# University of Alberta

Cognitive Impairment Following Transient Ischemic Attack and Minor Stroke

by

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# Dedication

I dedicate this thesis to my beloved parents, without whom none of my success would be possible.

# Thesis Abstract

**Background:** Ischemic stroke is associated with cognitive impairment, but the acute cognitive sequelae of transient ischemic attack (TIA) and minor stroke is unknown. We hypothesized that transient cognitive impairment can be predicted by diffusion-weighted imaging (DWI) lesion volume.

**Methods:** TIA/minor stroke patients (NIH Stroke Scale ≤ 3) underwent Montreal Cognitive Assessment, Mini-Mental Status Examination and MRI at baseline, days 7 and 30.

**Results:** One hundred patients were included. MoCA detected cognitive impairment in 54% of patients at baseline. Recall deficits resolved, while deficits in language were persistent. WMH volumes were inversely predictive of MoCA scores after 30 days ($\beta$=-0.519, $p<0.0001$). Patients with persisting deficits were more likely to have frontal cortical lesions (86%, $p=0.038$) and higher WMH volumes (9.56mL, $p=0.04$).

**Conclusions:** TIA/minor stroke patients have evidence of temporary acute cognitive impairment. Deficits are correlated with chronic WMH load. Temporary cognitive deficits should be considered in the management of TIA/minor stroke.

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# Abbreviations

| | |
|---|---|
| ADDTC | State of California Alzheimer's disease Diagnostic and Treatment Centers |
| AHA | American Heart Association |
| AICS | Acute Ischemic Cerebrovascular Syndrome |
| ASA | American Stroke Association |
| CMB | Cerebral Microbleeds |
| CT | Computed Tomography |
| DSM-IV | Diagnostic and Statistical Manual of Mental Disorders, 4th Edition |
| DTI | Diffusion Tensor Imaging |
| DWI | Diffusion Weighted Imaging |
| FLAIR | Fluid-Attenuated Inversion Recovery |
| GCS | Glasgow Coma Scale |
| GRE | Gradient Recalled Echo |
| HIS | Hachinski Ischemic Scale |
| ICD-10 | International Classification of Diseases, 10th Revision |
| MCI | Mild Cognitive Impairment |
| MMSE | Mini-Mental State Examination |
| MoCA | Montreal Cognitive Assessment |
| MRI | Magnetic Resonance Imaging |
| mRS | Modified Rankin Scale |
| NIHSS | National Institute of Health Stroke Scale |
| NINDS-AIREN | National Institute of Neurological Disorders and Stroke and *Association Internationale pour la Recherché et l'Ensignement en Neurosciences* |
| TIA | Transient Ischemic Attack |
| VaD | Vascular Dementia |
| VCI | Vascular Cognitive Impairment |
| WHO | World Health Organization |
| WMG | White Matter Grade |
| WMH | White Matter Hyperintensity |

# Chapter 1:

# Introduction to Transient Ischemic Attack and Vascular Cognitive Impairment

## Transient Ischemic Attack

### Acute Cerebrovascular Syndrome Pathophysiology

Acute ischemic cerebrovascular syndrome (AICS) describes a spectrum of disorders resulting from disrupted brain perfusion.[1] During reduced cerebral perfusion, adaptive homeostatic mechanisms, including vasodilation and increased oxygen extraction, are initiated to maintain sufficient rates of energy production.[2] When cerebral perfusion drops to critically low levels, the result is aerobic energy production failure and eventual cell death.

Cerebral ischemia is the result of insufficient blood flow to a specific area of the brain, diminishing available oxygen and metabolites required to meet metabolic demands.[2] When blood flow restriction is permanent, acute ischemic infarction ensues in the form of tissue death. Normal cerebral blood flow in grey matter lies between 40-60 ml/100 g/min in humans.[3] In less metabolically active white matter, cerebral blood flow is normally 22 ml/100g/min. During ischemia, grey matter cerebral blood flow falls below 20 ml/100g/min, and the oxygen extraction fraction, a measure of the fraction of oxygen extracted from the blood, increases

to its maximum.[3] Adenosine triphosphate levels drop rapidly and inadequate energy supply causes failure to maintain the electrochemical membrane gradient. The result is a loss of cell viability, leading to ischemic neuronal death that is often irreversible.[2] In the case of transient ischemic attacks (TIAs) however, blood flow is restored prior to infarction, generally within minutes to hours. Therefore, physiological changes during TIA manifest temporarily, resulting in reversible neuronal dysfunction.

## Defining Transient Ischemic Attack

The definition of a TIA has evolved many times over the years. According to the World Health Organization (WHO) in 1988, TIA was defined as rapidly developing clinical signs of focal or global disturbance of cerebral function, lasting less than 24 hours, with no apparent nonvascular cause.[4] In 1990, the National Institute of Neurologic Disorders and Stroke (NINDS) defined TIA as brief episodes of focal loss of brain function for less than 24 hours, thought to be caused by ischemia, usually localized to that portion of the brain supplied by one vascular system.[5] A common assumption of these traditional definitions was that TIAs were associated with the complete resolution of ischemia, demonstrating transient symptoms with no permanent tissue injury.

The arbitrary threshold set at 24 hours distinguishing TIA from ischemic stroke has been a source of controversy. It was eventually shown that the 24-hour time limit was inaccurate in demarcating patients with and without brain infarction.[6]

Brain imaging studies demonstrated that many patients with transient events lasting less than 24 hours had an associated cerebral infarct. CT evidence of brain lesions in TIA patients ranged from 12% to 34% demonstrating that the traditional definition misclassified up to one third of patients who have suffered tissue injury as being free of ischemic damage.[7, 8]

The WHO and NINDS' definitions have been criticized for potentially impeding the effective administration of certain acute stroke therapies.[6] The 24-hour threshold encouraged physicians to wait and observe before administering interventions in case symptoms resolved spontaneously. This was an issue with acute stroke therapies such as intravenous tissue plasminogen activator, which must be administered sooner than later. The time-based definition was therefore considered inaccurate and inefficient in focusing diagnostic attention.

Advances in imaging, particularly magnetic resonance imaging (MRI), led to the proposal of a revised tissue-based definition of TIA in 2002.[9]In this revision, TIA was defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, with symptoms typically lasting less than one hour and without evidence of acute infarction. Although this definition was well supported by the current findings in literature, it was determined that like the 24-hour threshold, the 1-hour threshold did not accurately define TIA.[6] Accordingly by 2009, the American Heart Association (AHA) approved the

following definition: a transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischemia, without acute infarction.[6]

Several drawbacks have been identified with the new tissue-based definition of TIA. This definition relies on diagnostic imaging to verify the presence of an infarct. In many cases, the availability and sensitivity of neuroimaging methods are not consistent across centers. Imaging techniques with reduced sensitivity such as CT or conventional MRI would be expected to predict a falsely higher prevalence of TIA in comparison to diffusion-weighted MRI techniques that are highly sensitive for acute ischemic lesions. Epidemiological studies face the challenge of comparing present data with prior studies, as TIA prevalence and incidence rates vary with the changing definitions.

## Epidemiology

### Incidence

TIA incidence rates, i.e. the number of new cases annually, have been estimated from cohort studies conducted around the world. In the United States, the incidence of TIA is estimated at 200,000 to 500,000 per year.[10, 11]Based on the review of the National Hospital Ambulatory Medical Care Survey on 2 623 000 TIA patients diagnosed in US emergency departments between 1992 and 2000, the overall TIA incidence rate was estimated at 1.1 per 1000 US population.[12] TIA incidence was 0.83 per 1000 from population data between 1993 and 1994 in the Great Cincinnati/Northern Kentucky population.[13] In Canada, it is estimated that about 15,000 people experience a TIA each year.[14] The Oxford Vascular Study

investigating TIA incidence between 2002 and 2004,found a rate of 0.66 per 1000 people per year.[15] A study conducted in the rural and urban areas of Portugal found an overall TIA incidence of 0.67 per 1000 population.[16] The urban areas had lower incidence at 0.61 compared to rural areas with TIA incidence at 0.96.

TIAs have been more frequently diagnosed in African Americans than Caucasians and in men more frequently than women.[13, 17]Studies have also shown that TIA incidence increases exponentially with advancing age, regardless of age or gender. The Greater Cincinnati/ Northern Kentucky Stroke study with a population comprising 1.3 million people, reported the incidence of TIA in those aged 35 years and younger to be 1-3 cases per 100,000, compared to as many as 1500 cases in those aged 85 and older.[18] The relationship between increasing age and likelihood of TIA was also supported in recent UK studies. In the Oxford Vascular Study between 2002 and 2004, TIA occurrence per 1000 population in patients aged 85 years and older was 6.41 compared to 0.24 in patients below 75 years.[15]

**Prevalence**

Population based studies of TIA prevalence rates, i.e. the number of existing cases in the population, have only been done in a few countries around the world. The methodological difficulty in accurately measuring TIA prevalence results in a range of reported rates between 1.6 and 8.2. The Rotterdam study conducted in the Netherlands reported a prevalence rate of 1.6 in a population of 7354

patients.[19] A study surveying individuals above 40 years of age residing in areas of Daisen and Ama in western Japan, reported TIA prevalence rates of 4.4 and 2.0 per 1000 population respectively.[20] In the People's Republic of China, a study conducting door-to-door surveys screened 63 195 individuals found TIA prevalence to be 1.8 per 1000.[21]A study in the United States of self-administered questionnaires in approximately 10,000 elderly people residing in public and private retirement facilities among eight cities suggested a TIA prevalence of 8.2 per 1000 in the total population and 5.8 among those without a history of prior stroke.[22].

Reported prevalence rates of TIA vary based on factors such as the age distribution of patient populations. In the Cardiovascular Health Study, women between the ages of 65-69 had a TIA prevalence of 1.6 compared to women aged 85 and above with a prevalence rate of 3.4.[23]TIA prevalence in males aged between 65 and 69 was 2.7 compared to males above 85 at 2.9.In the Atherosclerosis Risk in Communities study, comprising a younger patient population between 45 and 64 years, TIA prevalence was 0.4%.[24]

## Diagnosis of Transient Ischemic Attack

### Evaluating Transient Ischemic Attack

In routine clinical practice, patients arriving in the emergency department within 270 minutes of symptom onset are expected to undergo a thorough history and physical examination along with adequate diagnostic testing to determine if they

qualify for thrombolytic therapy.[25] Diagnosis of TIA relies heavily on accurate clinical history detailing symptom characteristics as well as results from diagnostic brain imaging.

### *Symptoms*

Symptoms associated with TIAs arise with sudden onset and in most cases have a maximum duration of 24 hours. It is estimated that symptoms in 60% of events resolve within an hour.[26] TIA symptoms are considered 'focal' and are attributed to dysfunction in the particular arterial territory of the brain. The most commonly observed are motor symptoms such as heaviness, clumsiness, loss of balance, or general weakness usually limited to one side of the body.[25] Sensory symptoms include numbness, tingling, loss of sensation and are often unilateral. Speech deficits can be observed in the form of dysphasia, dysarthria or both. Visual symptoms can manifest in the form of transient monocular blindness, also known as amaurosis fugax. 'Non-focal' symptoms, such as confusion, lightheadedness or headaches are not easily localized to any single brain region.

### *Diagnostic Imaging*

Advances in imaging have a central role in the diagnosis of TIA and exclusion of other possible diagnoses. Along with computed tomography (CT) imaging, conventional magnetic resonance imaging (MRI) and diffusion weighted imaging (DWI), are now increasingly used in assessing patients with TIA and stroke. The American Heart Association/American Stroke Association (AHA/ASA) currently

recommends that emergent neuroimaging be done within 24 hours in patients with TIA symptoms.[6] Unfortunately, imaging capabilities are not available in many centers and therefore do not get utilized in all TIA patients. In patients that are imaged, CT is the most commonly utilized, with studies reporting CT use in 56% to 92% of TIAs.[12, 27]

Brain imaging allows physicians to exclude conditions with transient neurological symptoms due to conditions that mimic TIAs. These include brain tumors, some aneurysms and subdural hematoma.[28, 29] In addition, occasionally patients with intracerebral hemorrhage present with transient symptoms.[30, 31] Finally, advanced imaging plays an important role in obtaining evidence for vascular origin and determining TIA etiology. This includes identifying large artery disease, small vessel disease, carotid stenosis or cardioembolic sources as well as the location and size of acute and chronic ischemic lesions. Diagnosis and treatment decisions are better informed with the support of imaging evidence.

**Risk Factors**

The risk factors for TIA are identical to those of ischemic stroke. Researchers have identified well-known modifiable risk factors that include hypertension, diabetes mellitus, high cholesterol, and smoking.[32] Studies of patients seen in the emergency department have provided evidence that more than half of patients diagnosed with TIA have a history of hypertension.[33-35] Diabetes mellitus is present in up to approximately 25% of TIA patients[36, 37] and is associated with

doubling the risk of ischemic stroke.[38, 39]Dyslipidemia however is not well established as an independent risk factor for ischemic stroke.[40] Cigarette smoking increases the relative risk of TIA by approximately 1.5 times.[41, 42]Atrial fibrillation (AF) is also associated with a high risk of thromboembolism and stroke. Other modifiable risk factors with less well-defined risk profiles in TIA include excessive use of alcohol, obesity, and physical inactivity.[32]

Inherent risk factors for TIA that cannot be altered include age, sex, ethnicity and a personal or family history of cerebrovascular disease.[40] Age is the most important population attributed factor for ischemic stroke, and a similar trend has been repeatedly identified in studies involving TIA patients.[13] Overall TIA incidence at age 75-84 is approximately 25 times higher than at age 45-54, as reported by the Oxford Vascular Study.[15] TIAs have also been more commonly identified in males than in females.[13] Studies comparing racial groups have identified a higher TIA burden in African American populations compared to Caucasian populations.[13, 17]

**Differential Diagnosis**

In addition to TIA, other conditions can cause transient neurological symptoms. These are sometimes referred to as stroke mimics. There is no gold standard test to confirm a TIA apart from a thorough clinical history and assessment by the physician following symptom onset. TIAs therefore are often misdiagnosed as other conditions and vice versa. A recent study done in the US found that of 100

patients admitted to the emergency department with transient focal neurological episodes diagnosed as TIA, 60% of these patients had other conditions.[43] In another prospective study of 303 patients with suspected TIA, about 1 out of 5 patients with a tentative TIA diagnosis had a TIA mimic rather than a true TIA.[44]

In conditions that cause transient neurologic symptoms, characteristics of the patient history can be useful in distinguishing such mimics from true TIAs. The two most commonly identified TIA mimics are epileptic seizures and migraines. In one study, epileptic seizures and migraine headaches were shown to account for 44% and 24% of TIA mimics respectively.[43] Occasionally, structural intracranial lesions such as a tumor, subdural hematoma or aneurysm can present with TIA like symptoms. In these cases, cerebral imaging is crucial to ruling out space occupying lesions including those related to neoplasia and infection. Other disorders that have been identified as mimicking TIA symptoms include multiple sclerosis, labyrinthine disorders, metabolic dysfunction (hyper/hypoglycemia) and transient global amnesia.[44, 45] In general, diagnosing a TIA mimic involves the consideration of timing and onset (non-sudden) of symptoms, presence of positive or non-focal symptoms or an accompanying aura in the case of migraines.

## Management of Transient Ischemic Attack

The primary goal in TIA management is prevention of future debilitating strokes. Studies in TIA patients report the risk of ischemic stroke within 90 days at being between 10 and 20%, with approximately 50% of these strokes taking place

within the first 48 hours of symptom onset.[46] Early initiation of a combination of lifestyle changes and pharmacological treatments can significantly reduce the risk of subsequent stroke.

**Lifestyle Factors**

Lifestyle factors that predispose to stroke include cigarette smoking, excessive use of alcohol and physical inactivity. A meta-analysis of 32 studies found that smokers had a 50% higher risk of stroke than in non-smokers, after controlling for sex and age.[47] In smokers that suffer a TIA, it is strongly encouraged that cigarette smoking be discontinued.[40] Alcohol consumption has been associated with stroke risk in many trials. Heavy consumption of more than 60 g of alcohol a day was associated with an increased relative risk of 1.64 in total stroke as reported in a meta-analysis.[48] Current AHA/ASA recommendations are to reduce excessive alcohol use and maintaining moderate habits of 1 to 2 drinks a day.[40] Studies investigating the association between physical fitness and stroke incidence have shown that highly active individuals have a 25% lower risk of stroke incidence.[49] The AHA/ASA recommends 30 to 60 minutes of physical activity 1 to 3 times a week.[40] Managing these lifestyle behaviors may also help reduce the chances of developing other conditions that increase the risk of future stroke.

**Pharmacological Therapies**

Of the pharmacological therapies, antiplatelets and anticoagulants currently have the most prominent role in stroke prevention following TIA. The other approach to stroke prevention is the identification and modification of risk factors that predispose patients to subsequent stroke. These include hypertension, diabetes mellitus and hypercholestoremia.

Antiplatelet agents have been recommended for patients with TIA or acute noncardioembolic stroke. The AHA/ASA guidelines have outlined the following therapies as accepted first line agents: aspirin, aspirin-dipyridamole (Aggrenox), and clopidogrel (Plavix).[40]For secondary prevention of stroke, combination therapy of aspirin + dipyridamole has shown to be more effective than aspirin or dipyridamole monotherapy.[50, 51]Two large studies have established the efficacy of early aspirin therapy in acute ischemic stroke.[52, 53] The International Stroke trial randomized 19,435 patients to aspirin 300mg daily or no aspirin.[52] Patients in the treatment group demonstrated a 1.1% reduction in recurrent ischemic stroke. The Chinese Acute Stroke Trial (CAST) included 21,106 acute ischemic stroke patients who were randomized to aspirin 160mg daily or placebo.[53] After 4 weeks, recurrent ischemic stroke was reduced from 201% to 1.6% and mortality from 3.9% to 3.3% in the aspirin treatment group. A recent meta-analysis involving 12 randomized controlled trials demonstrated that in comparison with mono antiplatelet therapy, dual therapy (aspirin + dipyridamole and aspirin+clopidogrel) significantly reduced stroke recurrence.[54]

Anticoagulation is the therapy of choice in patients with atrial fibrillation (AF). Oral anticoagulants such as warfarin are recommended for long-term risk reduction in AF patients. A meta-analysis of 29 studies, including over 28,000 elderly AF patients, demonstrated that stroke was reduced by 64% with adjusted-dose warfarin compared to 22% for antiplatelet therapy.[55] New oral anticoagulants, including dabigatran, apixaban and rivaroxaban, have been developed as alternatives to warfarin. A meta-analysis performed to compare the efficacy and safety of these new agents indicated that these anticoagulants were more efficacious than warfarin, as they demonstrated a decreased risk for intracranial bleeding and a higher safety profile. [56]

Controlling hypertension through reduction of both systolic and diastolic pressure has been shown to reduce the risk of stroke by 30% to 50% in randomized controlled trials of TIA and stroke patients.[57-59] These trials included the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) was designed to test the effects of BP-lowering in 6105 patients with stroke or TIA in the previous 5 years.[60] During a mean of 3.9 years of follow-up, active treatment with perindopril demonstrated a relative risk reduction of 26% among patients with ischemic stroke. The Heart Outcomes Prevention Evaluation (HOPE) study compared the effects of the ACEI ramipril with placebo and found a 24% risk reduction for stroke or vascular death among 1013patients with a history of stroke or TIA.[61] According to AHA/ASA, hypertension treatment is recommended for

the prevention of recurrent stroke. Benefits have been associated with an average reduction of 10/5 mmHg and normal BP has been define as < 120/80mmHg.[40]

Diabetes has been associated with increasing the risk of stroke by approximately 25 to 50%.[62] Most patients with type 2 diabetes mellitus develop cardiovascular disease (CVD). Two major randomized clinical trials sought to determine the effect of intensive glucose management on cardiovascular risk. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial involved 10,251 participants with type 2 diabetes and existing CVD or multiple risk factors, who were randomly assigned to intensive or standard glucose treatments.[63] The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial included 11140 patients with type 2 diabetes who were randomly assigned to intensive glucose control or standard glucose control.[64] Both trials failed to demonstrate a reduction in cardiovascular events or death in groups receiving intensive glucose therapy.

