Post-Stroke Cognitive Impairment and Vascular Dementia

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Newcastle Centre for Brain Ageing and Vitality
Newcastle University Campus for Ageing and Vitality

- Newcastle Brain Tissue Resource (NBTR)
- NIHR Biomedical Research Centre for Age Related Diseases (NBRB) and NE DenDroN
- H Wellcome Laboratories for Biogerontology
- Clinical Ageing Research Unit (CARU)
- Newcastle Magnetic Resonance Centre (NMRC) (old Newcastle General Hospital site)
Plan: Cognitive Function after Stroke

Overview

• Introduction: Prevalence, Types and Classification
• Vascular Cognitive Impairment, VaD and SIVD
• Neuropsychometric assessment post-stroke
• Newcastle and Ibadan (Nigeria) COGFAST studies
  ➢ Clinical and neuropsychological aspects
  ➢ Pathophysiology of Leukoencephalopathy, White matter changes
  ➢ Post-stroke and VaD in SSA
• Take home message
World-wide Stroke Incidence
Incidence decreased but total strokes increased worldwide

In HIC overall incidence, mortality and DALYs of all stroke types have declined in both younger (<75 years) and older (≥75 years) age groups, in LMIC these have increased (Krishnamurthi RV et al, 2014; Feigin et al, 2014)
Of all strokes, ~80-82% are ischaemic and 18-20% are haemorrhagic. Of the haemorrhagic strokes, 15% are due to an intracerebral haemorrhage, and 5% are due to a subarachnoid haemorrhage.
Classification of Stroke

(Oxford Community Stroke Project (OSCP); also known as the Bamford or Oxford classification)

Relies primarily on the initial symptoms; based on the extent of the symptoms, the stroke episode is classified as:

- **Total anterior circulation stroke (TAC)**
- **Partial anterior circulation stroke (PAC)**
- **Lacunar stroke (LAC)**
- **Posterior circulation stroke (POC)**

The type of stroke is then coded by adding a final letter to the above:

- I – for infarct (e.g. TACI)
- H – for haemorrhage (e.g. TACH)
- S – for syndrome; intermediate pathogenesis, prior to imaging (e.g. TACS)

Entities predict extent of the stroke, area of brain affected, underlying cause, and the prognosis.
Death rates from stroke and survival

- Risk increases exponentially for both stroke and dementia with age.

- Stroke is the third most common cause of death in developed nations.

- Rate of stroke related deaths has decreased continuously since 1970

- Stroke increases the risk of dementia x5 compared to age match controls (Pendlebury 2009).

- 30% of Stroke survivors develop PSD within 2 years (Leys 2005).

Oxfordshire data 2004: age-specific incidence of major stroke fallen by 40% in past 20 yrs (Rothwell et al, 2004)
Stroke, cerebrovascular diseases and vascular cognitive impairment in Africa

- Age is the strongest irreversible risk factor
- Hypertension is strongest modifiable risk factor
- Cerebral SVD is higher ≥30% in SSA
- Significant proportions of CVDs ascribed to various forms of infectious disease e.g. HIV
- Prevalence estimates: VaD (2-3%), delayed dementia after stroke (10-20%); VCI (30-40%)
### Common and rare causes of stroke pathophysiology in SSA

<table>
<thead>
<tr>
<th>Primary or 2º Vascular Disorder(s)*</th>
<th>Common conditions</th>
<th>Frequencies (Africa) (low+ to high+++)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embolic disease</td>
<td>Cardioembolism</td>
<td>+++</td>
</tr>
<tr>
<td>Arteriolosclerosis</td>
<td>Cerebral small vessel disease</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>Hypertensive vasculopathy</td>
<td>+++</td>
</tr>
<tr>
<td>Non-atherosclerotic non-inflammation vasculopathies</td>
<td>Arterial dissections, fibromuscular dysplasia, dolichoectatic basilar artery, large artery kinking and coiling, radiation induced angiopathy, moyamoya disease</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Aneurysms- sacular, berry, fusifom, cerebral</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Vascular malformations: cavernous hemangioma, arteriovenous, capillary</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Cerebral venous thrombosis</td>
<td>+</td>
</tr>
<tr>
<td>Amyloid angiopathies</td>
<td>Hereditary CAAs (Amyloid β, PrP, cystatin C, transthyretin, gelsolin)</td>
<td>+</td>
</tr>
<tr>
<td>Monogenic stroke disorders</td>
<td>CADASIL, CARASIL, retinal vasculopathy with cerebral leukodystrophies (RVCLs), Moyamoya disease, Hereditary angiopathy, nephropathy, HANAC, COL4 disorders</td>
<td>+</td>
</tr>
<tr>
<td>Monogenic disorders involving stroke</td>
<td>Fabry disease, FHM, HHT, Vascular Ehlers-Danlos syndrome, Marfan syndrome, Psuedoxanthoma elasticum, Arterial tortuosity syndrome, Loeys-Dietz syndrome, polycystic kidney disease; Neurofibromatosis type 1 (von Ricklinghausen disease), Carney syndrome (Facial lentiginosis and myxoma)</td>
<td>+</td>
</tr>
<tr>
<td>Metabolic disorders</td>
<td>MELAS, MERRF, Leigh’s disease, MIRAS, Fibromuscular dysplasia, Menkes disease, Homocystinuria, Tangier’s disease</td>
<td>++</td>
</tr>
<tr>
<td>Haematological disorders</td>
<td>Paraproteinaemia, coagulopathies (antiphospholipid antibodies, SLE, nephrotic syndrome, Sneddon syndrome, protein S, C, Z, antithrombin III, plasminogen)</td>
<td>++</td>
</tr>
<tr>
<td>Vasosspastic disorders</td>
<td>SAH, Migraine related strokes, paroxysmal hypertension, drug induced vasconstriction</td>
<td>+</td>
</tr>
</tbody>
</table>
Dementia in Africa

• In 2010 there were estimated to be 36 million people who had dementia worldwide
• With demographic transition the prevalence will rise faster in developing countries
• Currently, it is estimated that 58% of people with dementia live in low- and middle-income countries; rising to 71% by 2050
• There are 2.1 million people living with dementia in SSA (2012 estimate)

Prevalence of dementia in SSA (~2.2 million people!)

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Age range</th>
<th>Screening tool used</th>
<th>Dementia prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longdon, 2013</td>
<td>Rural Tanzania</td>
<td>70 +</td>
<td>CSI-D</td>
<td>6.4% (age-adjusted)</td>
</tr>
<tr>
<td>Paraiso, 2011</td>
<td>Benin, urban</td>
<td>65+</td>
<td>CSI-D, 5WT</td>
<td>3.7%</td>
</tr>
<tr>
<td>Guerchet, 2009</td>
<td>Benin, rural</td>
<td>65+</td>
<td>CSI-D, 5WT</td>
<td>2.6%</td>
</tr>
<tr>
<td>Guerchet, 2010</td>
<td>CAR</td>
<td>65+</td>
<td>CSI-D, 5WT</td>
<td>8.1% (CAR)</td>
</tr>
<tr>
<td></td>
<td>Congo</td>
<td></td>
<td></td>
<td>6.7% (Congo).</td>
</tr>
<tr>
<td>Yusuf, 2011</td>
<td>Nigeria, Zaria</td>
<td>75.5 ± 9.4</td>
<td>CSI-D</td>
<td>2.79%</td>
</tr>
<tr>
<td>Ochayi &amp; Thacher</td>
<td>Nigeria, Jos</td>
<td>65+</td>
<td>CSI-D</td>
<td>6.4%</td>
</tr>
<tr>
<td>Ogunniyi, 2000</td>
<td>Nigeria</td>
<td>65+</td>
<td>CSI-D</td>
<td>2.29% (age-adjusted)</td>
</tr>
<tr>
<td>Gureje, 2006</td>
<td>Nigeria</td>
<td></td>
<td>10 word learning list</td>
<td>‘probable dem’ 10.1%</td>
</tr>
</tbody>
</table>
Towards Clinicopathological Criteria and Mechanisms of Dementia in after Stroke (VaD)?

