

# Factors Associated with Cognitive Decline in Transient Ischemic Attack Patients

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**ABSTRACT:** Chronic cerebrovascular disease and large ischemic stroke are both associated with cognitive impairment. Much less is known about the acute cognitive sequelae of transient ischemic attack (TIA). Although often overlooked, there is increasing evidence that cognitive impairment does occur following TIA. In some patients, cognitive changes persist after resolution of focal neurological deficits, but the temporal profile of these symptoms is unknown. In addition, clinical and imaging correlates of cognitive impairment after TIA have not been systematically studied. This under-studied and recognized problem has significant implications for TIA patient management. In this review, we summarize the evidence currently available and identify future research priorities.

**RÉSUMÉ:** Facteurs associés au déclin cognitif chez les patients présentant un accident ischémique transitoire. La maladie vasculaire cérébrale chronique et l'accident vasculaire cérébral extensif sont tous deux associés à un déficit cognitif. On connaît moins bien les séquelles cognitives aiguës d'un accident ischémique transitoire (AIT). Bien que ce soit rarement pris en compte, il y a de plus en plus de données en faveur de la présence d'un déficit cognitif suite à un AIT. Chez certains patients, les changements cognitifs persistent après la résolution des déficits neurologiques focaux, mais le profil temporel de ces symptômes demeure inconnu. De plus, les corrélats cliniques et d'imagerie du déficit cognitif après un AIT n'ont pas été étudiés systématiquement. Ce problème peu étudié comporte des implications importantes pour le traitement des patients ayant présenté un AIT. Dans cette revue, nous faisons un sommaire des données disponibles et nous identifions les priorités à considérer dans des études futures.

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Stroke is the leading cause of prolonged disability in the elderly and the second most common cause of death.<sup>1,2</sup> Prior to stroke individuals often experience minor cerebrovascular events such as transient ischemic attacks (TIAs). According to the World Health Organization criteria, a TIA is defined as a focal neurological deficit lasting for less than 24 hours and presumed to be of vascular origin.<sup>3</sup> These events 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.<sup>4</sup> Without early detection and proper treatment, TIAs can be followed by more severe ischemic stroke.

Cerebrovascular disease is associated with cognitive impairment that significantly impacts patients in the long term. Up to 25% of stroke survivors meet the criteria for dementia within 12 months of an ischemic event.<sup>5,6</sup> 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.<sup>7-9</sup> 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 imaging and clinical factors correlated with impairments in cognition function, describe existing temporal profiles of cognitive change and address current therapeutic strategies for treating cognitive decline in TIA patients.

## IMAGING STUDIES IN TIA PATIENTS

### Imaging Modalities Used in TIA

It has been estimated that approximately one third of patients diagnosed with a TIA on clinical grounds alone, actually have evidence of an infarct on magnetic resonance imaging (MRI) scan.<sup>10,11</sup> 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

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**Table 1: Computed tomography studies in transient ischemic attack patients**

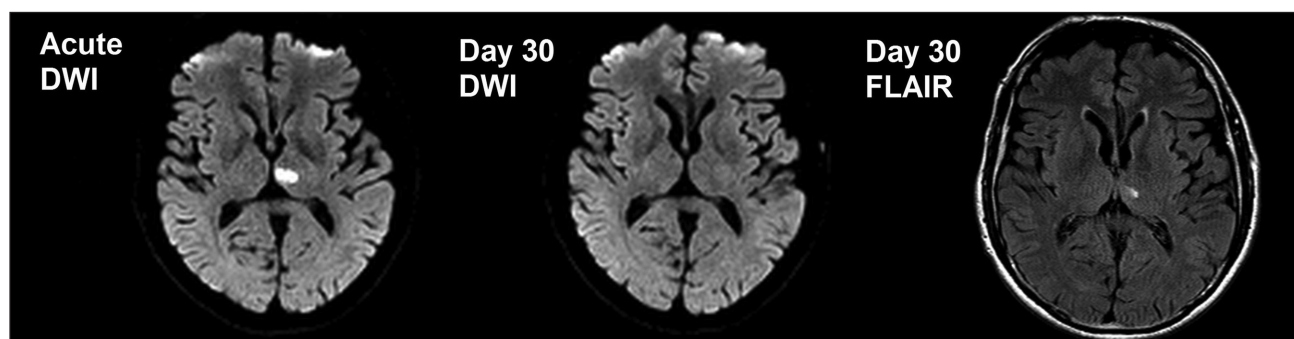
Study (Reference)	Time from Symptom Onset to Scan	TIA Inclusions	# of Patients	% of TIA Patients With Infarct
Perrone et al. <sup>14</sup> 1979		All TIAs	35	34
Calandre et al. <sup>15</sup> 1984	Mean 50 days	All TIAs	88	25
Awad et al. <sup>16</sup> 1986		All TIAs	22	32
Davalos et al. <sup>17</sup> 1988			122	21
Murros et al. <sup>18</sup> 1989	Within 4 weeks	Carotid TIA	284	12
Dennis et al. <sup>19</sup> 1990	Median 11 days (IQR 5-23 days)	All TIAs	120	27
Evans et al. <sup>20</sup> 1991	Within 4 weeks	All TIAs	350	17
Eliasziw et al. <sup>21</sup> 1995		All TIAs	164	28
Douglas et al. <sup>22</sup> 2003	Within 48h	All TIAs	478	4
Al-Khaled et al. <sup>23</sup> 2012	Within 48h	All TIAs	1533	3