Traditionally, large epidemiological studies involving ischemic and hemorrhagic strokes have demonstrated a weak association between elevated total cholesterol and increased risk of ischemic stroke, but a stronger association between low cholesterol and greater risk of ICH. However recently, increased cholesterol levels have consistently been associated with a high risk of cerebral ischemia.[65] A meta-analysis including more than 90 000 patients included in statin trials showed that the larger the reduction in LDL-C levels, the greater the reduction in stroke

risk.[66] AHA/ASA has recommended the use of statins to reduce risk of future stroke in TIA or ischemic stroke patients who have evidence of atherosclerosis and LDL-C level ≥100mg/dL.[40]

Many clinical trials have also compared medical therapy with surgical interventions such as carotid endarterectomy (CEA), and carotid angioplasty and stenting (CAS). Randomized controlled trials have demonstrated the superiority of CEA plus medical therapy over medical therapy alone.[67-69] In TIA patients with carotid stenosis of 70% or greater, revascularization with CEA is considered an extremely robust interventions. Two of the largest randomized trials, the European Carotid Surgery trial[67] and the North American Symptomatic Carotid Endarterectomy Trial,[68] demonstrated a 10 to 15% absolute reduction in subsequent stroke following surgical intervention. These trials also showed that for patients with stenosis of <50%, surgical intervention did not offer a benefit in reducing stroke risk. In recent years, CAS has emerged as a therapeutic alternative to CEA for treatment of extracranial carotid artery occlusive disease in patients at high risk for CEA.[40] The proposed advantages of CAS are its less invasive nature, decreased patient discomfort, and a shorter recuperation period, but its durability remains unproven. Randomized controlled trials have shown CAS success and failure rates to be comparable to CEA.[70]

## Vascular Cognitive Impairment

Dementia as defined by the Diagnostic and Statistical manual of Mental Disorders (DSM), involves impairment in memory and at least one other area of cognitive functions, as well as documented functional disability.[71] Dementia affects approximately 7% of the general population older than 65 years and 30% of the people above 80.[72] Vascular dementia is the second leading cause of dementia after Alzheimer's disease.[73] The incidence of both stroke and dementia rise exponentially with age.[74] Cerebrovascular disease and larger ischemic stroke are both associated with a high risk of subsequent cognitive impairment and dementia. Studies show that up to one third of stroke patients develop dementia within 3 months of stroke.[72] Recent evidence shows that cognitive impairment does occur following TIA and minor ischemic stroke as well.[75, 76] VaD increases the morbidity, disability and healthcare costs of the growing elderly population, while decreasing their quality of life and chances of survival.

## History of Vascular Cognitive Impairment

Dementia related to cerebrovascular disease was first described as 'arteriosclerotic dementia,' based on the view that dementia was a result of cerebral arteriosclerosis.[77] This was followed by term 'multi-infarct dementia' (MID), coined by Hachinski et al., who implied that dementia was the cumulative result of multiple strokes, not occurring at the same time.[78] Later, MID was replaced by terms like 'post-stroke dementia'[79] and 'vascular dementia' (VaD).[80]

It is now known that cognitive impairments associated with cerebrovascular disease, encompass more than what these traditional concepts defined.
The term vascular cognitive impairment (VCI) was introduced to refer to all forms of mild to severe cognitive impairment caused by or associated with cerebrovascular disease. On this scale, VaD would be considered the most severe form of VCI. According to the American Heart Association and American Stroke Association (AHA-ASA), VCI is defined as "a syndrome with evidence of clinical stroke or subclinical vascular brain injury and cognitive impairment affecting at least one cognitive domain."[81]

## Subtypes of Vascular Dementia

The main subtypes of VaD are distinguished based on the patterns of vascular brain lesions leading to dementia. Current classifications divide VaD into multi-infarct dementia (or cortical VaD), strategic infarct dementia and subcortical vascular dementia.

### *Multi-Infarct Dementia*

Multi-infarct dementia is based on the traditional concept that multiple cortical infarcts are required for the development of dementia.[78] This type of dementia is characterized by multiple lacunar infarcts in the cortex and in subcortical areas.[82] The cumulative amount of damaged brain tissue therefore passes the threshold for cognitive impairment, causing significant incapacities.[82] The vascular mechanisms of MID involve large vessel disease, cardio embolic events and hypoperfusion.

### *Strategic Infarct Dementia*

Strategic infarct dementia includes unilateral or symmetric lesions, usually involving functionally important brain regions and neuronal circuits. Examples of critical cortical sites include the hippocampus and angular gyrus. Subcortical sites include the thalamus, fornix, basal forebrain, caudate, and the genu of the internal capsule.[53] The clinical features of strategic infarct dementia vary considerably with the precise location of each lesion. However, only a very small total infarct volume is required to observe clinically significant features of VCI.

### *Subcortical Vascular Dementia*

Subcortical vascular dementia is the most commonly observed subtype and incorporates clinical entities of the lacunar state and Binswanger's disease. The underlying damage can be described as widespread demyelination and confluent axon loss in the white matter.[82] In this type of VaD, small vessel disease is considered the main vascular mechanism, while lacunar infarcts and ischemic white matter lesions are the primary type of brain lesion.

## Diagnostic Criteria of Vascular Dementia

As a newly introduced concept, several diagnostic criteria for VCI have been proposed, although there is a pressing need for adequate validation. The Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD) have been considered more clinical and epidemiologically applicable, while the ADDTC and the NINDS-AIREN

criteria were formulated largely for use research settings as diagnostic instruments for VaD.

***Hachinski Ischemic Scale***

The traditional Hachinski Ischemic Scale (HIS) was a clinical tool designed to provide a preliminary discrimination between degenerative dementia, vascular or multi-infarct dementia and mixed dementia.[83] This scale assigns a 1 or 2 point value to each clinical feature and a summation of these points is the Ischemic Score. Patients with an HIS score ≤4 are diagnosed with Alzheimer's disease, an intermediate score of 5-6 suggests diagnosis of mixed dementia and a score ≥7 suggests multi-infarct dementia.

***DSM-IV (1994)***

The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) requires focal neurological signs/symptoms or significant cerebrovascular diseases, such a multiple infarcts in the cortex and subcortical white matter, which are etiologically related to the disturbances.[71] The DSM-IV however has no requirement concerning brain imaging.

***ICD-10 (1993)***

The International Classification of Diseases, 10th Revision (ICD-10) criteria defines dementia as a decline in memory and other cognitive abilities that have been present for at least 6 months.[84] The ICD-10 criteria for vascular dementia

require the presence of focal neurological deficits and an unequal distribution of cognitive function. There is also no requirement of brain imaging.

***ADDTC (1992)***

The State of California Alzheimer's disease Diagnostic and Treatment Centers (ADDTC) criteria were initially designed to diagnose ischemic vascular dementia.[85] These criteria define dementia as "deterioration from a known or estimated prior level of intellectual function sufficient to interfere broadly with the patient's customary affairs of life, which is not isolated to a single narrow category of intellectual performance and which is independent of level of consciousness."[85] According to the ADDTC criteria, patients are classified as having probable or possible vascular dementia based on evidence of dementia, previous stroke and infarcts evidenced by imaging.

***NINDS-AIREN (1993)***

The National Institute of Neurological Disorders and Stroke and *Association Internationale pour la Recherché et l'Ensignement en Neurosciences* (NINDS-AIREN) criteria are currently the mostly widely used in diagnosing VaD.[86] These criteria rely on neuroimaging by computed tomography (CT) or magnetic resonance imaging (MRI) for evidence of focal brain damage as well as cognitive deficits in at least 3 cognitive domains (one of which must be memory). Patients are diagnosed as having probably, possible or definite vascular dementia based on

the strength of the association between cerebrovascular disease and cognitive impairment.

## Risk Factors of Vascular Cognitive Impairment

Non-modifiable risk factors of VaD include demographic and genetic factors. As with most cognitive disorders, VCI is likely to be more common with age. After 65 years of age, there is an exponential increase in the prevalence and incidence of VaD.[87, 88] Some studies report a higher incidence of VaD in men than in women.[89] In other studies, the incidence of VaD appears to be higher in blacks than in whites or Hispanics with a history of stroke.[90] The apolipoprotein E ε4 allele is a strong indication of genetic risk for Alzheimer's disease, however there is currently no apparent association between apolipoprotein E ε4 and VCI.[91]

Lifestyle factors may be risk factors for VCI, and in many cases there is current evidence for the biological mechanisms by which these factors may heighten the risk of VCI. Low education level has been reported to be associated with an increased risk for VaD.[92] Physical activity has been identified as having potential protective benefits in brain health as well as in VCI. Long-term physical activity, including vigorous activity and walking is therefore strongly associated with higher levels of cognitive function, and less VaD. Some studies have also found a benefit to cognition associated with more use of alcohol compared with infrequent or no use of alcohol.[93, 94]Obesity is also an emerging risk factor.[95] Mid-life body

mass index measures are strongly associated with VCI, whereas later life measures have an inverse association with cognitive impairment.[96] Finally, based on the known of effects of smoking on the cardiovascular system, several studies show an increased risk for cognitive decline in smokers compared to non-smokers.[97, 98]

Physiological risk factors are biomarkers of diseases processes and can be measured through imaging or clinical examinations. The major physiological risk factors associated with VCI include blood pressures, hyperglycemia and lipids.[81] Midlife hypertension is considered the most significant modifiable risk factor for mild cognitive impairment and VaD.[99, 100] Chronic hyperglycemia and diabetes are associated with VCI and VaD.[99, 101] Studies suggest that poorer cognitive function is associated with a longer duration of diabetes.[101-103] Finally, studies have suggested that higher midlife measures of total cholesterol significantly predict cognitive impairment developing years later.[104]

## Summary

Transient ischemic attacks are episodes of reversible neurological deficits that are also considered an important warning sign for future ischemic stroke. Diagnosis is made based on history, neurologic examination, and neuroimaging with absence of infarction. Management of these patients through lifestyle factors and pharmacological therapies strongly focuses on stroke prevention. However, there

are a number of questions that remained unanswered regarding the acute cognitive sequelae of TIA and minor stroke.

The aim of this Masters project is to outline a temporal profile of the acute cognitive deficits that follow TIA and minor stroke. It is possible that cognitive changes in many of these patients are temporary. Identifying clinical and imaging correlates of cognitive deficits would be an asset to predicting long-term functional outcomes. This under-studied and recognized problem has significant implications for TIA/minor stroke patient management.

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# Chapter 2:

## Cognitive Impairment Following Transient Ischemic Attack

### Introduction

Stroke is the leading cause of prolonged disability in the elderly and the second most common cause of death.[1, 2] Prior to stroke individuals often experience minor cerebrovascular events such as transient ischemic attacks (TIAs). According to the American Heart Association, transient ischemic attack is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischemia, without acute infarction.[3] TIAs have been considered crucial "warning signs" for increased risk of an upcoming stroke. Stroke has been shown to follow a TIA in 12 to 30% of patients, and the highest risk of recurrent cerebral ischemia is within the first 24 hours of the initial event.[4] Without early detection and proper treatment, TIAs can be followed by more severe ischemic stroke.

Cerebrovascular disease is associated with cognitive impairment that significantly impact patients in the long term. Up to 25% of stroke survivors meet the criteria for dementia within 12 months of an ischemic event.[5, 6]. Chronic cerebrovascular changes, without overt clinical evidence of an ischemic stroke, can lead to cognitive decline, ultimately resulting in vascular dementia. In TIA patients, symptoms and tissue deficits are by definition considered temporary, but cognitive impairments have been identified in some studies after initial focal symptoms have resolved.[7-9] Imaging studies in TIA/minor stroke patients have identified correlates of cognitive deficits, but a profile describing how cognitive

changes evolve over time has not been established. It is unknown whether cognitive impairments remain stable, worsen, or resolve in time and what factors may significantly predict these changes. These factors are relevant to managing patient rehabilitation and making informed decisions related to return to previous activities including work and driving.

The purpose of this review is to provide an overview of the chronic microvascular changes and imaging findings correlated with impairments in cognition function, describe existing temporal profiles of cognitive change and address current therapeutic strategies for treating cognitive decline in TIA/minor stroke patients.

## Vascular Disease and Cognitive Changes: Etiologies

Chronic microvascular changes have been associated with an increased risk of vascular cognitive impairment following TIA or minor stroke. These microvascular changes include cerebral microbleeds, lacunar infarcts and leukoaraiosis.[10] Microvascular disease is linked to the pathology of the small penetrating arteries and arterioles in the brain. It has been hypothesized that patients with pre-existing microvascular changes are at increased risk of cognitive decline after an incident clinical stroke.[11]

### Cerebral Microbleeds

Cerebral microbleeds (CMBs) are small collections of hemosiderin deposits resulting from chronic microscopic bleeding from cerebral vessels affected by

small vessel disease.[12] Susceptibility-weighted MRI sequences, such as Gradient Recalled Echo (GRE) are required to detect CMBs in vivo, which appear as small, round hypointense lesions.[13] CMBs have been defined with various sizes, but most investigators agree the maximum diameter of a CMB is 5-10mm.[14] These chronic bleeds are often found distributed in deep/infratentorial regions as well as cortico-subcortical (or lobar) regions. Deep and infratentorial microbleeds are thought to represent the sequelae of hypertensive microangiopathy (lipo or fibrohaylinosis) and are therefore more frequently observed in hypertensive patients.[15] Lobar microbleeds have been attributed to cerebral amyloid angiopathy (CAA), an age related condition characterized by the deposition of β-amyloid in the walls of small arteries and arterioles.[16] CMBs have been detected in 5% of the general healthy population and show increasing prevalence with age.[14]

Microbleeds are considered clinically silent lesions, but recent studies indicate an association between CMBs and cognitive changes.[17] Demonstrating a direct relationship between CMBs and cognition is challenging because CMBs rarely occur in isolation. They are strongly associated with radiological makers of small vessel disease, and indeed cognitive impairment, such as white matter hyperintensities (WMH) and lacunes, making their effects more difficult to differentiate.[18] In stroke patients, CMBs vary from 35% in patients with first ever or recurrent ischemic stroke to 60% in intracerebral hemorrhage.[19]

Despite their prevalence, studies of the relationship between CMBs and cognitive function in healthy adults are scarce. The Rotterdam Scan study investigated CMBs and cognitive performance in 3979 non-demented patients.[20] The presence of numerous microbleeds was significantly associated with lower MMSE scores and worse performance in all cognitive domains except memory. The Reykjavik Study of Healthy Aging for the New Millennium (AGES-Reykjavik) with 3906 participants demonstrated a similar association with cognitive scores that were strongest in individuals with multiple CMBs and microbleeds in deeper locations.[21] A recent study in Japan including 678 healthy adults found CMBs in 6.8% of patients.[22] Lower MMSE scores were predicted by the presence of both CMBs and severe WMHs.

One of the first studies to show the relation between CMBs and cognitive dysfunction in cerebrovascular disease examined 55 stroke and TIA patients with and without microbleeds.[23] Executive dysfunction was more common in microbleed patients compared to controls (60% vs. 30%). Patients with impairments in multiple cognitive domains also had significantly more microbleeds. In another study of 86 patients diagnosed with subcortical vascular dementia, 85% showed evidence of CMBs, which was an independent predictor of dysfunction in all cognitive domains, with the exception of language.[24] Another study focused on 152 patients with mild cognitive impairment being followed for an average of 2 years.[25] Microbleeds showed a 3-fold increase in significant risk for progression to non-Alzheimer dementia.

**Lacunar Infarcts**

Lacunae are small cavities no more than 2cm in diameter that result from the occlusion of small deep penetrating arterioles in the brain.[26] These small lesions are largely confined to the cerebral white matter and subcortical structures including the thalamus, basal ganglia and brainstem. Approximately 25% of ischemic strokes are lacunar in type.[27] Along with advancing age, arterial hypertension and diabetes are the risk factors most strongly associated with lacunar stroke. When symptomatic, these lesions may present clinically as one of several specific lacunar syndromes, including pure motor hemiparesis, pure sensory syndrome, sensorimotor stroke, ataxic hemiparesis or dysarthria–clumsy hand. More commonly, up to 89% of lacunar infarcts are asymptomatic or clinically silent.[28, 29]

Although cognitive impairment is generally not associated with acute lacunar infarction, this has never been systematically studied. In contrast, multiple chronic lacunar infarcts are associated with more than half of vascular dementia cases.[30] Isolated lacunae have been considered a rare cause of cognitive impairment; however, the presence of lacunae in strategic sites or in combination with other lesions is considered a significant cause of cognitive impairment and dementia.[31-34] Following lacunar stroke, the risk of developing dementia is estimated between 11%-23%[35] and increases with coexisting white matter disease.[36]

A number of studies have investigated the relationship between lacunar stroke and cognitive dysfunction. In 1992, Loeb et al. found that patients with lacunar infarcts were 4-12 times more likely to suffer dementia than the normal population.[37] Another study found that many patients with lacunar infarcts demonstrated associated cognitive impairments in memory.[38] A longitudinal study of 77 patients with probable vascular dementia measured changes in cognition through MMSE at 1 week and 1 year.[39] Patients with lacunar infarcts showed an annual deterioration in MMSE scores by 1.44 ± 1.8 points. In a study of 160 patients, cognitive performance was tested using MMSE during the first year following first ever stroke.[40] Patients with lacunar infarcts showed a mean decline of 1.8 points after one year compared to the mean increase of 1.8 points observed in other stroke subtypes.

**Leukoaraiosis**

Chronic cerebral white matter changes are radiological manifestations of small vessel disease commonly observed in cerebrovascular patients, but also the healthy elderly.[41] The terms white matter hyperintensities (WMH) or leukoaraiosis are both used to refer to periventricular/sub-cortical hypodensities on CT scan and hyperintensities on T2-weighted MRI (Figure 2.1). Pathological correlates of WMHs include myelin loss, gliosis, axonal loss, and enlarged perivascular spaces.[41] In the general population, they occur in approximately 30-90% of individuals over the age of 60.[42] Age and hypertension are consistently identified as risk factors in white matter disease.