Dogma, problems, pitfalls
Mechanisms: Cerebral SVDs and Dementia

Vascular risk factors, genetic factors, age, lifestyle

Large Vessel Occlusion

Small Vessel Disease/Occlusion

Partial Vessel Occlusion

Hypotensive Disorders

Large Cortical Infarcts

Small Infarcts (Lacunes)

White Matter Lesions

Brain Atrophy

MID

SIVD

VCI: Cognitive impairment, Dementia, Non-cognitive features (e.g. depression).

After O’Brien J et al, 2003
WHO DEFINITION OF DEMENTIA

‘Dementia is a syndrome that affects memory, thinking, behaviour and ability to perform everyday activities’

Currently a WHO priority – ‘Dementia a Global Health Priority’ report published 2012

Dementia is NOT part of the normal ageing process
Diagnosis of Dementia

• **What is dementia?**
  
  • A progressive deterioration in cognitive function
  • Causes problems with social interactions, work, relationships
  • Need to distinguish dementia from DELIRIUM and PSYCHIATRIC problems
NOT dementia

• **DELIRIUM**: an acute confusional state (causes include infection, malignancy, etc.)

• **PSYCHIATRIC PROBLEMS** (“pseudodementia”): e.g. depression, anxiety. Relatively abrupt onset often with identifiable trigger. Should not progress
How to diagnose dementia?

THE HISTORY

– Try and speak to the patient and also a relative
– Ask about:
  » Symptoms at onset
  » Speed of evolution
  » Impact on work/family life
  » Family history
  » Risk factors (e.g. vascular, alcohol)
  » Past medical history
ICD-10 Dementia criteria

- **G1**- Decline in memory (first, inability to learn new information then loss of previously learned information)
- This should be supported by cognitive testing and interview of a reliable informant
- AND
- **Decline in other cognitive areas** such as judgement and thinking and planning and organising (must be decline from previous level of functioning NB learning disability)
- **G2** - no clouding of consciousness (i.e. no delirium)
- **G3** Decline in social functioning, motivation or emotional control (apathy, coarsening of social behaviour, irritability) Essentially evidence of a change in functional ability
- **G4** Present for at least 6 months
- Mild/Moderate/Severe
- **With additional symptoms** (behavioural and psychological symptoms of dementia (depression, delusions, psychosis) Up to 90% have these
DSM-V Major Neurocognitive Disorder (Dementia)

• 1. Evidence of significant cognitive decline from a previous level of performance in **one or more** cognitive domains – such as complex attention, executive function, learning, memory, language, perceptual-motor or social cognition

Evidence should consist of history of significant decline (from patient, reliable informant or clinician)

AND

• Impairment in cognitive performance from standardised neuropsychological testing (or another assessment if this is not available)

• 2. The cognitive deficits interfere with independence in everyday (functional) activities (at a minimum, assistance with complex activities of daily living such as paying bills)

• 3. Not occurring only in delirium and not better explained by another mental disorder

• Specify subtype (see criteria for subtypes of dementia)
Differences with DSM-V criteria

• NCD – acquired, rather than developmental disorders - represent decline. Due to underlying brain pathology.
• ‘Dementia’ typically refers to degenerative diseases in older people, whereas NCD expands category to diseases in younger people.
• Allows for one area of deficit only (i.e. amnestic syndrome, cognitive impairment post head injury) except in Alzheimers disease
• For degenerative dementias, use consensus guidelines for dementia subtype in addition to DSM-V.
Neuropsychometric Assessment

- Cognitive function tests have been used and developed over several years.

- Neuropsychometric batteries may contain several components to test different cognitive abilities, e.g. CANTAB, CAMCOG, ADAS-Cog etc.

- The Mini-Mental State Examination (MMSE)- widely used. Montreal Cognitive Assessment (MoCA) test.

- Value of informant questionnaires
Mini-Mental State Examination

• MMSE is a short test which measures general cognitive status including short-term memory (Folstein, et al, 1975)

• MMSE includes tests for orientation (e.g. year, season, etc.), registration, attention and calculation, recall, and language

• MMSE is a 30 points score test. Mildly cognitively impaired subjects can have scores 26 to 21
VCI: Definitions and Recent refinements in understanding clinical entity
Difficulties with spectrum of VCI?
Vascular Cognitive Impairment

Vascular = all causes of CVD (cardiovascular also)
Cognitive Impairment = early to late and severe forms of dementia syndromes (VaD and MCI)
Prevalence of VCI: expected to be very high!

- Early-onset VaD (<65 yrs) ranges 3-44 % clinic and population-based studies; Recent US study medicare prevalence ~15%
- Pathologically diagnosed VaD 0.03-60% with an overall mean estimate 18%

Original Contributions

National Institute of Neurological Disorders and Stroke–Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards

Vladimir Hachinski, MD, DSc; Costantino Iadecola, MD; Ron C. Petersen, MD, PhD; Monique M. Breteler, MD, PhD; David L. Nyenhuis, PhD; Sandra E. Black, MD; William J. Powers, MD; Charles DeCarli, MD; Jose G. Merino, MD; Raj N. Kalaria, PhD, FRCP; Harry V. Vinters, MD; David M. Holtzman, MD; Gary A. Rosenberg, MD; Anders Wallin; Martin Dichgans, MD; John R. Marler, MD; Gabrielle G. Leblanc, PhD

Background and Purpose—One in 3 individuals will experience a stroke, dementia or both. Moreover, twice as many individuals will have cognitive impairment short of dementia as either stroke or dementia. The commonly used stroke scales do not measure cognition, while dementia criteria focus on the late stages of cognitive impairment, and are heavily biased toward the diagnosis of Alzheimer disease. No commonly agreed standards exist for identifying and describing individuals with cognitive impairment, particularly in the early stages, and especially with cognitive impairment related to vascular factors, or vascular cognitive impairment.

Methods—The National Institute for Neurological Disorders and Stroke (NINDS) and the Canadian Stroke Network (CSN) convened researchers in clinical diagnosis, epidemiology, neuropsychology, brain imaging, neuropathology, experimental models, biomarkers, genetics, and clinical trials to recommend minimum, common, clinical and research standards for the description and study of vascular cognitive impairment.

Results—The results of these discussions are reported herein.

Conclusions—The development of common standards represents a first step in a process of use, validation and refinement. Using the same standards will help identify individuals in the early stages of cognitive impairment, will make studies comparable, and by integrating knowledge, will accelerate the pace of progress. (Stroke. 2006;37:2220-2241.)
VCI: Neuropsychological Tools

Proposed 30-Minute and 5-Minute Neuropsychological Protocols

30-Minute Test Protocol
- Semantic Fluency (Animal Naming)
- Phonemic Fluency (Oral Word Association Test)
- Digit Symbol-Coding from the Wechsler Adult Intelligence Scale, Third Edition
- Hopkins Verbal Learning Test
- Center for Epidemiologic Studies-Depression Scale
- Neuropsych Inventory, Questionnaire Version (NPI-Q)
- Supplemental: MMSE, Trail Making Test

5-Minute Protocol
- MoCA subtests
- 5-Word Memory Task (registration, recall, recognition)
- 6-Item Orientation
- 1-Letter Phonemic Fluency
- Supplemental: Remainder of the MoCA, Semantic Fluency (Animal Naming), Trail Making Test, MMSE (to be administered at least 1 hour before or after the above tests).