CT indicates computed tomography; TIA, transient ischemic attack.

entities.<sup>12</sup> 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. Transient ischemic attack-related infarcts can be difficult to detect because they are often very small - generally less than 1mL in volume.<sup>13</sup>

Although evidence of infarction can be seen on computed tomography (CT) after TIA, these are often chronic infarcts and unrelated to the acute presentation. Nonetheless, these lesions are of prognostic value. In 1979, Perrone *et al* found that 34% of TIA patients had small hypodense areas on CT.<sup>14</sup> Subsequent studies have reported lower percentages ranging from 3% to 32%<sup>15-23</sup> (Table 1). Interestingly a study in 1983, examining the case reports of two patients with TIA symptoms, demonstrated evolving infarcts on cranial CT.<sup>24</sup> 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. In the most recent CT study, a cohort of 1533 TIA patients were scanned within 48 hours of symptom onset.<sup>23</sup> Evidence of a suspected new infarct was detected in 3.1% of patients, but this is much lower than that seen with MRI.<sup>11</sup>

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. The DWI sequence is particularly 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.<sup>25</sup> 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%).<sup>16</sup> More recently, a study of 161 TIA patients, who underwent both CT and MRI, indicated focal CT abnormalities in seven (4.3%) patients.<sup>26</sup> 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.



**Figure:** MRI findings including DWI and FLAIR sequences in a TIA patient scanned acutely and at day 30. Acute DWI demonstrates a small ischemic lesion, which is seen to resolve by day 30. Bright signal intensity seen on the day 30 FLAIR image indicates a chronic infarct. MRI indicates magnetic resonance imaging; DWI, diffusion-weighted imaging; FLAIR, fluid attenuated inversion recovery; TIA, transient ischemic attack.