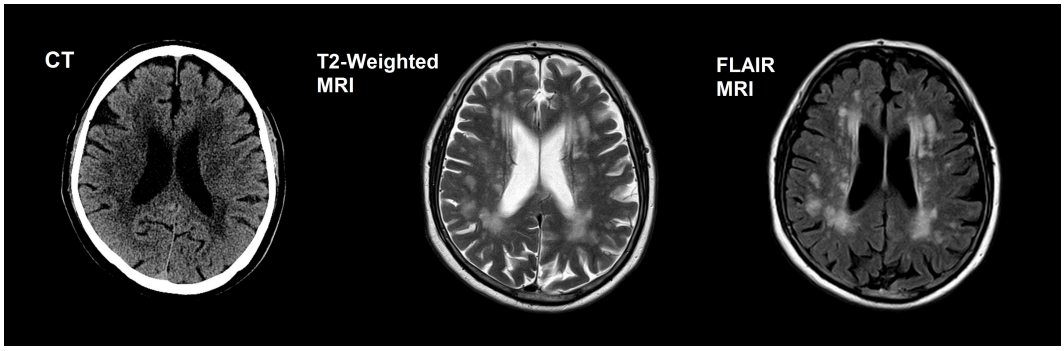


**Figure 2.1** Chronic white matter changes as seen on CT, T2-weighted and FLAIR (Fluid Attenuated Inversion Recovery) MRI.

Cerebral WMHs are a well-recognized risk factor for post stroke dementia. The presence of WMHs has been correlated with decline in cognitive performance in many previous studies. In the Rotterdam Study, presence of white matter lesions and a broad range of cognitive domains were assessed in 90 non-demented patients.[43] Patients with white matter lesions demonstrated worse cognitive performance on all neuropsychological tests compared to those without. More recently, a prospective cohort study of 1024 patients evaluated imaging and functional outcomes within 1 year of acute stroke or TIA.[44] The presence of mild to moderate leukoaraiosis predicted poor function recovery and low quality of life compared to no leukoaraiosis during the first year of stroke onset.

Increasing severity of white matter load has also been shown to be a powerful predictor of progression of cognitive decline.[45, 46] The Cardiovascular Health Study followed 1919 individuals aged 65 and older, who underwent 2 MRI scans separated by 5 years.[47] This study aimed to determine predictors of worsening white matter grade (WMG), which was assessed on a semi-quantitative 10-point WMG (0 to 9) scale using 8 reference cases as visual standards. Results indicated

that a worsening of 1 grade in 28% of participants was associated with impaired performance on the MMSE and digit symbol substitution test. The Austrian Stroke Prevention Study examined 329 community dwellers that underwent MRI and cognitive testing at baseline, 3 and 6-year follow-ups.[48] The average increase in white matter lesion load was significantly correlated with deteriorated performance on tasks of memory, conceptualization and visuopractical skills.

**Silent Stroke**

Silent stroke is defined as a brain parenchymal lesion of vascular origin, without any history of corresponding symptoms or signs of prior stroke.[49] Silent strokes are commonly found on brain CT or MRI, not only among patients presenting with first ever stroke, but also in the healthy elderly. The Rotterdam Scan Study reported presence of silent infarcts in 20% of healthy elderly individuals, between the ages of 60 and 90 years.[50] In healthy and asymptomatic individuals, silent strokes mainly comprise lacunar infarcts, which are often associated with white matter changes.[49] Age and hypertension are two significant risk factors for silent brain infarct, followed by diabetes, smoking and excessive alcohol consumption.[51]

Although silent infarcts fail to produce sensory or motor deficits, these lesions can still disrupt subcortical circuits that control cognitive function. Silent strokes have therefore been associated with an increased risk of dementia and cognitive decline. One study examined 84 middle-aged neurologically normal adults using MRI and neuropsychological testing.[52] The MMSE scores were significantly in

subjects with than without silent cerebral infarcts. Another study used 1015 elderly participants from the population-based Rotterdam Scan Study, aged 60-90 years and free of dementia and stroke at baseline.[53] Patients underwent neuropsychological testing and cerebral MRI at baseline and followed up at a mean 3.6 years later. Silent brain infarcts present at baseline more than doubled the risk of dementia and were associated with a steeper decline in global cognitive function. The Memory and Morbidity in Augsburg Elderly Study in south Germany studied 267 healthy elderly patients aged 65 to 83.[54] Individuals with silent stroke showed impairments on the MMSE, in the cognitive domains of memory, procedural speed and motor performance.

## Imaging Studies in Transient Ischemic Attack Patients

### Imaging Modalities Used in TIA

It has been estimated that approximately one third of patients diagnosed with a TIA on clinical ground alone, actually have evidence of an infarct on magnetic resonance imaging (MRI) scan.[55, 56] This has resulted in a paradigm shift in the approach to TIA/minor stroke, which are now viewed as a spectrum of the acute cerebrovascular presentation, rather than discrete entities.[57] The fact that patients with transient symptoms often have evidence of parenchymal brain injury indicates that the condition is not as benign as once believed. TIA-related infarcts can be difficult to detect because they are often very small - generally less than 1mL in volume.[58]

Although evidence of infarction can be seen on CT after TIA, these are often chronic infarcts and unrelated to the acute presentation (Table 2.1). Nonetheless, these lesions are of prognostic value. In 1979, Perrone et al. found that 34% of TIA patients had small hypodense areas on CT.[59] Subsequent studies have reported lower percentages ranging from 3% to 32%[60-68] (Table 2.1). Interestingly a study in 1983, examining the case reports of two patients with TIA symptoms, demonstrated evolving infarcts on cranial CT. These authors suggested that patients, who fit the temporal profile of TIA, but showed evidence of infarction on CT, should be classified separately as cerebral infarction with transient signs.[69] In the most recent CT study, a cohort of 1533 TIA patients were scanned within 48 hours of symptom onset.[68] Evidence of a suspected new infarct was detected in 3.1% of patients, but this is much lower than that seen with MRI.[56]

More recent MRI studies have changed the approach to diagnosis of the TIA/minor stroke patient. The MRI Diffusion weighted imaging (DWI) sequence in particular has a high sensitivity for detecting acute cerebral ischemia. DWI is sensitive to the movement of protons, and therefore water molecules in the brain. Areas of increased intensity on DWI represent diffusion restriction. The latter is associated with bio-energetic compromise and cytotoxic edema formation during an ischemic event.[70] Studies of TIA patients utilizing DWI have demonstrated higher infarct detection rates in comparison to CT. A prospective study of 22 TIA patients, found focal CT changes in 7 (32%) patients, however using DWI, focal abnormalities were detected in as many as 17 (77%).[61] More recently, a study of

161 TIA patients, who underwent both CT and MRI, indicated focal CT abnormalities in 7 (4.3%) patients.[71] The overall agreement between CT and MRI in detecting ischemic lesions was 69%, indicating that approximately one third of identified DWI lesions were missed or misidentified (i.e. chronic lesions classified as acute relevant infarct) on CT.

Systematic MRI studies have found that the proportion of TIA patients with positive DWI changes ranges from 11% to 68%[58, 72-97] (Table 2.1). Serial imaging studies indicate that some DWI lesions do not result in a visible chronic infarct (Figure 2.2). In a study of 42 TIA patients, relevant DWI abnormalities were reported in nearly half of patients.[72] Of the 9 DWI positive patients who had a follow up imaging study 2-7 months after the event, 4 did not reveal any infarct relevant to the original abnormality. In another multicenter study, DWI scans were performed within 24 hours of symptom onset in 458 patients and acute ischemic lesions were found in 96 (21%) patients.[97] A follow-up MRI was done on 48 patients showing that in 5 (10.4%), DWI lesions visible on admission had disappeared. In a study by Oppenheim and colleagues, 21% of TIA patients with baseline positive DWI scans showed no permanent injury when assessed 11.6 months later.[89] Lesions that 'reversed' had smaller initial DWI volumes than those that infarcted. Although this phenomenon has been referred to as 'DWI reversal' it more likely represents a very small infarct that is below the resolution of standard MR imaging.

## Table 2.1: CT and MRI (DWI) Studies in TIA/Minor Stroke Patients

| Imaging Modality | Study (reference) | Time from Symptom Onset to Scan | TIA Inclusions | No. Pts | % of TIA Pts With Infarct |
|---|---|---|---|---|---|
| **CT** | Perrone et al.[59] 1979 | | All TIAs | 35 | 34 |
| | Calandre et al.[60] 1984 | Mean 50 days | All TIAs | 88 | 25 |
| | Awad et al.[61] 1986 | | All TIAs | 22 | 32 |
| | Davalos et al.[62] 1988 | | | 122 | 21 |
| | Murros et al.[63] 1989 | Within 4 weeks | Carotid TIA | 284 | 12 |
| | Dennis et al.[64] 1990 | Median 11 days | All TIAs | 120 | 27 |
| | Evans et al.[65] 1991 | Within 4 weeks | All TIAs | 350 | 17 |
| | Eliasziw et al.[66] 1995 | | All TIAs | 164 | 28 |
| | Douglas et al.[67] 2003 | Within 48h | All TIAs | 478 | 4 |
| | Al-Khaled et al.[68] 2012 | Within 48h | All TIAs | 1533 | 3 |
| **MRI** | Kidwell et al.[72] 1999 | Mean 17h | Cerebral and brainstem | 42 | 48 |
| | Engelter et al.[73] 1999 | Mean 36.5h | Focal deficit <24h | 40 | 35 |
| | Takayama et al.[74] 2000 | Within 48h | All TIAs | 19 | 37 |
| | Kamal et al.[75] 2002 | Within 6h | All TIAs | 28 | 46 |
| | Ay et al.[58] 2002 | Mean 39h | Cerebral and brainstem | 57 | 47 |
| | Marx et al.[76] 2002 | Mean 10.7h | Brainstem | 14 | 29 |
| | Kastrup et al.[77] 2002 | Mean 5 days (DWI +)<br>Mean 6 days (DWI -) | Carotid TIA | 42 | 45 |
| | Rovira et al.[78] 2002 | Mean 5 days | Cerebral and brainstem | 58 | 67 |
| | Crisostomo et al.[79] 2003 | Mean 23h | All TIAs | 75 | 21 |
| | Nagura et al.[80] 2003 | Median 17.3h | All TIAs | 45 | 31 |
| | Nakamura et al.[81] 2003 | Within 48h | All TIAS | 18 | 50 |
| | Restrepo et al.[82] 2004 | Mean 56min (DWI +)<br>Mean 33min (DWI -) | All TIAs | 22 | 55 |
| | Purroy et al.[83] 2004 | Within 7 days | Cerebral and brainstem | 83 | 33 |
| | Winbeck et al.[84] 2004 | Within 24h | Anterior circulation | 60 | 30 |
| | Schulz et al.[85] 2004 | Median 17 days | All TIAs | 136 | 13 |
| | Inatomi et al.[86] 2004 | Median 4 days | Cerebral and brainstem | 129 | 44 |
| | Ay et al.[87] 2005 | Mean/SD 22 ± 26h | Cerebral and brainstem | 87 | 41 |
| | Coutts et al.[88] 2005 | Median 8.5h | TIA and MS | 143 | 68 |
| | Oppenheim et al.[89] 2006 | Median 24h | All TIAs | 103 | 35 |
| | Lamy et al.[90] 2006 | Mean 42.4h | Cerebral and brainstem | 98 | 35 |
| | Prabhakaran et al.[91] 2007 | Within 48h | All TIAs | 146 | 25 |
| | Redgrave et al.[92] 2007 | Within 72h | All TIAs | 200 | 16 |
| | Calvet et al.[93] 2009 | Median 19.5h | All TIAs | 339 | 40 |
| | Mlynash et al.[94] 2009 | Mean/SD 23.2 ± 12.5h | All TIAs | 43 | 35 |
| | Adeoye et al.[95] 2010 | Within 48h | All TIAs | 323 | 15 |
| | Al-Khaled et al.[96] 2013 | Within 48h | Time defined TIA | 1862 | 11 |
| | Miyagi et al.[97] 2013 | Within 7 days | All TIAs | 458 | 21 |

TIA indicates transient ischemic attack; CT, computed tomography; MRI, magnetic resonance imaging; DWI, diffusion-weighted imaging.

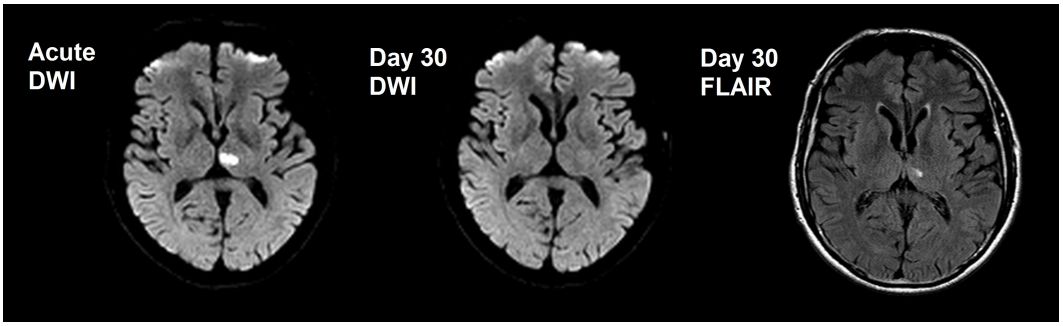


**Figure 2.2** Acute MRI demonstrates a small ischemic DWI lesion, which is seen to resolve by day 30. A small lesion can also be seen as bright signal intensity on they day 30 FLAIR sequence in the corresponding area.

### Imaging Correlates of Cognitive Impairment

Studies identifying clinical characteristics associated with the presence of DWI abnormalities in TIA patients focus more strongly on functional impairments than cognitive deficits. A longer duration of neurological symptoms and the presence of motor weakness are both associated with the presence of DWI lesions.[79,86] The impact of DWI lesion presence, location, volume and number on cognitive performance is unknown. Studies correlating MRI findings in TIA/minor stroke patients with neuropsychological testing are lacking. There is an increased likelihood of aphasia in TIA/minor stroke patients with DWI lesion, but the relationship to other cognitive domains is unknown.[90, 96] One study found that TIA patients with a positive DWI scan were 25 times more likely to have aphasia than those with negative scans.[79] In a study of 147 TIA patients, disturbance of higher cortical function evidence as aphasia and spatial neglect was a significant factor associated with DWI abnormalities.[86]

Although DWI lesion characteristics in TIA patients such as volume, location and frequency have been reported, studies investigating the association of these parameters with cognitive impairments are very scarce. In the Sydney Stroke Study, 170 patients with stroke or TIA and 96 age-matched controls were examined between 3 to 6 months following the event. [98] Patients were categorized as having vascular dementia (VaD), vascular cognitive impairment (VCI) or no cognitive impairment by consensus and administered detailed neuropsychological test along with an MRI scan. Although VaD subjects had larger infarct volumes than VCI subjects, cognitive impairments were not significantly correlated with volume or number of infarctions. Instead, a significant relationship was observed between chronic deep white matter hyperintensities and cognitive deficits.

## Cognitive Performance Testing After Stroke and TIA

### Assessments in Acute Ischemic Stroke

Cognitive function is often compromised after stroke, but is rarely assessed in stroke trials. Cognitive changes in acute stroke patients have been assessed quantitatively using different batteries of neuropsychological tests. While detailed neuropsychological testing represents the gold standard in terms of identifying cognitive impairment, this is generally impractical in the acute setting, partially motivating the need for brief yet accurate instruments. The two most commonly utilized tests in cognitive screening for acute stroke are the Mini Mental State Examination and the Montreal Cognitive Assessment.

The Mini Mental State Examination (MMSE), developed by Folstein et al., is a cognitive assessment of patient mental state and has been considered the clinical standard in stroke.[99] The assessment is comprised of a battery of individual tests that can be administered in approximately 10 minutes. The test is scored out of a total of 30 points, with higher scores indicating higher functioning. Items are grouped into categories to test orientation, registration, recall, calculation and attention, naming, repetition, comprehension, reading, writing and drawing. The MMSE has however been criticized for being insensitive to mild cognitive impairments. This test also primarily focuses on assessing memory and language abilities while it fails to assess executive function, a common impairment in cerebrovascular disease.

The Montreal Cognitive Assessment (MoCA) was a test designed more recently as a cognitive screening assessment with increased sensitivity to mild cognitive impairment (MCI). [100] The MoCA can be administered in a short 10 minutes, where patients can score a total of 30 points. The test is divided into 8 sections assessing the cognitive domains of visuo-executive function, naming, memory, attention, language, abstraction, delayed recall and orientation. Cognitive impairment based on MoCA scoring has been designated by a cutoff score less than 26.[100, 101]

A number of factors make accurate assessment of cognitive impairment following stroke/TIA challenging. Depression present following acute stroke has been

implicated in worse functional outcome and also exacerbates any acute/chronic cognitive impairment.[102-104] Cognitive assessments also vary in their sensitivity for mild impairment. A validation study by Nassreddine and colleagues in 2005 compared the sensitivities of MMSE and MoCA in 94 patients who met the criteria for mild cognitive impairment.[100] The MMSE had a sensitivity of 18% in MCI patients, whereas the MoCA had a sensitivity of 90%. Several studies comparing MoCA and MMSE in acute stroke and TIA patients have shown that MoCA is superior to the MMSE in detecting MCI.[101, 105-107] Despite this, many studies continue to utilize MMSE.

**Cognitive Impairment after TIA and Minor Stroke**

Cognitive studies in TIA/minor stroke patients have demonstrated that cognitive impairments in many cases do persist beyond the transient event. A comparative study of MoCA and MMSE in 20 patients diagnosed with TIA or stroke utilized the MMSE on admission and the MoCA 2 weeks later. [108] With cutoffs for impairment set at ≤26, MMSE detected cognitive impairment in 10% of patients, while MoCA detected impairment in 55%. In a larger population based study of 413 TIA and stroke patients, the MMSE and MoCA were administered at a 6-month or 5-year follow-up.[101] Defining cognitive impairment as a score of <27 on either test, 58% of patients with an MMSE score within normal limits had an abnormal MoCA. The MoCA indicated poor cognitive function in 70% of all patients.