VCI may include all cognitive domains, but there is likely to be a preponderance of so-called “executive” dysfunction (i.e., slowed information processing, impairments in the ability to shift from one task to another, and deficits in ability to hold and manipulate information or working memory)
Montreal Cognitive Assessment (MoCA)

- MoCA also includes tests for orientation (e.g. year, season, etc.), registration, attention and calculation, recall, and language biased towards Executive Dysfunction

- MoCA is a 30 points score test. Mildly cognitively impaired subjects can have scores 26 to 21
MoCA and ACE-R had good sensitivity and specificity for MCI defined using the NINDS-CSN Battery (Hachinski et al, 2006) 1 year after TIA and stroke but MMSE showed a ceiling effect.
VCI and Cognitive Function after Stroke

Neuropsychological Test Criteria: General considerations

- Quality of the standardization sample
- Psychometric qualities
- Portability
- Brevity
- Cost
- Ease of use
- Domain specificity (for 1-hour battery)
- Availability of multiple forms
- International or cross-cultural capability
- The lack of ceiling and floor effects
- Previous use of the test in VCI samples

*Trialled and Tested in sub-Saharan Africa!*

After Hachincki V et al, 2006
The spectrum of VCI

- Bowler JV. JNNP, 2005 – VCI concept refinement
- Hachinski V. et al, Stroke, 2006 -VCI Harmonization
- Sachdev P. et al, ADADJ, 2014 – Neurocognitive Disorders and VCD
- Skrobot O. et al, Alzheimers & Dementia, 2016 -VICCCS
- Skrobot O. et al, Alzheimers & Dementia, 2017 -VICCCS
Diagnostic criteria for vascular cognitive disorders: a VASCOG statement

• Cognitive disorders of vascular etiology are a heterogeneous group of disorders with diverse pathologies and clinical manifestations as VCD.
• Continuum of VCI recognized by categories of **Mild Vascular Cognitive Disorder, and Vascular Dementia or Major Vascular Cognitive Disorder**. Diagnostic thresholds, clinical/ceuroimaging criteria proposed for establishing vascular etiology.
• Subtypes of VCD with frequent co-occurrence of AD pathology emphasized
• Proposed criteria for VCD provide a coherent approach to diagnosis of diverse group of disorders and stimulate clinical-pathological validation studies
• Harmonized with the DSM-5 criteria

From P Sachdev et al, 2014
### The Vascular Impairment of Cognition Classification Consensus Study

<table>
<thead>
<tr>
<th>Subtypes in the VICCCS</th>
<th>Descriptive terms in the VICCCS</th>
<th>O'Brien concept classification and causes of sporadic VCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post stroke dementia</td>
<td></td>
<td>Post stroke dementia</td>
</tr>
<tr>
<td>Multi-infarct (cortical)</td>
<td></td>
<td>Vascular dementia</td>
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<tr>
<td>Subcortical ischaemic</td>
<td></td>
<td>Multi-infarct dementia (cortical vascular dementia)</td>
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<td></td>
<td>Strategic infarct</td>
<td>Subcortical ischaemic vascular dementia</td>
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<td>Hypoperfusion</td>
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<td></td>
<td>Haemorrhagic</td>
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<td></td>
<td>Specific arteriopathies*</td>
<td>Dementia caused by specific arteriopathies</td>
</tr>
<tr>
<td>Mixed dementias*</td>
<td></td>
<td>Mixed AD and vascular dementia</td>
</tr>
<tr>
<td>Mild VCI</td>
<td></td>
<td>Vascular mild cognitive impairment</td>
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<tr>
<td></td>
<td></td>
<td>Vasculitis§</td>
</tr>
</tbody>
</table>

- **Towards universal acceptance of VCI criteria**
  - impacting on clinical diagnosis rates, prevalence estimates, research and treatment
- VICCCS consortium by an online Delphi consensus study
- VICCCS redefined VCI including classification of mild and major forms of VCI and subtypes.
- Proposed new standardized VCI-associated terminology and future research priorities to address gaps in current knowledge
- VICCCS proposed a consensus-based updated conceptualization of VCI intended to facilitate standardization in research

*From O Skrobot et al, 2016*
Progress towards standardised diagnosis of VCI guidelines from VICCCS

- Diagnosis of VICCCS-revised *Mild and Major forms of VCI* and endorsed the NINDS-CSN (Hachinski et al, 2006) neuropsychological assessment protocols and recommendations for imaging
- Core domains for assessment should include: executive function, attention and memory as well as language and visuospatial function

**Mild VCI:** Impairment in at least ONE cognitive domain and mild to no impairment in ADL (independent of motor/sensory sequelae of vascular event)

**Major VCI (VaD):** Clinically significant deficits of sufficient severity in *at least* ONE cognitive domain (deficits may be present in multiple domains) and severe disruption to ADL (independent of the motor/sensory sequelae of the vascular event)

From O Skrobot et al, 2017 in press
Diagnosis of VaD: NINDS-AIREN Criteria

Dementia
- Impaired memory
- ≥ 2 other cognitive domains impaired

Cerebrovascular disease
- Neurological exam
- Neuroimaging

Probable/Possible diagnosis
- Temporal relationship between CVD and dementia
  - Abrupt onset / stepwise progression
  - Absence of disorders that could account for deficits (eg, AD)

Definitive diagnosis by autopsy?

THE NINDS-AIREN CRITERIA
Probable Vascular Dementia

1) Dementia

2) Cerebrovascular disease
   a) Focal signs consistent with stroke

   AND

   b) Relevant CVD by brain imaging
      • Multiple large-vessel infarcts
      • Single strategically placed infarct
      • Multiple lacunes
      • Extensive periventricular WMLs

3) Relationship between 1) and 2)
   a) Dementia onset within 3 months

   b) Abrupt deterioration in cognitive functions. Fluctuating stepwise progression

Roman G et al 1993
Principles of diagnosis

- Is dementia syndrome present? Refer to DSM/ICD-10 criteria
- Are two (generally) areas of brain function affected (from cognitive assessment, consider educational level)
- Functional impairment (assess IADLs)
- Always get a collateral history (for functional impairment, timescale (6 months for ICD-10))
- Exclude common differentials,
- DELIRIUM (is attention affected?)
- DEPRESSION (if in doubt, trial of treatment before diagnose dementia)
- Exclude reversible causes of dementia (hypothyroid, B12/folate/anaemia, HIV?, alcohol (thiamine))
- Consider dementia subtype (pattern of cognitive deficit, risk factors, neurological examination)
Frequency of Cognitive Impairment and Dementia after Stroke Injury

What type(s) of dementia do stroke survivors develop?
Cognitive Function after Stroke

- Pre-stroke dementia ranged 9-14%
- PSD (≤1 year) rates ranged 7-41% in hospital-based studies of recurrent stroke
- Incidence of dementia >1st year was 3% per yr
- MTLA, female gender, family history of dementia strongly associated with pre-stroke dementia
- Characteristics and complications of stroke and multiple lesions in time and place strongly associated with PSD
- Interpretation: 10% of patients had dementia before first stroke, 10% developed new dementia soon after first stroke, and >third had dementia after recurrent stroke.

