition time = 4 min 28 s) and TSE T2 (TR/TE/excitation = 2500/120/1, turbo factor = 15, FOV = 230 mm, slice thickness/gap = 5 mm/0.5 mm, matrix = 2566256, acquisition time = 1 min 39 s) images were also acquired.

The thesis author assessed the participants' MRIs 6-12 months after their neuropsychological interviews without reference to their cognitive status diagnosis. MRI assessment was conducted with information only on name, identity card number, sex, and age. Reliability tests of the MRI variables were carried out by two neurologists (XYC and YYX).

All measurements were performed with General Electric (GE) Advantage station system except for those of the WMLs. The MRI parameters analyzed included the following.

Brain infarcts

Acute infarcts were identified on the DWI, with hypointensive signals on the corresponding apparent diffusion coefficient (ADC) map. Old infarcts were identified on the T1 weighted images and confirmed on the corresponding T2 weighted images. The regions of interest (ROI) of the acute and old infarcts were outlined manually, and the area was produced automatically. The total volume was calculated by multiplying the total area by the sum of the slice thickness and gap. The sites of the infarcts included the frontal, temporal, parietal, and occipital lobes, subcortical white matter, basal ganglia, thalamus, and infratentorial region. Multiple infarcts and those involving more than one location were counted in all locations in which they occurred. Inter- and intra-rater reliability tests of the infarct measurements were carried out on 20 participants. For the volume of infarcts, the inter-rater intraclass correlation coefficients (ICC) were 0.86 (acute) and 0.84 (old), and the

intra-rater ICC 0.95 (acute) and 0.92 (old); for the number of infarcts, the inter-rater ICC were 0.93 (acute) and 0.89 (old), and the intra-rater ICC 0.96 (acute) and 0.91 (old).

WMLs volume

WMLs were measured with Easy Vision 4.3 on the FLAIR sequence using the semi-automated segmentation method. Seeds dropped on the structure of interest grew automatically to include all connected pixels until the entire structure was outlined, as illustrated in Figure 4-1. The volume of the pixels outlined was then shown automatically. This method has been used in a previous study (Mok et al., 2008). Inter- and intra-rater reliability tests of the measurement of WML volume were performed on 20 participants, with an inter-rater ICC of 0.92 and an intra-rater ICC of 0.94.

Hippocampal volume

Hippocampal volume was measured on the T1 weighted 3D-MPR sequence with a slice thickness of 1.5 mm. The hippocampus boundary

was defined according to the widely accepted description in Watson et al. (1992). The hippocampus contains 17-22 slices from the first visible anterior portion of the hippocampal head (the pes hippocampus) through the most posterior aspect of the hippocampus (hippocampal tail) at the point of the crus of the fornix from its fimbria (excluded at this level are the crus of the fornix, the isthmus of the cingulate gyrus and the parahippocampal gyrus). This boundary is estimated to cover 90-95% of the total hippocampal formation (Watson et al., 1992). The measurement of hippocampal volume is shown in Figure 4-2. The ROI was outlined manually using an electronic cursor and an area given automatically. The volume was obtained by the multiplication of the area and the slice thickness (1.5 mm). Inter- and intra-rater reliability tests of this measurement were performed on 20 participants (inter-rater ICC = 0.88; intra-rater ICC = 0.92).

CMBs

CMBs were defined as small (2-10 mm) hypointense lesions on the $T2^*$ weighted gradient echo sequence, with symmetric basal ganglia calcification and flow void artifacts of the pial blood vessels excluded

(Dichgans et al., 2002). A sample of the CMBs is shown in Figure 4-3. The CMB locations included the frontal, parietal, temporal, and occipital lobes, basal ganglia, thalamus, and infratentorial region, with the number in each location recorded. Inter- and intra-rater reliability tests of the CMB measurement were performed on 30 participants. Both inter- and intra-rater agreement was good (presence of CMBs: inter-rater kappa = 0.78; intra-rater kappa = 0.85; number of CMBs: inter-rater ICC = 0.91; intra-rater ICC = 0.95).

Intracranial volume, lateral ventricular volume, and ventricle-to-brain ratio (VBR)

Intracranial volume (ICV) was calculated by outlining the outer surface of the forebrain (excluding the pons and medulla at the level of the brachium pontis) in consecutive axial T1WI sections; the resulting areas were then multiplied by slice thickness and summed over the slices (Williamson et al., 2008). Lateral ventricular volume (LVV) was measured using the same method and restricting the lateral ventricle boundary. The ventricle-to-brain ratio (VBR) is considered to be an acceptable measure of whole brain atrophy (Papageorgiou et al., 1982).

Measurements were made on two portions of the same image in which the lateral ventricle was visualized with the maximal size (Mizumasa et al., 2004). The VBR is defined as the ratio of the value of the ventricular area to the value of the brain area (Figure 4-4). Inter- and intra-rater reliability tests of these parameters were performed on 20 participants (ICV: inter-rater ICC = 0.95, intra-rater ICC = 0.97; LVV: inter-rater ICC = 0.92, intra-rater ICC = 0.94; VBR: inter-rater ICC = 0.91, intra-rater ICC = 0.95.

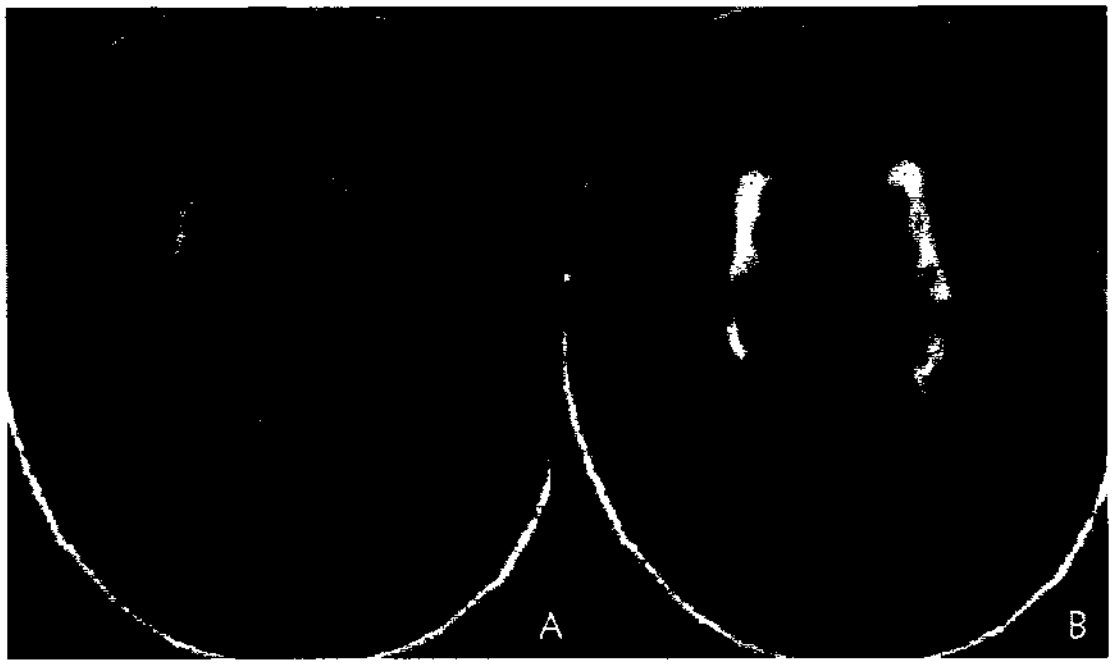


Figure 4-1. Measurement of WML volume on FLAIR image. (A) Original image. (B) After semi-automatic segmentation.

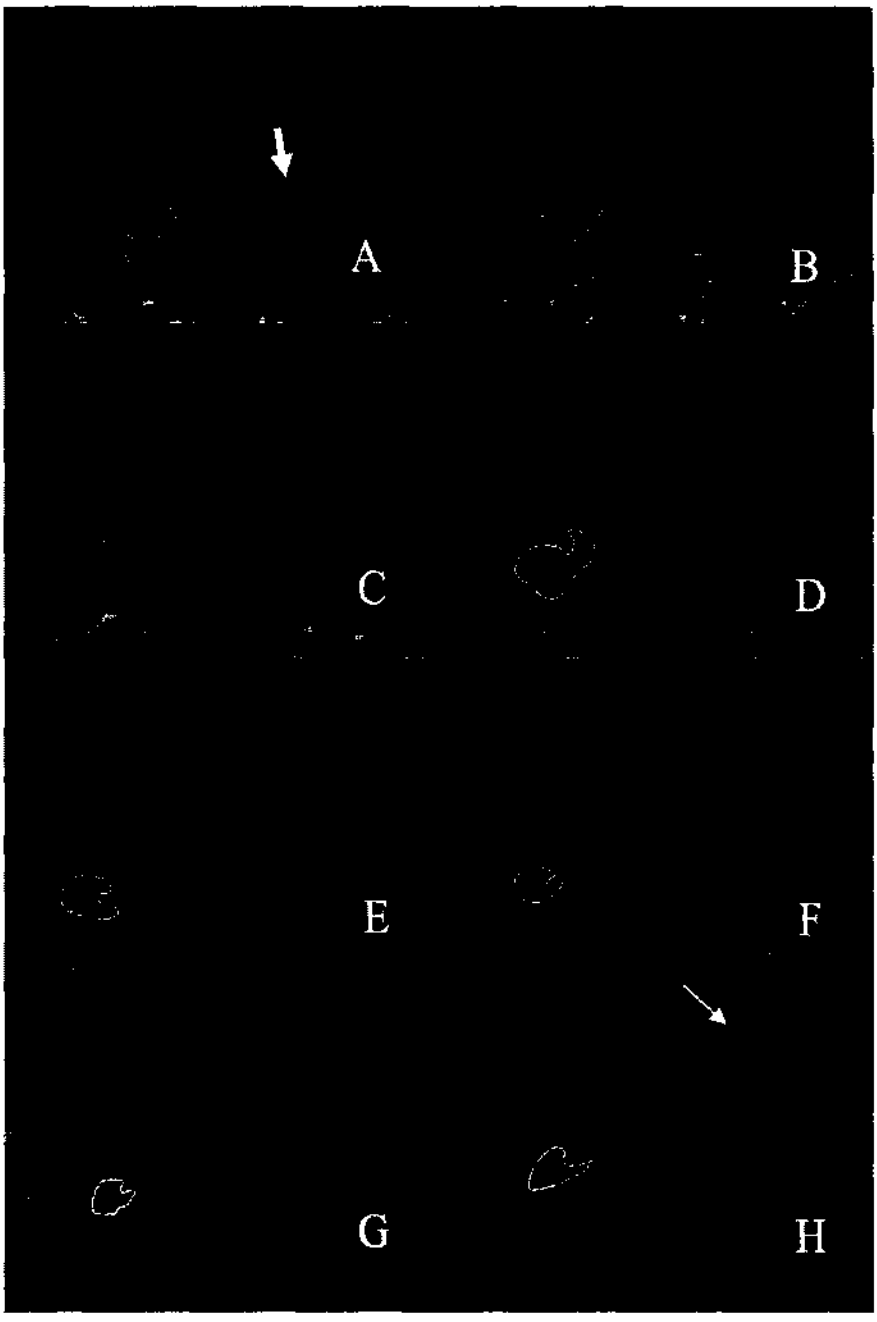


Figure 4-2: Selection of slices showing the measurement of hippocampal volume. (A) The first visible slice of the hippocampal head; the thick arrow refers to the amygdala. (H) The last slice of the hippocampus; the thin arrow refers to the crus of the fornix

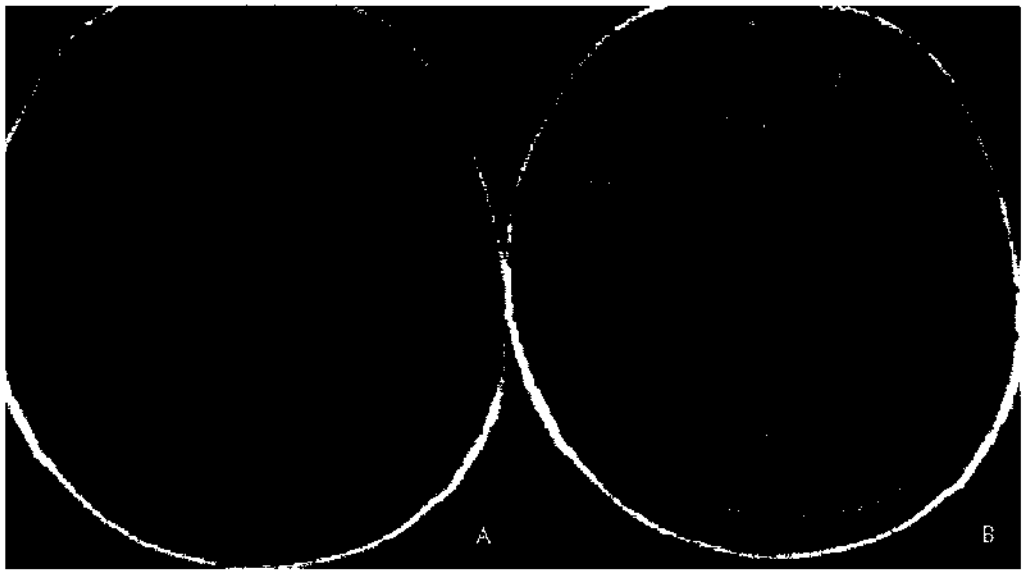


Figure 4-3: Measurements of the VBR were made on two portions of the same image in which the lateral ventricle was visualized with the maximal size. VBR = ROI area (A)/ROI area (B).

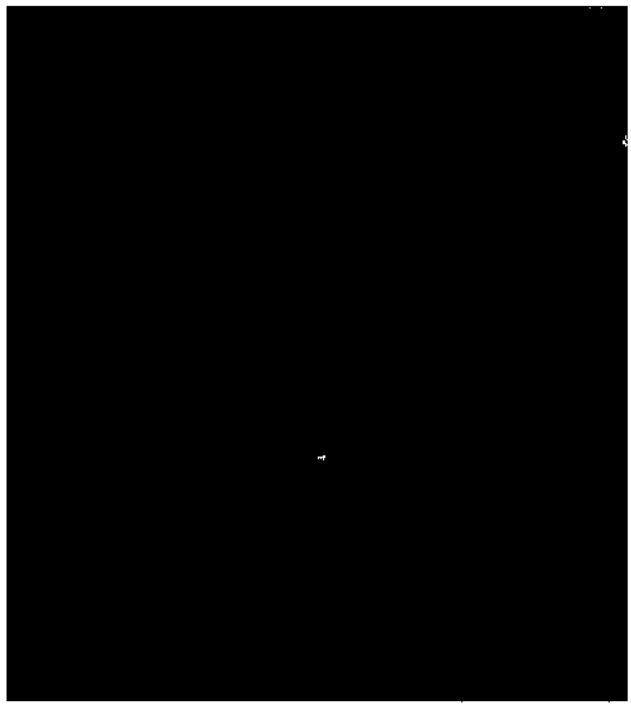


Figure 4-4: CMBs detected on $T2^*$ weighted gradient echo image.

4.2.6. Statistical analysis

All statistical analyses were performed using SPSS, Version 16.0 (SPSS, Chicago, Illinois).

Analysis of predictors of cognitive impairment, cognitive decline, and delayed dementia

Participants were first divided into two groups: "cognitive impaired" (all of these had CIND) and "cognitive intact" at three and 15 months after stroke. The difference in the proportions of the two groups was analyzed with Fisher's exact test or the Chi-square test. The continuous data were compared with t-tests or Mann-Whitney U tests, as appropriate. Variables with $p < 0.05$ in the univariate comparisons were included in the subsequent multivariate logistic regression model after assessing the correlation between the variables. To detect the effect of hippocampal atrophy on cognitive impairment, hippocampal volume was simultaneously entered into the logistic regression. Multivariate

logistic regressions were performed to determine the factors associated with cognitive impairment, with the level of significance set at < 0.05 (two-sided).

Participants were then classified into "with" and "without" cognitive decline groups, with the foregoing analysis repeated. Cognitive decline was defined as a change in cognitive status from "cognitive intact" to CIND or from CIND to dementia.

Finally, they were classified into "with delayed dementia" and "without delayed dementia" groups. Delayed dementia was defined as the development of dementia by the 15-month follow-up. Two logistic regression models were performed, with WMLs and hippocampal volume entered into them together with the other variables selected from the univariate analysis. The power was calculated in the non-significant predictor(s) with $\alpha = 0.05$ (two-sided) using PASS 2008 (NCSS, Utah, USA).

Analysis of the effects of WMLs and hippocampal volume on individual cognitive domain

Participants were classified into "impaired" or "unimpaired" in each of the seven cognitive domains at three months after stroke. Logistic regressions were conducted to test whether WML and hippocampal volume are significant predictors of impairment in each cognitive domain, adjusted for age, sex, years of education, NIHSS, and infarct location. The same procedure was repeated for new-onset impaired cognitive domains. Significance was set at < 0.01 (two-sided) due to multiple comparisons.

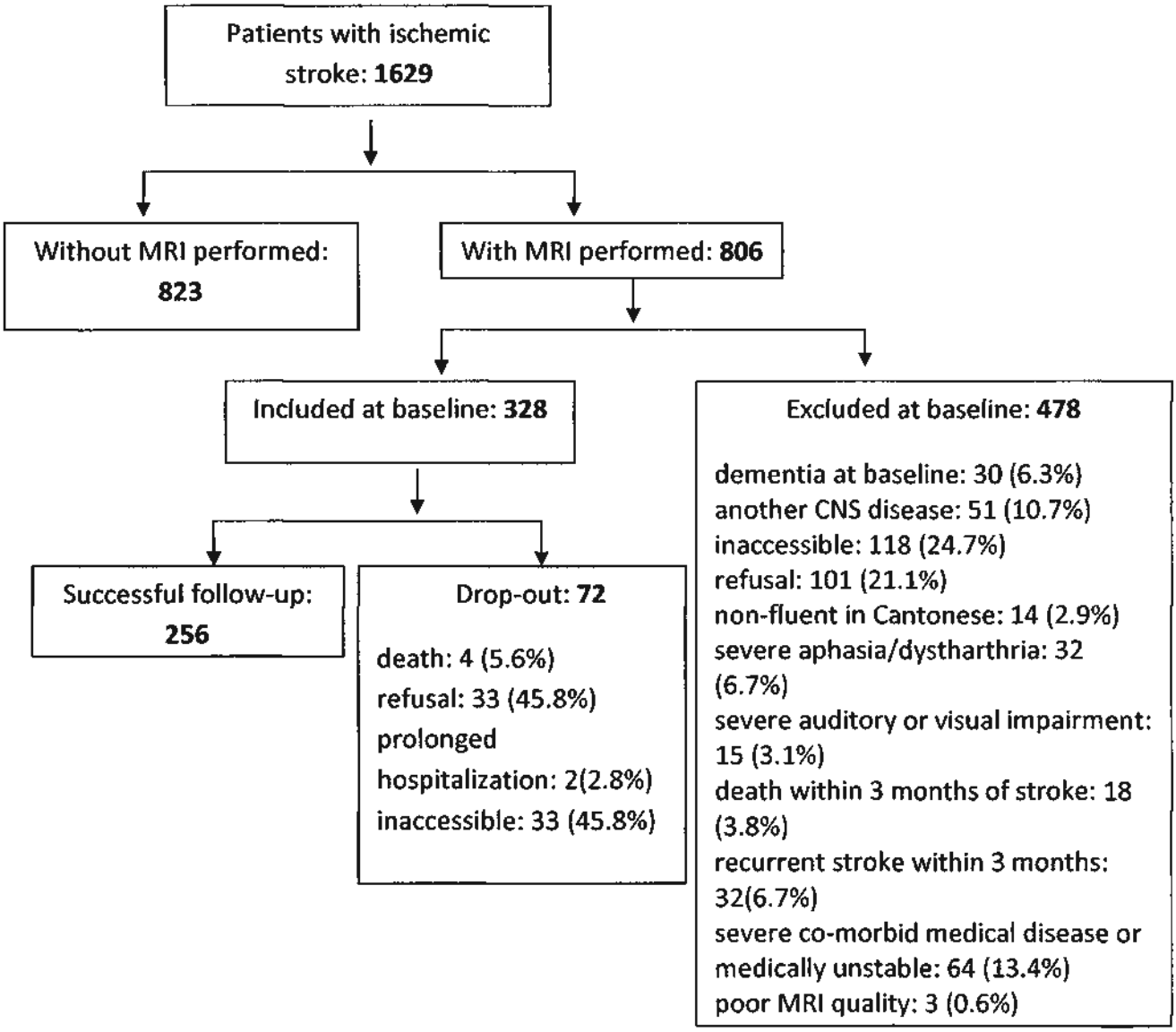
4.3. Results

4.3.1. Participants

As noted previously, between June 2006 and July 2008, 1629 patients were admitted to the ASU of PWH due to acute ischemic stroke and later discharged from hospital. Of these, 806 (49.5%) underwent MRI examination, although 478 (59.3%) were subsequently excluded from the study because they either failed to meet the inclusion criteria or met the exclusion criteria (Figure 4-5). The reasons for exclusion were:

30 (6.3%) had dementia at baseline; 51 (10.7%) had a CNS disease(s) other than stroke; 118 (24.7%) were inaccessible; 101 (21.1%) refused to participate; 14 (2.9%) were not fluent in Cantonese; 32 (6.7%) had severe aphasia/dysarthria on admission; 15 (31.%) had severe auditory or visual impairment; 18 (3.8%) died within three months of stroke; 32 (6.7%) had recurrent stroke within three months of the index stroke; 64 (13.4%) had a severe co-morbid disease or were medically unstable; and 3 (0.6%) had poor MRI quality. The final sample for the baseline (three months after index stroke) assessment thus included 328 (20.1%) patients. In comparison with the subjects who were excluded, those included were significantly younger (mean age: 68.2 ± 9.9 versus 73.0 ± 11.7, $p < 0.001$), more likely to be male (56.7% versus 47.2%, $p = 0.001$), and had fewer severe neurologic deficits (median of NIHSS: 4 versus 10, $p < 0.001$).

Figure 4-5. Participants included at baseline.



4.3.2. Baseline features of the participants

The mean (s.d.) age of the 328 subjects at the baseline assessment was 68.2 (9.9) years (range: 43-88 years). One hundred and eighty-six (56.7%) were male, 60 (18.3%) had a history of stroke, 218 (66.5%) had hypertension, 103 (31.4%) had diabetes, and 19 (5.8%) had ischemic heart disease. The median (interquartile range [IQR]) of NIHSS on admission was 4 (2-6), and the mean (s.d.) MMSE score at three months after stroke was 25.8 (3.4) (Table 4-2).