**Temporal Pattern of Cognitive Changes after TIA and Minor Stroke**

The temporal pattern of motor, speech and sensory deficits in TIA/minor stroke is an acute onset and relatively rapid resolution with no long-term sequelae. It is unknown to what extent, if any cognition is affected in this population hyperacutely and whether these deficits actually resolve with the other neurological symptoms. Longitudinal studies that adequately assess this pattern in TIA and minor stroke patients are scarce. Most studies in TIA and minor stroke patients lack serial assessment of cognition at multiple time points, including immediately after symptom onset, and only assess deficits several days after symptom onset. In a cross-sectional study of 280 TIA and minor stroke patients (National Institutes of Health Stroke Scale ≤ 3), MMSE was administered both at the initial assessment (baseline) and 1 month later and then repeated at 1, 2 and 5 years.[7] Patients were divided into 2 baseline groups: those seen between 1 and 7 days and those seen between 8 and 20 days. Transient cognitive impairment was defined as a baseline MMSE score ≥ 2 points lower than the 1-month follow up MMSE. The rate of transient cognitive impairment in patients initially assessed within 7 days (median 4 days) was 38.9%. This was higher than the rate of 19% seen in those examined between 8 and 20 days (median 12 days). Patients with TCI did show a recovery in mean MMSE scores from 23.9 ± 3.6 at baseline to 27.2 ± 3.0 at 1 month. Sachdev and colleagues examined 128 stroke or TIA patients aged 49 to 87 years, with no history of dementia or aphasia as a limiting factor (<3 on the Aphasia Severity Rating Scale).[8] The initial assessment was done within 3 and 6 months post stroke, and a follow-up assessment 14 months

later. At baseline, patients were categorized based on severity into 3 groups: vascular dementia (VaD), vascular cognitive impairment no dementia (VCI-ND) and no cognitive impairment (NCI). Cognitive tests showed a mean decline of 0.83 points on MMSE between the two time points. Patients impaired at baseline assessment (VaD + VCI-ND), showed a greater decline in visuoconstructive function and abstraction domains than NCI patients. In this study, higher white matter hyperintensity load was a significant predictor of cognitive decline. Education level emerged as a protective factor against cognitive decline following the TIA/stroke. Another study assessed cognitive function in 252 patients with TIA or non-disabling ischemic stroke at baseline (within 6 months of symptom onset) and again after 1 year.[9] At baseline, after administering MMSE along with the vascular dementia battery, 56% of patients were 'cognitively intact', 40% were 'cognitively impaired but not demented' and 4% were 'demented'. Of the 252 patients, only 155 were reassessed at the 1-year follow-up. Of these patients, 120 remained in the same categories as at baseline. Nineteen patients (12%) cognitively impaired but not demented at baseline, improved to the point they were considered cognitively intact at one year. Nine patients cognitively intact at baseline, deteriorated to cognitively impaired but not demented at the 1-year follow-up and seven patients who were cognitively impaired but not demented at baseline were demented at 1 year. Demographic variables that differentiated those who deteriorated from those who remained stable or improved included hypertension, age, years of education and MMSE score.

### Knowledge Gaps

Most of these studies included patients with large and often disabling strokes. It is therefore unsurprising that cognition is affected in these patients, particularly as many have pre-existing deficits. What remains unknown is the extent that TIA/minor stroke affects cognition and what the temporal profile of any changes is. Accurate predictors of improvement/worsening in cognitive status of time after TIA/minor stroke are also unknown.

## Therapeutics and Management of Cognitive Decline

Treatment and management of cognitive decline is critical to patient care and preventing prolonged disability following stroke. There is currently no standard treatment for vascular cognitive impairment.

### Prevention of Vascular Dementia: Vascular Risk Factor Management

#### *Hypertension*

Hypertension is an established risk factor for cardiovascular disease and stroke, but has also been implicated in affecting cognitive function. A recent systematic review investigated the association of arterial hypertension with increased risk of vascular dementia.[109] Results demonstrated that people with midlife hypertension have a doubled risk of developing vascular dementia comparing to those without hypertension.

There is some evidence suggesting treatment of hypertension decreases the risk of dementia. Published studies have found that lowering blood pressure in the middle aged or younger elderly population can be useful for the prevention of late life dementia. A few major randomized controlled trials have reported positive effects of antihypertensive treatment on cognitive function in patients with cerebrovascular disease. The Heart Outcomes Prevention Evaluation (HOPE) study was a randomized double blind study of 1013 high-risk patients with a history of stroke or TIA.[110] The study showed a relative risk reduction of 59% when treated with angiotensin-converting enzyme inhibitor (ACE-I) ramipril compared to placebo. In the Systolic Hypertension in Europe (Syst-Eur) trial, 2148 patients were randomized to active treatment with nitrendipine or placebo control.[111] Results showed that the rate of incident dementia was reduced by 50%. The PROGRESS study was a randomized, double blind, placebo controlled trial of 3015 patients with prior stroke or TIA.[112] Patients were assigned to the active treatment group (with perindopril or indapamide) or the matched placebo group, with cognitive function assessed at baseline, 6-month and 12-month visits with MMSE. At the mean follow-up of 3.9 years, the actively treated group demonstrated a 12% reduced risk of dementia and a 19% reduced risk of cognitive decline, compared to matched placebo group.

***Dyslipidemia***

High cholesterol has also shown a consistent association with both increased risk of AD and VaD. In the Kaiser Permanente Northern California Medical Group

study of 469 individuals between the ages of 40-45, serum total cholesterol levels were strongly associated with the increased risk of VaD and AD 3 decades later.[113] This study echoed the results of previous trials including the Finnish Cohort of the Seven Countries Study[114] and the CAIDE study,[115] where high midlife cholesterol levels were associated with VaD and AD later in life.

As a result, various trials have investigated the use of statins and serum cholesterol reduction in the prevention of dementia and cognitive impairment. In a recent study, 3005 participants were recruited from the Baltimore Longitudinal Study of Aging after the age of 50, and followed for a mean 25 years to investigate incidence of dementia and MCI.[116] Participants with incident dementia had higher total cholesterol measured at the first visit and statin users had a two – three fold lower risk of developing dementia. Similarly, data from the Rotterdam study demonstrated that statin use was associated with a decreased risk of AD compared to never using cholesterol-lowering drugs, in patients that were followed up to 15.3 years (mean 9.2).[117] Based on a recent Cochrane review, the use of statins has not consistently demonstrated positive results in all randomized controlled trials.[118]

***Diabetes Mellitus***

Diabetes is a strong risk factor for cerebrovascular disease but epidemiological evidence has shown a relationship between cognitive impairment and Type II diabetes. Hypoglycemia and hyperglycemia have both been linked to impairments

in cognitive function suggesting there may be an optimal neuroglygemic range within which cognitive functioning takes place.[119, 120] In a systematic review investigating the association between diabetes and incidence of major types of dementia, 14 longitudinal studies identified higher incidence of "any dementia" in individuals with diabetes, this highest risk being for AD and VaD.[121]

There has been no evidence to suggest that control of glucose levels reduces the risk of dementia or prevents cognitive impairment. A recent systematic review identified 5 randomized controlled trials assessing the effects of different treatments for Type II diabetes on cognitive function.[122] One study compared ginseng with placebo 36 patients being treated by diet alone (no insulin or oral hypoglycemic agents prescribed).[123] Cognitive function was tested after 8 weeks using digit span and a timed diagram test. Ginseng treated patient had better scores in the diagram test and no differences in digit span compared to placebo, but scores at baseline were not reported, making this result somewhat difficult to interpret. In three of the identified studies, patients given different diabetic treatments were assessed using quality of life questionnaires as opposed to a validated quantitative measure of cognitive function.[124, 125] The final study compared the effect of intensive inpatient diabetic therapy with unchanged regular diabetic therapy on 20 patients already being treated by diet and oral anti-diabetic drugs.[126] Cognitive function was assessed on admission, at discharge and at 6 weeks. At 6 weeks mean cognitive scores of the intensive therapy group were significantly better than those of the regular therapy group. There is still therefore

a lack of convincing evidence relating diabetes management to the prevention or improvement of cognitive impairment.

## Symptomatic Management of Cognitive Symptoms

### Pharmacological

#### *Cholinesterase Inhibitors*

Cholinesterase inhibitors are commonly used in temporarily treating or stabilizing symptoms of Alzheimer's disease. Evidence that disrupted cholinergic pathways may contribute to the pathophysiology of vascular dementia as well, have led to several clinical trials of cholinesterase inhibitors in the management of vascular dementia. Controlled clinical trials with donepezil and galantamine in patients with vascular dementia have demonstrated improvement in cognition, behavior and activities of daily living (Table 2.2).[127]

Donepzeil is a non-competitive, reversible antagonist of cholinesterase, licensed for the treatment of Alzhemier's disease in the United Kingdom and the United States. Two large-scale multi-center, randomized controlled trials (Study 307[128] and Study 308[129]) were conducted in patients with probable or possible vascular cognitive impairment according to the NINDS-AIREN criteria. Patients in both studies were randomized to 24 weeks of donepezil treatment (5 mg/d or 10 mg/d) or placebo with primary efficacy outcome measures being the Alzheimer's disease Assessment Scale-cognitive subscale (ADAS-cog) and the Clinician's

Interview Based Impression of Change (CIBIC). In study 307, 603 patients were assessed at baseline, 6, 12, 18 and 24 weeks.[128] Both donepezil treatment groups demonstrated a significant improvement in cognition versus the placebo on the ADAS-cog at all time points. In study 308 (n = 616 patients), the donepezil treatment group showed the same statistically significant improvement in cognition by week 24 when measured with the ADAS-cog.[129] A recent larger double-blind randomized controlled trial was conducted at 111 centers in 9 countries investigating 974 patients with probable or possible VaD.[130] Patients were randomized to receive donepezil 5 mg/d or placebo for 24 weeks. Patients treated with donepezil showed significant improvement from baseline to end point based on the Vascular AD Assessment Scale-Cognitive Subscale (VADAS-cog), compared to the relative stability of the placebo group. It is therefore recommended by the AHA/ASA that Donepezil can be useful for cognitive enhancement in patients with vascular dementia.[131]

Galantamine is a specific, competitive and reversible acetylcholinesterase inhibitor that has been shown to improve cognition and behavior in patients with Alzheimer's type dementia.[132, 133] In one randomized, placebo controlled trial, 592 patients with probable vascular dementia or Alzheimer's disease with cerebrovascular disease were randomized to placebo or galantamine 24mg/day for 6 months following a 4-week placebo period.[134] According to the ADAS-cog scores, treatment group patients significantly improved from baseline to the 6month period compared to those assigned placebo, whereas placebo group

deteriorated below baseline. Another randomized placebo controlled trial investigated galantamine in 788 patients with probable VaD using slow dose escalation up to 26 weeks.[135] After a 4-week placebo run, patients were randomized to receive increasing doses of placebo or galantamine, initiated at 4mg twice daily and escalated to a final dose of 8 or 12mg twice daily. Improvements in ADAS-cog scores in those treated with galantamine were significantly greater compared with placebo after 26 weeks. The AHA/ASA guidelines therefore suggest that galantamine can be beneficial to patients with mixed Alzheimer's disease or vascular dementia.[131]

***Glutamate Receptor Antagonists***

Glutamate is the principal excitatory neurotransmitter that stimulates NDMA receptors in cortical neurons. There is some evidence that sustained elevation of glutamate may underlie the neuronal loss that is observed in dementia.[136] Ischemia has been associated with the repeated stimulation of NMDA receptors; agents that block the stimulation of this receptor may play a protective role, preventing further neurodegeneration leading to cognitive decline. Memantine is a NMDA receptor antagonist, shown to have neuro-protective effects that help improve cognitive performance in vascular dementia patients.[137, 138] There have been several clinical studies demonstrating memantine's effects on improving cognitive performance in dementia patients (Table 2.2).[137, 139, 140] In one multicenter, randomized controlled trial, 321 patients with mild to moderate VaD were randomly allocated to receive placebo or memantine.[137] After a 2-week placebo

run-in period, patients received doses of 20 mg/d for 28 weeks to follow. Mean ADAS-cog scores showed that patients in the memantine group improved from baseline while the placebo group deteriorated in function. In a larger randomized controlled trial, 579 patients with probable VaD were randomized to placebo or treatment with 20-mg/d memantine for 28 weeks.[139] Memantine resulted in improvement in ADAS-cog scores, not seen in placebo patients. According to AHA/ASA, the benefits of memantine are not well established in VaD.[131]

**Table 2.2: Pharmacological Evidence for Treatment of Vascular Dementia**

| Treatment | Study Reference | Trial | Dosage | Participants | Measured Outcomes |
|---|---|---|---|---|---|
| **Donepezil** | Black et al.[128] (Donepezil 307) | 24 wks | 5mg daily and 10 mg daily | 603 patients with probable or possible VaD by NINDS-AIREN | ADAS-cog and CIBIC improvement in both treatment groups |
| **Donepezil** | Wilkinson et al.[129] (Donepezil 308) | 24 wks | 5mg daily and 10 mg daily | 616 patients with probable or possible VaD by NINDS-AIREN | ADAS-cog and CIBIC improvement in both treatment groups |
| **Donepezil** | Roman et al.[130] | 24 wks | 5mg daily | 974 patients with probable or possible VaD by NINDS-AIREN | VADAS-cog improvement in treatment group |
| **Galantamine** | Erkinjuntti et al.[134] | 24 wks | 24mg daily | 592 patients with AD and CVD or VaD by NINDS-AIREN | ADAS-cog improvement in treatment group |
| **Galantamine** | Auchus et al.[135] | 26 wks | Escalated to 8 or 12 mg twice daily | 788 patients with probable VaD by NINDS-AIREN | ADAS-cog/11 improvement in treatment group |
| **Memantine** | Orgogozo et al.[137] (MMM300) | 28 wks | 20mg daily | 321 patients with probable VaD by NINDS-AIREN | ADAS-cog improvement in treatment group |
| **Memantine** | Wilcock et al.[139] (MMM500) | 28 wks | 20mg daily | 579 patients with probable VaD by NINDS-AIREN | ADAS-cog improvement in treatment group |

VaD indicates vascular dementia; AD, Alzheimer's disease; NINDS-AIREN, The National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Ensignement en Neurosciences; ADAS-cog, Alzheimer's disease Assessment Scale-cognitive subscale; CIBIC, Clinician's Interview Based Impression of Change; VADAS-cog, Vascular AD Assessment Scale-Cognitive Subscale; CVD, cerebrovascular disease.

## Non-Pharmacological

### *Physical Activity*

Physical exercise has been associated with several beneficial effects including the reduced risk of Alzheimer's disease and cognitive decline. Many longitudinal studies in the health elderly have consistently found that regular physical activity was associated with better cognitive function and less cognitive decline later in life. A meta-analysis including 16 prospective studies of non-demented patients suggested that physical activity reduced the risk of dementia and Alzheimer's disease by 28% and 45% respectively.[141]

Studies targeting patients with Alzheimer's disease, vascular dementia and cognitive impairment have reported similar findings. A recently conducted systematic review included a total of 24 longitudinal studies of 1378 patients with VaD.[142] The meta-analysis technique was used to demonstrate a significant reduced risk for VaD in people who were naturally more physically active compared to those who were not. A 4 month randomized controlled trial conducted in 40 patients diagnosed with Alzheimer's disease assessed the effectiveness of a community based home exercise program on improving cognitive and physical function.[143] Patients were randomly assigned to usual treatment plus exercise or usual treatment alone groups. When assessed at baseline and the 4-month follow-up, patients who exercised had improved cognition compared to controls when assessed with MMSE. One meta-analysis

reviewed 30 randomized controlled trials evaluating exercise in patients with cognitive impairments.[144] Exercise was associated with statistically significant improvements in cognitive function as well as physical fitness.

***Education***

Higher levels of education have been associated with a reduced risk dementia and cognitive impairment during aging. It has yet to be determined if education protects from development of neurodegenerative brain pathology or if it increases the brain's resilience against dementia related pathology. The cognitive reserve hypothesis suggests that individuals exposed to an enriched environment through higher education will maintain higher cognitive function in later years by functionally compensating for any neurological load.[145]

Studies have examined the relationship between education levels and cognitive changes in both normal and demented adults. A recent systematic review aimed at investigating the cognitive reserve hypothesis in 133 quantitative studies including both healthy and AD patients.[146] A meta-analysis of this data showed that those with lower education levels had a higher risk for dementia. A longitudinal study of 630 cognitively healthy individuals aged 50 to 80 assessed educational level and mental demands at work as related to cognitive decline.[147] At the 3-year follow up, persons with low education (primary education and lower vocational secondary education) and lower mental workload showed accelerated

cognitive decline in speed (Stroop Test) memory (Verbal Learning Test) and general cognitive status (MMSE).

Participation in cognitively stimulating activities has been hypothesized to reduce the risk of dementia cognitive decline, although evidence of this association is scarce. A longitudinal cohort study tested this hypothesis in 801 non-demented individuals evaluated at baseline and a mean follow-up of 4.5 years.[148] Results showed that an individual reporting frequent cognitive activity at baseline had a 47% reduced changed of developing AD. Another interesting study of 488 cognitively intact individuals assessed the effect of self-reported cognitive activities on the onset of cognitive decline.[149] Findings showed that every additional self-reported day of cognitive activity at baseline, delayed the onset of accelerated memory decline by 0.18 years. These findings provide hope that engaging in cognitively stimulating activities may reduce the risk of dementia.

***Smoking***

Smoking has been associated with both cognitive decline and a significantly increased risk of VaD and AD. A meta-analysis conducted in 2007 identified 19 studies with at least 12 months of follow-up showing current smokers had an increased risk of dementia and cognitive decline ranging from 40-80% compared with people who have never smoked.[150] Recently, a population based cohort study of 21,123 patients surveyed between 1978 and 1985 demonstrated that heavy

smoking in midlife was associated with a greater than 100% increase in risk of dementia, AD and VaD more than 20 years later.[151]

Evidence that smoking cessation prevents cognitive impairment of onset of dementia is limited. The Honolulu-Asia Aging Study was one of the first to investigate smoking cessation and cognitive function.[152] This study found that the odd of cognitive impairment was 36% higher among continuous smokers than never smokers and significantly decline in long term quitters. A recent smoking cessation trial recruited 229 older smokers and 98 never smokers to assess how cessation in chronic smokers would affect rate of change in ADAS-cog scores measured over 24 months.[153] Results demonstrated that chronic smokers who continued to smoke or stopped smoking for less than 18 months experienced greater cognitive decline and greater deterioration of memory scores over 2 years when compared with never smokers.

## Conclusion

Cognitive changes are common in cerebrovascular patients. Although there is good evidence that patients with disabling stroke also have cognitive symptoms, there are less data related to TIA/minor stroke patients. Arguably, these are the more relevant patients to study, as they make functional recoveries, returning to live and work in the community. Assessment of cognition in acute stroke patients is challenging, due to the presence of other neurological deficits. This has led to under-recognition of the seriousness of cognitive changes in acute

cerebrovascular disease patients, particularly those with minor or even apparently transient symptoms. Reliable predictors of cognitive impairment have not been identified, although imaging correlates may hold some promise. The temporal pattern of cognitive impairment after TIA/minor stroke has not yet been adequately characterized. Given the implications for patient rehabilitation, return to work, and activities of daily living, we suggest that this is a research priority.

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# Chapter 3:

# Montreal Cognitive Assessments Demonstrate Acute Cognitive Impairment in Transient Ischemic Attack and Minor Stroke Patients

## Introduction

Long-term cognitive impairment is a well-known consequence of ischemic stroke.[1-4] Approximately two thirds of patients develop cognitive impairment within 3 months of stroke.[5] A history of transient ischemic attacks (TIAs) and minor strokes is also associated with vascular cognitive impairment. Cognitive changes are often overlooked or not assessed in the acute setting. Although detailed neuropsychological testing is ideal, it is time consuming and impractical in the very large TIA/minor stroke population.