Causal role of stroke, optimum acute stroke care and secondary prevention important in reducing the burden of cognitive impairment

(Pendlebury ST and Rothwell P, TLN, 2009)
Cognitive Impairment in Lacunar Stroke

- 24% had MCI or PSD
- Similar proportions: lacunar and non-lacunar strokes had MCI or dementia (1-4 yrs after stroke)
- Prevalence: 20% dementia after lacunar stroke
- Incidence: 37% MCI or dementia
- Limitations: short follow-up, subtype classification methods and confounding factors
- Conclusions: cognitive impairment common after lacunar strokes.
- New prospective studies required with accurate stroke subtyping to assess long term outcomes while accounting for cofactors

Neuroimaging Correlates of Cognitive Impairment and Dementia

SVD type(s) of VCI most common
Cerebral Small Vessel Disease: Clinical Features

Varied manifestations

• Much of SVD can be clinically silent
• Sudden-onset stroke symptoms or syndromes e.g. lacunar syndrome
• Mostly covert neurological symptoms and signs
• Motor slowing, dysarthria, short-stepped gait
• Cognitive: Self-reported cognitive difficulties e.g. executive slowing, processing speed, forgetfulness, dementia
• Behavioural: apathy (20-25%), depression (20-30%)
Neuroimaging of SVD: lacunar infarction

Male 61 yr old, lacunar infarct

Symptoms: left side hemiparesis, dysarthria. Reported as normal, but with information later MRI a faint hypodensity discerned at lateral border of right thalamus

What Neuropsychometric changes can you predict?

Rather than amnestic type memory impairment features associated with frontal lobe function i.e. Executive Function tasks, processing speed, working memory are more evident.
Lacunes and Lacunar infarcts

Lacunes

• complete or cavitating infarcts; up to 15 mm; common in subcortical structures
SVD Pathophysiology

Neuroimaging (MR)
1. Periventricular and Deep WMH
2. Lacunes and macro infarcts
3. Cortical: small infarcts
4. Subcortical: macroinfarcts
5. Cerebral Microbleeds
6. Amyloid deposition (PET)
7. Superficial siderosis
8. Perivascular spaces

Neuropathology
1. Periventricular WM changes (myelin loss)
2. Subcortical infarcts: Lacunes and macro infarcts
3. Cortical: small infarcts
4. Subcortical and cortical: microinfarcts
5. Microhaemorrhage/haemosiderin
6. Superficial haemosiderin (some)
7. Cerebral Amyloid Angiopathy
8. Perivascular spaces Arteriolosclerosis
Lacunar Infarcts in relation to WMH in SVD

Proposed model for a typical evolution of WMH and lacunes in SVD

- Spread of changes towards subcortical regions in SVD (ASPS and CADASIL cohorts)
- Majority (>90%) of lacunes were found at the edge (proximal predilection) of WMH
- Pathophysiology of lacunes and WMH is intimately connected

Modified after M Duering et al, 2011
Secondary cortical neurodegeneration after subcortical ischemia (SVD) as a mechanism for brain atrophy

From M Duering et al, 2012

A causal relationship between incident subcortical infarcts and morphologic alterations in connected cortical regions

Implies a role for secondary neurodegeneration within cortical GM (focal cortical thinning) after axonal damage e.g. infarct in WM

From M Duering et al, 2012
## Subtypes of VaD/VCI: Vascular Mechanisms and Brain Changes

<table>
<thead>
<tr>
<th>Vascular mechanisms</th>
<th>Cortical VaD</th>
<th>Strategic infarct VaD</th>
<th>Subcortical ischemicVaD SVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large-vessel disease</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>Cardiac embolic events</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>Hypoperfusion (focal or global)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Small-vessel disease</td>
<td>×</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

| Clinical and Cognitive Features            |              |                       |                             |
| Focal neurological signs                   | ✓            | ✓ / ×                 | ×                           |
| Stepwise progression                       | ✓            | ×                     | ×                           |
| Cognition (memory/executive)               | ✓            | ✓                     | ✓                           |
| Changes in the brain                       |              |                       |                             |
| Large cortico-subcortical                  | ✓            | ×                     | ×                           |
| Arterial territorial infarct               | ✓            | ✓                     | ×                           |
| Distal field (watershed) infarct           | ✓            | ✓                     | ×                           |
| Lacunar infarcts                           | ×            | ✓                     | ✓                           |
| Focal, diffuse WMLs                        | ×            | ✓                     | ✓                           |
| Incomplete ischaemic injury                | ×            | ×                     | ✓                           |
| Heterogeneity                              | ++           | +++                   | +                           |

*WMLs- white matter lesions*

T Erinkunjuntti and R Kalaria, 2005
Accumulation of Focal Cortical Symptoms

Large-vessel disease

Cortical infarcts in strategic locations

Frontal lobe: Aphasia, apraxia, disinhibition, apathy
Hippocampus, basal forebrain: Amnesia
Gyrus angularis: Constructional problems
Parietal lobe: Alexia, agraphia

Cortical type of dementia
Non-Specific Disconnection of the Cortex

Small-vessel disease

Diffuse white matter lesions

Disruption of cortico-cortical pathways

Frontal, temporal and parietal cortical deficits

Mixed cortical / subcortical type of dementia
Disruptions of Subcortico-cortical Circuits

Small-vessel disease

Subcortical infarcts in strategic locations
- Thalamus, caudate nucleus, internal capsule

Disruption of specific fronto-subcortical circuits or non-specific thalamo-cortical projections

Executive dysfunction, Apathy, Attentional deficit, Personality change

Subcortical type of dementia
Vascular Basis for Dementia and Neurodegeneration in Stroke Survivors

What type(s) of dementia do stroke survivors develop?
Stroke and Dementia are risks for each other

Modified from K Nagata, 2007
COGnitive Function After STroke (COGFAST – Newcastle Study)

Baseline Recruitment at 3 months:
COGFAST- first ever (overt) stroke
Original screen ~702 Non- demented elderly (>70 years) stroke survivors

- 415 participants
  - 356 stroke survivors (dementia free)
  - 59 Vascular Dementia cases
- 103 sub study (MRI and Cardiovascular Assessment)

Demented/severe disability 3 months post stroke: n=287 removed
COGFAST study: Overall Clinical and Neuropsychometric Findings

- Elderly group
- After 5 years, nearly half will have died.
- Only 1 third will be alive without dementia
- Greater decline to death or dementia if >2 vascular risk factors or baseline cognitive impairment but no dementia
- Incident depression 36.9 episodes per 100 person years

- Already lived to 80
- Improvement in cognitive function (CAMCOG) in ~25% post stroke
- Approx. 50% chance of another 5 years
- Better outcomes if no other risk factors (to CI or death)
- >60% free of depressive illness

MRC 15-year Longitudinal study of post-stroke survivors: Lead PI R Kalaria

COGFAST study: Overall Clinical and Neuropsychometric Findings

- Elderly group
- After 5 years, nearly half will have died.
- Only 1 third will be alive without dementia
- Greater decline to death or dementia if >2 vascular risk factors or baseline cognitive impairment but no dementia
- Incident depression 36.9 episodes per 100 person years

MRC 15-year Longitudinal study of post-stroke survivors: Lead PI R Kalaria

Long term incidence of dementia, predictors of mortality and pathological diagnosis in older stroke survivors