4.3.3. Univariate analysis of cognitive impairment at baseline

One hundred and eighty (54.9%) of the 328 patients had cognitive impairment (all were CIND) at baseline. The patients with CIND were significantly older (71.6 versus 64.2, $p < 0.001$), were more likely to be female (54.4% versus 29.7%, $p < 0.001$), had fewer years of education (median, 3 versus 6, $p < 0.001$), were more likely to suffer from diabetes (37.8% versus 23.6%, $p = 0.006$), were more likely to have had

a prior stroke (22.2% versus 13.5%, p = 0.042), and were less likely to have a smoking history (35.8% versus 47.6%, p = 0.030). These patients also had significantly higher NIHSS scores on admission (median, 4 versus 3, p < 0.001) and lower MMSE scores (median, 25 versus 28, p < 0.001) at three months after stroke (Table 4-3).

Comparison of the imaging variables showed the patients with CIND to have a larger old infarct volume (median, 0.15 mm versus 0.0 mm, p = 0.023), WML volume (median, 9.9 versus 4.7, p < 0.001), VBR (13.1% versus 11.1%, p < 0.001), and LVV (41.5 versus 31.6, p < 0.001). There was only a borderline significant difference in hippocampal volume between the two groups (p = 0.066) (Table 4-4).

4.3.4. Logistic regression of cognitive impairment at baseline

Age, sex, years of education, NIHSS, prior stroke, diabetes, old infarct volume, WMLs, VBR, and hippocampal volume were included into the logistic regression. LVV was not entered, as it was highly correlated with age (Pearson's r = 0.538) and VBR (Pearson's r = 0.834). In the logistic regression, age (odds ratio [OR] = 1.057, 95%

confidence interval [CI] = 1.025-1.090, $p < 0.001$), sex (female) (OR = 2.564, 95% CI = 1.463-4.494, $p = 0.001$), years of education (OR = 0.931, 95% CI = 0.874-0.991,$p = 0.024$), NIHSS (OR = 1.147, 95% CI = 1.046-1.257, $p = 0.024$), prior stroke (OR = 2.157, 95% CI = 1.023-4.546, $p = 0.043$), and WMLs volume (OR = 1.039, 95% CI = 1.015-1.063, $p < 0.001$) were found to be significant predictors of cognitive impairment at baseline (Table 4-5). WMLs volume was the only significant imaging variable in the regression model.

Table 4-2 Demographic and clinical characteristics of the subjects at baseline (n = 328).

Variables	Mean (s.d.)/median (IQR)/n (%)
Age	68.2 (9.9)
Sex (male)	186 (56.7%)
Education in years,	5 (1-9)*
Hypertension	218 (66.5%)
Diabetes	103 (31.4%)
Ischemic heart disease	19 (5.8%)
Hyperlipidemia	178 (54.3%)
Previous stroke	60 (18.3%)
Atrial fibrillation	18 (5.5%)
Smoking history	134 (40.9%)
NIHSS on admission	4 (2-6)*
BI	20 (19-20)*
MMSE	27 (24-29)*
GDS	4 (2-7)*

NIHSS = National Institutes of Health Stroke Scale; BI = Barthel Index; MMSE = Mini-Mental State Examination; GDS = Geriatric Depression Scale.

* Median (IQR)

Table 4-3 Comparison of demographic and clinical variables between CIND and cognitive intact groups at baseline.

Variables	CIND n = 180	Cognitive intact n = 148	p
Age*	71.6 ± 8.9	64.2 ± 9.5	<0.001
Sex (female)†	98 (54.4%)	44 (29.7%)	<0.001
Education in years ¶	3 (0-8)	6 (3-10)	<0.001
Hypertension†	117 (65.0%)	101 (68.2%)	0.536
Diabetes mellitus†	68 (37.8%)	35 (23.6%)	0.006
Hyperlipidemia†	94 (52.2%)	84 (56.8%)	0.412
Prior stroke†	40 (22.2%)	20 (13.5%)	0.042
Smoking history†	64 (35.8%)	70 (47.6%)	0.030
NIHSS on admission¶	4 (2-6)	3 (2-5)	<0.001
MMSE¶	25 (22-27)	28 (27-29)	<0.001
GDS¶	4 (2-7)	3 (2-6)	0.081

CIND = cognitive impairment no dementia; NIHSS = National Institutes of Health Stroke Scale; BI = Barthel Index; MMSE = Mini-Mental State Examination; GDS = Geriatric Depression Scale. *mean ± s.d., t-test; †n (%), x^2 test; ¶median (IQR)., Mann-Whitney U test.

Table 4-4 Comparison of imaging features between CIND and cognitive intact groups at baseline.

Variable	CIND n = 180	Cognitive intact n = 148	p
Index infarcts			
Location involvement			
frontal lobe[+]	19 (10.6%)	16 (10.8%)	0.941
parietal lobe[+]	8 (4.4%)	13 (8.8%)	0.110
occipital lobe[**]	5 (2.8%)	2 (1.4%)	0.464
temporal lobe[+]	5 (2.8%)	8 (5.4%)	0.225
subcortical white matter[+]	63 (35.0%)	42 (28.4%)	0.201
basal ganglia[+]	19 (10.6%)	18 (12.2%)	0.647
thalamus[+]	13 (7.2%)	13 (8.8%)	0.602
infratentorial[+]	36 (20.0%)	27 (18.2%)	0.688
num. of index infarcts[¶]	1 (0-1)	1 (0-1)	0.340
index infarct volume (mm^3)[¶]	0.5 (0-1.5)	0.5 (0-1.8)	0.251
Old infarcts (including silent infarcts)			
frontal lobe[**]	6 (3.3%)	3 (2.0%)	0.521
parietal lobe[**]	5 (2.8%)	3 (2.0%)	0.734
occipital lobe[**]	3 (1.7%)	1 (0.7%)	0.630
temporal lobe[**]	7 (3.9%)	2 (1.4%)	0.193
subcortical white matter[+]	12 (6.7%)	10 (6.8%)	0.974
basal ganglia[+]	57 (31.7%)	42 (28.4%)	0.519
thalamus[+]	25 (13.9%)	12 (8.1%)	0.100
infratentorial[+]	8 (4.4%)	5 (3.4%)	0.622
num. of old infarcts[¶]	1 (0-2)	0 (0-1)	0.100
old infarct volume (mm^3)[¶]	0.2 (0-0.4)	0 (0-0.3)	0.023
old lacunes num.[¶]	0 (0-1)	0 (0-1)	0.479
WML volume[¶]	9.9 (3.7-23.5)	4.7 (1.5-11.2)	< 0.001

CMBS (n,%)[†§]	47 (26.1%)	37 (25.3%)	0.875
Num. of CMBs [¶]	0 (0-1)	0 (0-1)	0.810
VBR[*]	13.1 ± 6.1%	11.1 ± 3.0%	< 0.001
LV volume[*]	41.5 ± 20.8	31.6 ± 14.4	< 0.001
Hippocampal volume[*‡]	2.66 ± 0.42	2.73 ± 0.33	0.066

CIND = cognitive impairment no dementia; CMBs = cerebral microbleeds; VBR = Ventricle-to-brain ratio; LV = lateral ventricular.

*mean ± s.d., t-test; [†]n (%), x^2 test; [¶]median (IQR)., Mann-Whiteney U test; ** n (%), Fisher's exact test; [§]N = 326; [‡]N = 316.

Table 4-5 Logistic regression of CIND at baseline.

Variable	β	p value	Odds ratio (95% C.I.)
Age	0.056	< 0.001	1.057 (1.025-1.090)
Sex (female)	0.942	0.001	2.564 (1.463-4.494)
NIHSS on admission	0.137	0.003	1.147 (1.046-1.257)
WML volume	0.038	0.001	1.039 (1.015-1.063)
Education in years	-0.072	0.024	0.931 (0.874-0.991)
Prior stroke	0.769	0.043	2.157 (1.023-4.546)
Diabetes mellitus	0.444	0.133	1.559 (0.873-2.785)
VBR	0.070	0.167	1.073 (0.971-1.185)
Old infarct volume	0.035	0.409	1.036 (0.953-1.126)
Hippocampal volume	-0.087	0.818	0.916 (0.435-1.930)

CIND = cognitive impairment no dementia; NIHSS = National Institutes of Health Stroke Scale; GDS = Geriatric Depression Scale; WML = white matter lesion; VBR = ventricle-to-brain ratio.

4.3.5. Follow-up at 1 year after the baseline

One year after the baseline assessment (15 months after the index stroke), 256 (78.1%) patients attended the follow-up assessment, and 72 (22.0%) dropped out. No significant differences in terms of sex, NIHSS, baseline MMSE, or frequency of CIND at baseline were found except that the drop-outs were younger (65.6 ± 10.9 versus 69.0 ± 9.5, p = 0.020) (Tables 4-6).

Of the 256 patients assessed at the one-year follow-up, 134 (52.4%) were diagnosed as cognitively impaired, including 117 (45.5%) cases of CIND and 17 (6.6%) of dementia. Twenty-one (18.4%) of the 113 patients diagnosed as cognitively intact at baseline had developed cognitive impairment (including 20 with CIND and one with dementia). Sixteen (11.2%) of the 143 patients with CIND at baseline had developed dementia, but 30 (21.0%) had reverted to cognitive intact status (Table 4-7).

Table 4-6 Comparison of subjects with and without follow-up.

Variable	With follow-up n = 256	Without follow-up n = 72	p
Age*	69.0 ± 9.5	65.6 ± 10.9	0.020
Sex (male)[+]	139 (54.3%)	47 (65.3%)	0.097
NIHSS on admission[¶]	4 (2-6)	4 (2-6)	0.281
Baseline MMSE[¶]	27 (23-28)	27 (24-29)	0.220
CIND at baseline (n, %)[+]	143 (55.9%)	37 (51.4%)	0.501

NIHSS = National Institutes of Health Stroke Scale; MMSE = Mini-Mental State Examination; CIND = cognitive impairment no dementia.

* mean (s.d.), t-test; [+]n (%); [¶]median (IQR)., Mann-Whiteney U test.

Table 4-7 Evolution of cognitive status at 1-year follow-up.

Baseline cognitive status	1-year follow-up			
	Cognitive intact	CIND	Dementia	CIND + dementia
Cognitive intact (n = 113)	92 (81.4%)	20 (17.7%)	1 (0.9%)	21 (18.6%)
CIND (n = 143)	30 (21.0%)	97 (67.8%)	16 (11.2%)	113 (79.0%)

CIND = Cognitive impairment no dementia.

4.3.6. Predictors of cognitive decline at 1 year follow-up

Thirty-seven (14.5%) patients had declined cognitively by the one-year follow-up relative to their baseline cognitive status. Those with cognitive decline were older (73.9 versus 68.1 years, $p < 0.001$) and had a higher frequency of acute infratentorial infarcts (29.7% versus 14.2%, $p = 0.018$), old parietal infarcts (10.8% versus 2.3%, $p = 0.023$), old subcortical infarcts (32.4% versus 16.4%, $p = 0.021$), and old infarcts in the thalamus (21.6% versus 9.1%, $p = 0.024$). They also had a significantly greater old infarct number and volume. The LV (42.5 versus 36.3, $p = 0.048$) and WML (median, 11.3 versus 6.4, $p = 0.009$) volumes were also higher in the patients with cognitive decline (Table 4-8). There was no difference in VBR or hippocampal volume between the two groups.

As only 37 patients had experienced cognitive decline, only three variables with $p < 0.01$ (age, WML volume, and old infarct volume) were included in the univariate analyses, with hippocampal volume added in the logistic regression. The number of old infarcts was not

included because it was highly correlated with old infarct volume ($r = 0.903$, $p < 0.001$). Age (OR = 1.065, 95% CI = 1.020-1.116, $p = 0.005$) and WML volume (OR = 1.022, 95% CI = 1.002-1.043, $p = 0.034$) remained significant in the logistic regression (Table 4-9), but hippocampal volume was not found to be a significant predictor of cognitive decline.

Table 4-8 Comparison of subjects with and without cognitive decline at follow-up.

Variable	Cognitive decline n = 37	Without cognitive decline n = 219	p
Age*	73.9 ± 7.4	68.1 ± 9.5	< 0.001
Sex (male)†	19 (51.4%)	98 (44.7%)	0.456
Education in years¶	5 (2-8)	5 (1-9)	0.804
Hypertension†	28 (75.7%)	148 (67.6%)	0.326
Diabetes†	10 (27.0%)	72 (32.9%)	0.481
Hyperlipidemia†	18 (48.6%)	126 (57.5%)	0.314
Previous stroke†	9 (24.3%)	37 (16.9%)	0.276
Smoking history†	19 (51.4%)	83 (38.2%)	0.133
NIHSS on admission¶	4 (3-7)	3 (2-5)	0.226
MMSE (3m)¶	27 (22-28)	27 (23-29)	0.545
GDS (3m)¶	4 (2-6)	4 (2-7)	0.901
Recurrence before follow-up†	5 (13.5%)	13 (5.9%)	0.095
Index infarcts			
Location involvement			
frontal lobe†	5 (13.5%)	19 (8.7%)	0.350
parietal lobe**	2 (5.4%)	14 (6.4%)	1.000
temporal lobe**	1 (2.7%)	9 (4.1%)	1.000
occipital lobe**	1 (2.7%)	5 (2.3%)	1.000
Subcortical white matter†	10 (27.0%)	77 (35.2%)	0.334
basal ganglia**	4 (10.8%)	27 (12.3%)	1.000
thalamus**	1 (2.7%)	21 (9.6%)	0.217
infratentorial†	11 (29.7%)	31 (14.2%)	0.018
num. of index infarcts¶	1 (0-1)	1 (0-1)	0.559

index infarcts vol. (mm^3)[¶]	0.8 (0.1-1.6)	0.4 (0-1.6)	0.431
Old infarcts			
Location involvement			
frontal lobe	3 (8.1%)	6 (2.7%)	0.126
parietal lobe	4 (10.8%)	5 (2.3%)	0.027
temporal lobe	2 (5.4%)	6 (5.7%)	0.326
occipital lobe	1 (2.7%)	1 (0.5%)	0.269
subcortical white matter	12 (32.4%)	36 (16.4%)	0.021
basal ganglia	12 (32.4%)	65 (29.7%)	0.736
thalamus	8 (21.6%)	20 (9.1%)	0.024
infratentorial	2 (5.4%)	8 (3.7%)	0.641
num. of old infarcts[¶]	1(0-2)	0 (0-1)	0.004
num. of lacunes[¶]	1 (0-2)	0 (0-1)	0.060
old infarct vol. (mm^3)[¶]	0.3 (0-0.8)	0 (0-0.3)	0.002
CMBs (n, %)[ǂξ]	8 (21.6%)	60 (27.5%)	0.453
num. of CMBs[¶ξ]	0 (0-1)	0 (0-1)	0.552
VBR[*]	13.1 ± 2.9%	12.3 ± 5.6%	0.449
LV volume[*]	42.5 ± 19.4	36.3 ± 17.2	0.048
Hippocampal volume[*]	2.59 ± 0.38	2.69 ± 0.38	0.166
WMLs volume[¶]	11.3 (5.2-27.1)	6.4 (2.5-15.4)	0.009

NIHSS = National Institutes of Health Stroke Scale; MMSE = Mini-Mental State Examination; CMBs = cerebral microbleeds; VBR = ventricle-to-brain ration; LV = lateral ventricular; WMLs=white matter lesions. *mean ± s.d, t-test; [ǂ]n (%), x^2 test; [¶]median (IQR)., Mann-Whiteney U test; [**]n (%), Fisher's exact test; [ξ]N = 255; [ǂ]N = 246.

Table 4-9 Logistic regression of cognitive decline at 1-year follow-up.

Variable	β	p	Odds ratio (95% C.I.)
Age	0.065	0.005	1.067(1.020-1.116)
WMLs volume	0.022	0.034	1.022(1.002-1.043)
Old infarct volume	0.070	0.107	1.073(0.985-1.169)
Hippocampal volume	-0.055	0.914	0.947(0.351-2.555)

WMLs=white matter lesions.

4.3.7. Delayed dementia

Seventeen patients were diagnosed with dementia according to the DSM-IV criteria. Fifteen (88.2%) of them were judged to be VaD, and two (11.8%) to have "dementia due to multiple etiologies" (AD plus CVD). Sixteen (94.1%) had CIND at baseline, and only one (5.9%) patient was cognitively intact at baseline. The one-year rate of progression to dementia in the CIND at baseline group was significantly higher than that in the cognitive intact at baseline group (11.2% versus 0.9%, $p<0.001$).

The patients with delayed dementia were older (77.6 versus 68.4 years, $p < 0.001$), more likely to be female (70.6% versus 43.9%, $p = 0.033$) and to have had a prior stroke (41.2% versus 16.3%, $p = 0.010$), and had higher NIHSS scores on admission (median, 7 versus 3, $p = 0.002$). In terms of their imaging features, they had a higher frequency of old infarcts in the thalamus (29.4% versus 9.6%, $p = 0.012$), more old infarcts (median , 2 versus 0, $p = 0.003$), and a larger old infarct (median , 0.6 mm^3 versus 0.0 mm^3, $p < 0.001$), LV (47.6 versus 36.5, $p = 0.011$), and WMLs volume (median, 23.1 versus 11.5, $p = 0.003$). Hippocampal volume was also significantly smaller in the subjects with

delayed dementia (2.45 versus 2.69, p = 0.011). The univariate comparions are shown in Table 4-10.

In the logistic regressions, when age, NIHSS, and old infarct volume were entered into the regression model, WMLs volume remained a significant preditor of delayed dementia (p = 0.007, OR = 1.045, 95% CI = 1.012-1.079), whereas hippocampal volume became non-significant. Hippocampal volume's power to detect delayed dementia was 0.757, with $\alpha = 0.05$ (two-sided).

Table 4-10 Comparison of clinical and imaging features between subjects with and without delayed dementia.

Variable	Delayed dementia n = 17	No-dementia n = 239	p
Age*	77.6 ± 5.4	68.4 ± 9.4	<0.001
Sex (female)†	12 (70.6%)	105 (43.9%)	0.033
Education in years¶	3 (0-6)	5 (1-9)	0.284
Hypertension†	11 (64.7%)	165 (69.0%)	0.710
Diabetes†	7 (41.2%)	75 (31.4%)	0.403
Hyperlipidemia†	8 (47.1%)	136 (56.9%)	0.429
Previous stroke†	7 (41.2%)	39 (16.3%)	0.010
Smoking history†	5 (29.4%)	97 (40.9%)	0.349
NIHSS on admission¶	7 (4-9.5)	3 (2-5)	0.002
MMSE (3m)¶	22 (20-24)	27 (24-29)	< 0.001
GDS (3m)¶	55 (3-6.8)	4 (2-7)	0.440
Recurrence before follow-up†	3 (17.6%)	15 (6.3%)	0.106
CIND at 3 months	16 (94.1%)	127 (53.1%)	0.001
Index infarcts			
Location involvement			
frontal lobe**	2 (11.8%)	22 (9.2%)	0.665
parietal lobe**	0 (0.0%)	16 (6.7%)	0.609
temporal lobe**	0 (0.0%)	10 (4.2%)	1.000
occipital lobe**	0 (0.0%)	6 (2.5%)	1.000
Subcortical white matter†	6 (35.3%)	81 (33.9%)	0.906
basal ganglia**	1 (5.9%)	30 (12.6%)	0.703
thalamus**	0 (0.0%)	22 (9.2%)	0.375
Infratentorial†	5 (29.4%)	37 (15.5%)	0.134

num. of index infarcts[¶]	1 (0.5-1)	1 (0-1)	0.835
index infarct volume (mm^3)[¶]	0.8 (0.1-1.4)	0.4 (0-1.6)	0.715
Old infarcts (including silent infarcts)			
frontal lobe[**]	2 (11.8%)	7 (2.9%)	0.113
parietal lobe[**]	2 (11.8%)	7 (2.9%)	0.113
temporal lobe[**]	1 (5.9%)	7 (2.9%)	0.427
occipital lobe[**]	1 (5.9%)	1 (0.4%)	0.129
subcortical white matter[†]	6 (35.3%)	42 (17.6%)	0.070
basal ganglia[†]	6 (35.3%)	71 (29.7%)	0.627
thalamus[†]	5 (29.4%)	23 (9.6%)	0.012
infratentorial[**]	2 (11.8%)	8 (3.3%)	0.136
num. of old infarcts[¶]	2 (1-2.5)	0 (0-1)	0.003
num. of lacunes	1 (0-2)	0 (0-1)	0.071
old infarcts vol. (mm^3)[¶]	0.6 (0.2-2.1)	0 (0-0.3)	< 0.001
CMBs (n, %)[†ξ]	8 (21.6%)	60 (27.5%)	0.453
Num. of CMBs [¶ξ]	0 (0-1.5)	0 (0-1)	0.969
VBR[*]	14.1 ± 3.3%	12.3 ± 5.4%	0.193
LV volume[*]	47.6 ± 23.9	36.5 ± 16.9	0.011
Hippocampal volume[*ǂ]	2.45 ± 0.36	2.69 ± 0.37	0.011
WML volume[¶]	23.1 (5.2-48.0)	7.2 (2.6-15.2)	0.003

NIHSS = National Institutes of Health Stroke Scale; MMSE = Mini-Mental State Examination; CMBs = cerebral microbleeds; VBR = ventricle-to-brain ratio; LV = lateral ventricular; WML = white matter lesion.

*mean ± s.d., t-test; [†]n (%), x^2 test; [¶]median (IQR)., Mann-Whiteney U test; [**] n (%), Fisher's exact test; [ξ]N = 255; [ǂ]N = 246.

Table 4-11. Logistic regression analysis of delayed dementia.

Variables	Model 1*		Model 2†	
	p	Odds ratio (95% CI)	p	Odds ratio (95% CI)
Age	0.006	1.150 (1.041-1.269)	0.001	1.169 (1.063-1.284)
NIHSS	0.007	1.259 (1.065-1.487)	0.006	1.239 (1.063-1.443)
Old infarct volume	0.094	1.128 (0.985-1.079)	0.073	1.114 (0.990-1.253)
WML volume	0.007	1.045 (1.012-1.079)	--	--
Hippocampal volume	--	--	0.307	0.455 (0.100-2.063)

NIHSS = National Institutes of Health Stroke Scale; WML = white matter lesion.

*Age, NIHSS, old infarct volume, and WML volume were included in the logistic regression.

†Age, NIHSS, old infarct volume, and hippocampal volume were included in the logistic regression.

4.3.8. Effects of WML and hippocampal volume on cognitive domains in non-demented stroke patients

At three months after stroke, the most common impaired cognitive domain was visuomotor speed (35.7%), succeeded by executive function (27.1%), visual memory (16.5%), verbal memory (15.9%), visuoconstruction (15.2%), language (8.8%), and attention (4.3%). The frequency of cognitive domain impairment at three and 15 months after stroke is shown in Figure 4-7.

In the univariate logistic regressions, WMLs were significantly correlated with executive function, attention, visual memory, visuoconstruction, and visuomotor speed, but not with language or verbal memory (Table 4-12). Even when adjusted by age, years of education, sex, NIHSS, and infarct location, WMLs remained significant predictors of the domains detected in univariate analysis (Table 4-13). Hippocampal volume was correlated with verbal and visual memory in the univariate logistic regressions (Table 4-12), but these associations became non-significant after adjustment by the foregoing factors (Table 4-13). An association trend was detected only with verbal and visual memory.