**Table 2: MRI (DWI) studies in transient ischemic attack patients**

Study (Reference)	Time from Symptom Onset to Scan	TIA Inclusions	# of Patients	% of TIA Patients With Infarct
Kidwell et al. <sup>27</sup> 1999	Mean 17h	Cerebral and brainstem	42	48
Engelter et al. <sup>28</sup> 1999	Mean 36.5h	Any focal deficit <24h	40	35
Takayama et al. <sup>29</sup> 2000	Within 48h	All TIAs	19	37
Kamal et al. <sup>30</sup> 2002	Within 6h	All TIAs	28	46
Ay et al. <sup>13</sup> 2002	Mean 39h	Cerebral and brainstem	57	47
Marx et al. <sup>31</sup> 2002	Mean 10.7h	Brainstem	14	29
Kastrup et al. <sup>32</sup> 2002	Mean 5 days (DWI +) Mean 6 days (DWI -)	Carotid TIA	42	45
Rovira et al. <sup>33</sup> 2002	Mean 5 days	Cerebral and brainstem	58	67
Crisostomo et al. <sup>34</sup> 2003	Mean 23h	All TIAs	75	21
Nagura et al. <sup>35</sup> 2003	Median 17.3h	All TIAs	45	31
Nakamura et al. <sup>36</sup> 2003	Within 48h	All TIAs	18	50
Restrepo et al. <sup>37</sup> 2004	Mean 56 min (DWI +) Mean 33 min (DWI -)	All TIAs	22	55
Purroy et al. <sup>38</sup> 2004	Within 7 days	Cerebral and brainstem	83	33
Winbeck et al. <sup>39</sup> 2004	Within 24h	Anterior circulation	60	30
Schulz et al. <sup>40</sup> 2004	Median 17 days	All TIAs	136	13
Inatomi et al. <sup>41</sup> 2004	Median 4 days	Cerebral and brainstem	129	44
Ay et al. <sup>42</sup> 2005	Mean/SD 22 ± 26h	Cerebral and brainstem	87	41
Coutts et al. <sup>43</sup> 2005	Median 8.5h	TIA and MS (NIH <6)	143	68
Oppenheim et al. <sup>44</sup> 2006	Median 24h	All TIAs	103	35
Lamy et al. <sup>45</sup> 2006	Mean 42.4h	Cerebral and brainstem	98	35
Prabhakaran et al. <sup>46</sup> 2007	Within 48h	All TIAs	146	25
Redgrave et al. <sup>47</sup> 2007	Within 72h	All TIAs	200	16
Calvet et al. <sup>48</sup> 2009	Median 19.5h	All TIAs	339	40
Mlynash et al. <sup>49</sup> 2009	Mean/SD 23.2 ± 12.5h	All TIAs	43	35
Adeoye et al. <sup>50</sup> 2010	Within 48h	All TIAs	323	15
Al-Khaled et al. <sup>51</sup> 2013	Within 48h	Time defined TIAs	1862	11
Miyagi et al. <sup>52</sup> 2013	Within 7 days	All TIAs	458	21

MRI indicated magnetic resonance imaging; DWI, diffusion-weighted imaging; TIA, transient ischemic attack.

Systematic MRI studies have found that the proportion of TIA patients with positive DWI changes ranges from 11% to 68%<sup>13,27-52</sup> (Table 2). The discrepancy in this large range of reported values may be explained by variations in study design, study population and sample size. For example, time from symptom onset to MRI scan varied from within six hours to a median 17 days later. In studies reporting later time points, DWI infarcts may have resolved, while acute studies may have more frequently reported positive DWI scans. Additionally, although all studies included TIA patients, some also included minor stroke and population sizes ranged from 14 to 1862 patients. Serial imaging studies indicate that some DWI lesions do result in a visible chronic infarct (Figure), while others do not. In a study of 42 TIA patients, relevant DWI abnormalities were reported in nearly half of patients.<sup>27</sup> Of the nine DWI positive patients who had a follow-up imaging study two to seven months after the event, four 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.<sup>52</sup> A follow-up MRI was done on 48 patients showing that in five (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.<sup>44</sup> 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 MRI.

### 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.<sup>34,41</sup> The impact of DWI lesion presence, location, volume and number on cognitive performance is unknown. Studies correlating MRI findings in TIA patients with neuropsychological testing are lacking. There is an increased likelihood of aphasia in TIA patients with DWI lesion, but the relationship to other cognitive domains is unknown.<sup>45,51</sup> One study found that TIA patients with a positive DWI scan were 25 times more likely to have aphasia than those with negative

scans.<sup>34</sup> In a study of 147 TIA patients, disturbance of higher cortical function evidence such as aphasia and spatial neglect was a significant factor associated with DWI abnormalities.<sup>41</sup>

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 three to six months following the event.<sup>53</sup> Patients were categorized as having vascular dementia, vascular cognitive impairment (VCI) or no cognitive impairment by consensus and administered detailed neuropsychological testing along with an MRI scan. Although vascular dementia 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

### Cognitive Screening 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 (MMSE) and the Montreal Cognitive Assessment (MoCA).

The MMSE, developed by Folstein *et al*, is a cognitive assessment of patient mental state and has been considered the clinical standard in stroke.<sup>54</sup> The assessment comprises a battery of individual tests that can be administered in approximately ten 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 impairment (MCI). 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 MoCA was a test designed more recently as a cognitive screening assessment with increased sensitivity to MCI.<sup>55</sup> The MoCA can be administered in a short ten minutes, where patients can score a total of 30 points. The test is divided into eight 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.<sup>55,56</sup>

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.<sup>57-59</sup> 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 MCI.<sup>55</sup> 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.<sup>56,60-62</sup> Despite this, many studies continue to utilize MMSE.