Louise M. Allan, Elise N. Rowan, Michael J. Firbank, Alan J. Thomas, Stephen W. Parry, Tuomo M. Polvikoski, John T. O’Brien and Raj N. Kalaria

Institute for Ageing and Health, Newcastle University, Wolfson Research Centre, Campus for Ageing and Vitality, Newcastle upon Tyne, NE4 5LP, UK
Correspondence to: Prof. Raj N. Kalaria

- During mean follow-up of 3.8 years, ~25% developed PSD
- Duration of survival (days from baseline stroke to death) or overall burden of vascular and minimal neurodegenerative pathology (Braak <2.5) similar between PSD and PSND
- Elderly stroke survivors in this age group likely to develop VaD: Pathological diagnosis indicated ~75% VaD, rest Mixed (AD type pathology with vascular lesions) and frontotemporal dementia (1)
- Microinfarction differentiated PSD from non-demented PS survivors

Neuropathology in Elderly Stroke Survivors
What are the pathological substrates of PSD?
Newcastle Categorization of the Major CV lesions Associated with Cognitive Impairment

I
- large infarct or several infarcts
- multi-infarct dementia

II
- multiple small or microinfarcts
- white matter lesions

III
- strategic infarcts
- thalamus hippocampus basal forebrain

IV
- cerebral hypoperfusion
- hippocampal sclerosis

V
- cerebral hemorrhage
- lobar ICH SAH

VI
- CV lesions with AD pathology
- mixed dementia

Slide courtesy of Dr Ken Nagata
COGFAST study: Carotid Artery Disease (CAD) and Stroke Injury

a

b

Oxford Handicap Scale

<table>
<thead>
<tr>
<th></th>
<th>No symptoms</th>
<th>Minor symptoms</th>
<th>Minor handicap</th>
<th>Moderate handicap</th>
<th>Severe handicap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>17%</td>
<td>83%**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>23%</td>
<td>56%</td>
<td>14%**</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>7%</td>
<td>53%</td>
<td>33%**</td>
<td>7%</td>
<td></td>
</tr>
</tbody>
</table>

Hase Y et al, Submitted 2018
COGFAST study: Carotid Artery Disease (CAD) and Stroke Injury

Location of brain infarcts

- Mild: 45% Cerebral cortex, 22% White matter, 18% Basal ganglia/Thalamus, 14% Brainstem, 2% Cerebellum
- Moderate: 31% Cerebral cortex, 17% White matter, 43% Basal ganglia/Thalamus, 2% Brainstem, 8% Cerebellum
- Severe: 3% Cerebral cortex, 5% White matter, 20% Basal ganglia/Thalamus, 8% Brainstem, 63% Cerebellum

Distribution of brain infarcts size

- Mild: 74% <5mm, 18% 5-15mm, 2% 16-30mm, 6% 31-50mm, 2% >51mm
- Moderate: 74% <5mm, 13% 5-15mm, 4% 16-30mm, 4% 31-50mm, 6% >51mm
- Severe: 76% <5mm, 6% 5-15mm, 6% 16-30mm, 5% 31-50mm, 6% >51mm

Hase Y et al, Submitted 2018
Staging and natural history of cerebrovascular pathology in dementia

Deramecourt V et al, 2012

ABSTRACT
Objective: Most pathologic studies indicate that significant vascular changes are found in the majority of elderly persons, either alone or in association with neurodegenerative processes such as Alzheimer disease (AD) or dementia with Lewy bodies (DLB). Cumulative burden of cerebrovascular lesions can explain cognitive decline described as vascular cognitive impairment, but because there is a lack of consensus in the best way to quantify vascular pathology, the relationship between cognitive decline and cerebrovascular disease remains uncertain. We developed a rating scheme for cerebrovascular lesions using postmortem brains from patients with dementia from 2 European tertiary care memory clinics.

Staging and Natural history of cerebrovascular pathology

Semiquantitative scoring of CVL

0 1 2 3

Arteriolosclerosis

Amyloid angiopathy

Perivascular hemosiderin leakage

Perivascular spaces dilatation

Myelin loss

<table>
<thead>
<tr>
<th>Final neuropathological diagnosis</th>
<th>Vessel wall modifications</th>
<th>Perivascular and white matter modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteriolosclerosis</td>
<td>Amyloid angiopathy</td>
<td>Perivascular hemosiderin leakage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deep white matter</td>
</tr>
<tr>
<td></td>
<td></td>
<td>perivascular spaces dilatation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Autocortical white matter</td>
</tr>
<tr>
<td></td>
<td></td>
<td>perivascular spaces dilatation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Myelin loss</td>
</tr>
</tbody>
</table>

SCORE VI
SCORE V
SCORE IV
SCORE III
SCORE II
SCORE I
White Matter Changes: do they matter?

Leukoencephalopathy

1) periventricular versus deep WM
2) anterior versus posterior deep WM
White matter hyperintensities (WMHs) associated with an increased risk of
- Stroke (HR 3.3)
- Dementia (1.9)
- Death (2.0)

Association of WMH with a faster decline in global cognitive performance, executive function, and processing speed.

WMH indicate an increased risk of CBV events when identified as part of diagnostic investigations.

Fig 3: Inverse variance meta-analysis of studies testing association of white matter hyperintensities with incident dementia.
Leukoencephalopathy

WMLs predict functional decline over a 3 yr period in elderly without disability at baseline (LADIS study)

• Annual rates of transition to disability or death were 29.5% in those with severe vs. 10.5% in mild WMLs

*Inzitari D et al, 2009*
Neuroimaging defined SVD: What are the substrates of dementia?

- Silent Infarcts increase with age and are a risk for dementia (increases risk for AD by >2.5-fold)
- White matter changes (WMHs on T2w MRI) increase risk for dementia (and AD)
- Greater baseline CVD risks or WMHs are associated with cognitive impairment (and AD)
- Vascular risk factors contribute to dementia (even AD) through additive effects but not necessarily independent of amyloid (PiB tracer studies) pathway

Severe Frontal WM Myelin Loss in VaD

- Degree of myelin loss in related to greater %dMBP
- %dMBP inversely correlated with the mean size of oligodendrocytes
- Greatest degrees of myelin loss in VaD versus other dementias

Ihara M et al, 2010
Chronic hypoxic state in deep WM: a common finding

- Dementia related to deep WM rather than periventricular WMLs
- Arteriolar changes restricted to Deep WM; ↑WM rarefaction (lesional) correlated with severity in degree of (cortical) CAA
- ↑ ICAM/Collagen IV ratio for lesional deep WM vs normal WM
- ↑ CD68 +ve cells in lesional deep WM (VCI) vs normal WM
- ↑ HIF1α +ve cells in lesional deep WM vs normal WM

Fernando M et al, 2003; Simpson S et al, 2007; 2008; Ihara M et al 2010
Strategic role of frontal white matter tracts in vascular cognitive impairment

- Most prominent feature: processing speed
- Predominantly affected cognitive domain in lacunar stroke SVD and CADASIL
- Strategic locations included *anterior parts of thalamus*, the genu and anterior limb of the internal capsule, anterior corona radiata and genu of the corpus callosum
- Interpretation: anterior thalamic radiation as a major anatomical structure impacting on processing speed.
- Strong support for a central role of frontal-subcortical circuits in SVD and VCI

*Duering M et al, Brain, 2011; Benjamin et al, 2014*
## What factors in WM Pathology are important in Elderly Stroke Survivors who develop Dementia?