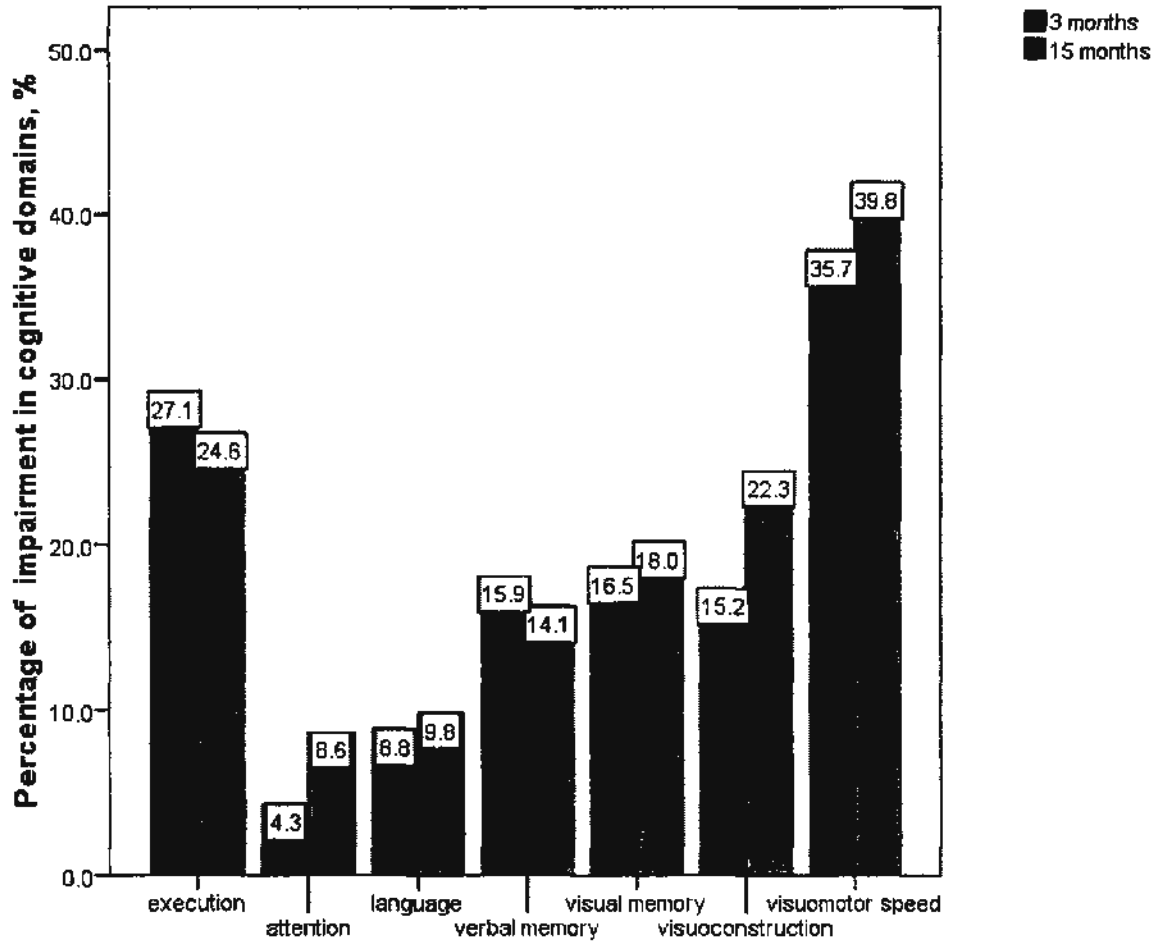


Figure 4-6 Frequency of cognitive domain impairment at 3 and 15 months after stroke.

Table 4-12. Univariate logistic regressions of WMLs and hippocampal volume in the prediction of impairment in seven cognitive domains.

Dependent variable	Independent variables			
	WML volume*		Hippocampal volume*	
	OR (95%CI)	p	OR (95%CI)	p
Executive Function	1.035(1.017-1.053)	<0.001	0.379(0.190-0.754)	0.006
Attention	1.031(1.008-1.055)	0.007	1.645(0.419-6.452)	0.475
Language	1.024(1.005-1.044)	0.015	0.621(0.215-1.179)	0.378
Verbal Memory	1.019(1.002-1.037)	0.028	0.295(0.125-0.694)	0.005
Visual Memory	1.026(1.009-1.044)	0.003	0.285(0.124-0.656)	0.003
Visuo-construction	1.024(1.006-1.042)	0.007	0.488(0.209-1.136)	0.096
Visuomotor Speed	1.034(1.016-1.052)	<0.001	0.604(0.325-1.122)	0.111

WMLs = white matter lesions; OR = odds ratio.

Table 4-13. Multivariate logistic regressions of WMLs and hippocampal volume in the prediction of impairment in seven cognitive domains.

Dependent variable	Independent variables			
	WMLs volume		Hippocampal volume	
	OR (95%CI)	p	OR (95%CI)	p
Executive Function	1.033 (1.012-1.055)	0.002	--	0.272
Attention	1.072 (1.029-1.117)	0.001	--	0.517
Language	1.024 (1.004-1.045)	0.019	--	0.679
Verbal Memory	--	0.122	--	0.057
Visual Memory	1.029 (1.011-1.048)	0.002	0.360 (0.155-0.835)	0.017
Visuo-construction	1.032 (1.010-1.054)	0.004	--	0.368
Visuomotor Speed	1.028 (1.008-1.049)	0.005	--	0.419

*adjusted by age, sex, years of education, NIHSS, and location of infarcts.

4.4. Discussion

This is the first longitudinal study of VCI in Chinese stroke patients to include imaging analysis. It involved a relatively large sample size, a series of repeated neuropsychological tests, and integrated MRI analysis, particularly of the volumetry of WMLs and the hippocampus. We found a high prevalence of cognitive impairment in Chinese stroke patients, although most patients remained cognitively stable one year after baseline. WMLs rather than hippocampal atrophy appear to be predictors of poststroke cognitive impairment and decline. This is the first longitudinal study to confirm the relationship between WMLs and cognitive decline in stroke patients using WML volumetry.

Prevalence of cognitive impairment

The prevalence of cognitive impairment in our cohort was 54.9% (CIND) at three months after stroke and 52.4% (45.7% CIND, 6.6% dementia) at 15 months after stroke. These results are within the range of those obtained in previous studies with a similar assessment timeframe. For example, the Helsinki Stroke Ageing Study (Pohjasvaara et al., 1997) reported a 62% prevalence of cognitive impairment at three

months poststroke. Sachdev et al. (2006) reported a prevalence of 47.7% (after excluding VaD), and Rasquin et al. (2004) reported the prevalence of CIND to be 61.3% at six months and 51.5% at 12 months after stroke.

Prior data on cognitive impairment in Chinese stroke patients are limited. In the cross-sectional study carried out by Zhou et al. (2005), the frequency of cognitive impairment at three months poststroke was 37.5%. However, their study employed only the IQCODE and MMSE as diagnostic tools, and these tools are inadequate for the assessment of cognitive impairment in stroke patients. A cross-sectional study carried out among Hong Kong Chinese patients with SVD-related stroke reported a similar prevalence (40.0%), with CDR = 0.5 (Mok et al., 2004). The only longitudinal study involving Chinese stroke patients (83% of the participants were Singaporean Chinese) (Tham et al., 2002) found that the prevalence of cognitive impairment at three months after stroke was 44.0% (40.0% CIND, 4.0% dementia), but only 33.6% (29.0% CIND, 4.5% dementia) at 15 months after stroke.

It appears that cognitive impairment is prevalent in Chinese stroke patients, even in those with relatively mild neurological deficits on admission. However, as there are no confirmative and operational

criteria for VCI, it may be difficult to compare its prevalence among studies, as they employed different cognitive tests, cutoffs, and VCI criteria. Additionally, we did not try to classify the origins of cognitive impairment in stroke, as there is still a lack of valid imaging criteria for such classification. It is more common for cognitive impairment in stroke cohorts to be labeled VCI (Sachdev et al., 2004, 2009; Zhou et al., 2005).

Evolution of CIND in stroke

In the present study, 11.2% of the patients with CIND at baseline progressed to dementia within one year, whereas 21.0% of them reverted to cognitively intact. Most of the patients (85.6%) remained cognitively stable or even improved. The first-year evolution of CIND in this study is in accordance with previous data, with 5.8% to 11.0% progressing to dementia and 15.7 to 45.2% reverting to cognitively intact (Tham et al., 2002; Ballard et al., 2003; Srikanth et al., 2004; Serrano et al., 2007), which suggests that the evolution of CIND is bilateral and that more patients will improve rather than decline in the

first poststroke year. Nevertheless, of the 17 patients who had developed dementia by the follow-up, 16 (94.1%) had been diagnosed as CIND at baseline, thus suggesting that patients with CIND at baseline are at high risk of developing delayed dementia relative to those who are cognitively intact at baseline (11.2% versus 0.9%, $p < 0.001$). In the longitudinal study carried out by Serrano et al. (2007), which was based on different diagnostic criteria, approximately 12-15% of patients who had been diagnosed with vascular MCI within three months of stroke had developed dementia by the two-year follow-up, whereas the rate was only 0-1.4% among the cognitively intact poststroke patients. Another study reported that 32.7% of those who presented with impaired cognition at the baseline assessment after the first stroke had dementia at the second-year assessment (Srikanth et al., 2006), compared with 10.6% of the cognitively intact poststroke patients.

Predictors of cognitive impairment, cognitive decline, and delayed dementia

As expected, an older age, female sex, lower educational level, higher NIHSS on admission, and previous stroke were significant predictors of cognitive impairment at baseline, which is in line with the findings of previous cross-sectional studies. The only imaging variable to be significantly associated with cognitive impairment in this study was WMLs volume, which is consistent with most previous studies (Tang et al., 2004; Mok et al., 2005; Sachdev et al., 2006), but not all (Vakhnina et al., 2009). It is not surprising that WMLs volume rather than stroke location or volume played an important role, as we excluded those with a diagnosis of dementia (including pre- and poststroke dementia) at baseline. Those whose poststroke dementia was directly due to a large stroke or strategic stroke location (e.g., thalamus, hippocampus, angular gyrus) were thought likely to develop dementia soon after the index stroke. Thus, in these non-demented subjects recruited at baseline, the pre-existing ischemic changes in the brain would be critical in cognitive impairment. Of course, we could not preclude the presence of MCI or CIND before the index stroke.

WMLs volume was found to be a significant predictor of cognitive decline and delayed dementia at follow-up, a finding never before reported in a longitudinal study using the volumetry of WMLs. This

relationship is supported by the findings of a longitudinal study employing the MRI visual rating method (Dufouil et al., 2009) and two studies using CT rating methods (Henon et al., 2001; Cordoliani-Mackowiak et al., 2003), although not by those of others (Rasquin et al., 2004, 2005, 2007; Altieri et al., 2004; Firbank et al., 2007; Sachdev et al.,2009). Most of the latter studies, however, adopted only a visual rating method (Rasquin et al., 2005; Williamson et al., 2008; Dufouil et al., 2009) or merely rated WMLs as "absent" or "present" (Rasquin et al., 2004, 2007). It seems that the volumetric assessment of WMLs is more accurate. Additionally, the measurement of hippocampal volume is also necessary. Only two prior longitudinal studies employed WMLs volumetry and assessed MTLA (Firbank et al., 2006; Sachdev et al., 2009) at the same time, and neither confirmed that WMLs volume is a significant predictor of cognitive decline. Firbank et al. (2006) found MTLA to contribute to cognitive decline one year after stroke. There are several explanations for the discrepancy between our results and those of these two studies. First, there are some methodological concerns about the earlier studies. Firbank et al. (2006), for example, failed to assess the volume of infarcts or the severity of global atrophy (or cortical atrophy), and they had only a small sample size (n = 79). The

sample size was also small (n = 94) in Sachdev et al., 2009). Second, the sample in the former was significantly different from ours. All of their subjects were older than 75, with a mean age of more than 80, which is more than 10 years older than ours. It is well-known that the pathological changes of AD significantly increase with age. Thus, it is possible that the underlying AD-related structural changes (e.g., MTLA) in this sample would be more severe than those in our sample and, consequently, would also have a greater weight in cognitive decline. Third, the three studies use different definitions of cognitive decline. Given recent improvements in the integrity of MRI analytical methods and the larger sample size included in our study, we are confident in concluding that WMLs not only predict baseline cognitive impairment, but also predict cognitive decline and delayed dementia at follow-up in Chinese stroke patients. Previous longitudinal MRI studies have suggested that patients with higher WMLs volume at baseline are more likely to have more WMLs progression at follow-up (Sachdev et al., 2007; Gouw et al, 2008). Given the substrate of SVD as progressive arteriosclerosis, SVD may probably have a progressive effect on cognitive function. Interventions that attempt to slow down the

progression of WMLs may possibly prevent or postpone the development of dementia in stroke.

In this study, hippocampal atrophy was not associated with cognitive impairment at baseline or cognitive decline and delayed dementia at follow-up. It has been linked to prestroke cognitive decline (Henon et al., 1998; Pohjasvaara et al., 1999; Barba et al., 2001). Hippocampal atrophy has also been reported to be a correlate of dementia in SIVD (Fein et al., 2000). However, Sachdev et al. also failed to confirm the presence of a relationship between hippocampal volume and cognitive impairment in either their cross-sectional study (2007) or longitudinal study (2009). The only longitudinal study that has found hippocampal atrophy to predict cognitive decline in non-demented stroke patients aged > 75 years is that conducted by Firbank et al. (2007), as discussed above. However, the number of delayed dementia cases in our study was small possibly due to the short follow-up period. Thus, the power of hippocampal atrophy to predict delayed dementia may be inadequate (power = 0.757). Further studies with a longer follow-up period and a larger sample size are warranted.

Effects of WMLs and hippocampal atrophy on cognitive domains in non-demented stroke patients

WMLs volume was found to be associated with a wide range of cognitive domains. The correlation between WMLs and poor executive function performance has been found in previous studies too (Burton et al., 2003; Wen et al., 2004; Jokinen et al., 2006), and may be due to the interruption of FSC, which dominate executive function through extensively distributed WMLs (Desmond, 2002). The findings of our study were also in agreement with those of others that attention and psychomotor speed are commonly impaired by WMLs in the community elderly (de Groot et al., 2000; Fukui et al., 1994) and in stroke patients (Burton et al., 2003,2004; Jokinen et al., 2006). Interestingly, we also found WMLs to be predictive of impairment in visual memory and visuoconstruction, which accords with Jokinen et al. (2005). The effects of WMLs on visual memory and visuoconstruction may be secondary to impairment of executive function and attention (Edwards and Grainger, 2006). The diffuse effects of WMLs are considered to be the major mechanism (Edwards and Grainger, 2006).

We did not find hippocampal atrophy to be associated with verbal or visual memory after controlling for WMLs, although there seemed to be a trend of association. Two studies have found MTLA to be strongly related to immediate and delayed poststroke memory function (Van der Werf et al., 2003; Jokinen et al., 2004). The conflicting result in our study may be the result of our exclusion of those with prestroke dementia at baseline; thus, the baseline hippocampal atrophy in our cohort may have been less severe. Moreover, our sample did not have dementia, and thus the effect size of hippocampal atrophy on memory dysfunction may have been reduced. Our finding is restricted to poststroke subjects without dementia. Further study is still warranted to confirm the association between hippocampal atrophy and cognitive functions.

Limitations

This study had a few limitations. First, the inclusion rate for baseline assessment was relatively low in comparison with the whole stroke cohort, which can mainly be attributed to just under half of them undergoing MRI examination. Our cohort thus represented a younger

stroke sample with relatively mild neurological deficits. Second, we did not construct a stroke-free control group. Third, we followed up for only one year, and the number of delayed dementia cases was small. Forth, we did not record and compare the usage of drugs (e.g. antiplatlet drugs, antihypertensive drugs, glucose-lowering drugs or statin) which might be a confounder for cognitve impairment and cognitive decline as satisfactory control of vascular risk factors may prevent or postpond dementia.

Conclusion

In summary, the prevalence of cognitive impairment is high in Chinese stroke patients, although most remain cognitively stable one year from baseline. WMLs volume rather than hippocampal atrophy is predictive of poststroke cognitive impairment, cognitive decline, and delayed dementia. WMLs affect a wide range of cognitive domains, including executive function, attention, visual memory, visuoconstruction, and visuomotor speed, in ischemic stroke patients without dementia.

CHAPTER 5 VERBAL FLUENCY IN ELDERLY POSTSTROKE WOMEN AND ITS RELATIONSHIP WITH LEFT DORSOLATERAL PREFRONTAL CORTEX ATROPHY

5.1. Introduction

Verbal fluency is a linguistic ability mediated by the frontal lobes, particularly the prefrontal cortex (PFC), that has been found to be involved in the verbal fluency network of healthy individuals (Cabeza and Nyberg, 2000). The PFC is the largest component of the frontal lobe, comprising two major portions: the dorsolateral prefrontal cortex (DLPFC) and the orbital-frontal cortex (OFC) (Benarroch et al., 2007). The DLPFC is largely responsible for attention, executive function, and working memory, whereas the OFC is associated with decision making and affect control (Benarroch et al., 2007). Poor word-list retrieval has been associated with the dominant prefrontal region in functional MRI activating studies (Frith et al., 1991; Cuenod et al., 1995; Warburton et al., 1996), and decreased verbal fluency has been observed in patients with left frontal lobe lesions (Henry and Crawford, 2004). In patients

with frontal-temporal dementia (FTD), poor verbal fluency is associated with atrophy of the left DLPFC (Huey et al., 2009).

Sex differences in cognition have been reported in a number of domains, such as verbal fluency, visual-spatial skills, motor function (Collaer and Hines, 1995), and verbal working memory (Duff and Hampson, 2001). Women tend to perform better than men on language tasks (Brucki and Rocha, 2004). Structural differences, as well as functioning differences in the brain, between the sexes have been identified using MRI (Welborn et al., 2009). For example, men tend to have greater brain volume and greater white matter volume (Gur et al., 1999), whereas women tend to have more grey matter tissue and greater cortical complexity in the frontal and parietal regions (Luders et al., 2004), as well as a larger OFC volume (Goldstein et al., 2005). Several reports have demonstrated that, in the elderly, more men than women have whole-brain and frontal atrophy (Gur et al., 1998; Lavretsky et al., 2004). Functional MRI studies have shown the areas of the brain associated with pain, verbal fluency, and imagination to be more robustly activated in women than men (Cahill, 2003; Cahill and Stegeren, 2003; Cahill et al., 2004; Andreano and Cahill, 2006).

PFC atrophy is common in ischemic stroke patients. Vascular risk factors may exacerbate brain aging and account for part of the observed decline in volume, as the PFC exhibits increased vulnerability to vascular lesions (Chen et al., 2009). A study using MRI volumetry showed that atrophy of the superior frontal and fronto-orbital gyri predicted decline in executive function independent of WML volume in patients with cerebral SVD (Mok et al., 2008). Verbal fluency impairment has been found in elderly patients with SIVD (Jokinen et al., 2009), and has been linked to the atrophy of the corpus callosum in the otherwise healthy elderly (Jokinen et al., 2007).

We could locate no studies exploring the effects of regional brain atrophy on verbal fluency in stroke patients. It is not known whether atrophy in the PFC or subdivisions of the PFC contribute to verbal fluency impairment in stroke patients or whether there is a sex difference with regard to this impairment. Accordingly, we conducted an MRI volumetric study of the PFC and its subdivisions in non-aphasic stroke patients with the aim of investigating the effect of atrophy in these regions on executive function and verbal fluency in men and women.

5.2. Methods

5.2.1. Participants

Eighty-three elderly (age ≥ 60 years) patients with acute ischemic stroke who had been admitted to the ASU of PWH in Hong Kong between June 2006 and June 2007 were included in a longitudinal study with baseline and annual neuropsychological examinations. All of the subjects underwent MRI examination, were of Chinese descent, and fluent in the Cantonese dialect. None had language impairment (NIHSS best language score = 0) (Lyden et al., 1999). They were all free of any central nervous system disease other than stroke, and none had prior dementia or depression, significant dysarthria, or visual or hearing impairment. Thirty-three elderly ischemic stroke women participated in the neuropsychological interview three months after stroke, but three dropped out before the one year from baseline assessment, and thus 30 cases of elderly poststroke women were included in the study. Simultaneously, a group of 30 age-matched elderly men with ischemic stroke who had completed the follow-up assessment were constructed

from the same cohort to serve as the control group. Each female case was age-matched using the list of ischemic stroke men, with each matched to the man with the closest admission date. The study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong, and all participants signed a consent form.

Basic socio-demographic and clinical data, including age, sex, education (in years), hypertension, diabetes mellitus, previous stroke, and NIHSS score on admission were retrieved from the ASU stroke registry. Hypertension was defined as repeated blood pressure measures of ≥ 140/90 mm Hg or the need for chronic antihypertensive medication; and diabetes mellitus was defined as fasting blood glucose ≥ 7.0 mmol/l, postprandial blood glucose ≥ 11.1 mmol/l, or current treatment for the disease.

5.2.2. Neuropsychological tests

All subjects completed a series of neuropsychological tests both three and 15 months after the index stroke. Global cognitive function was assessed using the CC-MMSE (Chui et al.,1994), and the Chinese

version of the Frontal Assessment Battery (FAB) (Dubois et al., 2000) was used to evaluate executive function. The Chinese FAB contains six items that assess conceptualization, lexical fluency, motor programming, sensitivity-to-interference, go-no-go, and environmental autonomy. The maximum score for each item is 3, and the total test score is 18. The FAB takes about 10-15 minutes to administer depending on the patient's level of impairment. It has been widely used in the evaluation of executive function in elderly stroke and degenerative dementia patients (Tang et al., 2009; Torralva et al., 2009). In the Semantic Verbal Fluency Test (VFT) (Chui et al., 1997), patients were asked to retrieve words belonging to the categories of "food" and "animal." The time limit was 60 seconds for each task. The VFT score was the sum of both category tests. The severity of depressive symptoms was also evaluated with the GDS-15 (Lim et al., 2000) to detect the possible effects of depressive symptoms on cognitive function.

5.2.3. MRI measurements

MRI assessment included DWI, T1 weighted imaging, T2 weighted imaging, FLAIR, $T2^*$ weighted gradient echo, and T1 3D-MPR for each participant with a 1.5 T system (Sonata, Siemens Medical, Erlangen, Germany) within seven days of admission. Whole-brain volume was acquired using a T1-weighted FLASH sequence.

Brain infarcts

Brain infarctions were identified on the T1 weighted images and confirmed on the corresponding T 2-weighted images, with the volumetric measurements carried out on the former. Infarct location was classified by site: cortical, subcortical, infratentorial, or multiple. The infarct area in each visible slice was measured with manual outlines, and the total volume was calculated by multiplying the total area by the sum of the slice thickness and gap.