There is no consensus on the cognitive test most appropriate for assessment of post stroke cognitive impairment. A number of studies have compared MoCA and MMSE after TIA with other methods of evaluation including the Addenbrooke's Cognitive Examination Revised (ACE-R), telephone MoCA (T-MoCA) assessment and specific batteries of neuropsychological tests.<sup>63-65</sup> In a population-based study of 100 patients assessed  $\geq$  one year after TIA or stroke, MoCA and MMSE were compared to the ACE-R for detecting MCI, defined using the Neurological Disorders and Stroke-Canadian Stroke Network Vascular Cognitive Impairment Battery.<sup>63</sup> Both the MoCA and ACE-R had better sensitivity and specificity for MCI compared to the MMSE, which demonstrated a ceiling effect. A study by the same group assessed the T-MoCA against face-to-face cognitive tests in 91 patients with TIA or stroke.<sup>64</sup> After one year, MoCA subtest scores for repetition, abstraction and verbal fluency were significantly worse by telephone than face-to-face testing. The T-MoCA was therefore considered limited in its ability to assess visuoexecutive and complex language tasks. Another study aimed to compare the MoCA with a computerized battery of neuropsychological tests for memory, attention and executive functions to detect mild to moderate cognitive impairments in patients with TIA or stroke.<sup>65</sup> In comparison to stroke, TIA patients presented significantly better scores through both methods. However, the MoCA was able to identify many more subjects with low scores (<26) compared to the neuropsychological battery.

### Cognitive Assessments in Vascular Dementia

The most widely used criteria for diagnosis of vascular dementia is the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria.<sup>66</sup> These criteria rely on neuroimaging by CT or MRI for evidence of focal brain damage as well as cognitive deficits in at least three 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. The Alzheimer's disease Assessment Scale (ADAS) is used to assess cognitive dysfunction in individuals with Alzheimer disease and other dementias.<sup>67</sup> Its subscale, the Alzheimer's disease Assessment Scale-cognitive subscale (ADAS-cog), is the most popular cognitive testing instrument used in clinical trials of nootropics.<sup>68</sup> It consists of 11 tasks measuring the disturbances of memory, language, praxis, attention and other cognitive abilities.



## Cognitive Impairment after TIA

Cognitive studies in TIA 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 two weeks later.<sup>69</sup> With cutoffs for impairment set at  $\leq 26$ , 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 six month or five year follow-up.<sup>56</sup> 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. In a more recent study, cognitive impairment in 97 first time TIA patients was assessed using MoCA and compared to 100 healthy control patients.<sup>70</sup> TIA patients exhibited declined cognitive function with impairments in verbal fluency, memory recall, abstraction, and visuospatial/executive abilities.

## 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  $\leq 3$ ), MMSE was administered both at the initial assessment (baseline) and one month later and then repeated at one, two and five years.<sup>7</sup> Patients were divided into two baseline groups: those seen between one and seven days and those seen between 8 and 20 days. Transient cognitive impairment (TCI) was defined as a baseline MMSE score  $\geq 2$  points lower than the one month follow-up MMSE. The rate of TCI in patients initially assessed within seven days (median four 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  $23.9 \pm 3.6$  at baseline to  $27.2 \pm 3.0$  at one 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).<sup>8</sup> The initial assessment was done within three and six months post stroke, and a follow-up assessment 14 months later. At baseline, patients were categorized based on severity into three groups: vascular dementia, vascular cognitive impairment no dementia (VCI-ND) and no cognitive impairment. Cognitive tests showed a mean decline of 0.83 points on MMSE between the two time points. Patients impaired at baseline assessment (vascular dementia + VCI-ND), showed a greater decline in visuoconstructive function and abstraction domains than patients with no cognitive impairment. 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 six months of symptom onset) and again after one year.<sup>9</sup> 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 one 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 one year follow-up and seven patients who were cognitively impaired but not demented at baseline were demented at one 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 affects cognition and what the temporal profile of any changes is. Accurate predictors of improvement/worsening in cognitive status 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 VCI.