<table>
<thead>
<tr>
<th>WM Marker</th>
<th>PSND† (Stable)</th>
<th>PSD† (Decliners)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukoaraiosis (WMH on MRI)</td>
<td>+</td>
<td>++</td>
<td>SD↑</td>
</tr>
<tr>
<td>Total Vascular pathology score</td>
<td>+++</td>
<td>+++</td>
<td>nsd</td>
</tr>
<tr>
<td>Microinfarction</td>
<td>++</td>
<td>+++</td>
<td>SD↑</td>
</tr>
<tr>
<td>Myelin Index</td>
<td>++</td>
<td>+++</td>
<td>trend↑</td>
</tr>
<tr>
<td>Degenerated MBP</td>
<td>+</td>
<td>++</td>
<td>trend↑</td>
</tr>
<tr>
<td>Axons: SMI32/SMI31</td>
<td>++</td>
<td>+++</td>
<td>trend↑</td>
</tr>
<tr>
<td>Sclerotic Index / PVS</td>
<td>+++</td>
<td>+++</td>
<td>nsd</td>
</tr>
<tr>
<td>Astrocyte degeneration/BBB damage</td>
<td>++</td>
<td>+++</td>
<td>SD↑</td>
</tr>
<tr>
<td>Pericyte degeneration/Capillary coverage</td>
<td>++</td>
<td>+++</td>
<td>SD↑</td>
</tr>
<tr>
<td>Microglial Activation/Perivascular</td>
<td>++</td>
<td>+++</td>
<td>SD↑</td>
</tr>
</tbody>
</table>

† Mean Braak stage = 2.6 in PSND and PSD

Which markers of WM pathology differentiate demented (PSD) and non-demented (PSND) survivors?

Frontal WMH volume was an independent predictor of survival to dementia

Data analysis: n=106 subjects; Cox multivariate models; p=0.037, HR 95%1.90 (1.04 to 3.48)
Screening, Diagnosis and Risk Factors for Dementia in SSA

Arms of Newcastle Longitudinal studies
COGnitive Function After STroke (COGFAST – Nigeria Study)

Longitudinal study of post-stroke survivors in Africa (Ibadan, Nigeria, Nairobi, Kenya and Hai District Tanzania: Pls R Kalaria, A Ogunniyi, M Owolabi, R Akinyemi, R Walker)
Map of Nigeria showing the study area in Southwestern part of the country  

[A] Political map of Nigeria showing Abeokuta and Ibadan north of Lagos  

[B] An ethno-linguistic map showing the Yoruba speaking Southwestern region of the country with location of study centres
CogFAST – Nigeria: Vascular Neuropsychological Battery

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive Function/Activation</td>
<td>Category (Animal) Fluency Test</td>
</tr>
<tr>
<td></td>
<td>Phonemic (Letter) Fluency Test</td>
</tr>
<tr>
<td></td>
<td>Verbal Reasoning (Similarities Test)</td>
</tr>
<tr>
<td></td>
<td>Ideational Fluency Test</td>
</tr>
<tr>
<td>Language/Lexical Retrieval</td>
<td>Boston Naming Test (2nd version)</td>
</tr>
<tr>
<td>Memory/Learning</td>
<td>Word List Test (Learning, Recall, Recognition)</td>
</tr>
<tr>
<td></td>
<td>Delayed Recall of Stick Design</td>
</tr>
<tr>
<td>Visuospatial/Visuoconstruction</td>
<td>Stick Design Test</td>
</tr>
<tr>
<td>General Cognitive Functioning</td>
<td>Modified Tokens Test (IU Token Test)</td>
</tr>
<tr>
<td></td>
<td>Community Screening Instrument for Dementia (CSID MMSE)</td>
</tr>
</tbody>
</table>

- Based on the 60 min VCI Harmonization Standards – Neuropsychological Protocol proposed by the NINDS – CSN (Hachinski et al, 2006).

- Multiple test items assessing each cognitive domain were selected in consonance with the recommendations of the Harmonization standards.

- Utility of tests in previous cognitive evaluations in environment of study population

Refs: Folstein, 1995; Hall et al, 1993; 2000; Gureje et al., 1995; Blessed et al, 1991; Unverzaght et al., 1999; Ballard et al, 2002; Baiyewu et al., 2005; Akinyemi et al., 2008
CogFast- Nigeria: Stroke and Cognition

- First ever stroke survivors mean age = 61 yrs
- 80% Ischaemic stroke; 41% lacunar stroke
- Median modified Rankin score = 2
- 8.4% demented at baseline and 30% cognitive impairment no dementia (CIND)
- Pre-stroke cognitive decline
- Medial temporal lobe atrophy (MTA) [OR = 2.25 (1.16–4.35)] was independently associated with cognitive dysfunction
- High frequency of early VCI

Pattern of performance on Choice Reaction Time (CRT) in controls and impaired subjects.

Akinyemi R et al, 204; 2015
## Predictors of Post-stroke VCI - COGFAST Nigeria

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis OR (95%CI)</th>
<th>Multivariate analysis: OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Age (years)</td>
<td>1.06 (1.02 – 1.10)</td>
<td>1.05 (1.00 – 1.09)</td>
</tr>
<tr>
<td>Female Gender</td>
<td>2.27 (1.15 -4.45)</td>
<td>1.87 (0.80 – 4.40)</td>
</tr>
<tr>
<td>&lt; 6 years of education</td>
<td>4.84 (2.36 – 9.92)</td>
<td>5.09 (2.17 – 11.95)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.18 (0.30 4.58)</td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>1.29 (0.59 -2.79)</td>
<td></td>
</tr>
<tr>
<td>Previous stroke</td>
<td>1.38 (0.51 -3.10)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>1.253 (0.51 – 3.10)</td>
<td>1.19 (0.47 -3.00)</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>2.01 (1.01 – 4.00)</td>
<td></td>
</tr>
<tr>
<td>Daily fish intake pre-stroke</td>
<td>0.42 (0.20 – 0.88)</td>
<td>0.37 (0.15 -0.89)</td>
</tr>
<tr>
<td>Moderate to strenuous physical activity pre-stroke</td>
<td>0.17 (0.04 – 0.84)</td>
<td>1.00 (0.99 -1.02)</td>
</tr>
<tr>
<td>Modified Rankin Score</td>
<td>1.03 (0.53 – 1.98)</td>
<td></td>
</tr>
<tr>
<td>Barthel Index</td>
<td>0.98 (0.90 -1.06)</td>
<td></td>
</tr>
<tr>
<td>CESD score</td>
<td>1.04 ( 0.96 – 1.12)</td>
<td></td>
</tr>
</tbody>
</table>

Factors associated with PS VCI include older age at baseline, female gender and lower educational attainment.

While pre-stroke moderate- heavy physical activity and daily fish intake were protective.

*Significant results are shown in bold (p <0.01)*

_Akinyemi R et al, JNS, 2014; BMC Res Notes 2015_
Medial temporal lobe atrophy (MTLA) was independently associated with VCI/VaD in PS survivors at 12 months.