Volumetry of brain regions

Volumetric analysis of the brain regions was performed using an automatic imaging analysis program, the Insight Segmentation and Registration Toolkit (ITK) (http://www.itk.org). The analysis procedures were as follows.

1. Data pre-processing

MRI pre-processing was performed to enable non-uniformity correction, spatial standardization, and brain extraction. The N3 algorithm (Sled et al., 1998) was employed to automatically correct the non-uniform image intensity for the volume data. The MRI data were transformed from their original space into a common stereotactic space using multi-scale affine registration (Collins et al., 1994). In affine registration, translation, rotation, scaling, and shearing are allowed to maintain inter-subject anatomical variability. The voxel size of the re-sliced data was $1 \times 1 \times 1 mm^3$. A brain extraction tool (Smith, 2002) was used to segment the brain from the MRI data. Afterwards, the deformable model with a 1000 vertex was used to extract the boundary of the brain surface.

2. Tissue Classification

Tissue classification was performed using the supervised k-nearest neighbor classifier to classify the entire 3-D image (Cocosco et al., 2003). The initial classification was defined by a set of samples generated from prior tissue probability maps in the standard brain space. After sufficient quality control, the volumes of white matter, grey matter and cerebrospinal fluid (CSF) were calculated as the number of voxels multiplied by the size of each voxel.

3. Quantification of WMLs

A fully automated clustering-based quantitative WMLs detection technique was adopted to analyze FLAIR, with the intensities on the white matter mask generated from the segmentation results from the T1 images and co-aligned with the FLAIR data (Jansen et al., 2008).

4. Quantification of ICV

ICV was calculated by automatically adjusting the prior atlas intensity model to the new input data. The label of the intracranial region was transformed to the input data non-rigidly (using demon registration) (Thirion, 1998).

5. Grey matter/white matter surface generation and topology correction

The binary masks of grey matter and white matter were extracted as described in the tissue classification section. Based on these masks, the white matter and grey matter outer bounding surfaces were generated using the tessellation of their boundaries. Topological error correction was performed automatically using the method proposed by Segonne (2007).

6. Cortical surface parcellation

The parcellation of the cerebral cortex into different cortical regions was carried out by non-rigid registration to a cortical surface atlas (Fischl et al., 2004). Registration to the spherical atlas was performed using the cortical folding patterns to match the cortical geometry between each subject and the surface atlas. This registration algorithm modeled the gray scale warping in the images as the flow of fluid using the Navier-Stokes partial differential equations (Christensen et al., 1997). The labels of the anterior cingulate cortex (ACC) and OFC were given by the atlas (Fischl et al., 2004), whereas the labels of the DLPFC and PFC were defined manually according to the literature (Venkatasubramanian et al., 2008). The parcellation of the aforementioned brain regions is shown in Figure 5-1. All brain region volumes were adjusted by the ICV (= 1000 × raw volume/ICV). The

grey matter ratio (GMR) was defined as the grey matter volume divided by the volume of the whole brain.

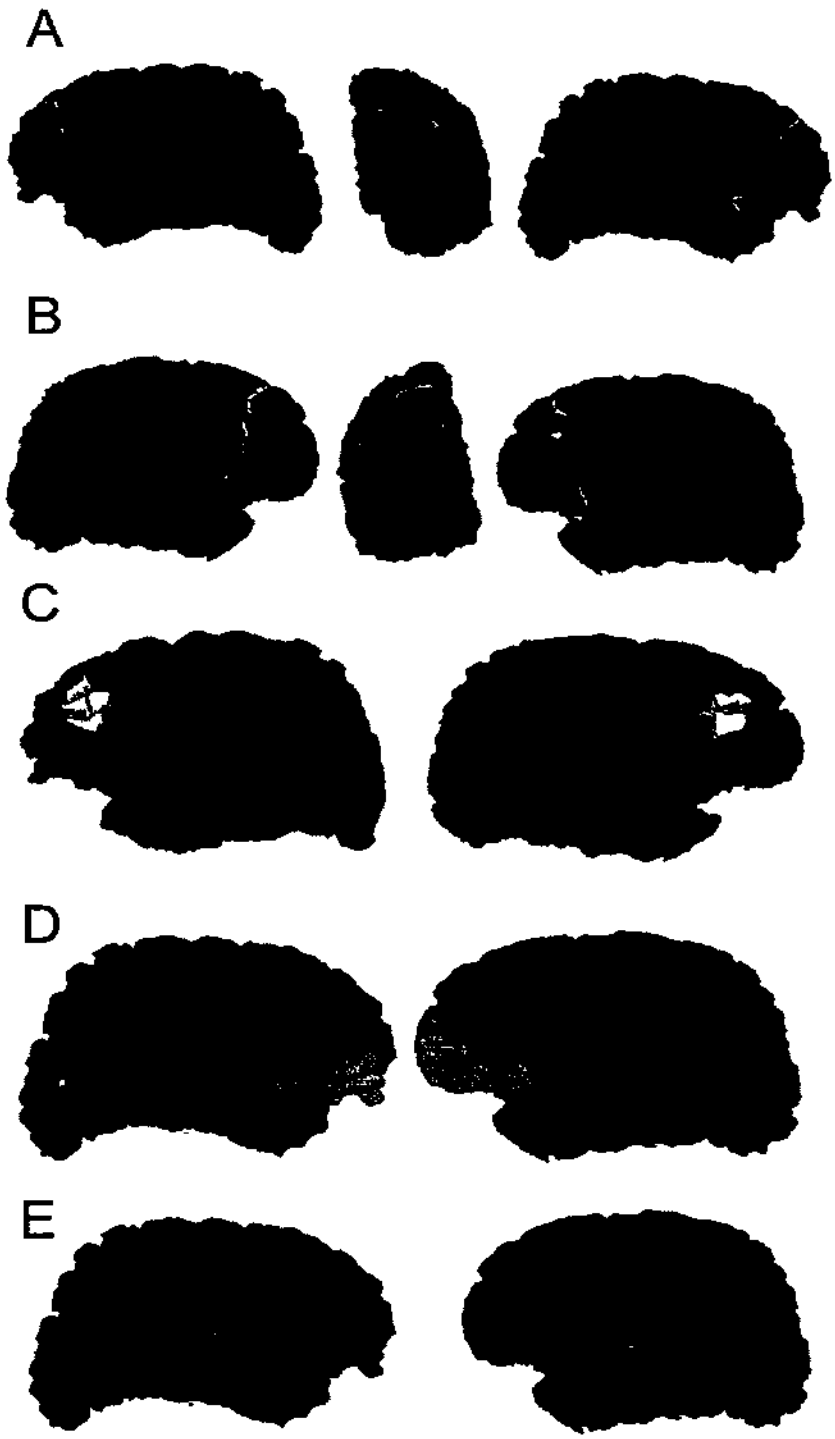


Figure 5-1. Parcellation of the brain regions. (A) left PFC; (B) right PFC; (C) left and right DLPFC; (D) left and right OFC; (E) left and right ACC anterior.

5.2.4. Statistical analysis

The subjects were divided into two groups according to sex. The difference in the proportions of the groups was analyzed with a χ^2 test. The continuous data were compared with t-tests or Mann-Whitney U tests, as appropriate. Correlation calculations were performed between the volumes of the brain regions and WMLs and VFT (Pearson's correlation), MMSE and FAB (Spearman's correlation) separately for women and men. At this stage of the univariate correlations, significance was set at $p < 0.01$ (two-sided) due to multiple comparisons. The significant correlations were then retested by partial correlation after controlling for possible confounders. The level of significance in the partial correlations was set at $p < 0.05$ (two-tailed). All statistical analyses were performed using SPSS, Version 16.0 (SPSS, Chicago, Illinois).

5.3. Results

The mean ages of the women and men were 73.3 ± 7.2 and 72.1 ± 6.9 years, respectively. The subjects' demographic, clinical, and radiological features according to sex are shown in Table 5-1. No differences were found between the sexes except that the women had less education, more diabetes mellitus, and lower MMSE and FAB scores ($p < 0.05$). They also had a significantly higher volume of right OFC and right ACC.

At three months after stroke, in the univariate analysis, the volume of the left DLPFC was significantly correlated with the VFT scores in the women but not in the men (Table 5-2). After controlling for age, education, NIHSS score, diabetes mellitus, location and volume of infarcts, and WML volume, the correlation between the left DLPFC and the VFT in the women remained significant (partial coefficient = 0.477, $p = 0.018$).

At 15 months after stroke, in the univariate analysis, the volumes of the left DLPFC and PFC were significantly correlated with the VFT scores in the women but not in the men (Table 5-3). After the aforementioned adjustment, the significant associations between the left DLPFC and VFT (partial coefficient = 0.548, $p = 0.006$) and the left

PFC and VFT (partial coefficient = 0.467, p = 0.021) remained in the women (Table 5-4).

Table 5-1. Demographic, clinical, neuropsychological, and radiological features of the subjects.

Variable	Female n = 30	Male n = 30	p
Age*	73.3 ± 7.2	72.1 ± 6.9	0.490
Education in years¶	3 (0-6)	6 (3-9)	0.010
Hypertension‡	22 (73.3%)	18 (60.0%)	0.273
Diabetes‡	16 (53.3%)	6 (20.0%)	0.007
Previous stroke‡	5 (16.7%)	5 (12.8%)	0.653
NIHSS¶	5(2-6.5)	4 (3-6)	0.485
MMSE (3 m)†	23.4 ± 3.2	26.4 ± 2.9	0.001
FAB (3 m)†	11.5 ± 2.8	13.6 ± 2.6	0.005
VFT (3 m)†	22.3 ± 6.5	21.9 ± 6.2	0.976
GDS (3 m)†	4.4 ± 4.3	3.7 ± 3.2	0.734
MMSE(15 m)†	24.1 ± 3.6	26.7 ± 3.6	0.001
FAB (15 m)†	11.9 ± 3.4	14.3 ± 3.0	0.004
VFT (15 m)†	22.8 ± 6.2	24.0 ± 8.3	0.559
GDS (15 m)†	6.6 ± 4.8	5.5 ± 3.9	0.390
No. of infarcts¶	2 (1-2)	2 (1-3)	0.736
Location of infarcts			0.062

cortical	3 (10.0%)	3 (10.0%)	
subcortical	12 (40.0%)	15 (50.0%)	
infratentorial	10 (33.3%)	2 (6.7%)	
multiple sites	5 (16.7%)	10 (33.3%)	
volume of infarcts (cm^3) ¶	0.9 (0.2-1.8)	1.3 (0.7-3.7)	0.529
WML volume¶§	2.7 (1.5-4.0)	3.0 (2.1-5.3)	0.193
GM ratio*	55.6 ± 4.2%	54.1 ± 4.5%	0.179
Volume of brain regions§			
Left PFC*	21.61 ± 2.61	20.52 ± 2.30	0.094
Right PFC*	21.35 ± 2.38	20.25 ± 2.12	0.064
Left DLPFC*	1.03 ± 0.31	1.02 ± 0.22	0.928
Right DLPFC*	1.05 ± 0.23	1.04 ± 0.28	0.870
Left OFC*	7.12 ± 0.83	6.84 ± 0.85	0.197
Right OFC*	7.23 ± 0.74	6.84 ± 0.75	0.047
Left ACC*	2.40 ± 0.44	2.27 ± 0.46	0.240
Right ACC*	2.51 ± 0.41	2.29 ± 0.34	0.029

NIHSS = National Institutes of Health Stroke Scale; MMSE = Mini-Mental State Examination; WML = white matter lesion; GM = grey matter; VR = volume ratio; PFC = prefrontal cortex; DLPFC = dorsolateral prefrontal cortex; OFC = orbital-frontal cortex; ACC = anterior cingulate cortex.

*mean (s.d.), t-test; †mean(s.d), Mann-Whitney U test; ‡n (%), χ^2 test; ¶median(IQR), Mann-Whitney U test.

§Volumes were calculated as: raw volume × 1000/ICV.

Table 5-2. Correlations between volumetric variables and cognitive tests at 3 months after stroke.

Volumetric variable	Female			Male		
	MMSE[a]	VFT[b]	FAB[a]	MMSE[a]	VFT[b]	FAB[a]
GMR	0.212	0.088	0.072	0.293	0.305	0.498*
Volume of WMLs or brain regions[¶]						
WMLs	-0.408	-0.437	-0.538*	0.048	-0.188	-0.089
L-PFC	0.191	0.326	0.135	0.241	0.259	0.371
R-PFC	0.059	0.309	0.285	0.239	0.208	0.319
L-DLPFC	0.064	0.496*	0.079	0.133	-0.162	0.104
R-DLPFC	-0.101	0.067	-0.085	-0.034	0.055	0.129
L-OFC	0.150	0.008	0.072	0.348	0.304	0.416
R-OFC	0.262	0.086	0.275	0.208	0.232	0.284
L-ACC	0.210	0.173	0.457	0.079	0.088	0.238
R-ACC	-0.183	0.052	0.028	-0.249	0.037	-0.002

MMSE = Mini-Mental State Examination; VFT = verbal fluency test; FAB = Frontal Assessment Battery; GMR = grey matter ratio; PFC = prefrontal cortex; DLPFC = dorsolateral prefrontal cortex; OFC = orbital-frontal cortex; ACC = anterior cingulate cortex.

*$p < 0.01$. [¶]Volumes were calculated as: raw volume × 1000/ICV.

a: Spearman's correlation; b: Pearson's correlation.

Table 5-3. Correlations between volumetric variables and cognitive tests at 15 months after stroke.

Volumetric variable	Female			Male		
	MMSE[a]	VFT[b]	FAB[a]	MMSE[a]	VFT[b]	FAB[a]
GMR	0.122	0.375	0.338	0.439	0.267	0.434
Volume of WMLs or brain regions[¶]						
WMLs	-0.477*	-0.514*	-0.612*	-0.046	-0.098	-0.147
L-PFC	0.049	0.617**	0.348	0.402	0.030	0.295
R-PFC	0.274	0.537*	0.433	0.332	0.180	0.204
L-DLPFC	0.045	0.631*	0.331	0.201	-0.181	0.053
R-DLPFC	0.084	0.216	0.068	0.082	0.128	0.095
L-OFC	0.045	0.423	0.210	0.480*	0.092	0.242
R-OFC	0.343	0.402	0.359	0.151	0.056	0.218
L-ACC	0.226	0.179	0.298	0.260	-0.021	0.126
R-ACC	0.124	0.225	0.226	-0.109	0.012	0.130

MMSE = Mini-Mental State Examination; VFT = verbal fluency test; FAB = Frontal Assessment Battery; GMR = grey matter ratio; PFC = prefrontal cortex; DLPFC = dorsolateral prefrontal cortex; OFC = orbital-frontal cortex; ACC = anterior cingulate cortex.

*$p < 0.01$; [¶]Volumes were calculated as: raw volume × 1000/ICV.

a: Spearman's correlation; b: Pearson's correlation.

Table 5-4 Partial correlation of L-DLPFC and L-PFC volume and verbal fluency test score in elderly female stroke patients.

	Verbal Fluency Test (3 months)		Verbal Fluency Test (15 months)	
Volume¶	**Partial coefficient**	**p**	**Partial coefficient**	**p**
Left DLPFC*	0.477	0.018	0.548	0.006
Left PFC*	-	-	0.467	0.021

*controlled by age, education, NIHSS, diabetes mellitus, location of infarcts, and volume of infarcts and WMLs.

PFC = prefrontal cortex; DLPFC = dorsolateral prefrontal cortex.

¶Volumes were calculated as: raw volume × 1000/ICV.

5.4. Discussion

To the best of our knowledge, this was the first study to investigate the sex difference in the association between the PFC and cognitive functions in stroke patients. Our main finding was that the volume of the left DLPFC was positively correlated with verbal fluency performance in women at three and 15 months after stroke, even after adjusting for possible confounders. This correlation was absent in the age-matched male stroke patients.

Our finding that verbal fluency is impaired in stroke patients mainly when left frontal lesions is present echoes the findings of previous studies of patients with traumatic brain injuries (Jurado et al., 2000; Henry and Crawford, 2004). The findings of this study also suggest that, in addition to focal damage or acute injures, chronic, degenerative, or ischemic changes in the left DLPFC may also contribute to verbal fluency impairment in non-aphasic stroke in women. The absence of any correlation between executive functions and atrophy of the PFC and its subdivisions in women may be due to co-existing WMLs, which have been linked to poststroke executive dysfunction (Wen et al., 2004) and may lessen the effect of PFC atrophy. The relationship between

PFC and DLPFC atrophy and executive function warrants further studies with more sensitive tests of executive function.

Our results also indicate that the left DLPFC and left PFC may play different roles in the neuropsychological processing of verbal fluency for elderly male and female stroke patients. Although the elderly female patients scored significantly lower in tests of global cognition and executive function, their verbal fluency performance was comparable to that of their male counterparts, which accords with the notion that language function is predominant in women (Duff and Hampson, 2001; Brucki and Rocha, 2004). Sex differences in PFC functions and volume may be linked to gonadal hormones that can modulate PFC functions (Duff and Hampson, 2001). Animal experiments have shown that gonadal hormones are responsible for the sexual differentiation of both the structure and function of the central nervous system via organizational and activational effects (Collins et al., 1994). That gonadal hormones may influence PFC functions in humans is supported by the finding that the PFC is one of the strongest binding sites for estrogen in female brain specimens (Bixo et al., 1995).

Whether there is a sex difference in executive function in stroke patients remains unknown. In the comparison of women and men in this

study, the latter had significantly lower right OFC and right ACC volumes than the former, as well as a trend toward a lower volume of both sides of the PFC. However, men and women had a similar DLPFC size. It is possible that there may be selective atrophy in the brain regions of both men and women.

Notwithstanding these findings, this study had significant limitations. First, the subjects presented with relatively mild neurological deficits, which limits the generalizability of the findings. In addition, patients with aphasia and large frontal lobe infarcts had to be excluded. Second, volumetry was not conducted in every part of the cerebral cortex. Third, only the FAB was used to assess executive functions, and it may have a ceiling effect in doing so. Moreover, phonemic verbal fluency was not tested. Finally, the sample size was too small to have sufficient power in detecting associations between the FAB score and PFC or DLPFC atrophy.

In conclusion, atrophy of the left DLPFC is associated with semantic verbal fluency impairment in elderly women suffering from a stroke, but not in their male counterparts. Sex may thus be a contributing factor in the neuropsychological pathomechanism of poststroke cognitive impairment.

CHAPTER 6 POSTSTROKE DEPRESSION IN PATIENTS WITH SMALL SUBCORTICAL INFARCTS

6.1. Background

Small subcortical infarcts (SSIs) occur more frequently among the Chinese than among Caucasians (Huang et al., 1990), and have been associated with a favorable prognosis (Grau et al., 1990). The most common etiological type of SSI is small vessel disease (SVD) (Bamford and Warlow, 1988), but recent studies have revealed that SSIs can also result from intracranial large artery disease (LAD), extracranial large artery disease and cardioembolism (Jung et al., 2001; Seifert et al., 2005). It is thought that the higher frequency of SSIs in Chinese has contributed to a higher frequency of intracranial large artery stenosis (Mok et al., 2003). SSIs resulting from LAD may have an unstable clinical course (Adachi et al., 2000) and a worse physical outcome (Mok et al., 2003) than those resulting from SVD.

Poststroke depression (PSD) is a common disabling outcome of stroke that is thought to be associated with cerebral hypoperfusion

(Yamaguchi et al.,1992). As a deficit of cerebral perfusion is related to the degree of large artery stenosis (Hori et al.,2002), and the physical outcome is worse in LAD, we postulate that the frequency of PSD may be higher in patients with SSIs resulting from LAD than from SVD. No study has been conducted to investigate poststroke depressive symptoms among patients with different etiological types of SSI. Hence, to test our hypothesis, we investigated these symptoms in patients with SSIs three months after stroke.

6.2. Methods

From December 2004 to May 2007, all ischemic stroke patients admitted to the ASU of PWH in Hong Kong were screened. The inclusion criteria for recruitment were (1) at least 18 years old, (2) a well-documented acute first or recurrent ischemic stroke occurring within seven days of admission, (3) a score $\geq$ 17 on the CC-MMSE (Chui et al., 1994) on admission, (4) of Chinese descent and fluent in the Cantonese dialect, (5) able and willing to be informed consent, and (6) no history of psychiatric disorders. Patients were excluded from the

study if (1) they had a neurological disease other than stroke, (2) no MRI had been performed, and (3) they had significant aphasia or dysarthria, i.e., they had scored ≥2 on the NIHSS (Lyden et al., 1999) language or dysarthria component. This poststroke psychiatric study was approved by the Ethics Committee of the Chinese University of Hong Kong.

Patients with relevant SSIs were included for further analysis. SSIs were defined as hypodense lesions ranging from 0.2~2 cm in the longest dimension (except for infarcts in the infratentorial region). Two centimeters was selected as the cutoff point because infarcts are often larger in live patients than at autopsy (Adachi et al., 2000). A relevant SSI was defined as an SSI in T2-weighted MRI and DWI that could account for a patient's neurological deficit (Mok et al., 2003).

6.2.1. MRI examination

All examinations were performed with a 1.5T scanner (Sonata, Siemens Medical System, Erlangen, Germany). The parameters of MRI examination are the same as those in Section 4.2.5 of Chapter 4.

MRI assessment included an examination of both brain infarcts and WMLs. (1) For brain infarcts, the number, type, site, and volume of the acute lesions in DWI were examined. Multiple infarcts were defined as the presence of more than one acute infarct in DWI. The sites of the acute infarcts were classified according to the mapping template developed by Bogousslavsky and Regli (1992). The number and size of old infarcts were also recorded. (2) The extent of the WMLs was graded using the four-point scale developed by Fazekas et al. (1987). Periventricular hyperintensities (PVH) and deep WM hyperintensities (DWMH) were scored on proton density images. Inter- and intra-rater reliability tests were performed on 20 patients, and the level of both inter- and intra-rater agreement was acceptable (volume of acute infarcts: inter-rater r = 0.934, intra-rater r = 0.965; number of infarcts: inter-rater r = 0.892, intra-rater r = 0.945; WMLs: inter-rater kappa = 0.80~0.85, intra-rater kappa = 0.95).

6.2.2. Vascular evaluation

Extracranial carotid disease lesions were evaluated with carotid duplex sonography using a 7.5 MHz probe (Philip SD800) on patients with relevant SSIs. Moderate stenosis was defined as 50-69% stenosis, and severe as ≥ 70% stenosis. Intracranial LAD was evaluated by 3D time-of-flight magnetic resonance angiography (MRA), and its severity was described in accordance with previously published protocols (Wong et al., 2002; Kumral et al., 2002).