## Prevention of Vascular Dementia: Vascular Risk Factor Management

### Hypertension

Hypertension is an established risk factor for cardiovascular disease and stroke. A number of studies have identified a blood pressure threshold of 130/80 mmHg above which strokes are more likely to occur.<sup>71,72</sup> Hypertension has also been implicated in affecting cognitive function. A recent systematic review investigated the association of arterial hypertension with increased risk of vascular dementia.<sup>73</sup> 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.<sup>74</sup> The study showed that significantly fewer patients

demonstrated cognitive impairment when treated with angiotensin-converting enzyme inhibitor (ACE-I) ramipril compared to placebo. Given the mild lowering of blood pressure however, it is hard to be certain that these cognitive benefits were a direct result of ramipril. In the Systolic Hypertension in Europe (Syst-Eur) trial, 2148 patients were randomized to active treatment with nitrendipine or placebo control.<sup>75</sup> Results showed that the rate of incident dementia was reduced by 50%. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) was a randomized, double blind, placebo controlled trial of 3015 patients with prior stroke or TIA.<sup>76</sup> 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 Alzheimer's disease and vascular dementia. 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 vascular dementia and Alzheimer's disease three decades later.<sup>77</sup> This study echoed the results of previous trials including the Finnish Cohort of the Seven Countries Study<sup>78</sup> and the CAIDE study,<sup>79</sup> where high midlife cholesterol levels were associated with vascular dementia and Alzheimer's disease 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.<sup>80</sup> 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 Alzheimer's disease compared to never using cholesterol-lowering drugs, in patients that were followed up to 15.3 years (mean 9.2).<sup>81</sup> Based on a recent Cochrane review, the use of statins has not consistently demonstrated positive results in all randomized controlled trials.<sup>82</sup>

### *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 neuroglycemic range within which cognitive functioning takes place.<sup>83,84</sup> 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 Alzheimer's disease and vascular dementia.<sup>85</sup>

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 five randomized controlled trials assessing the effects of different treatments for Type II diabetes on cognitive function.<sup>86</sup> One study compared ginseng with placebo 36 patients being treated by diet alone (no insulin or oral hypoglycemic agents prescribed).<sup>87</sup> Cognitive function was tested after eight weeks using digit span and a timed diagram test. Ginseng treated patients had better scores on 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.<sup>88,89</sup> 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.<sup>90</sup> Cognitive function was assessed on admission, at discharge and at six weeks. At six 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. Compared to other studies, controlled clinical trials with donepezil and galantamine in patients with vascular dementia have demonstrated improvement in cognition, behavior and activities of daily living<sup>91-98</sup> (Table 3).

Donepezil is a non-competitive, reversible antagonist of cholinesterase, licensed for the treatment of Alzheimer's disease in the United Kingdom and the United States. Two large-scale multi-center, randomized controlled trials (Study 307<sup>92</sup> and Study 308<sup>93</sup>) were conducted in patients with probable or possible VCI according to the NINDS-AIREN criteria. Patients in both studies were randomized to 24 weeks of donepezil treatment (5 mg/day or 10 mg/day) or placebo with primary efficacy outcome measures being the 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.<sup>92</sup> 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.<sup>93</sup> A recent larger double-blind randomized controlled trial was conducted at 111 centers in 9 countries investigating 974 patients with probable or possible vascular dementia.<sup>94</sup> Patients were randomized to receive donepezil 5 mg/day or placebo for 24 weeks. Patients treated

**Table 3: Pharmacological evidence for treatment of vascular dementia**

Treatment	Study Reference	Trial Duration	Dosage	Participants	Measured Outcomes
Donepezil	Black et al. <sup>92</sup> (Donepezil 307)	24 wks	5mg daily and 10 mg daily	603 patients with probable or possible vascular dementia by NINDS-AIREN	ADAS-cog and CIBIC improvement in both treatment group
Donepezil	Wilkinson et al. <sup>93</sup> (Donepezil 308)	24 wks	5mg daily and 10 mg daily	616 patients with probable or possible vascular dementia by NINDS-AIREN	ADAS-cog and CIBIC improvement in both treatment groups
Donepezil	Roman et al. <sup>94</sup>	24 wks	5mg daily	974 patients with probable or possible vascular dementia by NINDS-AIREN	VADAS-cog improvement in treatment group
Galantamine	Erkinjuntti et al. <sup>95</sup>	24 wks	24mg daily	592 patients with NINCDS-ADRDA Alzheimer's disease with cerebrovascular disease or vascular dementia by NINDS-AIREN	ADAS-cog improvement in treatment group
Galantamine	Auchus et al. <sup>96</sup>	26 wks	Escalated to 8 mg or 12 mg twice daily	788 patients with probable vascular dementia by NINDS-AIREN	ADAS-cog/11 improvement in treatment group
Memantine	Orgogozo et al. <sup>97</sup> (MMM300)	28 wks	20mg daily	321 patients with probable vascular dementia by NINDS-AIREN	ADAS-cog improvement in treatment group
Memantine	Wilcock et al. <sup>98</sup> (MMM500)	28 wks	20mg daily	579 patients with probable vascular dementia by NINDS-AIREN	ADAS-cog improvement in treatment group