MTLA correlated significantly with cognitive performance and white matter hyperintensities (WMHs) on T2W MRI.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal vs vCIND</th>
<th>vCIND vs PSD</th>
<th>Normal vs (vCIND + PSD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTLA rating</td>
<td>2.02 (1.05 – 3.87)</td>
<td>0.035</td>
<td>2.25 (1.16 – 4.35)</td>
</tr>
<tr>
<td>Log _ TBV</td>
<td>0.01 (0- 1996.50)</td>
<td>0.260</td>
<td></td>
</tr>
</tbody>
</table>
Hypertension and Incident dementia risk

<table>
<thead>
<tr>
<th>Effect</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1.52</td>
<td>1.01- 2.30</td>
</tr>
<tr>
<td>Systolic BP, X 10 mm Hg</td>
<td>1.09</td>
<td>1.03 – 1.16</td>
</tr>
<tr>
<td>Diastolic BP, X 10 mm Hg</td>
<td>1.22</td>
<td>1.07 – 1.38</td>
</tr>
<tr>
<td>Pulse Pressure, X 10 mm Hg</td>
<td>1.10</td>
<td>1.01 – 1.21</td>
</tr>
</tbody>
</table>

Screening Cognitive Function and Diagnosis of Dementia in Hai, Tanzania
Community Validation, Hai Dementia screening Study

Cut-off of ≤ 7

- Sensitivity: 60.0%
- Specificity: 84.2%
- LR: 3.80

Cut-off of ≤ 8

- Sensitivity: 88.6%
- Specificity: 64.2%
- AUROC curve: 0.846 (95% CI 0.776 - 0.915)

Educational level no association
Difficulties with cognitive assessment
Pilot MMSE used in Hai, 2011

<table>
<thead>
<tr>
<th>*=missing</th>
<th>Dementia n=17</th>
<th>MCI N=29</th>
<th>Normal cognition N=14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (med, IQR)</td>
<td>81.0 (16.50) *=1</td>
<td>85.0 (10.0)</td>
<td>80.00 (14.0)</td>
</tr>
<tr>
<td>Female (n, %)</td>
<td>11 (64.71)</td>
<td>19 65.52</td>
<td>11 (78.57)</td>
</tr>
<tr>
<td>Ever attended formal school (n, %)</td>
<td>4 (23.53)</td>
<td>10 34.48</td>
<td>7 (50.0)</td>
</tr>
<tr>
<td>Years of education (med, IQR)</td>
<td>0.00 (1.00)</td>
<td>0.00 (3.00)</td>
<td>0.50 (4.0)</td>
</tr>
<tr>
<td>Self-reported basic literacy (n, %)</td>
<td>4 (23.53)</td>
<td>7 (24.14)</td>
<td>7 (50.0)</td>
</tr>
<tr>
<td>Minimally adapted MMSE total score (med, IQR)</td>
<td>12.00 (4.50)</td>
<td>15.0 (5.0)</td>
<td>19.50 (3.75)</td>
</tr>
<tr>
<td>MMSE total disregarding literacy and numeracy based items /22</td>
<td>12.00 (4.50)</td>
<td>14.0 (4.0)</td>
<td>19.00 (2.5)</td>
</tr>
</tbody>
</table>
Screening and diagnosis of Dementia in LMICs

Epidemiological Studies

Population-based epidemiological studies (prevalence phase) in eight Latin American countries (Cuba, Brazil, Dominican Republic, Venezuela, Peru, Mexico, Argentina and Puerto Rico), India, China, Nigeria and South Africa.

A three year follow up of all prevalence phase participants (incidence phase) in Cuba, Dominican Republic, Venezuela, Peru, Mexico, Argentina and China, with a more limited follow-up in India.
Screening tools for dementia designed for use in SSA?

- MMSE is still the most widely used test – but almost useless in those with low education

- CSI-D validated in >2000 older people in LMICs (but only 20 from SSA)

- False positive rate still 25% in low edu.

- Both tests take over 30-40 min to complete – too long for screening

<table>
<thead>
<tr>
<th>Test</th>
<th>Questions</th>
<th>Sensitivity</th>
<th>AUROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSI-D</td>
<td>30 + 30</td>
<td>92</td>
<td>0.9191 (90–92)</td>
</tr>
<tr>
<td>TEST OF SENEGAL</td>
<td>39</td>
<td></td>
<td>0.967</td>
</tr>
</tbody>
</table>
The IDEA six-item cognitive screen

- Developed for low-literacy settings in sub-Saharan Africa
- Takes 5-10 minutes to administer
- Validated for dementia screening in community and geriatric OPD (Tanzania)
- Validated for major cognitive impairment (dementia or delirium) in older inpatients (Tanzania, Nigeria and Zambia)
The IDEA study brief screening test

- 6 item screening test
- Designed for non specialists and low literacy population
- Designed to cover all lobes of the brain
- Most discriminating questions from CSI-D (used in Hai dementia prevalence study)
- CERAD 10 word learning list
- Baiyewu matchstick test

<table>
<thead>
<tr>
<th></th>
<th>First attempt</th>
<th>Second attempt</th>
<th>Third attempt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siagi</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mkono</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barua</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mfalme</td>
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<td></td>
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<tr>
<td>Tikiti</td>
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<td></td>
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<tr>
<td>Nyasi</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Kona</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Jiwe</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kitabu</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fimbo</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# IDEA Screening tool -2

<table>
<thead>
<tr>
<th>Question</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>I will tell you the name of something and I want you to describe what it is.</td>
<td>Score: ____/2</td>
</tr>
</tbody>
</table>
| What is a bridge? (correct answer: something that goes across a river, canyon or road) | 0 if incorrect  
2 if correct |
| Number of animals named:____  
0 for 0-3 animals named  
1 for 4-7 animals named  
2 for 8 or more animals | Score: ____/2 |
| Who is the chief/head/leader of this village?                             | 0 if incorrect  
1 if correct |
| Score: ____/1 |
| What day of the week is it?                                               | 0 if incorrect  
2 if correct |
| Score: ____/2 |
| Can you tell me any of the words you learned earlier?                    | 1 one word  
2 two words  
3 three words  
4 four words  
5 5 or more words | Score: ____/5 |
Can you make the design shown below using these four matchsticks. I will show you once and then you have to copy exactly.

Score 1 for each part of the design that is performed correctly

| 1 Middle two matchstick heads pointing same way |
| 1 Outside two matchsticks pointing at an angle |
| 1 Matchstick heads are orientated correctly |

Total score: ____/15
Comparison with other cognitive screening tools commonly used in high income countries

<table>
<thead>
<tr>
<th>TEST</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Area under ROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE – specialist clinic (meta-analysis 34 studies)</td>
<td>79.8</td>
<td>81.3</td>
<td></td>
</tr>
<tr>
<td>MMSE - mixed hospital (meta-analysis)</td>
<td>71.1</td>
<td>96.6</td>
<td></td>
</tr>
<tr>
<td>RUDAS</td>
<td>89</td>
<td>98</td>
<td>0.95</td>
</tr>
<tr>
<td>Addenbrookes (meta-analysis 5 studies)</td>
<td>96.7</td>
<td>77.4</td>
<td></td>
</tr>
<tr>
<td>Six-item screener (for ER)</td>
<td>63</td>
<td>81</td>
<td>0.77</td>
</tr>
<tr>
<td>IDEA inpatients Tanzania</td>
<td>90.9</td>
<td>87.5</td>
<td>0.917</td>
</tr>
<tr>
<td>IDEA outpatients Tanzania &gt; 8</td>
<td>84.6</td>
<td>89.1</td>
<td>0.919</td>
</tr>
<tr>
<td>IDEA inpatients Nigeria</td>
<td>100</td>
<td>96.3</td>
<td>0.990</td>
</tr>
</tbody>
</table>
Instrumental Activities of Daily Living in high-income countries

**Instrumental Activities of Daily Living (IADL)**

**Instructions:** Circle the scoring point for the statement that most closely corresponds to the patient's current functional ability for each task. The examiner should complete the scale based on information about the patient from the patient him/herself, informants (such as the patient's family member or other caregiver), and recent records.