Screening tests for cognitive impairment include Folstein's Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). The MMSE, originally designed to screen for dementia of the Alzheimer's type, is currently widely used to assess for post-stroke cognitive impairment.[6] Previous studies have indicated that MMSE has reduced sensitivity for mild cognitive deficits and those associated with right-hemisphere lesions.[7-11] In contrast, the MoCA was developed more recently to detect mild cognitive impairment with higher sensitivity. This assessment has demonstrated high test-retest reliability, good internal consistency and a particular strength in detecting executive

function, a subtest not assessed by MMSE.[12] Although previous studies have compared these assessments in acute ischemic stroke, acute changes in specific cognitive domains following TIA/minor stroke have not been characterized.

In this prospective observational study, we tested the hypothesis that the MoCA is more sensitive than MMSE to acute cognitive changes after TIA/minor stroke. Using serial assessments, we also assessed the temporal pattern of overall and domain-specific cognitive changes within 90 days of TIA/minor stroke.

## Methods

### *Patients*

Acute TIA/minor ischemic stroke patients with a National Institute of Health Stroke Scale (NIHSS) score ≤ 3 at admission and aged 18 years or older were recruited within 72 hours of symptom onset. Exclusion criteria included stroke mimics (such as seizures, migraine), a prior history of dementia or severe aphasia. Subjects who were unable to complete baseline neuropsychological testing were excluded. Informed consent was obtained from all patients prior to enrollment. This was an observational study and secondary stroke prevention measures were implemented in accordance with current practice guidelines.[13]

### *Clinical Assessment*

All patients underwent a clinical evaluation at baseline, days 7, 30 and 90. At each visit, Folstein's MMSE and the MoCA were administered. Identical versions

of the MoCA were administered at all time points. Each MMSE version differed with respect to the 3 words used in recall and the orientation of the intersecting pentagons to be copied. Patients with an educational background less than 12 years in length were assigned one additional point on their MoCA score.[12] Patients with an MMSE ≤ 26 or MoCA score < 26 were considered cognitively impaired.[7]

Neurological function was assessed with the National Institutes of Health Stroke Scale (NIHSS) score at each time point. Functional outcome was assessed with the Modified Rankin Scale (mRS) at days 7, 30 and 90. All raters were certified in NIHSS and mRS administration.

***Statistical Analysis***

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 20.0.0 (SPSS Inc., 2007). Changes in MoCA and MMSE scores between baseline and day 90 were tested using Freidman's test followed by post-hoc analysis with Wilcoxon signed-rank tests. For both the MMSE and MoCA, performance within each cognitive domain was calculated as a percent score (median score/maximum possible score) to allow for relative comparisons between domains and assessments. Spearman's correlation was calculated to assess the relationship between NIHSS scores and cognitive function. A p-value $<0.05$ was considered significant.

## Results

### *Patient Characteristics*

A total of 118 TIA/minor stroke patients were enrolled in the study and 18 patients were excluded. The most common reason for exclusion was the presence of pre-existing dementia, determined after enrollment. The remaining 100 patients (68% males) had a median (IQR) NIHSS score of 1(2) on admission and median population age of 63 (20).

### *MoCA vs. Folstein MMSE*

Median (IQR) MoCA and MMSE scores at baseline were 26 (4) and 29 (2) respectively ($p<0.0001$). The MoCA indicated cognitive impairment in 54/100 patients (54%) at baseline. At the same time, the MMSE detected impairment in only 16/100 (16%, $p=0.001$). Thus, 38% of patients with cognitive impairment present at baseline went undetected by MMSE (Figure 3.1).

### *Temporal Pattern of Cognitive Changes*

Median MoCA scores progressively increased over time following the onset of symptoms. At days 7, 30 and 90, MoCA scores were 27 (5), 28 (3) and 28 (3) respectively. Median MMSE scores at the same time points remained stable at 29 (2). Wilcoxon signed rank test indicated a significant improvement in MoCA scores between baseline and day 90 ($p<0.0001$) while MMSE scores at remained the same after 90 days ($p=0.591$).

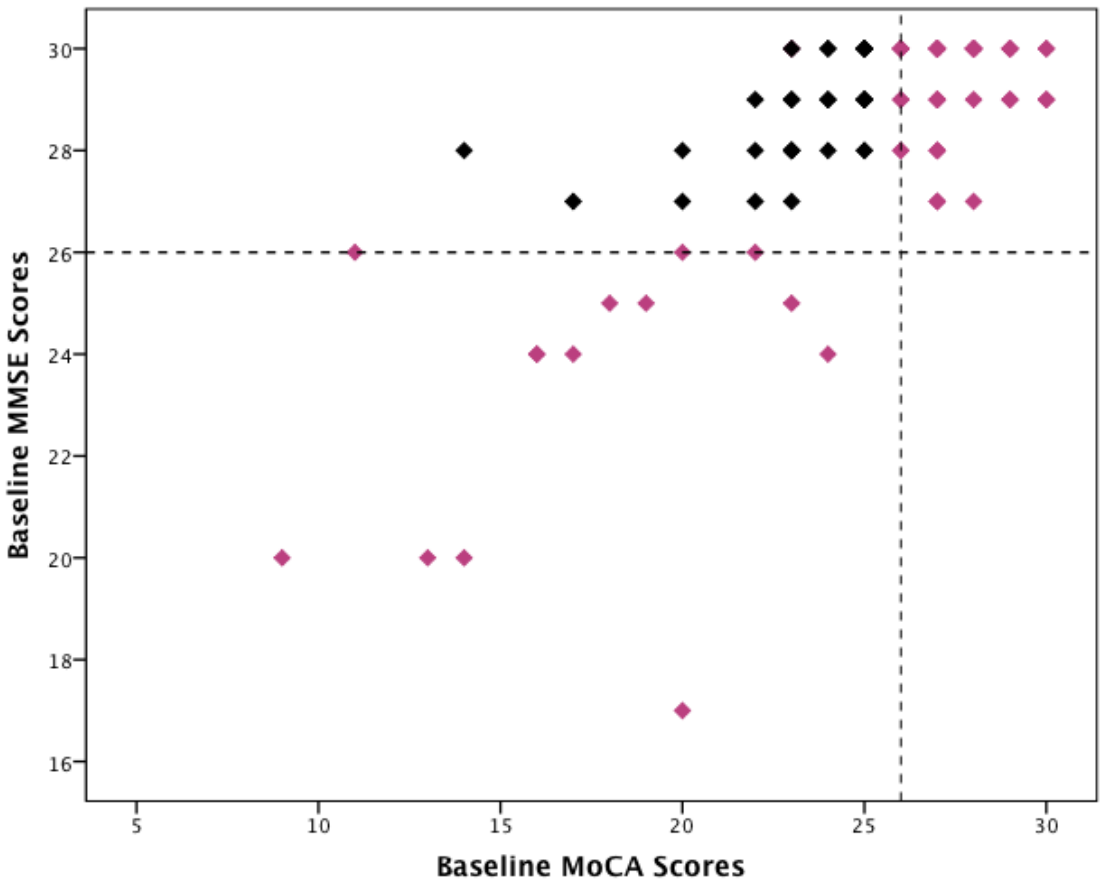


**Figure 3.1** Scatter plot comparing MMSE and MoCA scores for all patients at baseline. The horizontal dashed line shows the cutoff for MMSE at ≤ 26 and the vertical dashed line shows the cutoff for MoCA at < 26. The black data points indicate those patients who scored >27 on the MMSE but < 26 on the MoCA. MMSE indicates Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.

### *Cognitive Domains*

Assessment subtests were used to analyze performance differences in specific cognitive domains. The MoCA was divided into 7 cognitive domains, which included orientation, attention, recall, naming visuospatial, language and abstract reasoning. The MMSE was divided into 6 cognitive subtests assessing orientation, attention, recall, language, registration and constructional praxis. Mean (SD) raw scores and percent scores for each subtest are summarized in Table 3.1.

**Table 3.1: MoCA and MMSE Sub-Score Results**

| Subtest Details | | Mean Raw Scores (SD) and Mean Percent Scores | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | **Baseline** | **Percent Score** | **Day 7** | **Percent Score** | **Day 30** | **Percent Score** | **Day 90** | **Percent Score** |
| **MoCA Subtest /Max Score** | | | | | | | | | |
| Visuoexecutive /5 | Trail B test, cube copy, clock drawing | 3.9 (1.4) | 76.9 | 4.1 (1.2) | 82.6 | 4.2 (1.0) | 83.9 | 4.3 (1.0) | 85.8 |
| Naming /3 | Confrontation naming (lion, hippo, camel) | 2.8 (0.6) | 91.5 | 2.9 (0.4) | 96.1 | 2.9 (0.3) | 96.6 | 2.9 (0.4) | 96.5 |
| Attention /6 | Forward (5 digits), backward (3 digits)<br>Tapping the letter A in letter list<br>Serial 7 subtractions | 5.2 (1.3) | 87.4 | 5.3 (1.0) | 88.6 | 5.4 (1.1) | 90.7 | 5.6 (0.9) | 92.7 |
| Language /3 | Repetition of two complex sentences<br>≥11 words beginning with f in 1 min | 2.0 (1.0) | 66.7 | 2.1 (0.9) | 69.4 | 2.1 (0.9) | 68.2 | 2.3 (0.8) | 75.8 |
| Abstraction /2 | Similarities, eg, train and bicycle = transport | 1.6 (0.7) | 78.1 | 1.8 (0.5) | 89.5 | 1.8 (0.5) | 90.3 | 1.9 (0.5) | 93.2 |
| Recall /5 | Recall a list of 5 words | 2.7 (1.7) | 53.3 | 3.6 (1.5) | 72.8 | 3.6 (1.6) | 72.3 | 3.7 (1.5) | 74.5 |
| Orientation /6 | Date, month, year, day, place, city | 5.8 (0.6) | 96.3 | 5.8 (0.6) | 96.1 | 5.8 (0.6) | 97.2 | 5.8 (0.7) | 96.2 |
| TOTAL /30 | | 24.7 (4.1) | 82.3 | 26.0 (4.3) | 86.7 | 26.8 (3.4) | 89.3 | 27.0 (3.4) | 90.0 |
| **MMSE Subtest /Max Score** | | | | | | | | | |
| Orientation /10 | Orientation to place and time | 9.7 (0.6) | 96.8 | 9.5 (0.9) | 95.4 | 9.5 (0.9) | 94.9 | 9.6 (1.1) | 95.6 |
| Registration /3 | Repeat “ball, car, man” | 3.0 (0.1) | 99.7 | 3.0 (0.1) | 99.6 | 3.0 (0.1) | 99.6 | 3.0 (0.2) | 99.0 |
| Attention /5 | Serial 7 subtractions<br>WORLD backwards | 4.5 (1.1) | 87.8 | 4.7 (0.9) | 89.9 | 4.7 (0.9) | 88.2 | 4.7 (0.8) | 91.3 |
| Recall /3 | Recall “ball, car, man” | 2.4 (0.8) | 80.8 | 2.1 (1.0) | 69.3 | 2.1 (1.0) | 75.7 | 2.4 (0.9) | 80.4 |
| Language /8 | Confrontation naming (pen, watch)<br>Repeat “no ifs, ands or buts”<br>Perform 3-step command<br>Obey written instruction (close your eyes)<br>Write a complete sentence | 7.6 (0.8) | 95.0 | 7.7 (0.8) | 95.6 | 7.7 (0.8) | 96.3 | 7.7 (0.6) | 96.7 |
| Praxis /1 | Copy intersecting pentagons | 0.8 (0.4) | 79.4 | 0.8 (0.4) | 80.9 | 0.8 (0.4) | 78.7 | 0.8 (0.4) | 75.0 |
| TOTAL /30 | | 28.5 (2.4) | 95.0 | 28.1 (2.0) | 93.7 | 28.5 (2.0) | 95.0 | 28.7 (1.8) | 95.7 |

Mean percent scores calculated as a percent of maximum possible score. MoCA indicates Montreal Cognitive Assessment; MMSE, Mini-mental State Examination; SD, Standard deviation.

Baseline MoCA assessments indicated TIA/minor stroke patient performance was poorest in language and recall domains (Figure 3.2). While language subtest scores remained stable over 90 days, recall and abstract reasoning subtest scores improved by day 7 and remained stable to day 90. When assessed with MMSE, cognitive performance was poorest in the constructional praxis and recall domains at baseline. Recall performance worsened at day 7 and then gradually improved over days 30 and 90 (Figure 3.2). Deficits in the other five cognitive domains were stable between baseline and day 90.

Four cognitive domains were directly comparable between the MoCA and MMSE – attention, language, recall and orientation. The greatest difference between the two assessments at baseline was in recall (27.5%, $p = 0.014$) and language (28.3%, $p = 0.001$) domains (Figure 3.3). At baseline, the performance in recall was only 53.3% of the maximum possible score when assessed with MoCA. In contrast, recall performance was 80.8% when assessed with MMSE. Performance in language was 66.7% with MOCA and 95.0% with MMSE ($p=0.001$, Figure 3.3). Over the following 90 days, language impairments detected by MoCA remained stable at all time points (day 7, 69.4%, day 30, 68.2%; day 90, 75.8%, $p=0.088$), but more severe than indicated by MMSE. Impairments detected by MoCA in recall however, improved substantially from baseline to day 7 (19.5% increase, $p < 0.0001$), matching MMSE scores at day 7 and onwards (Figure 3.3).

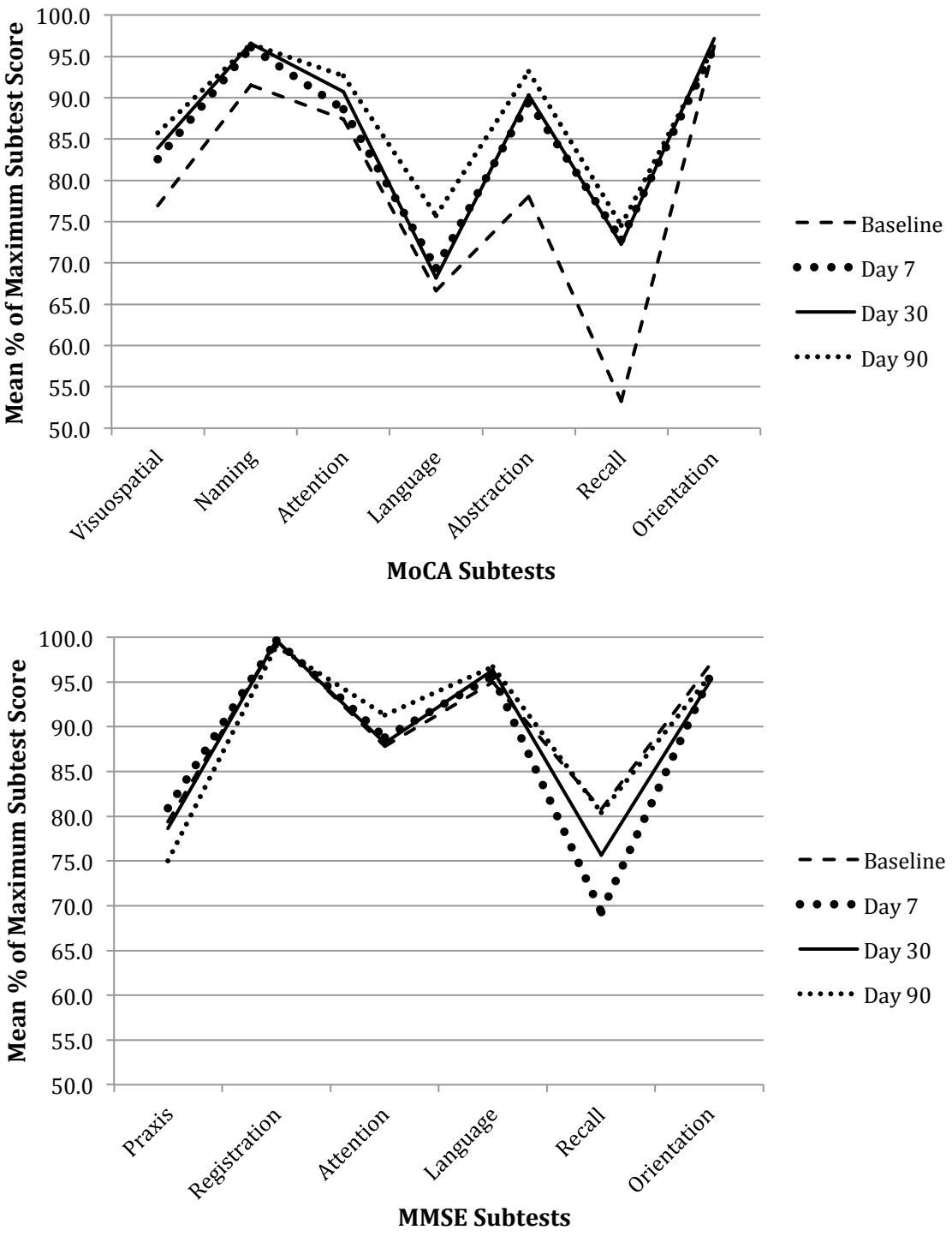


**Figure 3.2** Mean MoCA (upper figure) and MMSE (lower figure) subtest scores shown as a percentage of the maximum subtest score for all TIA/minor stroke patients at baseline, day 7, day 30 and day 90. MMSE indicates Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.