NINDS-AIREN indicates National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences; ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; CIBIC, Clinician Interview Based Impression of Change; VADAS-cog, Vascular Alzheimer's disease Assessment Scale-Cognitive Subscale; NINCDS-ADRDA, National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association.

with donepezil showed significant improvement from baseline to end point based on the Vascular Alzheimer's disease Assessment Scale-Cognitive Subscale (VADAS-cog), compared to the relative stability of the placebo group. It is therefore recommended by the American Heart Association/American Stroke Association (AHA/ASA) that Donepezil can be useful for cognitive enhancement in patients with vascular dementia.<sup>99</sup>

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.<sup>100,101</sup> 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 six months following a four week placebo period.<sup>95</sup> According to the ADAS-cog scores, treatment group patients significantly improved from baseline to the six month period compared to those assigned placebo, whereas placebo group deteriorated below baseline. Another randomized placebo controlled trial investigated galantamine in 788 patients with probable vascular dementia using slow dose escalation up to 26 weeks.<sup>96</sup> After a four 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.<sup>99</sup>

### Glutamate Receptor Antagonists

Glutamate is the principal excitatory neurotransmitter that stimulates N-methyl-D-aspartate (NMDA) receptors in cortical neurons. There is some evidence that sustained elevation of glutamate may underlie the neuronal loss that is observed in dementia.<sup>102</sup> 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.<sup>97,103</sup> There have been several clinical studies demonstrating memantine's effects on improving cognitive performance in dementia patients<sup>97,98,104</sup> (Table 3). In one multicenter, randomized controlled trial, 321 patients with mild to moderate vascular dementia were randomly allocated to receive placebo or memantine.<sup>97</sup> After a two week placebo run-in period, patients received doses of 20 mg/day 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 vascular dementia were randomized to placebo or treatment with 20-mg/d memantine for 28 weeks.<sup>98</sup> Memantine resulted in improvement in ADAS-cog scores, not seen in placebo treated patients. According to AHA/ASA, the benefits of memantine are not well established in vascular dementia.<sup>99</sup>



## 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.<sup>105</sup>

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 vascular dementia.<sup>106</sup> The meta-analysis technique was used to demonstrate a significant reduced risk for vascular dementia in people who were naturally more physically active compared to those who were not. A four 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.<sup>107</sup> Patients were randomly assigned to usual treatment plus exercise or usual treatment alone groups. When assessed at baseline and the four 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.<sup>108</sup> 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.<sup>109</sup>

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 Alzheimer's disease patients.<sup>110</sup> 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.<sup>111</sup> At the three 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).

There is current evidence that lifelong bilingualism is also a factor that protects against cognitive decline and the onset of dementia.<sup>112</sup> In a recent study of 211 patients diagnosed with

probable Alzheimer's disease, age, education and language history were recorded, classifying 102 patients as bilingual and 109 patients as monolingual.<sup>113</sup> Results demonstrated that compared to monolinguals, bilingual patients had been diagnosed 4.3 years later and had reported the onset of symptoms 5.1 years later. A study investigating possible neural correlates of this effect tested the hypothesis that bilingualism is associated with maintenance of white matter integrity in older individuals.<sup>114</sup> Results from diffusion tensor imaging showed stronger structural and functional connectivity in bilinguals compared to monolinguals.

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.<sup>115</sup> Results showed that an individual reporting frequent cognitive activity at baseline had a 47% reduced chance of developing Alzheimer's disease. Another interesting study of 488 cognitively intact individuals assessed the effect of self-reported cognitive activities on the onset of cognitive decline.<sup>116</sup> 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 vascular dementia and Alzheimer's disease. 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.<sup>117</sup> 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, Alzheimer's disease and vascular dementia more than 20 years later.<sup>118</sup>

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.<sup>119</sup> This study found that the odds of cognitive impairment was 36% higher among continuous smokers than never smokers and significantly declined 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.<sup>120</sup> 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 two 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 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 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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