6.2.3. Etiological classification of SSIs

Patients with cardioembolic infarction (which was determined by the presence or history of atria fibrillation, sick sinus syndrome, heart valve disease, acute congestive failure, resent myocardial infarction, atrial myxoma, or patent foramen ovale) were excluded. We also excluded patients with infarctions resulting from vasculitis, hematological disorder, or dissection. The etiologies of ischemic stroke among the remainder of the patients were divided into either LAD or SVD. Intracranial LAD or extracranial carotid artery disease were diagnosed if the stenosis was at least moderate (> = 50%) in severity and if the

relevant SSI was located within its arterial distribution. SVD was diagnosed if there was no evidence of intracranial or extracranial LAD.

6.2.4. Clinical characteristics

The following data were collected for all participants: age, sex, years of education, date of onset of stroke, psychiatric history, and presence of chronic vascular diseases (hypertension, diabetes mellitus, atrial fibrillation, ischemic heart disease, and history of stroke). NIHSS and MMSE on admission were assessed by stroke nurses in the ASU.

6.2.5. Physical status and psychiatric assessment

Psychiatric interviews were conducted three months after stroke at a research clinic, as it was assumed that most patients would have made initial emotional adjustments to their disability by that time. Poststroke depressive symptoms were assessed by the Chinese version the GDS-15 (Lim et al., 2000), which we previously validated as having a satisfactory level of accuracy in detecting PSD in Chinese populations

(Tang et al., 2004). According to our previous study, using 6/7 as the cut-off, the sensitivity and specificity of the GDS-15 in detecting PSD were 89% and 73%, respectively. Patients with GDS $\geq$ 7 were considered to have PSD (Tang et al., 2004). Global cognitive function was evaluated with the CC-MMSE. Ability to cope with daily life was evaluated with the BI (Mahoney and Barthel, 1965) and the Instrumental Activities of Daily Living Scale (IADL) (Lawton and Brody, 1969). The same psychiatrist (WKT) carried out all of the psychiatric assessments.

6.2.6. Statistical analysis

SPSS 12.0 was used to analyze the data. The patients with SSIs recruited for the study were divided into two groups, an LAD group and an SVD group. Age and years of education in the groups were compared using t-tests, and MMSE, NIHSS, BI, IADL, GDS, and number and volume of infarcts were compared using Mann-Whitney U tests, because they were not normally distributed. Variables of frequency were compared using Chi-square tests. The foregoing

variables were also compared between the PSD and non-PSD groups. Variables with $p < 0.05$ were entered into a binary logistic regression to determine the independent predictors of PSD. Significance was set at $p < 0.05$ (two-sided).

6.3. Results

Between December 2004 and May 2007, 618 patients met the criteria for inclusion in the poststroke psychiatric study, 591 of whom were recruited for subsequent psychiatric assessment. Of the other 27, 14 died during the three-month period immediately following their stroke (four suffered fatal recurrent strokes), 11 suffered nonfatal recurrent strokes, and two were diagnosed with MMSE < 17 three months after their strokes. MRI, MRA, and carotid duplex sonography were ultimately performed on 535 (90.5%) of the 591 patients recruited for poststroke psychiatric assessment.

Relevant SSIs were verified in 145 (24.5%), 127 (21.5%) of whom were included in the analysis, after the exclusion of six patients with cardiogenic embolism, one with protein S deficiency, two with cerebral

vasculitis, and nine who were without carotid duplex sonography results. SVD was diagnosed in 83 (65.4%) patients and LAD in 44 (34.6%) patients. Thirty-five of the patients in the LAD group had pure intracranial LAD, four had extracranial LAD, and five had concurrent intracranial and extracranial LAD. The distribution of SSIs is shown in Table 6-1.

Table 6-1 Distribution of SSIs.

Site of infarcts	Frequency (%)
Superficial perforators	22 (17.3)
Deep perforators	71 (55.9)
MCA territory	55 (43.3)
ACA territory	2 (1.6)
PCA territory	12 (9.4)
ICA territory	2 (1.6)
Internal border-zone	34 (26.8)
More than one site	5 (3.3)
Total	127 (100)

SSIs = small subcortical infarcts; MCA = middle cerebral artery; ACA = anterior cerebral artery; PCA = posterior cerebral artery; ICA = internal carotid artery.

The clinical and imaging variables of the SSI patients with LAD and SVD are compared in Table 6-2. Diagnoses of diabetes mellitus ($p = 0.002$) and multiple acute infarcts ($p < 0.001$) were significantly more frequent in the LAD group, which also had higher numbers of acute and total infarcts ($p < 0.05$). The LAD group also had a higher frequency of superficial infarcts (27.3% versus 12.0%, $p = 0.032$), and more depressive symptoms were observed in this group than the SVD group (median of GDS, 7 versus 4, $p = 0.014$). Twenty-three of the 44 (52.3%) patients in the LAD group had PSD, compared with only 21 of the 83 (25.3%) patients in the SVD group ($p = 0.002$). Four (9.1%) of those in the former were diagnosed with major depression, compared to five (6.0%) in the latter. Univariate analysis (Table 6-3) showed a significant difference in etiological type and BI at three months after stroke between the PSD and non-PSD groups. The PSD group had a higher percentage of LAD cases (52.3% versus 25.3%, $p = 0.002$) and a lower BI score. The correlation between the IADL and BI was > 0.50 ($r = -0.642$), and the IADL was not entered into the subsequent multivariate logistic regression model to avoid the problem of collinearity. In this regression model, the etiological type LAD was a significant

independent risk factor (OR = 3.249, p = 0.003) for PSD, although BI was not an independent predictor (Table 6-4).

Table 6-2 Comparison of the clinical features, radiological findings, physical status, and psychiatric assessment at 3 months after stroke of patients with SSIs resulting from SVD and LAD.

	SVD n = 83	LAD n = 44	p
Sex (male): N/(%)[a]	66 (79.5)	29 (65.9)	0.093
Age[b]	63.5 (10.7)	66.1 (11.1)	0.200
Years of education[b]	6.4 (4.6)	5.3 (4.2)	0.177
Hypertension: N/(%)[a]	60 (72.3)	37 (84.1)	0.136
Diabetes: N/(%)[a]	26 (31.3)	25 (56.8)	0.005*
MMSE on admission [c]	27 (22-29)	26 (24-28)	0.965
NIHSS on admission [c]	4 (2-5)	4 (2.25-5.75)	0.546
Previous stroke: N/(%)[a]	11 (13.3)	8 (18.2)	0.459
Location of infarcts: N(%)[a]			
Superficial perforator	10 (12.0)	12 (27.3)	0.031*
Deep perforator	50 (60.2)	21 (47.7)	0.177
Internal border zone	23 (27.7)	11 (25.0)	0.743
Volume of acute infarcts (cm^3)[c]	0.4 (0.2-0.7)	0.6 (0.2-1.2)	0.160
Multiple acute infarcts: N/(%)[a]	8 (9.6%)	20 (45.5%)	< 0.001*
Total number of infarcts [c]	2 (1-3)	2.5 (1-4)	0.029*

DWMH score[c]	1 (1-2)	1 (1-2)	0.686
PVH score[c]	1 (1-2)	1 (1-2)	0.982
Assessment at 3 months after stroke			
MMSE at 3 months[c]	28 (25-29)	27 (26-29)	0.570
IADL[c]	0 (0-2)	1 (0-7.75)	0.050
BI[c]	100 (95-100)	100 (95-100)	0.070
GDS[c]	4 (2-7)	7 (3-9)	0.014*
Depression (GDS ≥ 7): N/(%)[a]	21 (25.3%)	23 (52.3%)	0.002*

a. n (%), Chi-square test; b.mean (s.d), t-test; c. median (IQR), Mann-Whitney U test.

PVH = Periventricular hyperintensities; DWMH = deep white matter hyperintensities; MMSE = Mini-Mental State Examination; NIHSS = National Institutes of Health Stroke Scale; IADL = Instrumental Activities of Daily Living Scale; BI = Barthel Index; GDS = Geriatric Depression Scale.

*$p < 0.05$

Table 6-3 Comparison between the PSD and non-PSD groups in terms of clinical features, radiological findings, and physical status of patients with SSIs.

	PSD n = 44	Non-PSD n = 83	p
Sex (male): N/(%)[a]	33 (75.0)	62 (74.7)	0.970
Age[b]	63.9 (10.4)	64.6 (10.7)	0.721
Years of education[b]	5.8 (4.4)	6.2 (4.6)	0.603
Hypertension: N/(%)[a]	30 (68.2)	67 (80.7)	0.113
Diabetes: N/(%)[a]	21 (47.7)	30 (36.1)	0.205
MMSE on admission [c]	27 (23.5-28.5)	26(23-29)	0.996
NIHSS on admission [c]	4 (3-7)	3 (2-5)	0.171
Previous stroke: N/(%)[a]	5 (11.4)	14 (16.9)	0.408
Volume of acute infarcts (cm^3)[c]	0.5 (0.2-1.1)	0.4 (0.2-0.7)	0.315
Multiple acute infarcts: N/(%)[a]	12 (27.3%)	16 (19.5%)	0.318
Total number of infarcts [c]	2 (1-4)	2 (1-3)	0.175
DWMH score[c]	1 (1-2)	1 (1-2)	0.745
PVH score[c]	1 (1-2)	1 (1-2)	0.878
Etiological type[a]			0.002*
LAD: N/(%)	23 (52.3%)	21 (25.3%)	
SVD: N/(%)	21 (47.7%)	62 (74.4%)	
Assessment at 3 months after stroke			

MMSE at 3 months[c]	26.5 (3.2)	26.4 (3.4)	0.798
BI[c]	97.5 (90-100)	100 (100-100)	0.002*
IADL [c]	1 (0-6)	0 (0-2)	0.004*

PVH = Periventricular hyperintensities; DWMH = deep white matter hyperintensities; MMSE = Mini-Mental State Examination; NIHSS = National Instituted of Health Stroke Scale; IADL = Instrumental Activities of Daily Living Scale; BI = Barthel Index; GDS = Geriatric Depression Scale.

a. n (%), Chi-square test; b. mean (s.d), t-test; c. median (IQR), Mann-Whitney U test.

*$p < 0.05$

Table 6-4 Variables predicting PSD in logistic regression analysis.

Variable	*β*	p value	OR (95.0% CI)
Etiological type (LAD *versus* SVD)	1.178	0.003	3.249 (1.492~7.074)
BI	-0.130	0.129	0.878 (0.742~1.039)

OR = odds ratio; CI = confidence interval; SVD = small vessel disease; LAD = large artery disease; BI = Barthel Index.

6.4. Discussion

The percentage of patients with relevant SSIs in our cohort was 24.5% (145 of 591), a similar percentage to that found in previous studies of Chinese populations (Huang et al., 1990; Mok et al., 2003). We found that 34.6% of the SSIs in our group of patients originated from LAD, which is similar to the percentage found in a previous study of an Asian population (Bang et al., 2002), but higher than that in a study of a Caucasian population (Horowitz et al., 1992). It seems that LAD is a common etiological type of SSI in the Chinese.

SSIs occur in the deep perforator, border-zone, and superficial perforator regions. The major mechanisms of SSIs resulting from LAD are hypoperfusion, artery-to-artery embolism, or atheromatous plaques occluding the beginning of the intracranial perforators (Caplan et al., 1989; Lee et al., 2003). Our study shows multiple infarcts and infarcts in the superficial region to be more common in LAD than in SVD, which is consistent with previous reports (Horowitz et al., 1992; Mok et al., 2003; Lee et al., 2003).

Previous studies have suggested that PSD is associated with cerebral infarction in the left anterior hemisphere (Robinson et al., 1985), a

larger lesion size (MacHale et al., 1998), and WMLs (Bokura et al., 1994; Piamarta et al., 2004). Few studies have examined how a stroke's impact on PSD can be affected by its etiological type. Pohjasvaara (2003) reported depression to be more common in stroke patients with MRI-defined SIVD than with other types of stroke. He ascribed SIVD, a condition resulting from SVD (Roman et al., 2002), to patients with severe WMLs or multiple lacunar infarcts.

In our study, there was a significantly higher incidence of PSD in the LAD group, which suggests that LAD is an independent risk factor for PSD in patients with SSIs, regardless of physical status. As the size of the infarcts in the patients with SSIs was relatively small, the effects of acute infarction on depression may be less important. Prestroke chronic impairment of the brain may thus play a more important role in the development of PSD in SSI cases. Poor blood perfusion is an important prestroke chronic impairment. The internal carotid artery, together with its intracranial branches, the middle cerebral artery (MCA) and anterior cerebral artery (ACA), supplies the anterior three-fifths of the cerebral hemisphere. The most important structures associated with depression, the frontal-subcortical circuits (FSC) (Cummings, 1998) are located within this supplemental area. Severe stenosis of the carotid or

intracranial large artery affects cerebral blood flow significantly (Chaves et al., 2000). Hori et al. (2002) found that, in patients with CVD, a reduction in the mean increment ratio (IR) and regional IR, obtained by calculating the mean cerebral blood flow for pre- and post-acetazolamide tests, parallels the degree of artery stenosis seen using single-photon emission computed tomography (SPECT). It is possible that PSD is more common in LAD than in SVD because chronic significantly poor cerebral blood perfusion impairs the mood regulation pathway and the metabolism of the neurotransmitters associated with depression. This hypothesis is also supported by a previous study showing that a decrease in regional cerebral blood flow (r-CBF) in the frontal region is associated with PSD (Yamaguchi et al., 1992).

In recent years, recanalization techniques for stenosis of the extracranial and intracranial large artery, such as carotid endarterectomy (CEA), a carotid angioplasty stent (CAS), and intracranial angioplasty, have become increasingly commonplace. It may be that recanalizing stenosis and stimulating increased cerebral blood flow will help to reduce the incidence of poststroke psychiatric disorders. Certainly, further studies on these disorders could profitably concentrate on cerebral vessels and cerebral blood flow.

This poststroke psychiatric study had a number of limitations. First, selection bias may have been introduced by our exclusion of patients with aphasia, dysarthria, and low MMSE scores. The patients who were included had relatively younger ages and lower NIHSS scores on admission than those who were excluded. Second, we employed only the GDS-15 to determine PSD. Third, our classification of large and small vessel disease was based on the results of MRA and carotid duplex sonography. Compared with digital subtraction angiography (DSA), which is considered by most practitioners to be the most accurate method available for measuring large artery stenosis, MRA may sometimes overestimate the extent of stenosis. Fourth, echocardiography was not performed on all patients, which may have resulted in an underestimation of the number of cardioembolism cases.

6.5. Conclusion

The results of this study suggest that PSD may be more common in patients with SSIs resulting from LAD than SVD. The association between etiological type and PSD is independent of physical status.

These findings thus indicate that cerebral blood perfusion may play an important role in the development of PSD.

CHAPTER 7 POSTSTROKE EMOTIONAL LABILITY AND ITS RELATIONSHIP WITH CEREBRAL MICROBLEEDS

7.1. Introduction

As discussed in the introduction to this thesis, emotional lability (EL) is defined as virtually uncontrollable episodes of laughter, crying, or both (Kim and Choi-Kwon, 2000). These outbursts of laughing or crying either occur with no clear relationship to a stimulus or are triggered by minor, non-specific stimuli. In addition, patients may experience no concomitant or subsequent change in feelings. EL is a distressing and embarrassing complaint for the patient, is often socially disabling (Andersen et al., 1993), and may interfere with his or her rehabilitation. Other terms used for this clinical syndrome include emotionalism, pathological laughing and crying, pseudobulbar affect, pathological emotionality, and emotional incontinence (Kim and Choi-Kwon, 2000; Schiffer and Pope, 2005; Dark et al., 1996). Common methods of evaluating EL are clinical interviews, chart reviews, the

Pathological Laughing and Crying Scale (Robinson et al., 1993), and other questionnaires (Schiffer and Pope, 2005).

EL affects 11-52% of all stroke survivors (Tang et al., 2004; Schiffer and Pope, 2005). PSEL usually starts within weeks of a stroke (Kim, 1997), may last from one week to a few years (Ceccaldi et al., 1994; Kim, 1997), has a fluctuating clinical course (Dark et al., 1996), and may respond to selective serotonin reuptake inhibitors (Brown, 1998).

The neuropathological substrate of EL has yet to be determined. Wilson (1924) proposed that it is caused by bilateral corticobulbar motor tract lesions. Parvizi et al. (2001) more recently hypothesized that disconnection in the cortico-pontine-cerebellar pathways may also be an important link in the pathogenesis of PSEL. Black (1982) suggested three levels of injury (cortical, bulbar, and hypothalamic) as possible causes of pathological laughter, with the common factor being disinhibition at the upper brainstem level. House et al. (1989) proposed that frontal lesions may produce emotional disinhibition similar to the way in which frontal lobe damage produces disinhibition in terms of social behavior. EL has been found to co-occur with frontal release signs such as grasp reflex (Langworthy, 1940). Neuroimaging studies have shown that EL may be related to specific frontal areas, such as the

anterior cingulate and dorsolateral prefrontal cortices (Malloy et al., 1993) and the medial inferior frontal areas (Ghaffar et al., 2008). PSEL is associated with anterior cortical (Kim and Choi-Kwon, 2000; Morris et al., 1993), frontal lobe (Ross and Stewart, 1987), and lenticulocapsular lesions (Kim and Choi-Kwon, 2000), particularly those that involve the dorsal globus pallidus (Kim, 2002). Brainstem and parietal lesions can also generate EL (Ghaffar et al., 2008; Asfora et al., 1989).

The FSC are known to mediate emotion and affective behavior (Cummings, 1993). These circuits link specific areas of the frontal cortex to the striatum, basal ganglia, and thalamus (Cummings, 1993). Several lines of evidence suggest that they are involved in the development of EL (Ross and Stewart, 1987; Malloy et al., 1993; Kim, 2002; Ghaffar et al., 2008). Thalamic lesions can give rise to a variety of neuropsychiatric complications following stroke, including disinhibition, affective changes, apathy, amnesia, and dementia (Carrera and Bogousslavsky, 2006).

In addition to infarcts and WMLs, a common type of lesions involving the FSC is MBs. These MBs are focal deposits of hemosiderin that indicate prior micro-hemorrhages. MBs are related to cerebral

amyloid angiopathy, hypertension, and atherosclerosis (Vernooij et al., 2008) and are common in ischemic stroke (Werring et al., 2005). They may provide useful diagnostic and prognostic information, with potential therapeutic implications for the treatment of stroke (Cordonnier et al., 2007). MBs are also associated with advanced small artery disease of the brain (Kato et al., 2002) and leukoaraiosis (Gao et al., 2008), and they may also predict recurrent stroke (Naka et al., 2006).

MBs are generally considered to be clinically silent. Recent evidence suggests that they may be an important factor in causing cognitive impairments in subcortical VaD (Won et al., 2007), in which they are associated with cognitive dysfunction, particularly executive dysfunction (Werring et al., 2004). The clinical significance of MBs in psychiatric conditions following stroke remains unknown, as is the role they play in PSEL. The aim of the case-control study reported in this chapter was to assess the relationship between MBs and PSEL in stroke survivors.

7.2 Methods

7.2.1. Subjects

A total of 2,337 patients with first-ever or recurrent acute ischemic stroke were admitted to the ASU of the PWH in Hong Kong between December 2004 and June 2007, of whom 874 received an MRI examination. Of those who were admitted with a first-ever or recurrent ischemic stroke and received an MRI, 519 (59.4%) were recruited for this PSEL study. The inclusion criteria were (1) Chinese ethnicity; (2) age of 18 years or above; (3) well-documented (clinical presentation and CT scan of the brain) first or recurrent acute stroke occurring within the seven days before admission; (4) Cantonese as the primary language; and (5) ability and willingness to give consent. The exclusion criteria were (1) transient ischemic attacks; (2) cerebral, subdural, or subarachnoid hemorrhage; and (3) history of a central nervous system disease, such as tumor, trauma, hydrocephalus, multiple sclerosis, Parkinson's disease, etc. All participants were screened for PSEL by a qualified psychiatrist (WKT), and the study protocol was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. The consent of all participants was obtained in accordance with the Declaration of Helsinki.

7.2.2 Collection of demographic and clinical data

A research nurse, who was blind to the psychiatrist's diagnoses, collected patients' demographic data (age, sex, and education level) and assessed the severity of their stroke with the NIHSS (Brott, et al., 1989).

7.2.3. Assessment of PSEL

Psychiatric interviews were conducted three months after the stroke at a research clinic. A psychiatrist (WKT) administered a brief questionnaire to all participants. The diagnostic criteria of PSEL were based on those proposed by Kim (2002) and Choi-Kwon et al. (2006). PSEL was considered to be present if patients exhibited excessive or inappropriate laughing, crying, or both compared with their premorbid state. If the patient agreed that excessive or inappropriate laughing or crying had occurred on two or more occasions since the latest episode of stroke, then a diagnosis of PSEL was established. A research assistant

trained by the principal author administered the CC-MMSE (Chui et al., 1994) to measure participants' global cognitive function.

7.2.4. MRI analysis

Radiological examination by MRI, including DWI and sequence of proton density, was performed on each participant with a 1.5 T system (Sonata, Siemens Medical, Erlangen, Germany) within seven days of admission. For the parameters of MRI examination, readers are referred to Section 4.2.5 of Chapter 4.

Brain infarcts

Acute infarcts affecting the frontal, temporal, parietal, and occipital lobes, coronary radiata, centrums semiovale, internal capsule, basal ganglia, thalamus, brainstem, and cerebellum were recorded, as was the presence or absence of acute infarcts in these locations. Multiple infarcts or infarct(s) involving more than one location were counted in

all locations in which they occurred. The total area of acute infarcts on the DWI was measured with manual outlines, with restricted water diffusion identified on the diffusion weighted images with b values of 1000. The total volume was calculated by multiplying the total area by the sum of the slice thickness and gap.

MBs

MBs were defined as small (2-10 mm) hypointense lesions on the T2 weighted gradient echo sequence, although symmetric basal ganglia calcification and flow void artifacts of the pial blood vessels were excluded (Dichgans et al., 2002). The MB locations included the frontal, parietal, temporal, and occipital lobes; basal ganglia; thalamus as a whole and its anterior, paramedian, lateral, and posterior territories (Carrera et al., 2004); brainstem; and cerebellum. The number of MBs in each location was recorded. Inter- and intra-rater reliability tests of the MB measurements were performed on 30 participants, with good agreement achieved for both (presence of MBs: inter-rater kappa = 0.78; intra-rater kappa = 0.85; number of MBs: inter-rater ICC = 0.91; intra-rater ICC = 0.95).

White matter lesions

WML severity was graded using the four-point scale developed by Fazekas et al. (1987). Periventricular and DWMH were scored on the axial proton density images. Inter- and intra-rater reliability tests were performed on 20 participants, resulting in good agreement (kappa = 0.70-1.00).

7.2.5. Statistical analysis

All statistical tests were performed by SPSS for Windows (release 14.0, SPSS Inc., Chicago, Illinois). Demographic and clinical variables (age, sex, education level, and NIHSS and MMSE scores) and the scores of the PSEL subjects' psychometric tests were compared with those of matched controls using the χ^2 test, Fisher's exact test, Student's t test, and Mann-Whitney U test, as appropriate. Risk factors with a value of $p < 0.10$ were then analyzed by multivariate logistic regression

analysis using a forward stepwise selection strategy. If the correlations between any of these putative risk factors were > 0.50, then additional models were examined to rule out collinearity. In the analysis, the OR of any independent risk factor was interpreted as the risk of subsequent PSEL when all other risk factors were held constant. The level of significance was set at 0.05.