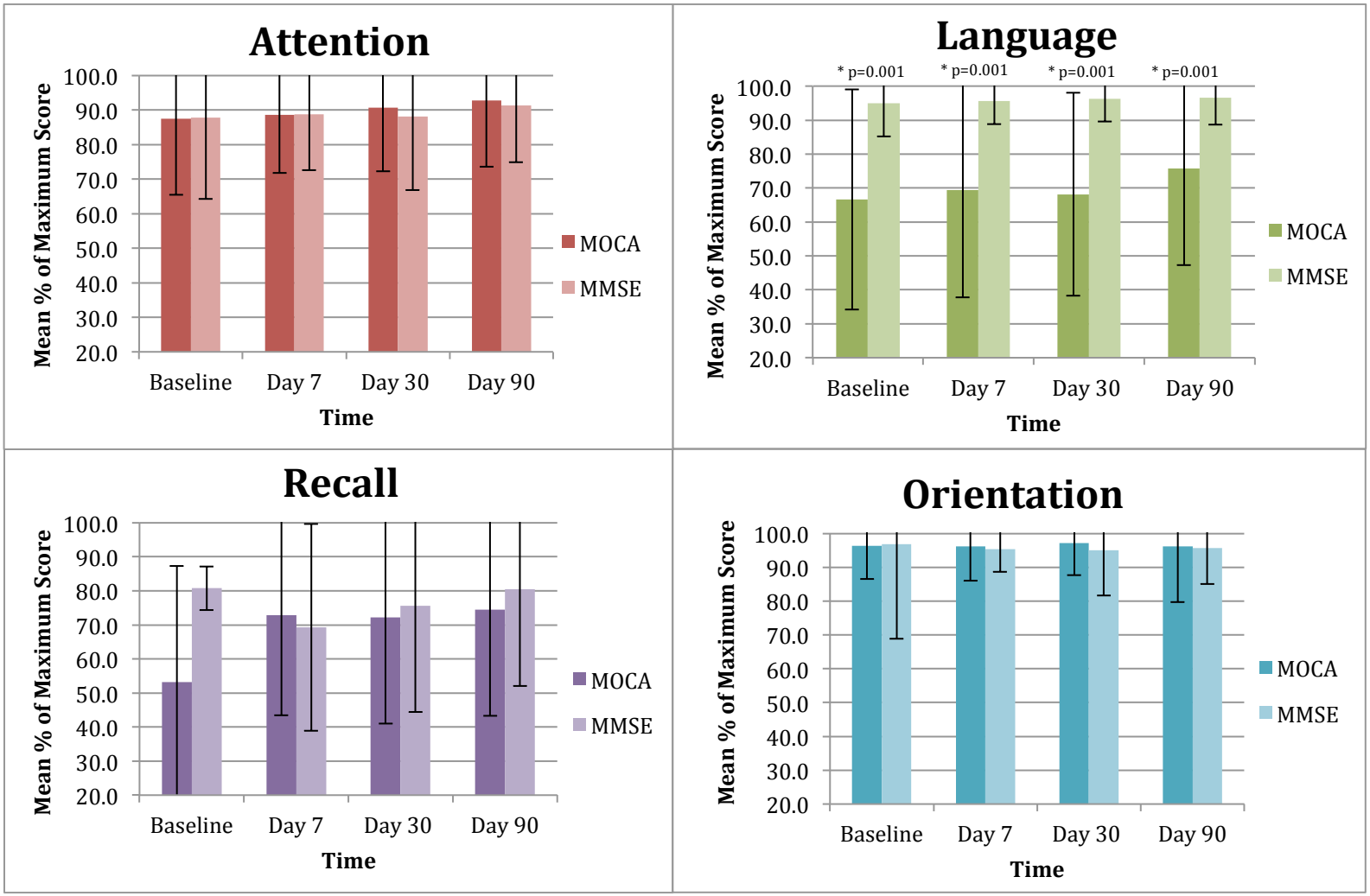


**Figure 3.3** Mean (SD) MoCA and MMSE subtest scores shown as a percentage of the maximum subtest score for all TIA/minor stroke patients in attention, language recall and orientation domains at baseline, day 7, day 30 and day 90. MMSE indicates Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.

***Resolution of Cognitive Deficits***

Patients with baseline impairment (N = 54, MoCA < 26) were then divided into 2 groups based on the improvement/worsening of cognitive function by day 30. Patients, in whom MoCA scores improved by ≥ 2 points by day 30, were defined as reverters (N = 35, 65%), as previously described.[14] Those with persisting or worse deficits by day 30 were defined as non-reverters (N = 19, 35%). Reverters improved from a baseline median (IQR) MoCA of 23(7) to 27(5) at day 30. MoCA scores in non-reverters worsened from 23(5) to 22(7) after 30 days.

A comparison of demographic characteristics showed that median (IQR) age was lower in reverters (68(19), than non-reverters (79(12), Table 3.2). Baseline neurological deficits as assessed by NIHSS were also more common in non-reverters (14/19, 74%), than in reverters (20/35, 57%; Table 3.2). Spearman's correlation indicated that NIHSS scores were significantly correlated with MoCA scores at baseline ($\varrho$=-0.517, p=0.023) and day 30 ($\varrho$=-0.514, p=0.041) in non-reverters. Reverters demonstrated significant improvements in all 7 subtests, with performance in the recall domain showing the greatest improvement (34% increase, p < 0.0001). In non-reverters, 6 out of 7 subtests remained the same after 30 days, while performance in the language domain worsened significantly (18% decrease, p=0.045, Table 3.2).

**Table 3.2: Demographic and Clinical Characteristics of Reverters and Non-Reverters**

| | Reverters N=35 | | Non-Reverters N=19 | |
|---|---|---|---|---|
| **Demographic Characteristics** | | | | |
| Age | 68 (19) | | 79 (12) | |
| Sex (male) | 17 (49%) | | 13 (68%) | |
| **Clinical Characteristics** | | | | |
| NIHSS = 0 | 15 (43%) | | 5 (26%) | |
| NIHSS = 1 | 7 (20%) | | 5 (26%) | |
| NIHSS = 2 | 7 (20%) | | 3 (16%) | |
| NIHSS = 3 | 6 (17%) | | 6 (32%) | |
| Median NIHSS (IQR) | 1 (2) | | 1 (3) | |
| **Baseline MoCA Subtests** | **Mean (SD)** | **% Score** | **Mean (SD)** | **% Score** |
| Visuospatial | 3.3 (1.5) | 66.1 | 3.1 (1.5) | 61.1 |
| Naming | 2.5 (0.8) | 82.8 | 2.6 (0.8) | 87.0 |
| Attention | 4.6 (1.7) | 72.3 | 4.7 (1.6) | 78.7 |
| Language | 1.6 (0.9) | 53.5 | 1.6 (1.1) | 53.7 |
| Abstraction | 1.2 (0.8) | 62.1 | 1.3 (0.8) | 63.9 |
| Recall | 1.9 (1.8) | 38.8 | 2.1 (1.7) | 43.3 |
| Orientation | 5.6 (0.7) | 93.9 | 5.6 (0.8) | 92.6 |
| Total | 21.0 (4.4) | | 21.1 (4.9) | |
| **Day 30 MoCA Subtests** | **Mean (SD)** | **% Score** | **Mean (SD)** | **% Score** |
| Visuospatial | 4.2 (1.0) | 83.1 | 3.4 (1.4) | 67.5 |
| Naming | 2.9 (0.3) | 96.9 | 2.6 (0.5) | 85.4 |
| Attention | 5.3 (1.1) | 88.5 | 4.5 (1.6) | 75.0 |
| Language | 2.3 (0.7) | 67.7 | 1.1 (0.7) | 35.4 |
| Abstraction | 1.8 (0.5) | 89.1 | 1.5 (0.7) | 75.0 |
| Recall | 3.6 (1.2) | 72.5 | 1.6 (1.8) | 32.5 |
| Orientation | 5.9 (0.3) | 99.0 | 5.3 (1.1) | 87.5 |
| Total | 25.8 (3.2) | | 20.1 (4.7) | |

Reverters were defined as patients with baseline impairment (MoCA <26) who showed an improvement of ≥ 2 points by day 30. Non-reverters were defined as patients with baseline impairment and persisting deficits by day 30. NIHSS indicates National Institute of Health Stroke Scale; MoCA, Montreal Cognitive Assessment; SD, Standard Deviation.

## Discussion

In this study, we have shown for the first time, a longitudinal assessment of domain specific cognitive impairment in TIA/minor stroke patients, including performance in acute stages following the event. The MoCA was more sensitive to language deficits, which were consistently present over the first 90 days. Memory deficits detected with MoCA at baseline, improved over time. Cognitive function in patients with persisting impairment after 30 days was significantly correlated with baseline neurological deficits.

Five studies have assessed the sensitivity of neuropsychological assessments to overall and domain specific cognitive impairments following TIA/minor stroke.[7-10, 15] These studies have primarily been cross-sectional, rather than longitudinal and none assessed cognitive function post acute TIA. No previous study has used serial assessment to examine the temporal profile of domain specific cognitive impairments following TIA/minor stroke.

Studies applying the MoCA are broadly consistent with our results. Pendlebury et al. assessed 413 patients with TIA or stroke at either 6-month or 5-year follow-ups using a cutoff score <26 to indicate impairment in both MoCA and MMSE.[7] According to MoCA, 291 (70%) patients were cognitively impaired, of whom 162 (56%) had normal MMSE scores. MMSE detected impairments in only 30% of all patients. A similar study by Dong et al. assessed 100 patients at a mean of 4.2±2.4 days post stroke.[9] Deficits detected by MoCA were present in 59% of patients,

while only 43% were impaired according to MMSE. In another study, 91 patients were administered the MMSE and MoCA ≥ 1 year after TIA or stroke.[8] The MoCA identified mild cognitive impairment with good sensitivity and specificity, whereas MMSE scores were consistently skewed toward higher values. The MMSE may be able to identify deficits in patients with more severe strokes.

Three cross-sectional studies have assessed domain specific changes in cognitive function following TIA and stroke.[7, 9, 15] Pendlebury et al. assessed patients with TIA (n=156) or stroke (n=207) at 6 months or more after symptom onset.[15] TIA subjects performed better that stroke patients on only one MMSE subtest versus six MoCA subtests (visuoexecutive tasks, attention, verbal fluency, abstraction, recall and orientation). In TIA patients, MoCA detected subtle deficits in recall and verbal fluency domains, areas were less impaired when assessed with the MMSE. In another study from the same group, 413 TIA/stroke patients were assessed 6 months or 5 years post-event.[7] The MoCA demonstrated deficits in executive function, attention, recall and repetition, which were not detected by the MMSE. Finally, Dong et al. compared the ability of MoCA and MMSE domain subtests scores to classify cognitive patterns in 100 patients with acute ischemic stroke or TIA within 14 days.[9] Based on baseline MoCA and MMSE cognitive screening scores, patients were divided into 3 groups: acute vascular cognitive impairment no dementia (VCIND) moderate (screened positive for both MoCA and MMSE), acute VCIND mild (positive for either MoCA or MMSE), and no cognitive impairment (negative for both MoCA and MMSE). The MMSE domain

subtest scores did not differentiate between these three groups. In contrast, MoCA subtest scores in visuospatial/executive function, attention and recall domains did.

Previous studies indicate that the MoCA is more difficult than the MMSE, which likely improves sensitivity for mild cognitive deficits in certain domains.[7, 9, 12] This is likely particularly relevant in the TIA/minor stroke population, where cognitive changes are very subtle. To test for attention, the MMSE uses only the serial 7's task, but the MoCA includes two additional tests (digit span and vigilance) for the same domain. The MoCA memory testing questions are more challenging, with more words, fewer learning trials, and a longer delay before patients are asked to recall. The MoCA also uses more tasks to thoroughly assess executive function, language abilities, and visuospatial processing. It is likely that these differences contributed to MoCA's higher overall sensitivity to acute impairment, as well as domain specific changes in memory and language in our patients.

Reverter status in TIA/minor stroke patients may be explained by the presence of baseline neurological deficits. The increased presence and severity of neurological deficits observed at baseline in non-reverters may have played a role in suppressing certain cognitive domains and affecting improvement over time. It would be useful to utilize magnetic resonance imaging (MRI) to compare the presence and extent of tissue injury between reverters and non-reverters. Reversion of cognitive impairment may have been related to the localization of acute lesions, affecting strategic regions of cognitive function more so in non-reverters than in reverters.

This study contains several important limitations. We used identical versions of the MoCA test at each time point, since alternate forms were not available at the time of study inception. It its possible that patients may have learned aspects of a task, contributing to the development of a learning curve. Modifying the details of certain tasks such as recall words and repetition sentences would help minimize learning effects. It is also important to recognize that cognition can be affected by different states of mood (i.e. fatigue, depression), both of which are common post-TIA/stroke.[16-18] Considering when cognitive assessments were completed (time of day/beginning vs. end of the visit), fatigue may have resulted in decreased capacity to sustain an effort, increasing the likelihood of error. Finally, language barriers may have hindered the patient's ability to thoroughly understand certain tasks, contributing to increased error.

## Conclusion

Assessment with the MoCA reveals greater cognitive impairments than the MMSE in the acute stages following TIA/minor stroke. Deficits are primarily in the memory and language domains. While memory deficits improved over time, language remained significantly impaired. Baseline neurological deficits were significantly correlated with cognitive function in patients with persisting cognitive impairment. These findings are relevant to TIA/minor stroke patient disposition and advice with respect to vocation, driving and activities of daily living.

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# Chapter 4:

# Temporary Cognitive Impairment in Transient Ischemic Attack and Minor Stroke Patients is Predicted by Chronic White Matter Hyperintensity Volume

## Introduction

Although neurological assessment of stroke patients is generally focused on motor deficits, cognitive impairment can also result in significant disability. Up to 25% of stroke survivors meet the criteria for dementia within 12 months of an ischemic event.[1, 2]Cerebrovascular disease and vascular risk factors including hypertension, diabetes and cholesterol are each independently associated with an increased risk of cognitive impairment and dementia.[3-5] While cognitive changes in patients with larger strokes have been well described,[6] much less is known about cognition in the acute period after TIA/minor stroke.

In TIA patients, symptoms are by definition considered temporary, but cognitive impairments have been identified in some studies after initial focal symptoms have resolved.[7-9] Chronic microvascular changes have been associated with an increased risk of vascular cognitive impairment following TIA/minor stroke.[10, 11]Cognitive deficits have been identified following TIA/minor stroke,[7-9, 12] but it is unclear if these symptoms improve with time. It is also unknown if these cognitive changes are correlated with the presence and extent of acute tissue infarction.

Using serial MRI and neuropsychological screening, we aimed to assess imaging abnormalities and temporal patterns of cognitive changes in acute TIA/minor stroke patients. We tested the hypothesis that ischemic injury identified with diffusion-weighted imaging (DWI) is predictive of changes in acute cognitive deficits. We also hypothesized that cognitive changes in these patients are temporary.

## Methods

### *Patients*

Acute TIA/minor ischemic stroke patients with a National Institute of Health Stroke Scale (NIHSS) score ≤ 3 at admission, aged 18 years or older were recruited within 72 hours of symptom onset. Stroke mimics (such as seizures, migraine), intracranial hemorrhage, pre-existing dementia, severe aphasia (NIHSS score >1 on item 9) and contraindications to MRI were all considered exclusion criteria. Our local human research ethics board approved the protocol and written informed consent was obtained from all patients.

### *Imaging Protocol*

All patients were initially screened with a non-contrast CT scan of the brain. MR imaging was performed within 72 hours of TIA/mild ischemic stroke and repeated at day 7 and day 30. The MRI protocol consisted of a T1-weighted sagittal localizer, time of flight MRA, gradient recalled echo (GRE), and diffusion weighted images (DWI), including Fluid-Attenuated Inversion Recovery (FLAIR) sequences. Patients were imaged using an 8-channel phased array radiofrequency head coil (MRI Devices, Waukesha, WI) on a 1.5-

T whole-body Siemens Sonata MRI scanner (Siemens Medical Systems, Erlangen, Germany). DWI was acquired with single-shot spin-echo diffusion echo planar imaging, 220-mm field of view, 20 5-mm axial slices with a 1.5-mm gap, b value of 1000 s/mm2 along 3 orthogonal directions, repetition time/echo time 2600/86 msec, GRAPPA R=2, and matrix size of 128x128 zero- filled to 256x256. Apparent diffusion coefficient (ADC) maps were calculated using the Stejskal-Tanner equation from raw DWI images.[13]

***Image Analysis***

The volume of acute ischemic lesions was measured on DWI sequences at baseline and day 7, using standard planimetric techniques (Analyze software package, Biomedical Imaging Resource, Mayo Clinic). Chronic lesion volumes were measured on day 30 FLAIR sequences. Signal intensity within the lesion was calculated for ADC at each time point, using contralateral normal values to determine relative ADC (rADC = ischemic ADC / contralateral ADC). User-assisted threshold based planimetric techniques were used to measure white matter hyperintensity (leukoaraiosis) included in the Quantomo software package (Cybertrial, Calgary). The Fazekas scale was also used to evaluate the presence and severity of chronic white matter changes on FLAIR sequences obtained at day 30.

***Clinical Assessment***

All patients were assessed clinically at the time of the baseline MRI scan, day 7, day 30 and day 90. On each visit, Modified Rankin (mRS) and NIHSS were recorded as well as Folstein's Mini Mental State Examination (MMSE), Montreal Cognitive Assessment

(MoCA), and the Glasgow Coma Scale (GCS). Identical versions of the MoCA were administered at all time points while each MMSE version differed with respect to two test items (recall and drawing). Cognitive impairment was defined as MoCA <26.[14, 15]

### *Statistical Analysis*

All statistical analyses were performed using the Statistical Package for Social Sciences version 20.0.0 (SPSS Inc., 2007). The intraclass correlation coefficient was calculated to assess inter-rater reliability for DWI lesion volume measurements. Changes in acute and chronic lesion volumes, rADC values, and MoCA scores were evaluated using related sample analysis of variance by ranks and post hoc pairwise comparisons. Stepwise multiple linear regression was used to identify independent predictors of cognitive change after 30 days. Linear regression was used to assess the relationship between ischemic lesion volumes, leukoaraiosis volumes and MoCA scores.

## Results

### *Patient Characteristics*

A total of 105 patients were enrolled in the study. Five patients were excluded, most commonly due to the presence of pre-existing dementia, determined after enrollment. Baseline demographic and clinical characteristics of the 100 patients included are summarized in Table 4.1. Of the 100 patients included, the median (IQR) age was 65(18) and 67% of the patients were male. The median (IQR) time to baseline imaging was 26.5 (28.5) hours after onset. Baseline median NIHSS and GCS scores were 1(2) and 15(1) respectively.

**Table 4.1: Baseline Patient Characteristics**

| **Characteristic** | |
|---|---|
| Age, years (IQR) | 65 (18) |
| Sex (male) | 67 (67%) |
| **Admission Assessments** (IQR) | |
| GCS | 15 (1) |
| NIHSS | 1 (2) |
| **Neuropsychological Assessments** (IQR) | |
| MoCA Impaired (<26) | 54 (54%) |
| **MRI Imaging** | |
| Ischemic lesion present | 76 (76%) |
| Chronic white matter changes present | 62 (62%) |
| **Leukoaraiosis (Fazekas Scale)** | |
| Absent (rating = 0) | 38 (38%) |
| Mild (rating = 1) | 51 (51%) |
| Moderate (rating = 2) | 10 (10%) |
| Severe (rating = 3) | 1 (1%) |
| **DWI Lesion Location** | |
| Cortical | 18/76 (24%) |
| Subcortical | **27/76 (36%)** |
| Cortico-Subcortical | 22/76 (29%) |
| Brainstem/Cerebellum | 9/76 (12%) |
| **DWI Lesion Location (Lobar)** | |
| Frontal | **47/76 (62%)** |
| Parietal | 19/76 (25%) |
| Temporal | 15/76 (20%) |
| Occipital | 6/76 (8%) |
| Deep Grey Matter | 12/76 (16%) |

IQR indicates inter-quartile range; GCS, Glascow Coma Scale; NIHSS, National Institute of Health Stroke Scale; DWI, diffusion-weighted imaging; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging.

### *Tissue Injury and Cognitive Impairment*

Acute ischemic lesions were present in 76 (76%) patients assessed within 72 hours of symptom onset. The most common locations of the acute lesions were cortical (frontal lobe; N=47, 62%) and subcortical (N=27, 36%; Table 4.1). Median (IQR) ischemic DWI lesion volume at baseline and day 7 was 0.87(2.9) mL and 0.57(1.8) mL respectively.

Median chronic FLAIR volume calculated at day 30 was 0.48(2.3) mL. Intraclass correlation coefficients for lesion volume measurements was 0.406 (0.20-0.58, p<0.0001).Friedman's ANOVA on ranks indicated that volumes were stable over time (p=0.074). The rADC at baseline, day 7 and day 30 was 0.86 (0.24), 0.93 (0.12), 1.08 (0.19) respectively, showing a significant gradual increase between baseline and day 30 (p<0.0001, Figure 4.1).

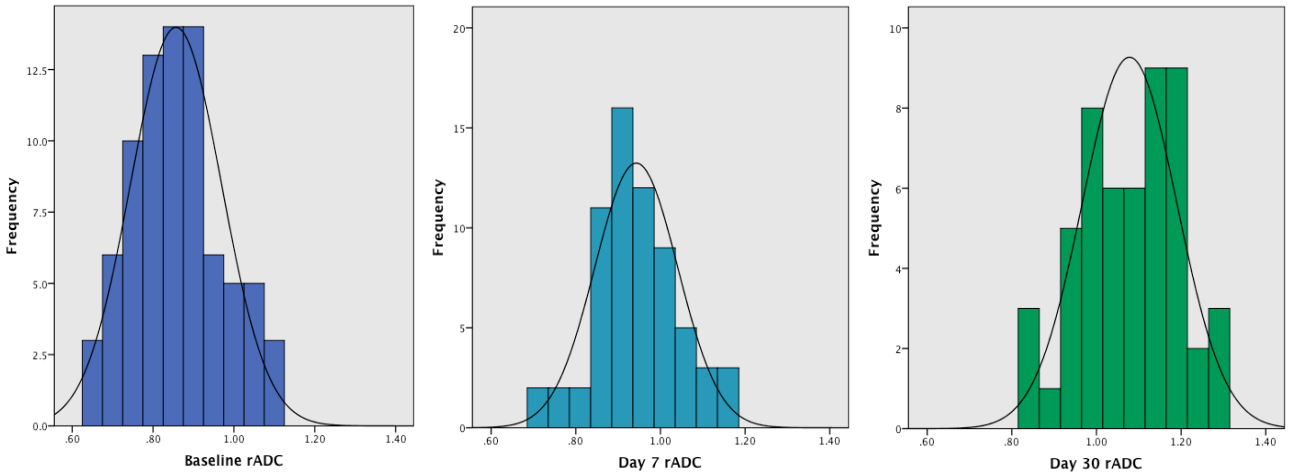


**Figure 4.1** Distribution of rADC (ischemic ADC/contralateral ADC) in patients at baseline, day 7 and day 30. rADC indicates relative apparent diffusion coefficient; ADC, apparent diffusion coefficient.

Chronic white matter changes (leukoaraiosis) were present in 64 (64%) patients. According to the Fazekas scale, leukoaraiosis was mild in 51 (51%) patients, moderate in 10 (10%) patients and severe in 1 (1%) patient (Table 4.1). Median (IQR) leukoaraiosis volume was 2.64 (9.2) mL. At baseline, the median MoCA score was 25(4). Over the following 90 days, MoCA scores were 27(5), 28(3) and 28(3) at days 7, 30 and 90 respectively.

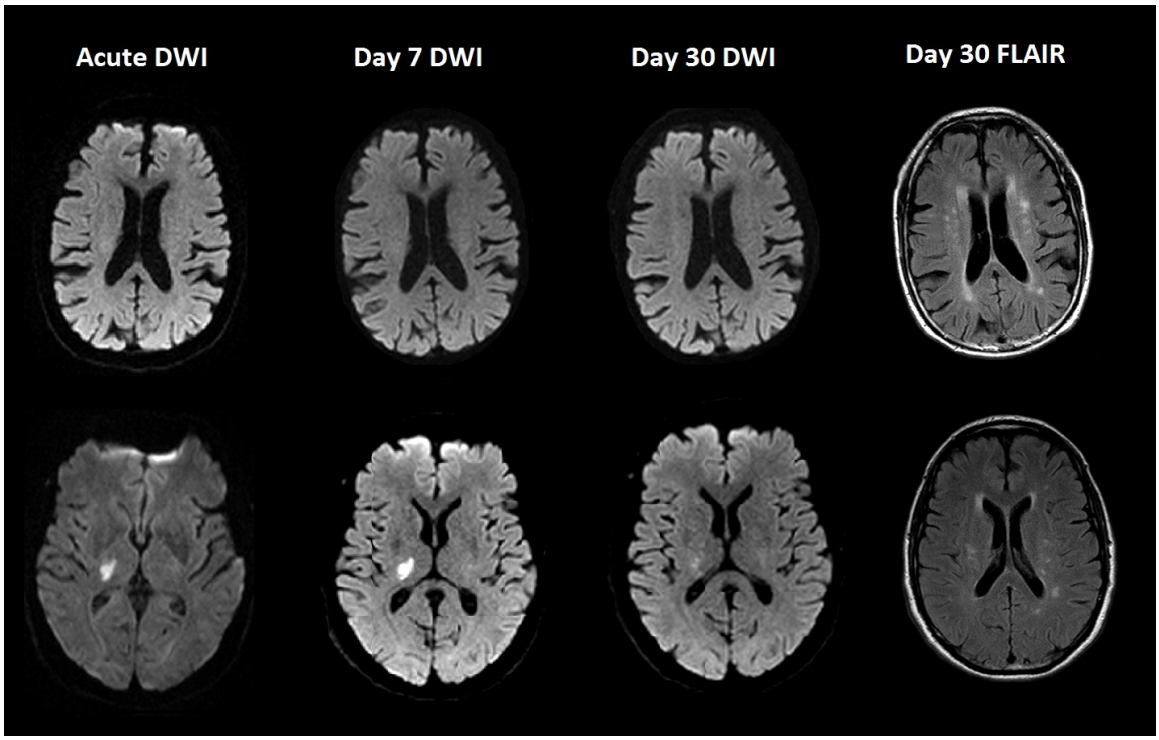


**Figure 4.2** DWI and FLAIR MRI scans in two TIA/minor stroke patients over 30 days following symptom onset. Patient 1 (top row): negative DWI, impaired baseline MoCA (24); Patient 2 (bottom row) positive DWI, unimpaired at baseline MoCA (27). Both patients show evidence of leukoaraiosis on day 30 FLAIR sequences.

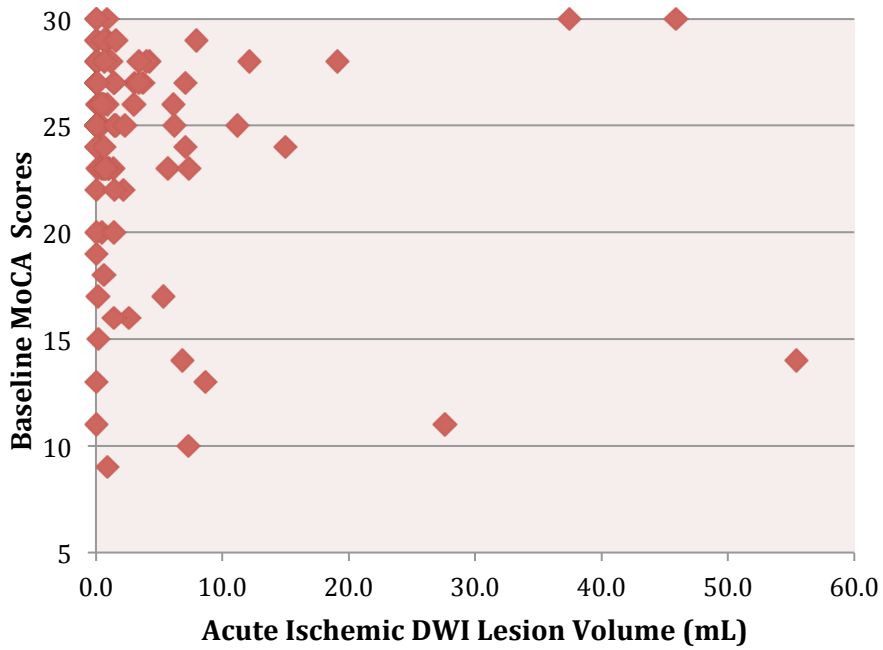


**Figure 4.3** Acute ischemic DWI lesion volume demonstrates no significant relationship to patient MoCA scores at baseline. DWI indicates diffusion-weighted imaging; MoCA, Montreal Cognitive Assessment.

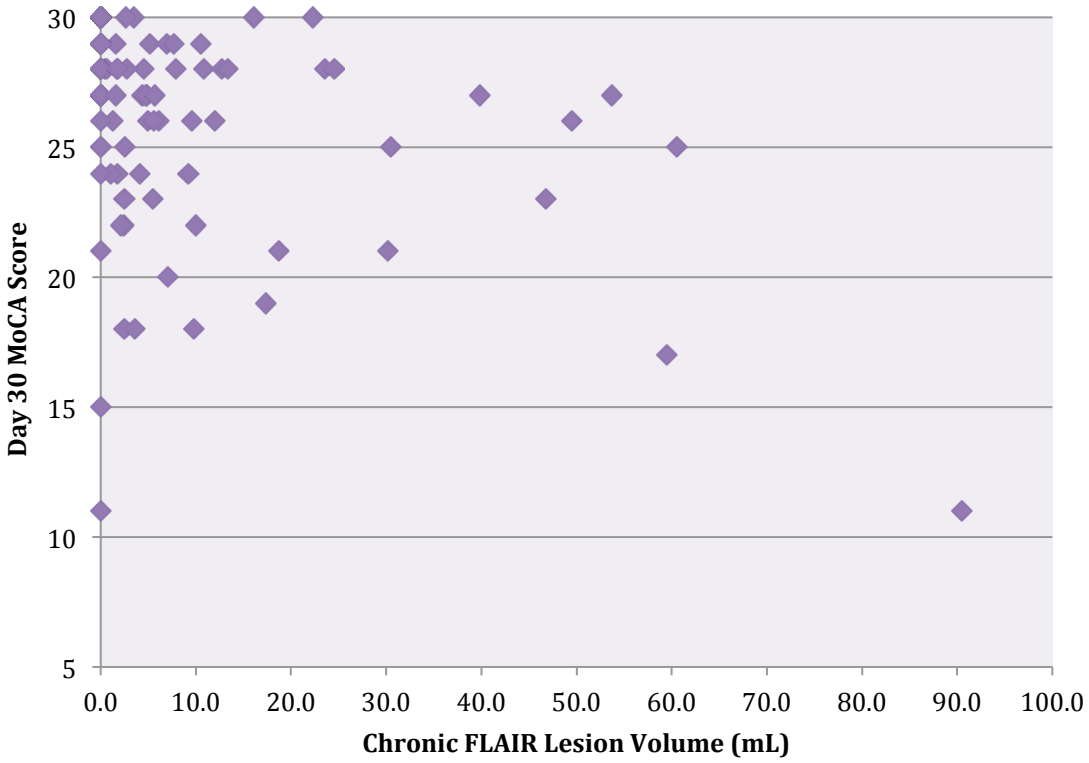


**Figure 4.4** Chronic day 30 FLAIR lesion volume demonstrates no significant relationship to patient MoCA scores at day 30. FLAIR indicates fluid attenuated inversion recovery; MoCA, Montreal Cognitive Assessment.

The proportion of patients with cognitive impairment was similar in those with (42/76, 55%) and those without DWI lesions (12/24, 50%; p=0.34; Figure 4.2). Linear regression indicated no relationship between acute ischemic DWI lesion volume and baseline MoCA scores (β = -0.146, [-0.179, 0.031], p=0.162; Figure 4.3). Regression analysis also indicated and insignificant relationship between chronic FLAIR volumes and day 30 MoCA scores (β = -0.89, [-0.231, 0.100], p=0.434; Figure 4.4). Chronic leukoaraiosis volumes however predicted MoCA scores at baseline (β = -0.332,95% CI [-0.152, -0.041], p = 0.001) and day 30 (β =-0.519, [-0.160, -0.077], p<0.0001; Figure 4.3).

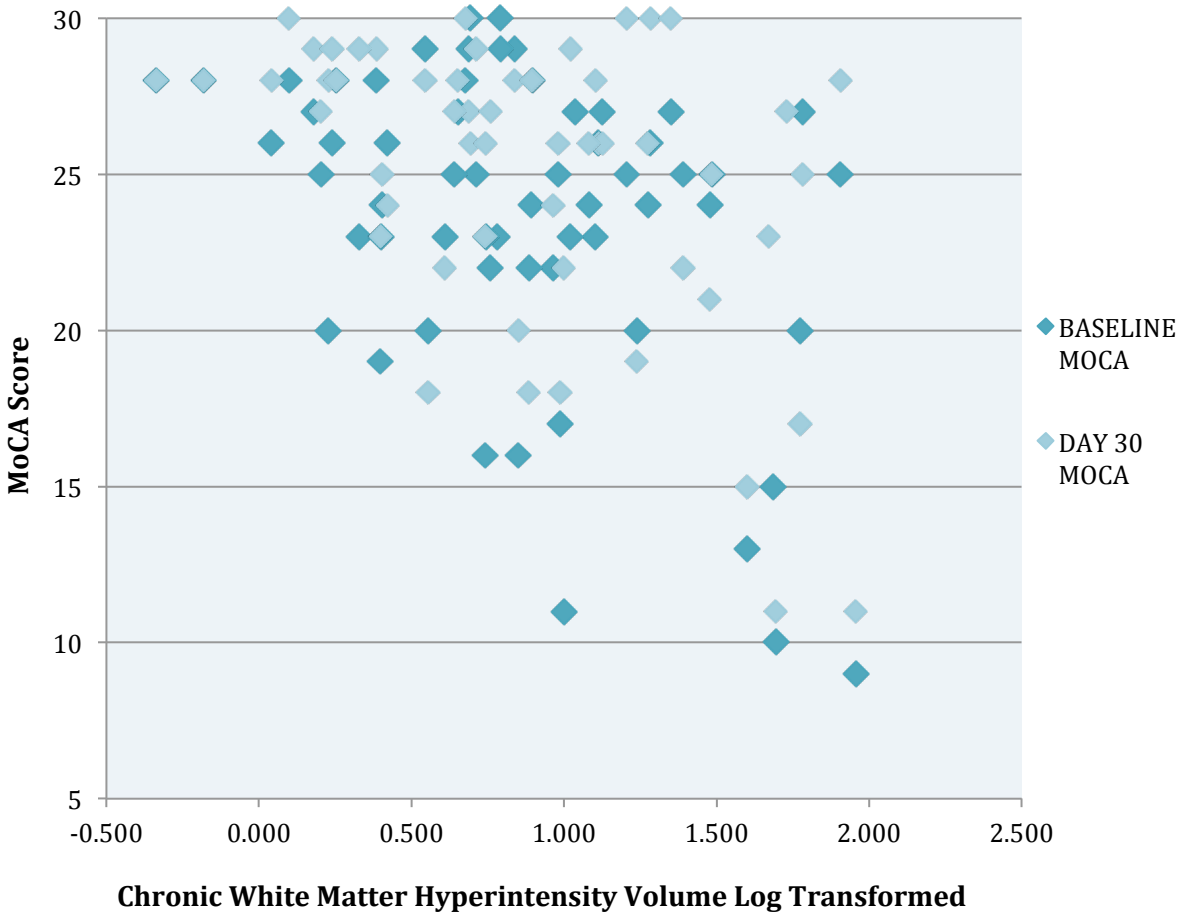


**Figure 4.5** Chronic white matter hyperintensity volume (log transformed) significantly predicts MoCA scores in patients at baseline and day 30. MoCA indicates Montreal Cognitive Assessment.

### *Temporal Pattern of Cognitive Changes*

Patients were divided into 3 groups based on changes in cognitive assessed by MoCA over time (Table 4.2). Reverters, or patients demonstrating transient cognitive impairment (N=35, 35%), were defined as those with baseline deficits (MoCA < 26), and improvement of ≥ 2 points by day 30 MoCA, as previously described.[7]Median MoCA scores in these patients improved from 23(7) at baseline to 27(5) at day 30. Non-

reverters, or patients demonstrating permanent cognitive impairment (N=19, 19%), were defined as those with baseline deficits and no change or improvement of <2 points by day 30 MoCA. Median MoCA scores in these patients were 23(5) at baseline and 22(7) at day 30. The final group consisted of patients with no cognitive impairment (N=46, 46%), whose MoCA scores were 27 (1) at baseline and 28 (3) at day 30.

Patients without impairment were younger than reverters, who were in turn younger than non-reverters (Table 4.2). Age did not predict reversion. Median age was significantly different between non-reverters and patients with no impairment ($p<0.0001$) as well as between non-reverters and reverters ($p=0.018$). Age was a significant predictor of cognition at day 30 in non-reverters ($\beta=-0.523$, [-0.413, -0.014], $p=0.038$), but not in reverters ($\beta=-0.302$, [-0.161, 0.013], $p=0.093$) or patients with no impairment ($\beta=-0.240$, [-0.064, 0.008], $p=0.127$).

***Ischemic Lesions and Temporal Pattern of Cognitive Changes***

The frequency of DWI lesions was similar in reverters (N=26, 74%), non-reverters (N=16, 84%) and patients with no cognitive impairment (N=34, 74%; $\chi^2 = 0.868$, $p=0.648$). In all three groups, lesions were primarily located in the frontal cortex or subcortically (Table 4.2). Frontal lobe lesions were more frequently observed in non-reverters (86%) than in reverters (48%; $\chi^2=4.29$, $p=0.038$). Acute lesion volumes were unrelated to baseline MoCA scores in non-reverters ($\beta=-0.116$, [-1.137, 0.726],$p=0.647$) and reverters ($\beta=-0.273$, [-0.312; 0.042], $p=0.131$).