7.3. Results

The patients who were excluded from this study were older (73.9 (12.0) versus 66.0 (11.7) years, $p < 0.001$ and more likely to be female (52.8% versus 39.3%, $p < 0.001$) and had higher NIHSS scores (10.1 (9.3) versus 4.5 (3.4), $p < 0.001$).

Of the 519 patients screened, 74 (14.3%) had PSEL. Patients' demographic and MRI characteristics and stroke-related data stratified by PSEL status are shown in Tables 6-1 and 6-2. The PSEL group had significantly more female subjects, a lower level of education, and lower MMSE but higher NIHSS scores. The number of MBs was significantly higher in the PSEL group. Bleeds located in the thalamus

were associated with PSEL, particularly those in the anterior and paramedian territories (Fig. 7-1). The number of MBs in the thalamus of subjects with PSEL ranged from 1 to 10, with a mean of 3.2 (2.7). The association between PSEL and MBs in the entire brain and in the frontal lobe was of borderline significance. PSEL was not associated with the volume and location of infarcts, the number of lacunar infarcts, or the extent of WMLs.

MMSE score and education were correlated ($r = 0.569$, $p < 0.01$). The correlation between MBs in the thalamus and those in the entire brain was 0.524 ($p < 0.01$). The following variables were entered into the regression model: sex, MMSE, NIHSS, MBs in the thalamus and frontal lobe, and number of MBs. MBs in the thalamus and MMSE score were significant independent predictors of PSEL. The OR of MBs in the thalamus was 4.7 (Table 7-3).

Table 7-1 Demographic, clinical, and MRI variables (microbleeds) of subjects with and without PSEL.

Variable	PSEL (n = 74)	No PSEL (n = 445)	p value
Age (years)[*] †	65.6 ± 9.9	65.6 ± 12.0	0.982
Female sex: N (%)[§]	38 (51.4%)	168 (37.8%)	0.027
Education (years)[*†]	4.2 ± 4.5	5.8 ± 4.8	0.008
MMSE score[*‡]	25 (22-28)	27 (25-29)	< 0.001
NIHSS score[* ‡]	5 (3-7)	4 (2-6)	0.004
Previous stroke: N (%)[§]	18 (24.3%)	82 (18.4%)	0.234
Presence of microbleeds (%)[§]	24 (32.4%)	100 (22.5%)	0.063
Number of microbleeds[*‡]	0 (0-1.25)	0 (0-0)	0.031
Location of microbleeds in (%)			
Frontal lobe[§]	9 (12.2%)	27 (6.1%)	0.056
Temporal lobe[§]	8 (10.8%)	30 (6.7%)	0.213
Parietal lobe[§]	8 (10.8%)	33 (7.4%)	0.316
Occipital lobe	2 (2.7%)	16 (3.6%)	1.000
Basal ganglia[§]	8 (10.8%)	39 (8.8%)	0.570
Thalamus as whole[§]	12 (16.2%)	29 (6.5%)	0.004
Anterior territory[§]	5 (6.9%)	9 (2.0%)	0.020

Lateral territory[§]	6 (8.1%)	17 (3.8%)	0.097
Paramedian territory[§]	6 (8.1%)	14 (3.1%)	0.040
Posterior territory[¶]	4 (5.4%)	10 (4.2%)	0.125
Brain stem[§]	8 (10.8%)	26 (5.8%)	0.110
Cerebellum[§]	5 (6.8%)	31 (7.0%)	1.000

MMSE = Mini-Mental State Examination; NIHSS = National Institutes of Health Stroke Scale; PVH = Periventricular hyperintensities; DWMH = Deep white matter hyperintensities.

[•]mean ± standard deviation; †t-test; ‡Mann-Whitney U test; [§]χ^2 test, [¶]Fisher's exact test.

Table 7-2 Demographic, clinical, and MRI variables of subjects with and without PSEL.

Variable	PSEL (n = 74)	No PSEL (n = 445)	p value
Number of acute infarcts†	1 (0-1.25)	1 (0-1)	0.604
Volume of acute infarcts (cm^3) †	0.6 (0-3.0)	0.4 (0-1.4)	0.200
Location of acute infarcts in (%)			
Frontal lobe‡	7 (9.5%)	25 (5.6%)	0.203
Temporal lobe§	2 (2.7%)	16 (3.6%)	0.698
Parietal lobe§	4 (5.4%)	30 (6.7%)	0.804
Occipital lobe§	3 (4.1%)	9 (4.0%)	0.392
Basal ganglia‡	18 (24.3%)	90 (20.2%)	0.421
Thalamus§	3 (4.1%)	26 (5.8%)	0.784
Brain stem‡	14 (18.7%)	61 (13.7%)	0.238
Cerebellum§	1 (1.4%)	7 (1.6%)	1.000
Coronary radiata‡	9 (12.2%)	62 (13.9%)	0.682
Centrums semiovale§	4 (5.4%)	19 (4.3%)	0.555
Internal capsule‡	11 (14.9%)	59 (13.3%)	0.708
No. of old infarcts †	0 (0-1)	0 (0-1)	0.977
Location of old infarcts			
Frontal lobe§	1 (1.4%)	10 (2.2%)	1.000

Temporal lobe[§]	2 (2.7%)	8 (1.8%)	0.641
Parietal lobe[§]	3 (4.1%)	8 (1.8%)	0.197
Occipital lobe[§]	1 (1.4%)	7 (1.6%)	1.000
Basal ganglia[‡]	18 (24.3%)	90 (20.2%)	0.421
Thalamus[‡]	7 (9.5%)	27 (6.1%)	0.275
Brain stem[§]	2 (2.7%)	19 (4.3%)	0.753
Cerebellum[§]	0 (0.0%)	6 (1.3%)	0.601
Coronary radiata[‡]	9 (12.2%)	42 (9.4%)	0.466
Centrums semiovale[§]	3 (4.1%)	11 (2.5%)	0.434
Internal capsule[§]	4 (5.4%)	25 (5.6%)	1.000
Lacunar infarcts			
Presence of lacunar infarcts[‡]	44 (59.5%)	249 (56.0%)	0.573
Number of lacunar infarcts[†]	1 (0-2)	1 (0-2)	0.626
WMLs			
DWMH score[†]	1 (1-2)	1 (1-2)	0.469
PVH score[†]	1 (0-2)	1 (0-1)	0.962

DWMH = deep white matter hyperintensities; MMSE = Mini-Mental State Examination; NIHSS = National Institutes of Health Stroke Scale; PSEL = poststroke emotional lability; PVH = periventricular hyperintensities; WMLs = white matter lesions.

† Median (IQR), Mann-Whitney U test; ‡ n (%), χ^2 test; §n (%), Fisher's exact test.

Table 7-3 Multivariate logistic model of the clinical and radiological determinants of poststroke emotional lability.

Variable	β	p value	OR (95.0% CI)
Microbleeds in thalamus	1.542	0.002	4.676 (1.743-12.544)
MMSE	-0.111	0.009	0.895 (0.823-0.972)
NIHSS	0.079	0.050	-
Microbleeds in frontal lobe	0.956	0.063	-
Sex (female)	0.517	0.076	-
Number of microbleeds	-0.090	0.093	-

MMSE = Mini-Mental State Examination; NIHSS = National Institutes of Health Stroke Scale.

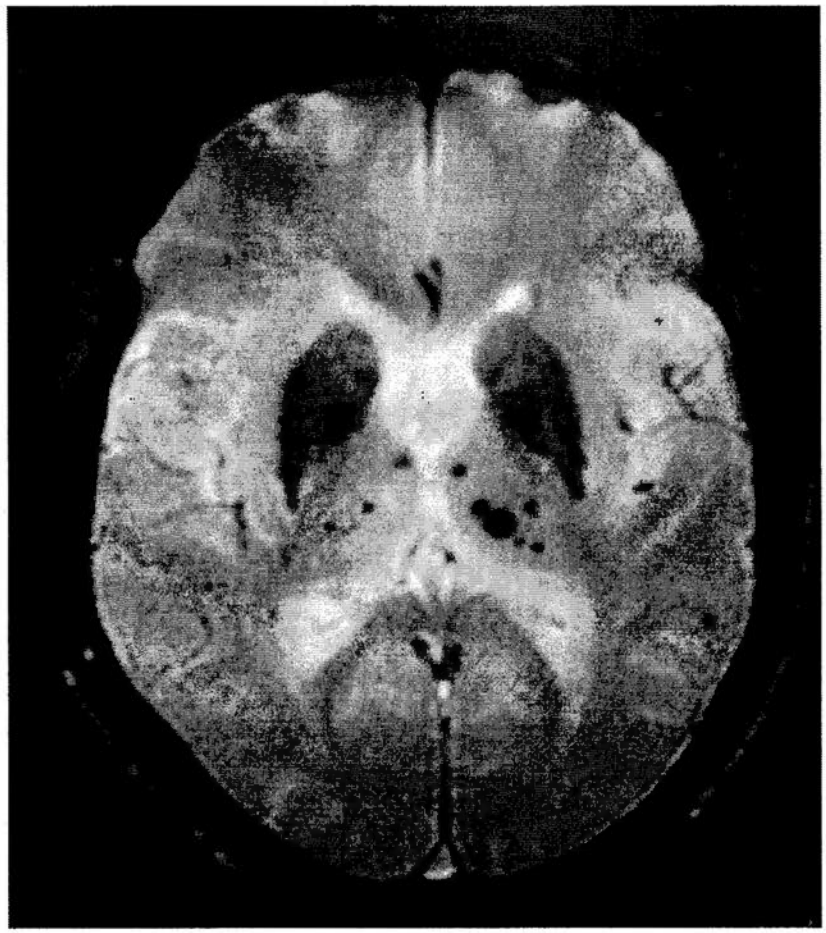


Figure 7-1. T2* weighted gradient echo MRI of a 78-year-old woman with poststroke emotional lability shows multiple microbleeds in the bilateral thalami (mostly on the left), ranging from 2 to 8 mm in diameter.

7.4. Discussion

To the best of our knowledge, this was the first study to examine the role of MBs in stroke patients with EL, and its findings challenge the prevailing view of these bleeds as clinically silent (Kato et al., 2002). The histopathological data reveal that MBs are involved not only in hemosiderin deposition, but also affect the surrounding gliosis and cause frank necrosis or infarction, which means that they may be of clinical importance (Tanaka et al., 1999).

The findings of this study suggest that microhemorrhages are important components of the pathomechanism of PSEL, with PSEL associated with MBs in the thalamus, particularly its anterior and paramedian territories. The thalamus can be divided into different regions according to the pattern of blood supply. The paramedian territory is supplied by the thalamoperforating arteries, which originate in the first part of the posterior cerebral artery (Carrera et al., 2004). The paramedian thalamic territory has connections between the cortical (prefrontal, orbitofrontal, and mediofrontal cortex) and subcortical (ventral pallidum and internal globus pallidus) structures (Guigere and Goldman-Rakic, 1988; Groenewegen and Berendse, 1994). Paramedian

thalamic lesions can cause personality changes and disinhibition (Bogousslavsky, 1988), such as crying spells, labile affect, and even frank manic symptoms (Gilchrist et al., 1993). It is thought that these behavioral symptoms are due to thalamofrontal disconnection (Gilchrist, 1993). A wide range of behavioral and personality changes have been associated with lesions in the anterior territory, including euphoria, a lack of emotional concern, and emotional central facial paralysis. The latter is characterized by facial weakness during such emotional displays as laughing and crying (Schmahmann, 2003). Patients with executive dysfunction have more MBs in the frontal region (Werring et al., 2004), and there is evidence to suggest that executive functions are impaired in patients with EL (McCullagh, 1999; Schmahmann, 2003). Further exploration of the relationship among MBs in the frontal lobe, executive functions, and PSEL is warranted.

The main limitation of this study is its relatively small sample size, which resulted in a low degree of power in detecting potential between-group differences with respect to frontal lobe MBs. Furthermore, PSEL assessments were carried out only once, at the three-month follow-up. As patients who died before this follow-up were not included in the study, the sample was biased to an unknown degree. In addition,

patients who were unable to give consent due to dementia or aphasia associated with left-side infarcts were excluded. The excluded group also included more female patients who were older and whose stroke was more severe. As cognitive impairment (House et al., 1989), left-side lesions (House et al., 1989), female sex (Kim and Choi-Kwon, 2000), a younger age (Tang et al., 2004), and neurological deficits (Kim and Choi-Kwon, 2000) are associated with PSEL, this selection bias may limit the generalizability of our findings.

It is interesting to note that thalamic MBs, which are prestroke lesions, can contribute to the development of an event such as EL after stroke. It is well known that prestroke abnormalities do contribute to poststroke psychiatric problems, including dementia and depression. WMLs and cerebral atrophy predict poststroke dementia (Tang et al., 2004), and, similarly, WMLs predict poststroke depressive symptoms (Verdelho et al., 2004).

In conclusion, the results of this study suggest that MBs in the thalamus may contribute to the development of PSEL. This assumption, although biologically plausible, should be regarded as speculative at this point. Further exploration of the importance of MBs in PSEL and other psychiatric sequels in stroke survivors is clearly warranted.

CHAPTER 8 INSOMNIA SYMPTOMS IN ISCHEMIC STROKE PATIENTS: CLINICAL AND RADIOLOGICAL CORRELATES

8.1. Introduction

Insomnia is a common complaint among stroke survivors (Palomaki et al., 2003). It involves difficulties in initiating or maintaining sleep or early awakening with the inability to fall asleep again (Estivill et al., 2003). As insomnia may affect stroke prognosis and quality of life for stroke survivors, it should be taken into consideration in their treatment and rehabilitation (Leppavuori et al., 2002). However, there is a paucity of studies on insomnia in stroke cohorts, and healthcare providers tend to neglect the complaint (Eaton et al., 1995).

Insomnia in stroke patients has been reported to be associated with the severity of disability, anxiety, dementia, and the use of psychotropic drugs (Leppavuori et al., 2002), thus suggesting that its development is multi-factorial. Depression and anxiety affect 16-40% of stroke patients (Chemerinski and Robinson, 2000; Pohjasvaara et al., 1998; Tang et al.,

2005) and partly account for insomnia. The fact that stroke patients have more pre-existing chronic vascular diseases (e.g., hypertension and diabetes) compared to the healthy elderly raises the possibility that there may be other factors related to insomnia in these patients.

The relationship between insomnia and brain lesions is poorly understood (Autret et al., 2001). The regulation of the sleep/wake cycle requires the anatomical and functional integrity of the neuronal networks in the cortical and subcortical structures (Nofzinger, 2004). It is unclear whether infarction location or other structural changes in the brain contribute to the development of insomnia in chronic stroke. To date, only one study (Leppavuori et al., 2002) has examined the neuroradiological concomitants of stroke-related insomnia, finding the major dominant stroke to be associated with new-onset insomnia in 277 ischemic stroke patients. The infarction locations considered, however, were only left and right hemisphere, deep lacunas, brainstem, or cerebellum, and the size of the infarctions was classified as major or minor. Moreover, they failed to measure WMLs or MBs.

The study reported in this chapter investigated the frequency of insomnia symptoms and their correlates in Chinese ischemic stroke survivors by analyzing both clinical and neuroimaging parameters.

8.2. Methods

8.2.1. Participants

All ischemic stroke patients consecutively admitted to the ASU of the PWH between December 2004 and June 2007 were screened for insomnia. Patients were invited to participate in the study if they (1) were aged ≥ 18 years; (2) had an acute first or recurrent ischemic stroke; (3) scored ≥ 15 on the CC-MMSE (Chui et al., 1994) on admission; (4) were of Chinese descent and fluent in the Cantonese dialect; and (5) were willing and able to give informed consent. Patients were excluded if they (1) had a central nervous system disease other than stroke; (2) did not have an MRI scan; (3) had significant aphasia or dysarthria to the extent of precluding meaningful communication; (4) had a recurrent stroke within three months of the index stroke; (5) had a history of depression and/or were being treated with an antidepressant; or (6) met the criteria for a major depressive disorder at the interview. Major depressive disorders were diagnosed using the Chinese-Bilingual

Structured Clinical Interview for the DSM-IV (CB-SCID-DSM IV; So et al., 2003).

Basic socio-demographic and clinical data, including age, sex, education level, hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), previous stroke, ischemic heart disease and atrial fibrillation, and scores on the NIHSS on admission, were retrieved from the stroke registry at the ASU. Hypertension was defined as repeated blood pressure measures of ≥ 140/90 mm Hg or the need for chronic antihypertensive medication; and diabetes mellitus was defined as fasting blood glucose ≥ 7.0 mmol/l, postprandial blood glucose ≥ 11.1 mmol/l, or current treatment for diabetes mellitus.

This study of poststroke psychiatric disorders was approved by the Ethics Committee of the Chinese University of Hong Kong and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All of the participants signed a consent form.

8.2.2. Assessment of insomnia

Insomnia and psychiatric and physical condition were assessed three months after the participants' index stroke. A trained research nurse administered the insomnia questionnaire and evaluated the participants' psychological and physical status. An insomnia questionnaire (Chui et al., 1999) soliciting information on the following sleep pattern items within the most recent one-month period was administered.

1. On average, how many hours do you spend asleep per night?

2. How many hours of sleep per night do you think you need?

3. Do you have difficulty in falling asleep?

4. Do you have frequent wakening in the night?

5. Do you wake up very early in the morning and have difficulty in going back to sleep?

6. Do you consider yourself as having insomnia?

7. Do you need to take sleeping pills at times in the past 1 month? If yes, how often?

8. Do you frequently feel tired in daytime?

This insomnia questionnaire has previously been used in the Chinese elderly in Hong Kong (Chui et al., 1999). Responses to questions 3, 4,

and 5 were coded as "never/rarely," "sometimes," and "frequently/all the time." Those to question 6 were coded as "no," "sometimes," and "frequently/all the time." Insomnia symptoms were confirmed if the answer to question 3, 4, or 5 was "frequent." The daytime consequences of insomnia were confirmed if the answer to question 8 was "yes." These definitions are consistent with those used in most epidemiological studies (Ohayon, 2002).

8.2.3. Assessment of physical and psychiatric status

The physical and psychiatric assessment included the administration of the following: (1) the BI (Mahoney and Barthel, 1965) for the assessment of subjects' functional disability; (2) the Chinese version of the GDS-15 (Lim et al., 2000) to evaluate depressive symptoms; (3) the Modified Life Event Scale (MLES; Bourque and Back, 1977) to identify 18 adverse life events in the six months before the examination; and (4) the CC-MMSE (Chui et al., 1994) to evaluate global cognitive functions.

8.2.4. MRI examination and assessment

All examinations were performed with a 1.5T scanner (Sonata, Siemens Medical System, Erlangen, Germany). The sequences acquired were T1-weighted, T2-weighted, protondensity, DWI, and gradient echo images.

The MRI assessment included brain infarctions, WMLs, and MBs. The number, site, and volume of the brain infarctions in the T1-weighted imaging were recorded, including those in the frontal, temporal, and occipital-parietal lobe, subcortical WM, basal ganglia, thalami, and infratentorial regions. The total area of infarcts in the T1-weighted imaging was measured by the manual outlines of all areas. The total volume was calculated by multiplying the total area by the sum of the slice thickness and gap. The severity of the WMLs was graded using the four-point scale developed by Fazekas et al. (1987). Periventricular hyperintensities (PVH) and deep white matter hyperintensities (DWMH) were scored on the protondensity images. MBs were defined as small (2-10 mm) hypointense lesions on the gradient echo sequences, excluding symmetric basal ganglia calcification and flow void artifacts of the pial blood vessels. The thesis author who was blind to the results of all other assessments evaluated

the neuroimaging variables. Inter- and intra-rater reliability tests were performed on 20 patients and involved the thesis author and another neurologist. The level of agreement for both tests was acceptable (volume of acute infarctions: inter-rater ICC = 0.93, intra-rater ICC = 0.97; number of infarctions: inter-rater ICC = 0.89, intra-rater ICC = 0.95; WMLs: inter-rater kappa = 0.85, intra-rater kappa = 0.95; MBs: inter-rater kappa = 0.78, intra-rater kappa = 0.85).

8.2.5. Statistical analysis

Participants were first divided into two groups: those with and without frequent insomnia symptoms. The difference in the proportion of the two groups was analyzed with Fisher's exact test or the Chi-square test. The continuous data were compared with t-tests or Mann-Whitney U tests. Variables with $p < 0.10$ were included in the subsequent multivariate logistic regression model after assessing the correlation between variables. Multivariate logistic regressions were performed to determine the factors associated with "frequent insomnia symptoms" and "frequent insomnia symptoms and daytime

consequences." The level of significance was set at < 0.05 (two-sided). All statistical analyses were performed using SPSS, Version 16.0 (SPSS, Chicago, Illinois).

All of the participants were then classified into two groups based on whether they were with or without "frequent insomnia symptoms and daytime consequences," and the foregoing analysis was repeated.

8.3. Results

Between December 2004 and May 2007, 874 patients were admitted to the ASU of PWH and had an MRI on admission. Five hundred and eight (58.1%) met the entry criteria and participated in the study. The demographic, clinical, and sleep characteristics of the whole sample are presented in Table 8-1. The patients who were excluded were older (70.6 versus 65.2 years, $p < 0.001$) and had higher NIHSS scores (median, 7 versus 5, $p < 0.001$) than the participants.

Frequency of insomnia symptoms

One hundred and eighty-six (36.6%) participants had insomnia symptoms (frequent difficulties initiating or maintaining sleep, or frequent early wakening), and 64 (12.6%) had insomnia symptoms with daytime consequences.

Factors associated with insomnia symptoms

The patients with insomnia symptoms had significantly higher GDS scores (5.2 ± 3.3 versus 3.9 ± 2.8, $p < 0.001$), a higher frequency of diabetes mellitus (40.9% versus 31.7%, $p = 0.037$), and a trend toward higher NIHSS scores (Table 8-2). The only neuroimaging variable associated with insomnia was frontal lobe infarction (12.4% versus 6.8% in the groups with and without insomnia symptoms; Table 8-3). In the logistic regression, only GDS score (OR = 1.157, 95% CI = 1.089-1.230; $p < 0.001$) and frontal lobe infarction (OR = 1.933, 95% CI = 1.034-3.613; $p = 0.039$) were significantly associated with insomnia symptoms (Table 8-4).

Factors associated with insomnia with daytime consequences

The patients who had insomnia with daytime consequences had significantly higher GDS scores (6.4 ± 3.2 versus 4.1 ± 2.9, $p < 0.001$) and a higher frequency of diabetes mellitus (51.6% versus 32.7%, $p < 0.001$; Table 2), both of which remained significant in the logistic regression. Having diabetes mellitus nearly doubled the risk of insomnia with daytime consequences (Table 8-4).

Table 8-1 Demographic, clinical, and sleep characteristics of the whole sample (n = 508).

Variable	n (%)/mean ± sd/median (IQR)
Age*	65.7 ± 11.7
Sex (male)	325 (64.0%)
Education (years)*	5 (2-8)
Hypertension	368 (72.4%)
Diabetes mellitus	178 (35.0%)
Ischemic heart disease	37 (7.3%)
Previous stroke	104 (20.5%)
NIHSS on admission*	4 (2-6)
Insomnia complaint	
No	321 (63.2%)
Yes (sometimes)	127 (25.0%)
Yes (frequent)	60 (11.8%)
Insomnia symptoms	
No	119 (23.4%)
Yes (sometimes)	203 (40.0%)
Yes (frequent)	186 (36.6%)
Insomnia with daytime consequence	64 (12.6%)

*median (IQR); NIHSS = National Institutes of Health Stroke Scale.

Table 8-2 Comparison of demographic and clinical features between participants with and without insomnia symptoms.

Variable	Frequent insomnia symptoms		Frequent insomnia with daytime consequences	
	Yes (n = 186)	No (n = 322)	Yes (n = 64)	No (n = 444)
Age*	65.5 ± 11.1	65.8 ± 12.0	65.9 ± 10.1	65.7 ± 11.8
Sex (female)	72 (38.7%)	111 (34.5%)	26 (40.6%)	157 (35.4%)
Years of education**	5 (2-8)	5 (2-8)	5 (2-8)	5 (2-8)
Married	138 (74.6%)	250 (77.6%)	47 (73.4%)	342 (77.0%)
Single/divorced/widowed	48 (25.4%)	72 (22.4%)	17 (26.6%)	102 (23.0%)
Smoker or ex-smoker	77 (41.6%)	151 (46.9%)	26 (40.6%)	202 (45.5%)
Alcohol use	41 (22.0%)	63 (19.6%)	13 (20.3%)	91 (20.5%)
Hypertension	141 (75.8%)	227 (70.5%)	49 (76.6%)	319 (71.8%)
Diabetes mellitus	76 (40.9%)†	102 (31.7%)	33 (51.6%)†	145 (32.7%)
Ischemic heart disease	15 (8.1 %)	22 (6.8%)	4 (6.3%)***	33 (7.7%)
Hyperlipidemia	124 (66.7%)	213 (66.1%)	46 (71.6%)	291 (65.5%)
Previous stroke	38 (20.4%)	66 (20.5%)	12 (18.8%)	92 (20.7%)
COPD	12 (6.5%)	25 (7.8%)	4 (6.3%)***	33 (7.7%)
NIHSS on admission**	4 (2-7)¶	4 (2-6)	4 (2-6)	4 (2-6)
Symptom laterality				
Left	76 (40.9%)	126 (39.1%)	31 (48.4%)	171 (38.5%)

Right	73 (39.2%)	145 (45.0%)	22 (34.4%)	196 (44.1%)
Both side/others	37 (19.9%)	51 (15.8%)	11 (17.2%)	77 (17.3%)
Assessment at 3 months after stroke				
GDS**	5 (3-8)†	3 (2-6)	7 (4-9) †	4 (2-6)
BI**	20 (19-20)	20 (19-20)	20 (19-20)	20 (19-20)
LSNS*	30.4 ± 7.7	31.4 ± 8.4	30.8 ± 7.7	31.1 ± 8.2
MMSE**	27 (25-29)	27(24-29)	27 (25-28)	27 (24-29)
Current medication				
Antidepressants***	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Hypnotics***	14 (7.5%)†	0 (0.0%)	12 (15.8%)†	2 (0.5%)

Variables are presented as mean ± sd or n (%).

All comparisons were examined by χ^2 test unless otherwise specified.

*mean (s.d), t-test, ** median (IQR), Mann-Whitney U test, *** N (%), Fisher's exact test; †$p < 0.05$;¶$p < 0.1$.

COPD = chronic obstructive pulmonary disease; MMSE = Mini-Mental State Examination; NIHSS = National Institutes of Health Stroke Scale; GDS = Geriatric Depression Scale; PSD = poststroke depression; BI = Barthel Index; LSNS = Lubben Social Network Scale.

Table 8-3 Comparison of neuroradiological characteristics between participants with and without insomnia symptoms.

Variable	Frequent insomnia symptoms		Frequent insomnia with daytime consequences	
	Yes (n = 186)	No (n = 322)	Yes (n = 64)	No (n = 444)
Location of infarcts				
Frontal lobe	23 (12.4%)†	22 (6.8%)	6 (9.4%)	39 (8.8%)
Temporal lobe	15 (8.1%)	15 (4.7%)	4 (6.3%)**	26 (5.9%)
Parietal lobe	19 (10.2%)	27 (8.4%)	6 (9.4%)	40 (9.0%)
Occipital lobe	8 (4.3%)	8 (2.5%)	1 (1.6%)**	15 (3.4%)
Subcortical white matter	54 (29.0%)	94 (29.2%)	23 (35.9%)	125 (28.2%)
Basal ganglia	51 (27.4%)	97 (30.1%)	14 (26.4%)	134 (29.5%)
Thalamus	15 (8.1%)	35 (10.9%)	5 (7.8%)	45 (10.1%)
Brainstem/cerebellum	44 (23.7%)	80 (24.8%)	17 (26.6%)	107 (24.1%)
No. of infarcts*	2 (1-3)	2 (1-3)	2 (1-3)	1 (1-3)
Volume of infarcts (ml)*	0.5 (0-2.0)	0.4 (0-1.2)	0.6 (0-1.6)	0.4 (0-1.4)
White matter lesions				
PVH score*	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-2)
DWMH score*	1 (1-1)	1 (0-1)	1 (1-2)	1 (0-1)
MBs	42 (22.6%)	82 (25.5%)	15 (23.4%)	109 (24.5%)
Num. of MBs*	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)

Variables were presented as median (IQR) or n (%).

All comparisons were examined by χ^2 test unless otherwise specified.

*Mann-Whitney U test, **Fisher's exact test; $^{+}p < 0.05$.

PVH = periventricular hyperintensities; DWMH = deep white matter hyperintensities; MBs = microbleeds.

Table 8-4 Logistic regression analysis of the correlates of insomnia symptoms.

Variable	Frequent insomnia symptoms			Frequent insomnia symptoms with daytime consequences		
	β	*p*	OR (95.0% CI)	*β*	*p*	OR (95.0% CI)
GDS	0.146	< 0.001	1.157 (1.089-1.230)	0.224	< 0.001	1.251 (1.148-1.363)
NIHSS on admission	0.024	0.403	1.024 (0.969-1.082)	--	--	--
Diabetes mellitus	0.303	0.127	1.353 (0.917-1.997)	0.672	0.017	1.959 (1.129-3.400)
Frontal lobe infarcts	0.659	0.039	1.933 (1.034-3.613)	--	--	--

OR = odds ratio; GDS = Geriatric Depression Scale score; NIHSS= National Institutes of Health Stroke Scale score.

8.4. Discussion

To the best of our knowledge, this was the first study of insomnia in Chinese stroke survivors. Depressive symptoms were found to be predictors of both insomnia and insomnia with daytime consequences. Furthermore, frontal lobe infarction was found to be a predictor of insomnia symptoms, and diabetes mellitus to be a predictor of insomnia symptoms with daytime consequences.

The prevalence of insomnia in the healthy elderly varies, mainly due to different sets of insomnia criteria being applied. In community studies, 10-41% of the elderly population has been found to have difficulty falling asleep or staying asleep or to wake up too early (Asplund, 1999; Ohayon, 2002). Patients suffering from chronic medical diseases also have a higher prevalence of insomnia relative to healthy controls (Taylor et al., 2007).

Data on the frequency of insomnia or insomnia symptoms in stroke patients are limited. A Finnish study (Leppavuori et al., 2002) found insomnia complaints in 56.7% of stroke patients, with 38.6% meeting DSM-IV criteria A-C for an insomnia diagnosis. Another study conducted in Finland (Palomaki et al., 2003) reported insomnia

complaints in 49% of these patients 18 months after their stroke. The rate of insomnia in our sample was 36.6%, but only 12.6% of patients had insomnia with daytime consequences. The diversity of results among the three studies may be due to differences in sampling, timeframe, or methods of insomnia assessment. The role played by ethnic factors in the development of insomnia in stroke remains uncertain. Another explanation is that the participants in this study were younger and less severely ill than the consecutively admitted ischemic stroke patients, which may have resulted in the underestimation of the frequency of insomnia symptoms.

Insomnia is thought to be multi-factorial in origin, both in the general population (Su et al., 2004) and in stroke survivors (Leppavuori et al., 2002). Insomnia symptoms are common in depression, with numerous studies reporting an association between depression and insomnia (Su et al., 2004). To eliminate the significant effect of depression on insomnia, patients with a diagnosis of a DSM-IV major depressive disorder were excluded from this study. Even so, the severity of depressive symptoms was a strong predictor of both insomnia symptoms and insomnia symptoms with daytime consequences, thus

indicating that even subclinical depression is an important contributing factor to insomnia in stroke.

Diabetes mellitus was an independent predictor of insomnia with daytime consequences in this study, an association that has been reported in the general population (Mallon et al., 2005; Vgontzas et al., 2009), but not in stroke patients. The results of the present study show that the odds of suffering insomnia with daytime consequences increased by nearly one fold with a diagnosis of diabetes mellitus. The activation of the hypothalamicpituitary-adrenal axis (Vgontzas et al., 2001; Rodenbeck et al., 2003) and sympathetic system (Bonnet and Arand, 1998) is elevated in insomniacs with objective short sleep duration, which is considered to be the basis for physiological hyperarousal, thus leading to short sleep duration in patients with Type 2 diabetes mellitus.

The association between diabetes mellitus and insomnia with daytime consequences may also be due to the higher rate of obstructive sleep apnea (OSA) in patients with this illness. The frequency of OSA associated with daytime sleepiness in diabetes mellitus has been reported to be as high as 23% (West et al., 2006; Idris et al., 2009). Further studies using polysomnography are warranted in a stroke cohort

because insomnia has far-reaching consequences for these patients' quality of life.

Frontal lobe infarction was significantly correlated with insomnia, but not with insomnia with daytime consequences, which is a novel finding that suggests a link between infarction site and insomnia in stroke. Similarly, Leppavuori et al. (2002) reported twice as many major dominant hemispheric strokes in insomnia patients than in those without insomnia; major dominant hemispheric strokes usually involve the frontal lobe (Leppavuori et al., 2002). There is further evidence to suggest the involvement of the frontal lobe in the physiology of sleep. Slow waves during non-rapid eye movement sleep on high-density electroencephalograms have been associated with large waves in the medial and middle frontal and inferior frontal gyri and cingulate (Murphy et al., 2008). Frontal and temporal lobe atrophy, as in Pick's dementia, is associated with decreased total sleep time and the duration and percentage of rapid eye movement sleep (Pawlak et al., 1986). However, frontal lobe infarction was not a significant predictor in our analysis of insomnia with daytime consequences. The relationship between frontal lobe infarction and insomnia needs to be confirmed with polysomnography studies.

This study had several methodological limitations. First, a large proportion (41.9%) of patients were excluded from the study, with those included representing patients with a younger age and less severe stroke. Patients with severe aphasia were also excluded, which may also have led to selection bias. Second, no healthy control group was included in the study. A community-based study in Hong Kong with age ≥ 70 years (half of them more than 80 years old) using the same instrument reported a 42.2% prevalence rate of insomnia symptoms (Chui et al., 1999). However, as this sample was much older than our stroke survivor sample, we cannot yet confirm how severely stroke affects insomnia symptoms. Third, insomnia was assessed with a questionnaire rather than via polysomnography, which would have provided far more accurate information about insomnia and related sleep disturbances such as OSA. Only one question was used to assess daytime consequences, which is insufficiently precise. Fourth, the subjects did not undergo complete psychiatric assessment. For example, anxiety disorders, which may also have had an impact on the outcomes, were not evaluated in these patients. Fifth, the cross-sectional study design was unable to provide sufficient evidence of causality between lesions and insomnia, as we had no accurate information on insomnia symptoms before stroke.

Interviews at three months after stroke may also be less precise in retrospectively collecting information on insomnia before stroke. Thus, these findings should be regarded as preliminary ones at this stage.

In conclusion, insomnia is common in Chinese stroke survivors and seems to be multi-factorial in origin. In addition to depressive symptoms, frontal lobe infarction and diabetes mellitus may be important factors in predicting insomnia symptoms. Further studies using polysomnography together with functional imaging techniques are needed to explore the relationship between frontal lobe infarctions and insomnia in stroke. A careful evaluation of behavioral and cognitive status, as well as a complete review of co-existing medical illness, should be regarded as the first steps in the effective management of insomnia symptoms in stroke survivors.

CHAPTER 9 FRONTAL LOBE ATROPHY AND CEREBRAL SMALL VESSEL DISEASE: AN MRI STUDY

9.1. Background

Brain atrophy is common in patients with ischemic stroke. Its pathogenesis is heterogeneous, with degeneration and ischemic injuries two possible mechanisms. Two studies have reported whole brain atrophy to be associated with subcortical ischemic lesions (Fein et al., 2000; Gainotti et al., 2004). Wen et al. (2004) carried out a brain MRI study on 397 asymptomatic individuals aged between 60 and 64 years, showing that gray matter reduction was significantly correlated with WML load.

Raz et al. (1997) reported the most substantial age-related decline in the cortex to be in the prefrontal gray matter in the healthy elderly, with the effects of age on hippocampal formation and the postcentral gyrus to be weak. This weak effect indicates the selective vulnerability of brain regions to aging and that vulnerability to ischemic changes may be different in different brain regions. However, the effects of WMLs on

the morphology of different lobes of the brain remain unclear. Temporal lobe atrophy (TLA), especially atrophy of the medial temporal lobe (MTLA), has been found to be highly correlated with the pathology of AD (Barkhof et al., 2007), thus suggesting that it may be mainly the result of aging. In a study of older hypertensive subjects, no association was found between MTLA and WMLs (Wiseman et al., 2004), although Fein et al. (2000) reported contradictory findings. The relationship between frontal lobe atrophy (FLA), parietal lobe atrophy (PLA), and WMLs has not yet been confirmed. The frontal lobe dominates execution, control, language, and mood regulation. FLA is associated with late-life depression (Almeida et al., 2003; Lai et al., 2000) and cognitive impairment (Mok et al., 2005) in ischemic stroke patients. Patients with subcortical ischemic vascular disease often have executive dysfunction, rather than memory loss. In addition, WMLs are predominant in the frontal white matter (Tullberg et al., 2004), and thus it is possible that FLA may be related to WMLs. Rossi et al. (2006) used voxel-based morphometry to assess the topographic correspondence between WMLs and grey matter atrophy in normal elderly and found that frontal WMLs are associated with frontal gray matter damage. However, confounders of silent infarcts and asymptomatic large artery

disease (LAD) were not compared. In ischemic stroke patients, no similar study has been performed. In addition, whether the two types of ischemic change – small vessel disease (SVD) or large artery disease (LAD) – are associated with FLA or the atrophy of other lobes in ischemic stroke patients is still unknown. In the study reported in this chapter, we examined the association between clinical variables, the neuroimaging parameters of vascular lesions, and lobar atrophy. We hypothesized that FLA is independently associated with WMLs.

9.2. Methods

9.2.1 Participants

All consecutive ischemic stroke patients admitted to the ASU of PWH between May 2005 and May 2007 who had had MRI performed were retrospectively included in this study. Those with cardioembolic infarction (determined by the presence, or a history, of atrial fibrillation, sick sinus syndrome, heart valve disease, acute congestive failure, recent myocardial infarction, atrial myxoma, or patent foramen ovale)

or infarctions resulting from other uncommon causes (such as vasculitis, hematological disorder, or dissection) were excluded, as were those with a central nervous disease other than stroke (such as AD, Parkinson's disease, or brain tumors). Patients with large territory acute or established infarcts involving the frontal, parietal, and temporal cortex were excluded, as these conditions would have affected the morphology of the lobes. The following data were collected for all participants from the ASU stroke registry and clinical management system: age, sex, education level, and presence of chronic vascular diseases (hypertension, diabetes mellitus, atrial fibrillation, ischemic heart disease, and history of stroke). Scores on the NIHSS and CC-MMSE (Chui et al., 1994), which were administered on admission, were assessed by stroke nurses in the ASU. This study was approved by the Ethics Committee of the Chinese University of Hong Kong, and all patients or their relatives signed a consent form.

9.2.2. MRI examination

All examinations were performed with a 1.5T scanner (Sonata, Siemens Medical System, Erlangen, Germany). Refer to Section 4.2.5 of Chapter 4 for the MRI parameters.

All MRI data were taken from a stroke registry database. MRI assessment was performed by two neurologists (the thesis authors and XYC), and inter- and intra-rater reliability were tested with 20 cases each. MRI assessment included the following. (1) The number and site of established brain infarcts were measured, with lacunar infarcts defined as hypointensive, small subcortical, or deep infarcts ranging from 0.2 to 2cm in the longest dimension in the T1WI. (2) WML severity was graded using the four-point (0-3) scale developed by Fazekas et al. (1987). PVH and DWMH were scored on the axial protondensity images, and were defined as severity beyond moderate (a Fazekas' score ≥ 2). Examples of different PVH and DWMH severities are shown in Figure 9-1. Thirty cases were randomly selected and rated according to Wahlund's age-related white matter changes (ARWMC) scale (Wahlund et al., 2001) by the thesis author who was blinded to the results of the Fazekas scale tests to check the level of agreement between the two rating scales. (3) Brain atrophy was assessed with the widely used three-point visual cortical atrophy rating method developed

by Victoroff et al. (1994), which was adopted to rate the severity of cortical (frontal, parietal, and temporal lobe) atrophy on the T1 weighted imaging. This rating method provides two standard images that represent different severities of lobar atrophy. Lobar atrophy is defined as the extent of atrophy on either side of the lobe being more severe than that on the first standard image. Mild-moderate atrophy is defined as more severe than the first standard image, but less severe than the second standard image. Severe lobar atrophy is defined as the extent of atrophy on either side of the lobe being more severe than that on the second standard image. Frontal, parietal, and temporal lobe atrophy were rated separately. Examples of different FLA severities are shown in Figure 9-2. (4) MBs were defined as small (2~10 mm) hypointensive lesions on the GE-MRI, although basal ganglia calcification and flow void artifacts of the pial blood vessels were excluded (Dichgans et al., 2002).

9.2.3. Assessment of intracranial and extracranial large artery

Lesions of extracranial carotid disease were evaluated with carotid duplex sonography using a 7.5 MHz probe (Philip SD800). The definitions of ICA stenosis and common carotid artery stenosis were more than 50% stenosis (Mok et al., 2003). Intracranial LAD was evaluated by 3D time-of-flight MRA. Stenosis of the large intracranial artery was defined as a more than 50% reduction in the diameter of the lumen (Wong et al., 2002). Three-dimensional time-of-flight MRA is considered to be an accurate technique for the screening of large vessel intracranial stenosis (Dagirmanjian et al., 1995).

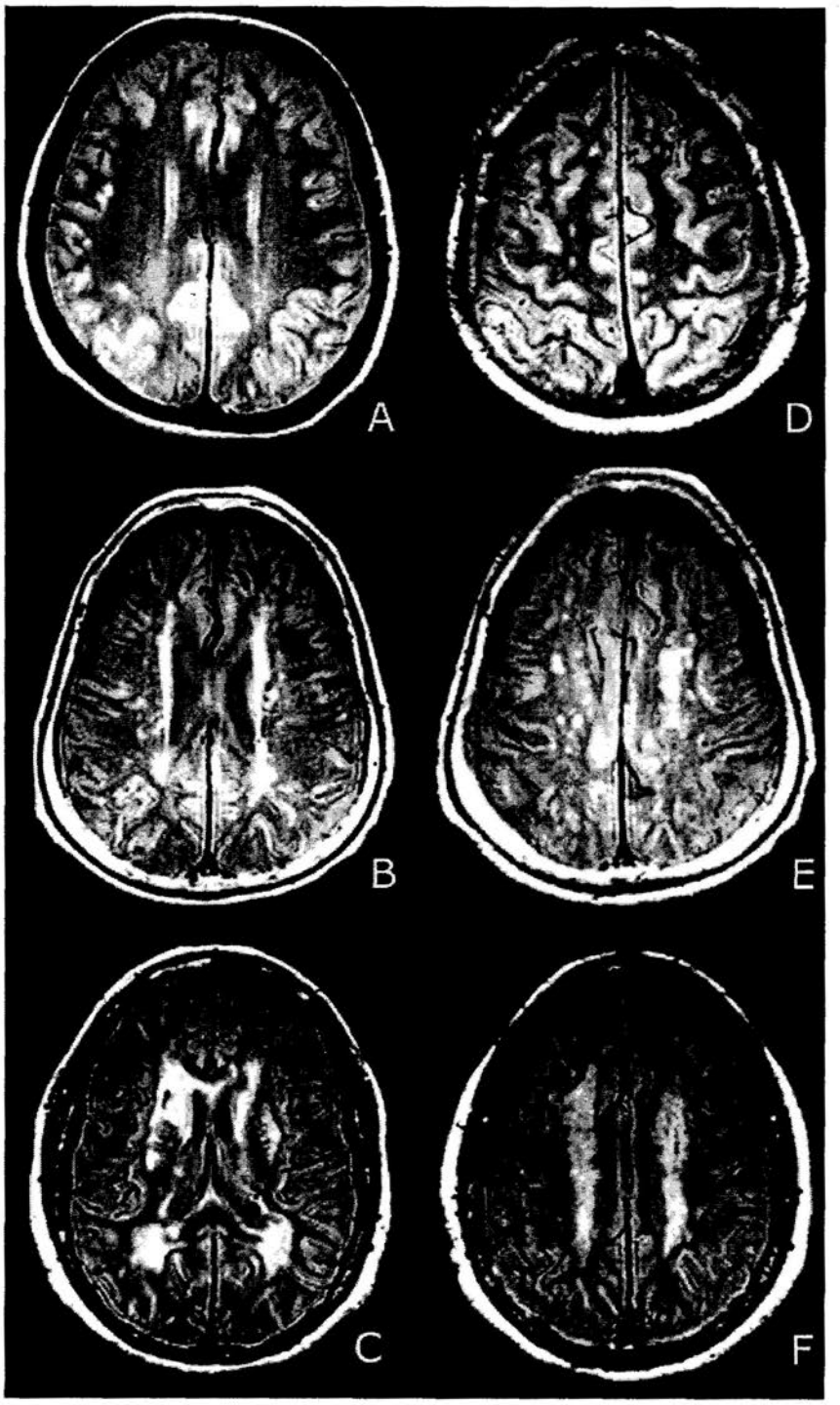


Figure 9-1. Examples of rating scores 1, 2, and 3 on the Fazekas scale. (A) Periventricular hyperintensities (PVH) score = 1; (B) PVH score = 2; (C) PVH score = 3; (D) deep white matter hyperintensities (DWMH) score = 1; (E) DWMH score = 2; (F) DWMH score = 3.