**Table 4.2: Clinical and Imaging Characteristics of Reverters and Non-Reverters**

| | Reverters N= 35 | Non-Reverters N=19 | No Impairment N=46 |
|---|---|---|---|
| **Baseline Characteristics** | | | |
| Age (IQR) | 68 (16) | 76 (13) | 63 (13) |
| Sex (male) | 14 (45%) | 13 (77%) | 37 (80%) |
| NIHSS on Admission | 1 (2) | 1 (2) | 1 (3) |
| **Imaging Characteristics** | | | |
| DWI Positive (%) | 26 (74%) | 16 (84%) | 34 (74%) |
| Acute DWI Lesion Vol (mL) | 0.89 (5.4) | 0.85 (1.2) | 0.87 (3.3) |
| Day 30 FLAIR Vol (mL) | 0.30 (2.4) | 1.16 (10.4) | 0.48 (2.7) |
| Leukoaraiosis Present (%) | 22 (63%) | 16 (84%) | 24 (52%) |
| Leukoaraisosis Volume (mL) | 4.76 (10.0) | 3.82 (17.3) | 1.10 (4.8) |
| **Leukoaraiosis (Fazekas Scale)** | | | |
| Absent (rating = 0) | 12 (34%) | 2 (13%) | 22 (48%) |
| Mild (rating = 1) | 18 (51%) | 11 (69%) | 23 (50%) |
| Moderate (rating = 2) | 4 (11%) | 4 (25%) | 1 (2%) |
| Severe (rating = 3) | 0 | 1 (6%) | 0 |
| **DWI Lesion Location** | | | |
| Cortical | **6/26 (23%)** | **5/16 (31%)** | 7/34 (21%) |
| Subcortical | **9/26 (35%)** | **6/16 (38%)** | 12/34 (35%) |
| Cortico-Subcortical | 7/26 (27%) | 4/16 (25%) | 11/34 (32%) |
| Brainstem/Cerebellum | 3/26 (12%) | 2/16 (13%) | 4/34 (12%) |
| **DWI Lesion Location (Lobar)** | | | |
| Frontal | **12/26 (46%)** | **12/16 (63%)** | 23/34 (68%) |
| Parietal | 4/26 (15%) | 6/16 (38%) | 9/34 (26%) |
| Temporal | 5/26 (19%) | 2/16 (13%) | 8/34 (24%) |
| Occipital | 2/26 (8%) | 2/16 (13%) | 2/34 (6%) |
| Deep Grey Matter | 5/26 (19%) | 1/16 (6%) | 6/34 (18%) |
| **Neuropsychological Testing** | | | |
| Baseline MoCA | 23 (7) | 25 (3) | 27 (1) |
| Day 7 MoCA | 26 (5) | 24 (50 | 29 (2) |
| Day 30 MoCA | 27 (5) | 24 (4) | 28 (3) |

Reverters defined aspatients with baseline impairment (MoCA <26), whose scores improved by ≥ 2 points by day 30. Non-reverters defined as patients with baseline impairment and persisting deficits. IQR indicates inter-quartile range; NIHSS, National Institute of Health Stroke Scale; DWI, diffusion-weighted imaging; MoCA, Montreal Cognitive Assessment.

Leukoaraiosis was present in 63% (N=22) of reverters, 84% (N=16) of non-reverters and 52% (N=24) of patients with no cognitive impairment ($\chi^2$=0.8.03, p=0.018). Median (IQR) leukoaraiosis volume was lower in reverters (4.37 (10.5) mL) than in non-reverters (9.56 (27.6) mL, p=0.04). Leukoaraiosis volume was not a significant predictor of day 30

MoCA scores in reverters (β=-0.171, [-0.096, 0.035], p=0.349) or patients with no impairment (β=-0.295, [-0.090, 0.002], p=0.058; Figure 4.6). In non-reverters however, leukoaraiosis volumes significantly predicted MoCA scores at day 30 (β=-0.714, [-0.203, -0.057], p=0.002; Figure 4.6). The stepwise multiple regression model indicated that both leukoaraiosis volume (β=-0.296, [-0.291, 0.049]) and age (β=-0.603. [-0.185, -0.034]) were significant independent predictors of cognition at day 30 (p=0.003) and together accounted for 58.5% ($R^2 = 0.585$) of the variance in MoCA scores.

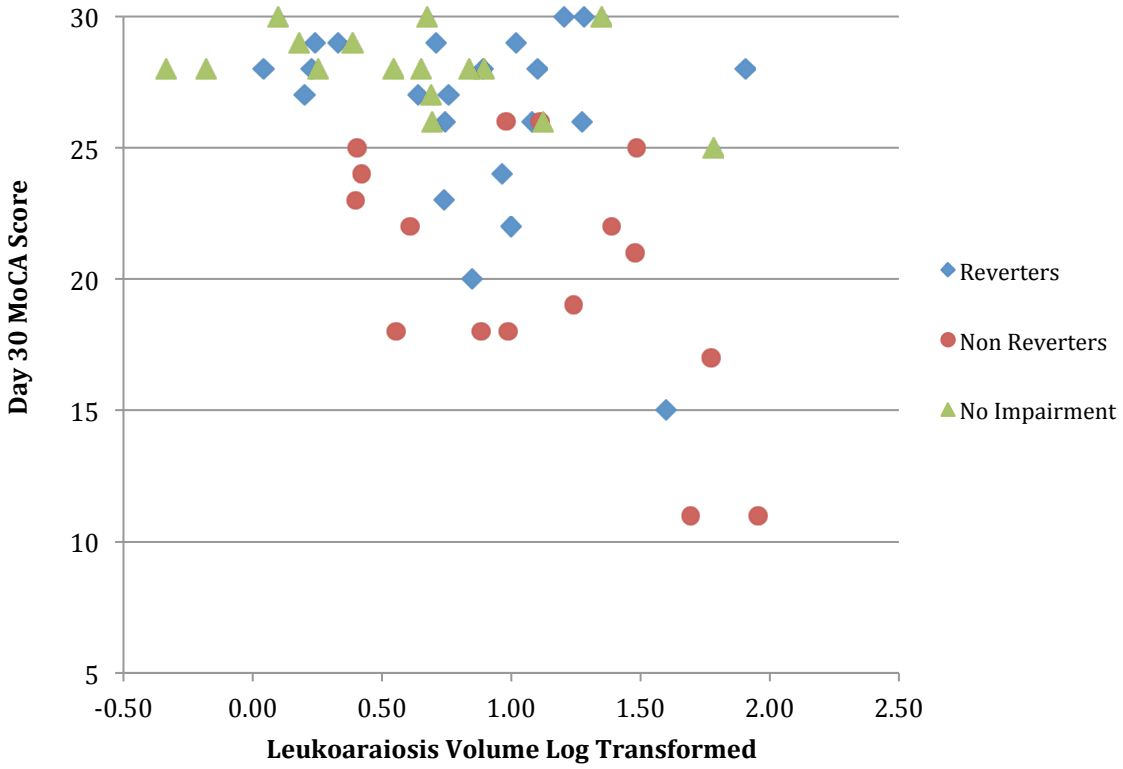


**Figure 4.6** Leukoaraiosis volumes (log transformed) and observed day 30 MoCA scores. Leukoaraiosis volumes significantly predicted day 30 MoCA scores in non-reverters. MoCA indicates Montreal Cognitive Assessment.

## Discussion

In this study, we have confirmed that cognitive impairment is common after TIA/minor stroke. For the first time, we have demonstrated that in the majority of patients, cognitive deficits are transient, resolving within 30 days of the event. Contrary to our original hypothesis, cognitive deficits were not predicted by DWI lesion presence or volume, but rather by chronic white matter disease burden. Age and greater chronic white matter disease burden also predicted persistent cognitive impairment.

### *Cognitive impairment following stroke*

Most studies of post TIA/stroke cognition have delayed assessment until after the acute phase of the illness. Sachdev et al,[12] assessed 170 patients with stroke or TIA 3 to 6 months post stroke. They found that cognitive impairment was correlated with chronic WMHs, but not with volume or number of discrete cerebral infarcts on T2-weighted MRI. This is consistent with our own findings that even the acute lesion volume, imaged with DWI, did not predict cognitive changes at any time point. Furthermore, we have found that the volume of chronic WMH predicts both transient and persistent cognitive deficits, when patients are assessed more acutely.

It is known that chronic white matter changes are related to cognitive impairment.[16-18] White matter lesions likely affect cortical connectivity by diminishing the efficiency of neural transmission, resulting in cognitive dysfunction.[19, 20] Our findings suggest that TIA/minor stroke may unmask subclinical cognitive impairment. Although we do not have pre-stroke/TIA cognitive assessments, the fact that in most patients, cognitive

changes are a transient phenomenon suggests an interaction of this type. Resolution of cognitive deficits after TIA/minor stroke has been reported previously, but only after one year.[21] Our results indicated these changes are much more transient, with restoration of normal cognitive function within 30 days.

***Reversion of cognitive impairment following stroke***

In our study, TIA/minor stroke patients with transient cognitive impairment had lower WMH volume than non-reverters. This is consistent with the results of a study by Williamson et al, who assessed cognition in 31 ischemic stroke patients at baseline (3-6 months post stroke) and 1-year post stroke.[21] In this study, 45% of patients reverted from vascular cognitive impairment to no cognitive impairment after 12 months. No differences in stroke severity, lesion volume or total number of lesions between patients who reverted and those who did not were observed.

Williamson et al. did report that a greater frontal white matter hyperintensity load was present in the non-reverter group. In our study, we also observed that non-reverters were more likely to have ischemic lesions in the frontal cortex. These finding are consistent with the hypothesis that frontal-subcortical pathology is the major deteriorative process in vascular cognitive impairment.[22, 23]There are five parallel circuits that link the frontal lobe to subcortical structures and are crucial to cognitive performance.[24] Presumably, damage at any point in these circuits leads to significant cognitive deficits. It is possible that the ischemic lesions present in non-reverters were located in areas critical to these pathways, disrupting communication with subcortical structures to cause persistent cognitive

deficits. A much larger MRI and cognitive study will be required to confirm this hypothesis however. Diffusion tensor imaging (DTI) studies of white matter tract integrity may also be useful in this patient population.[25] A serial DTI study indicated that white matter integrity improves over time following stroke.[26] A longitudinal analysis of white matter tract integrity may be useful in determining whether reverters and non-reverters may be differentiated based on how white matter tract integrity.

### *Limitations*

The main limitation of this study is its relatively small sample size. Furthermore, by administering identical versions of the MoCA test at each time point, a learning curve may have developed with some patients. Post-stroke fatigue may have also resulted in decreased capacity to sustain an effort, increasing the likelihood of error. Regardless of the precise underlying etiology, we still consider these to be post-stroke cognitive deficits that are relevant to patient disposition and management.

## Conclusion

Assessment of acute TIA/minor stroke patients with the MoCA indicates that temporary acute cognitive impairment is common. Our data suggests that changes in cognitive performance are correlated with chronic white matter hyperintensity volume and age. These temporary cognitive deficits should be considered in the management of TIA/minor stroke patients.

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# Chapter 5:

# Conclusions

The overall aim of the investigations described in this thesis was to assess the natural history of cognitive performance after TIA/minor stroke. We also sought to identify clinical and imaging predictors of improvement or worsening of cognitive function over the first 90 days after the event. The current literature is limited to cross-sectional studies that have only measured cognitive impairments in TIA/minor stroke patients as later time points ranging from one week to one year following the event.[1-3] No longitudinal changes of cognition in this population have been previously published. There are also no studies assessing the importance of both acute and chronic ischemic changes based on objective magnetic resonance imaging (MRI) findings.

## Assessment of Cognitive Impairment

Cognitive function is often compromised after stroke, but is rarely assessed in acute stroke trials. Assessments of cognitive function usually involve the use of different batteries of neuropsychological tests. Two commonly utilized tests in cognitive screening for acute stroke include the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State examination (MMSE), which is currently considered the clinical standard. We therefore compared the utility of the MoCA and the MMSE to detect cognitive impairments over 90 days following transient ischemic attack (TIA)/minor stroke. We hypothesized that the MoCA would be a

more sensitive tool for detecting mild cognitive impairment following TIA/minor stroke. For the first time, we showed that the MoCA was superior to the MMSE in tracking cognitive deficits and recovery in cognition over time. Unlike the MMSE, the MoCA was more sensitive to mild cognitive deficits following TIA/minor stroke. Cognitive scores determined by the MMSE plateaued at a maximum score, demonstrating a ceiling effect, which limited the MMSE from showing improvement over time.

We also described for the first time, cognitive domain specific changes over 3 months following TIA/minor stroke. When assessed at baseline, cognitive deficits were primarily evident in language and recall domains. Over the 90 days, improvement in overall cognitive function was attributed to significant improvements seen in the recall domain, while the language domain remained impaired. We also demonstrated that the MoCA can be used to track these minor improvements, while MMSE domain scores demonstrate a ceiling effect. This study also showed that the presence of baseline neurological deficits (measured by the National Institute of Health Stroke Scale), were significantly correlated with the temporal pattern of cognition in those patients who demonstrated persistent cognitive deficits.

These findings are relevant to the methods used to screen for mild cognitive impairment in TIA/minor stroke patients. We have shown that these symptoms are subtle, but common and may have implications for the timing of patient

disposition including return to work, driving and independent living. While detailed neuropsychological testing represents the gold standard in identifying cognitive impairment, these may not be ideal or practical in stroke patients, in whom extensive neuropsychological batteries are poorly tolerated and resource intensive. Although previous cross-sectional studies have suggested that the MoCA is more sensitive to cognitive impairment than the MMSE,[4-7] our data also indicates that the MoCA is superior to the MMSE in detecting trends of recovery (or lack thereof) in cognitive function. The MoCA should therefore be considered the more useful tool to include in future studies of post stroke cognitive impairment.

## Imaging Correlates of Cognitive Impairment

In this study, all stroke/TIA patients were assessed with serial MRI scans at the time of each cognitive assessment. Acute ischemic lesions identified by diffusion weighted imaging (DWI) and chronic white matter hyperintensities (WMH), were assessed as significant predictors of changes in cognitive impairment in TIA/minor stroke patients. We hypothesized that ischemic DWI lesions would be predictive of cognitive deficits in this patient populations. Contrary to our hypothesis, cognitive deficits were predicted by the volume of chronic white matter disease and not by the presence or volume of ischemic DWI lesions. Compared to TIA/minor stroke patients demonstrating transient cognitive impairment, those who remained persistently impaired had a higher WMH load and were also more likely to have frontal lobe lesions.

Our findings have implications for the management of TIA/minor stroke patients. Leukoaraiosis is a well-known risk factor for developing post-stroke cognitive impairment, which may ultimately adversely affect the course of a patients' treatment and recovery programs.[8,9] While it has already been demonstrated that the presence of cognitive deficits are correlated with WMH load in TIA/minor stroke patients,[1] our data suggests that this WMH burden is also an independent predictor of non-reversion of cognitive deficits within 90 days of TIA/minor stroke. The relationship between chronic white matter hyperintensities and cognitive deficits may be valuable in establishing a course for recovery and rehabilitation post-stroke as well as boundaries for activities of independent living (i.e. driving). Although it remains to be shown, it is plausible that therapies that slow the progression of white matter disease may also reduce the severity ad duration of cognitive deficits after TIA/minor stroke occurs.

## Strengths and Limitations

The studies included in this thesis had a number of strengths and limitations. The strengths include acute assessment of neuropsychological and imaging variables along with serial testing of both, blind assessment of DWI, FLAIR and WMH volumes with respect to clinical outcome using two raters, and the use of more than one well established neuropsychological test to assess cognitive deficits.

The main limitation of this study is its relatively small sample size, which has a major implication on the effect size and power of the results. This study also

lacked pre-stroke assessments, which would have been indicative of any pre-existing subclinical cognitive deficits that may have been present in some case. To assess cognitive function, we used identical versions of the MoCA test at each time point, since alternate forms were not available at the time of study inception. It is possible that patients may have learned aspects of a task, contributing to the development of a learning curve. Modifying the details of certain tasks such as recall words and repetition sentences would help minimize learning effects. Post-stroke fatigue may also have resulted in decreased capacity to sustain an effort, increasing the likelihood of error. Regardless of the precise underlying etiology, we still consider these to be relevant post-stroke cognitive deficits. Finally, it may be considered a caveat that when testing for the reversion of cognitive impairment, not all reverters were by definition returning to normal (MoCA >26). However, reversion was defined based on previous criteria, which still considered an increase of ≥2 points a significant improvement in cognition.[3, 6]

## Future Directions

### *Exploring Cognitive Changes*

Patients with suspected TIA are routinely screened for stroke risk, and are managed according to this risk. Evidence of visible cognitive deficits over the first few days following TIA/minor stroke, should be used to prognosticate longer-term changes in cognition. Attending to and treating such symptoms is important in improving patients' quality of life after TIA, but it could also inform

decisions of rehabilitation and tasks of independent living (i.e. return to work, driving). Our current data suggests that resolution of cognitive deficits in TIA/minor stroke patients is evident through improvements on tasks in the memory domain, while the language domain remains persistently impaired. With the MoCA however, it is difficult to understand the full complexity of these evolving deficits as certain cognitive domains are only briefly assessed. For example, language is only assessed through repetition of two syntactically complex sentences and a fluency task. However, this domain also entails reading, writing and naming abilities, all of which can be selectively impaired. Future research in this patient population should be aimed at utilizing different batteries of neuropsychological tests to perform a detailed evaluation of the progress of cognitive function in domains such as language and memory. This data would be valuable to decisions about treatment in TIA/minor stroke patients

It is also known that mild cognitive impairment contributes significantly to disability in the elderly and is consistently shown to have a high risk of progression to dementia.[10] Our findings suggest that in some TIA/minor stroke patients, cognitive deficits persist beyond 3 months post stroke. It would be valuable to investigate the role of short-term cognitive therapy in TIA/minor stroke patients and the effects of these therapies on long-term functional outcome. Although there is no standard treatment for vascular cognitive impairment, recent studies of symptomatic cholinergic treatment have shown promise in mild cognitive impairment. A meta-analysis showed that the long-term use of

cholinesterase inhibitors in subjects with mild cognitive impairment might attenuate the risk of progression to dementia.[11] Controlled clinical trials with donepezil and galantamine in patients with VaD, have demonstrated improvement in cognition, behaviour, and activities of daily living.[12] Exploring the efficacy of these treatments in TIA/minor stroke patients experiencing persistent cognitive impairment would be valuable to improving patient quality of life following stroke.

### *Exploring White Matter Changes*

Many questions remain unanswered regarding the relationship between white matter disease burden and clinical outcome. Our data suggests that TIA/minor stroke patients with persisting cognitive deficits have a higher WMH load along with cortical and subcortical lesions. Although it is suggested that these factors together may result in decreased functional connectivity of cortical regions, impeding recovery, the exact mechanisms remain unknown. Further research involving objective measures of cortical connectivity along side neuropsychological testing and volumetric measures of infarct evolution are needed to elucidate the exact mechanism between white matter disease burden and clinical outcome.

A potentially useful method of evaluating these changes may be to assess white matter tract connectivity and integrity in TIA/minor stroke patients. Diffusion tensor imaging (DTI) techniques have the ability to provide a more sensitive

measure of white matter tract integrity. DTI provides a quantification of the magnitude and directionality (anisotropy) of the diffusion of water molecules, which allows for a measurement of the apparent structural integrity of axonal fibres in white matter. This measure of white matter integrity may be a more sensitive marker for monitoring the effects of lesion progression following stroke and promote a better understanding of the recovery process after stroke. Previous studies have examined DTI fractional anisotropy (FA) values and found that white matter integrity improves following stroke. Wang et al. assessed 180 ischemic stroke patients and demonstrated a significant improvement in FA from baseline over 2 years of follow-up.[13] A longitudinal analysis of changes in white matter tracts and neuropsychological performance may be useful in determining whether reverters and non-reverters can be differentiated based on white matter tract integrity. It is reasonable to hypothesize that patients with persistent cognitive deficits will have lower FA values, reflecting the loss of white matter integrity, than those with transient cognitive deficits. This may shed light on differences in recovery rates after TIA/minor stroke as well as potential physiological and cognitive markers at baseline affecting prognosis.

## Closing Remarks

These studies provide a foundation for defining a temporal profile of cognitive function that follows TIA/minor stroke as well as clinical and imaging factors that affect temporary cognitive impairment. Ultimately, knowledge of the progression of cognitive deficits will be an important asset in the management of TIA/minor stroke patients.

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