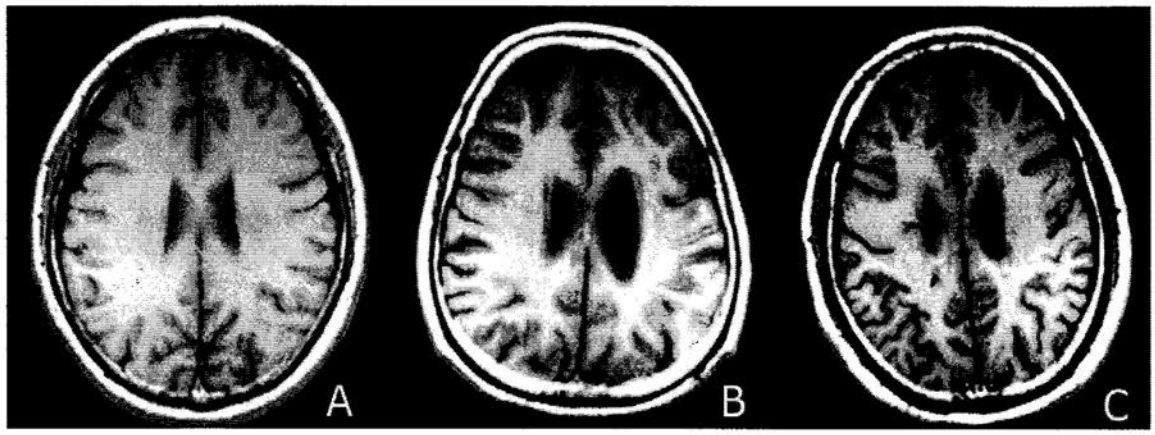


Figure 9-2. Examples of different severities of frontal lobe atrophy (FLA). (A) No FLA; (B) mild to moderate FLA; (C) severe FLA.

9.2.4. Statistical analysis

All of the patients were classified into groups according to the different severities (non-severe, mild to moderate, and severe) of FLA, TLA, and PLA. One-way ANOVA was performed to compare the ages between these groups. Age was categorized into five groups (< 50, 50-59, 60-69, 70-79, and ≥ 80 years old). Chi-square tests were performed to compare the category variables. A Kruskal-Wallis H test was performed to compare MMSE score on admission and the number of lacunar infarcts among the groups. Logistic regression was performed to ascertain the independent risk factors for FLA and severe FLA, PLA and severe PLA, and TLA and severe TLA. Statistical significance was set at 0.05 (two-sided). All statistical tests were performed with SPSS for Windows (Version 16.0, SPSS Inc, Chicago, Illinois).

9.3. Results

Four hundred and seventy-one consecutive ischemic stroke patients who were admitted to the ASU of the PWH between May 2005 and

May 2007 and who had had MRI performed were included in this study. Excluded were 67 cases with large territory infarcts involving the frontal, parietal, or temporal cortex (including 23 with cardioembolic stroke), 21 cases with cadioembolic stroke (but without large territory infarcts), 32 cases with other central nervous system diseases, two cases with stroke due to cerebral vasculitis, and one case with stroke due to protein S deficiency.

Reliability of WMLs and lobar atrophy ratings

Inter-rater agreement was good for both the PVH (weighted kappa: 0.82) and DWMH ratings (weighted kappa: 0.88). The intra-rater weighted kappa was 0.87-0.93 (PVH: 0.87; DWMH: 0.93). The PVH score, DWMH score, and the sum of the two were highly correlated with the Wahlund's ARWMC total score (Spearman correlations of 0.824, 0.887, and 0.858, respectively). The inter- and intra-rater agreements were also good for the lobar atrophy rating (inter-rater weighted kappa: frontal lobe, 0.82, parietal lobe, 0.73, temporal lobe, 0.64; intra-rater weighted kappa: frontal lobe, 0.90, parietal lobe, 0.81, temporal lobe, 0.71).

Relationship between lobar atrophy and WMLs

The frequency of FLA in our cohort was 36.5% (177/485), with severe FLA occurring in 31 (6.4%) patients. Table 9-1 compares the clinical and radiological features of the different severities of lobar atrophy. Age, MMSE score, previous stroke, DWMH, and PVH were associated with FLA, PLA, and TLA in the univariate comparison. Male sex and the presence of MBs were associated with PLA and TLA, but not PLA. Hypertension was associated with FLA and PLA, but not TLA. The features of LAD exhibited no significant association with lobar atrophy. The significant variables in the univariate analysis were entered into the subsequent logistic regressions. As PVH was highly correlated with DWMH ($r = 0.626$), only the one with the smaller p value was entered into these regressions. The correlation coefficients between all of the variables included were less than 0.3.

In the logistic regressions, age (OR = 2.666, 95% CI = 2.084-3.411, $p < 0.001$), previous stroke (OR = 2.111, 95% CI = 1.213-3.677, $p = 0.008$), and PVH (OR = 1.640, $p = 0.039$) were independent risk factors of FLA (Table 8-2). Age (OR = 3.161, 95% CI = 2.194-4.555, $p < 0.001$) and DWMH (OR = 3.634, 95% CI = 1.606-8.224, $p = 0.002$) were

independent risk factors of severe FLA (Table 8-3). Neither PVH nor DWMH was an independent risk factor of PLA or TLA.

Table 9-1. Comparison of clinical and radiological variables between different severities of lobar atrophy.

	FLA			PLA			TLA		
	Non	Mild-mod	Severe	Non	Mild-mod	Severe	Non	Mild-mod	Severe
	n=297	n=144	n=30	n=290	n=125	n=56	n=316	n=126	n=29
Age	61.4±11.1	71.5±9.4[a]	73.7±10.7[b]	61.7±11.5	69.7±9.3[a]	74.0±8.9[bc]	62.6±11.0	70.6±11.3[a]	71.9±9.1[b]
Sex (male, %)	173(58.2%)	104(72.2%)[a]	21(70.0%)[b]	173(59.7%)	88(70.0%)	37(66.1%)	190(60.1%)	85(67.5%)	23(79.3%)[b]
MMSE	25.7±3.3	24.8±3.5	24.4±3.3[b]	26.6±3.1	25.5±3.5[a]	24.9±3.6[b]	25.8±3.4	24.5±3.3[a]	25.2±3.2[b]
Hypertension	198(66.7%)	112(77.8%)[a]	26(86.7%)[b]	195(67.2%)	93(74.4%)	48(85.7%)[b]	219(69.3%)	95(75.4%)	22(75.9%)
Diabetes mellitus	105(35.4%)	57(39.6%)	16(53.3%)	105(36.2%)	48(38.4%)	25(44.6%)	118(37.3%)	48(38.1%)	12(41.4%)
Hyperlipidemia	200 (67.3%)	95(66.0%)	15(50.0%)	205(70.7%)	74(59.2%)	31(55.4%)[b]	214(67.7%)	80(63.5%)	16(55.2%)
Smoking history	119(40.1%)	74(51.4%)	13(43.3%)	119(39.7%)	60(48.0%)	31(55.4%)	132(43.8%)	56(44.4%)	18(62.1%)
Previous stroke	35(11.8%)	39(27.1%)[a]	8(26.7%)[b]	38(13.1%)	31(24.8%)[a]	13(23.2%)[b]	39(12.3%)	34(27.0%)[a]	9(31.0%)[b]
Radiological features related to SVD									
PVH (≥2)	61(20.0%)	65(40.3%)[a]	20(66.7%)[bc]	64(22.1%)	51(40.8%)[a]	24(42.9%)[b]	72(22.8%)	55(43.7%)[a]	12(41.4%)[b]
DWMH (≥2)	46(15.5%)	40(27.8%)[a]	17(56.7%)[bc]	50(17.2%)	36(28.8%)[a]	17(30.4%)[b]	54(17.1%)	38(30.2%)[a]	11(37.9%)[b]
Num.of Lacunes	1.2±2.0	1.6± 2.6	2.2±3.2	1.2±2.0	1.4±2.5	1.9±2.7	1.2±2.0	1.7±2.6	1.9±2.9
Microbleeds	59(19.9%)	48(33.3%)[a]	10(33.3%)[b]	66(22.8%)	36(28.8%)	15(26.8%)	69(21.8%)	36(28.6%)	12(41.4%)[b]
Radiological features related to LAD									
MCA stenosis	96(32.3%)	56(38.9%)	6(20.0%)	93(32.1%)	48(38.4%)	17(30.4%)	103(32.6%)	44(34.9%)	11(37.9%)
Carotid stenosis	18(6.1%)	17(11.8%)	3(10.0%)	21(7.2%)	12(9.6%)	7(12.5%)	24(7.6%)	11(8.7%)	5(17.2%)
ACA stenosis	21(7.1%)	6(4.2%)	1(3.3%)	21(7.2%)	4(3.2%)	3(5.4%)	19(6.0%)	6(4.8%)	3(10.3%)
Any LAD	129(40.7%)	65(45.1%)	11(36.7%)	119(41.0%)	56(44.8%)	22(39.3%)	132(41.8%)	50(39.7%)	15(51.7%)

FLA = frontal lobe atrophy; PLA = Parietal lobe atrophy; TLA = temporal lobe atrophy; MMSE = Mini-mental State Examination; PVH = periventricular hyperintensities; DWMH = deep white matter hyperintensities; SVD = small vessel disease; LAD = large artery disease; MCA = middle cerebral artery; ACA = anterior cerebral artery.

Values are mean (SD) or number (%); a: mild-moderate versus non-severe, $p < 0.05$; b: severe versus non-severe, $p < 0.05$; c: mild-moderate versus severe, $p < 0.05$.

Table 9-2 Logistic regression of risk factors of FLA, PLA, and TLA.

	FLA[a]		PLA[b]		TLA[c]	
Variable	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**P**	**OR (95% CI)**
Age	< 0.001	2.666 (2.084-3.411)	< 0.001	2.493 (1.989-3.126)	< 0.001	2.180 (1.742-2.748)
Previous stroke	0.008	2.111 (1.213-3.677)	0.040	1.735 (1.062-2.523)	0.001	2.345 (1.396-3.940)
PVH	0.039	1.640 (1.025-2.622)	--	--	--	--

a: The logistic regression model included age, sex, hypertension, previous stroke, PVH, and MBs.

b: The logistic regression model included age, hypertension, previous stroke, and PVH

c: The logistic regression model included age, sex, previous stroke, PVH, and MBs.

FLA = frontal lobe atrophy; PLA = Parietal lobe atrophy; TLA = temporal lobe atrophy; PVH = periventricular hyperintensities; MBs = microbleeds.

Table 9-3 Logistic regression of risk factors of severe FLA, PLA, and TLA.

Severe FLA[a]			Severe PLA[b]		Severe TLA[c]	
Variable	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**
Age	0.002	2.118 (1.328-3.377)	< 0.001	3.161 (2.194-4.555)	0.002	1.870 (1.258-2.782)
DWMH	0.002	3.634 (1.606-8.224)	--	--	--	--
Hypertension	--	--	0.026	2.567 (1.121-5.874)	--	--

a: The logistic regression model included age, sex, hypertension, previous stroke, DWMH, and MBs.

b: The logistic regression model included age, hypertension, previous stroke, and PVH.

c: The logistic regression model included age, sex, hypertension, previous stroke, PVH, and MBs.

FLA = frontal lobe atrophy; DWMH = deep white matter hyperintensities; PVH = periventricular hyperintensities; MBs = microbleeds.

9.4. Discussion

Previous studies have assessed brain atrophy using volumetric methods (Wiseman et al., 2004; Enzinger et al., 2005; Firbank et al., 2007), but a lack of data from a healthy Chinese population and differences in volumetric measurements make it difficult to determine the cut-off for brain atrophy. Hence, we adopted a widely used visual rating method for FLA that has demonstrated good inter- and intra-rater reliability (Victoroff et al., 1995; Anstey et al., 2006). The method's reliability for rating lobar atrophy remained good in our study.

The mechanisms of lobar atrophy are heterogeneous, and it is well known that aging plays an important role in the pathogenesis of brain atrophy (Meguro et al., 2001). In this study, as expected, age was found to be an independent risk factor of FLA, PLA, and TLA, which indicates that aging is also a critical reason for the pathogenesis of the different severities of lobar atrophy in stroke patients. It should be noted that a history of stroke was an independent risk factor for the atrophy of all lobes in this study, thus suggesting that cerebral infarction does contribute to brain atrophy.

WMLs, including PVH and DWMH beyond moderate (Pohjasvaara et al., 2003), and lacunar infarcts (Pohjasvaara et al., 2003) are considered to be features of SVD. In our study, PVH was significantly associated with FLA even when adjusted for age, sex, hypertension, and previous stroke, whereas DWMH was an independent correlate of severe FLA. This distinction suggests that FLA is associated with SVD. However, the association between WMLs and the atrophy of the parietal and temporal lobes was no longer significant when other confounders were adjusted.

Our findings thus suggest that the frontal lobe may be more vulnerable to subcortical ischemic changes than the parietal and temporal lobes. Global brain atrophy has been found to be related to severe WMLs (Fein et al., 2000; Longstreth et al., 2000). In addition to age-related degeneration, cortical atrophy in SVD may result from secondary axonal and trans-synaptic degeneration following primary subcortical injury (Fein et al., 2000). Occlusions of micro-vessels or chronic deep cerebral hypoperfusion may produce selective neuronal or axonal loss (Fein et al., 2000). Knopman et al. (2008) found the urine albumin/creatinine ratio, a measure of renal microvascular disease, to be associated with both brain atrophy and WMLs. A volumetric and

cerebral metabolism study revealed that a larger WML volume is associated with a larger volume loss of the brain (DeCarli et al., 1995). With regard to different brain regions, the effects of WMLs may be various. WMLs, which are generally considered to be possible markers of deep cerebral hypoperfusion, are more common in the frontal white matter, especially the prefrontal region, than in any other brain region (Tullberg et al., 2004). In a Positron Emission Tomography (PET) study, WMLs were associated with poorer frontal lobe cognitive function, and severe WMLs were found to reduce frontal lobe metabolism (DeCarli et al., 1995). Our findings are also supported by a recent study of the depressed and non-depressed elderly, which reported that reduced orbitofrontal cortex volume is associated with more severe WMLs (Taylor et al., 2007). However, the causality between FLA and WMLs remains unclear. The evidence provided by previous studies and that reported herein suggests only that FLA and WMLs may have a common mechanism.

In this study, PVH were significantly associated with FLA, whereas DWMH were an independent correlate of severe FLA. These two subtypes of WMLs may have different origins (Kono et al., 2004). DWMH and PVH are considered to be related to vascular risk factors

(Cook et al., 2004) and aging (Mirsen et al., 1991), although not all studies have confirmed the association between PVH and vascular risk factors, and DWMH are considered to represent a more ischemic change (Kono et al., 2004). As patients with severe FLA seem to be older and to have a higher frequency of vascular risk factors, it is possible that they have more DWMH than PVH. Although there has been debate in recent years about whether PVH and DWMH should be distinguished from each other (Sachdev et al., 2005; DeCarli et al., 2005), the Fazekas scale, which separates the two, is still in use. We compared this scale to the more recently developed and widely used ARWMC scale (also known as Wahlund's scale) and found the PVH and DWMH scores from the Fazekas scale to be highly correlated with the total score of the ARWMC scale ($r > 0.8$).

Another type of vascular lesion, large artery occlusion, was not related to FLA in this study. Theoretically, chronic hypoperfusion of the circle of Willis may play a role in the development of FLA. A Japanese study (Kin et al., 2007) reported the carotid plaque score and intima-media thickness to be associated with brain atrophy in the Japanese elderly. Atherosclerosis coexisting with SVD is also common in the elderly, but as their study did not compareWMLs, it could draw no

conclusions in that area. It remains unclear whether there is a severity threshold above which atherosclerotic stenosis affects FLA. Confirmation of the relationship between LAD and FLA requires further study.

In addition to medications used to reduce blood pressure in hypertensive patients, medications used to slow the progression of WMLs, such as statins (Bernick et al., 2005) and Vitamin B12 (Enns et al., 1999), have also been investigated in recent years. Do these medications also slow the progression of brain atrophy and reduce poststroke psychiatric disorders? Additional prospective studies are required to answer this question.

The strength of this study lies in its inclusion for the first time of LAD parameters for comparison with lobar atrophy. We also had a relatively large sample for MRI analysis. Nevertheless, the study does have a number of limitations, the first of which is our determination of atrophy. Although Victoroff's visual rating method is reliable and practical, there is still a need to develop a more accurate method, not only for research but also for practice. Moreover, the method does not rate the occipital lobe. The second limitation is that our classification of stenosis of the large artery was based on MRA and carotid duplex

sonography. MRA sometimes overestimates the extent of stenosis in comparison to DSA, which is considered to be the gold standard in the measurement of large artery stenosis. However, in a large sample study, it is reasonable to employ MRA and carotid duplex sonography to assess the intracranial and extracranial large arteries. The third limitation is that we did not measure the WMLs in specific sites of the brain, such as those in the frontal white matter. Finally, we excluded patients with cardioembolic stroke, which may limit the generalizability of our findings.

In conclusion, this study suggests that FLA in ischemic stroke patients is associated with the severity of WMLs. The association between WMLs and PLA and TLA is much weaker. SVD may thus play an important role in the pathogenesis of FLA. It would be helpful for neurologists to have a better understanding of the possible mechanisms of frontal dysfunction in stroke patients.

CHAPTER 10 CONCLUSION

This thesis has involved investigations of the clinical and imaging characterization of cognitive impairment and psychiatric morbidity in Chinese stroke patients. The main conclusions of the six studies reported herein can be summarized as follows.

(1) Cognitive impairment in Chinese stroke patients: a one-year follow-up study

This longitudinal study revealed the prevalence of VCI to be high in Chinese ischemic stroke patients, although most remain cognitively stable one year from baseline. The evolution of V-CIND at the one-year follow-up was bilateral, with 11.2% progressing to dementia and 21.0% reverting to cognitively intact. WML volume rather than hippocampal atrophy is predictive of poststroke cognitive impairment, cognitive decline, and delayed dementia, and WMLs inversely affect a wide range of cognitive domains in non-demented ischemic stroke patients.

(2) Verbal fluency in elderly poststroke women and its relationship with left dorsolateral prefrontal cortex atrophy

This case-control study employing accurate MRI segmentation techniques indicated that atrophy of the left DLPFC is associated with semantic verbal fluency impairment in non-aphasic, elderly stroke women after controlling for vascular risk factors, infarct features, and WMLs, but not in age-matched stroke men. This finding suggests that there may be a difference between the sexes in the neuropsychological and neuroanatomical mechanisms of poststroke cognitive impairment.

(3) Poststroke depression in small subcortical infarcts

This study suggests that PSD is more common in patients with small SSIs resulting from LAD than SVD. The vascular etiologies of SSIs were predictive of PSD, independent of physical status and other confounders. Our findings thus suggest that cerebral blood perfusion may play an important role in the development of PSD.

(4) Poststroke emotional lability and its relationship with cerebral microbleeds

This study suggests that MBs in the thalamus may play a role in the development of PSEL, although further exploration of the significance of MBs in PSEL and other psychiatric sequels in stroke survivors is clearly warranted.

(5) Insomnia symptoms in ischemic stroke patients: clinical and radiological correlates

Insomnia symptoms, which appear to be multi-factorial in origin, were present in 36.6% of the Chinese ischemic stroke survivors in this study. In addition to depressive symptoms, frontal lobe infarction and diabetes mellitus may be correlates of these symptoms in stroke survivors. Further studies using polysomnography together with functional imaging techniques are needed to explore the relationship between frontal lobe infarctions and insomnia in stroke.

(6) Frontal lobe atrophy and cerebral small vessel disease: an MRI study

This study of a large cohort of Chinese ischemic stroke patients revealed the severity of WMLs to be significantly associated with FLA, independent of age, vascular risk factors, and prior stroke. The association between WMLs and PLA and TLA is much weaker. SVD may thus play an important role in the pathogenesis of FLA. It may be helpful for practitioners to have a better understanding of the possible mechanisms of frontal dysfunction in ischemic stroke patients.

In future studies of VCI or poststroke cognitive impairment, it is suggested that a longer poststroke cognitive status follow-up and longitudinal imaging examination be employed. Improvements in the standardization of cognitive tests and the construction of widely accepted VCI criteria would make different studies more comparable. New imaging techniques, such as diffusion tensor imaging (DTI), have demonstrated greater power to detect subcortical ischemic lesions compared with conventional MRI scanning techniques (T2 WI or FLAIR). The better prediction of VCI and longitudinal cognitive decline

can be expected when conventional MRI is supplemented with DTI. Functional imaging techniques, such as functional MRI, MR Spectroscopy (MRS), and PET, provide useful information on the functioning of the brain. The substrate of VCI can be better understood with the integration of clinical feature, neuropsychology, and neuroimaging information, which can also facilitate the more effective prevention of VCI or VaD.

Studies of poststroke psychiatric morbidities in the Chinese remain very limited. It is essential that a national survey be conducted, as estimates suggest that there are huge numbers of poststroke survivors suffering from these disorders in China. The recognition and management of these morbidities by physicians need to see great improvements in future if the widely accepted concepts of the biopsychosocial model are to be realized. The mechanisms of poststroke psychiatric morbidities are not fully understood. In addition, the role played by pre-existing abnormalities of the brain, such as silent infarcts, atrophy, WMLs, and MBs, in the pathogenesis of these morbidities also remains unclear, although the aforementioned new imaging techniques are expected to enhance our understanding of that pathogenesis.

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APPENDIX I

DSM-IV criteria for diagnosis of dementia

A. The development of multiple cognitive deficits manifested by both of the following.

1. Memory impairment (impaired ability to learn new information or to recall previously learned information)
2. One or more of the following cognitive disturbances:

   (a) aphasia (language disturbance)

   (b) apraxia (impaired ability to carry out motor activities depite intact motor function)

   (c) agnosia (failure to recognize or identify objects despite intact sensory function)

   (d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. The deficits do not occur exclusively during the course of a delirium.

APPENDIX II

DSM-IV criteria for diagnosis of vascular dementia

A. The development of multiple cognitive deficits manifested by both of the following.

3. Memory impairment (impaired ability to learn new information or to recall previously learned information)
4. One or more of the following cognitive disturbances:

   (a) aphasia (language disturbance)

   (b) apraxia (impaired ability to carry out motor activities depite intact motor function)

   (c) agnosia (failure to recognize or identify objects despite intact sensory function)

   (d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. Focal neurological signs and symptoms (e.g., exggeration of deep tendon reflexes, extensor plantar response, psuedobulbar palsy, gait abnormalities, weakness of an extremity) or laboratory evidence indicative of cerebrovascular disease (e.g., multiple infarctions involving cortex and underlying white matter) that are judged to be etiologically related to the disturbance.

D. The deficits do not occur exclusively during the course of a delirium.