<table>
<thead>
<tr>
<th>A. Ability to use telephone</th>
<th>Score</th>
<th>E. Laundry</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Operates telephone on own initiative; looks up and dials numbers, etc.</td>
<td>1</td>
<td>1. Does personal laundry completely</td>
<td>1</td>
</tr>
<tr>
<td>2. Dials a few well-known numbers</td>
<td>1</td>
<td>2. Launder small items; rinses stockings, etc.</td>
<td>1</td>
</tr>
<tr>
<td>3. Answers telephone but does not dial</td>
<td>1</td>
<td>3. All laundry must be done by others</td>
<td>0</td>
</tr>
<tr>
<td>4. Does not use telephone at all</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Shopping</th>
<th>Score</th>
<th>F. Mode of transportation</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Takes care of all shopping needs independently</td>
<td>1</td>
<td>1. Travels independently on public transportation or drives own car</td>
<td>1</td>
</tr>
<tr>
<td>2. Shops independently for small purchases</td>
<td>0</td>
<td>2. Arranges own travel via taxi, but does not otherwise use public transportation</td>
<td>1</td>
</tr>
<tr>
<td>3. Needs to be accompanied on any shopping trip</td>
<td>0</td>
<td>3. Travels on public transportation when assisted or accompanied by another</td>
<td>1</td>
</tr>
<tr>
<td>4. Completely unable to shop</td>
<td>0</td>
<td>4. Travel limited to taxi or automobile with assistance of another</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5. Does not travel at all</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C. Food preparation</th>
<th>Score</th>
<th>G. Responsibility for own medications</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Plans, prepares, and serves adequate meals independently</td>
<td>1</td>
<td>1. Is responsible for taking medication in correct dosages at correct time</td>
<td>1</td>
</tr>
<tr>
<td>2. Prepares adequate meals if supplied with ingredients</td>
<td>0</td>
<td>2. Takes responsibility if medication is prepared in advance in separate dosages</td>
<td>0</td>
</tr>
<tr>
<td>3. Heats and serves prepared meals, or prepares meals but does not maintain adequate diet</td>
<td>0</td>
<td>3. Is not capable of dispensing own medication</td>
<td>0</td>
</tr>
<tr>
<td>4. Needs to have meals prepared and served</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D. Housekeeping</th>
<th>Score</th>
<th>H. Ability to handle finances</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Maintains house alone or with occasional assistance (e.g., “heavy work domestic help”)</td>
<td>1</td>
<td>1. Manages financial matters independently (budgets, writes checks, pays rent and bills, goes to bank), collects and keeps track of income</td>
<td>1</td>
</tr>
<tr>
<td>2. Performs light daily tasks such as dishwashing, bed making</td>
<td>1</td>
<td>2. Manages day-to-day purchases, but needs help with banking, major purchases, etc.</td>
<td>0</td>
</tr>
<tr>
<td>3. Performs light daily tasks but cannot maintain acceptable level of cleanliness</td>
<td>1</td>
<td>3. Incapable of handling money</td>
<td>0</td>
</tr>
<tr>
<td>4. Needs help with all home maintenance tasks</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Does not participate in any housekeeping tasks</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Scoring:** The patient receives a score of 1 for each item labeled A – H if his or her competence is rated at some minimal level or higher. Add the total points circled for A – H. The total score may range from 0 – 8. A lower score indicates a higher level of dependence.

**Sources:**
Instrumental Activities of daily living (IADL) Scale

1. **Wanatoa Historia/**They give histories of the family, their life, past events
2. **Wana suluhisha/**They settle conflicts
3. **Wanasaidia shughuli ndogo ndogo/**They assist in small works in the home
4. **Wanatoa ushauri/**They give advice
5. **Wanadumisha na kufundisha mila/unyago/**They teach traditions of society
6. **Ni walinzi wa nyumbani/**They watch over the house when others are out.
7. **Wanatunza wajukuu/**They look after the grandchildren
8. **Wanatoa ushawishi/**Persuasion, or changing people’s ideas for the better.
9. **Wanasaidia katika maswala mazito kama sherehe/**They preside over feasts and ceremonies
10. **Wanapangia watu majukumu/**Delegation of responsibilities to others.
11. **Wanasimamia haki/**They ensure fairness.
Results of combined screening, Hai Dementia screening programme

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Auroc</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDEA 6 item screen, used alone</td>
<td>0.846 (0.776-0.915)</td>
</tr>
<tr>
<td>IADL –SSA scale, used alone</td>
<td>0.896 (0.842-0.951)</td>
</tr>
<tr>
<td>IDEA 6 item screen and IADL-SSA used together</td>
<td>0.937 (0.896-0.979)</td>
</tr>
</tbody>
</table>

• Conclusions

- The IDEA brief dementia screening tool performed well in hospital inpatient, outpatient and community settings
- This screening test should prove useful in screening for dementia in SSA
- Less educationally biased than existing tools
- Performance in the community was improved by addition of a functional assessment tool
- Further testing in of this system of dementia screening in other low-resource and community settings is required
Matchsticks (Orientation) Test
(Baiyewu et al 2003)

Subject asked to make the design shown above using four matchsticks. He/She is shown once and then they have to copy exactly.

Score 1 for each part of the design that is performed correctly.
2010 Dementia Prevalence in Hai

- Six villages - Total population 34,078
- 1260 eligible >70 yr on census (56% female)
- 1198 screened - 184 Probable dementia, 108 possible dementia and rest no dementia
- 78 cases (22 male) ; DSM-IV

- Age-adjusted prevalence of dementia was 6.4% (95% CI: 4.9-7.9)
- Age-adjusted “10/66 dementia” prevalence 21.6% (95% CI 17.5-25.7%)
- Dementia Subtypes: 48.7% AD; 41.0% VaD; prevalence 3.9% AD and 2.9% VaD
- Vascular Risk Factors: Diabetes; Cholesterol and Hypertension

Longdon AR et al, 2013
Treatment of VaD/PSD

• There is no known treatment
• Medications to treat symptoms
  • Depression
  • Agitation
• Cholinesterase Inhibitors – no good evidence
• Behavioral strategies

• Potential Agents: several e.g. Cilostazol
  (PDE Inhibition)
# Risk factors for stroke

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Ischaemic Injury</th>
<th>Intracerebral haemorrhage</th>
<th>Subarachnoid haemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater age</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Hypertension</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Ischaemic Heart Disease</td>
<td>++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Raised haematocrit</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>High cholesterol</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Low cholesterol</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>High plasma fibrinogen</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Smoking</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Alcohol</td>
<td>_</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Obesity</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Transient ischaemic attack</td>
<td>++</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Hypertension

• Main modifiable risk factor for stroke
• Stroke risk doubles with each 7.5mmHg increase in usual diastolic BP\(^1\)
• Similar, and probably stronger, relationship with systolic BP
• Treatment of hypertension reduces stroke risk\(^2\)- an average BP reduction of 8.5mmHg results in a 42% reduction in stroke incidence

1) MacMahon et al. 1990 Lancet 335 765-774
2) Collins et al. 1990 Lancet 335 827-838
Hypertension management

• Population or opportunistic screening
• Three separate blood pressure measurements
• Non-pharmacological treatment, e.g. low salt diet, weight loss, exercise
• Drug treatment - costs, monitoring, compliance - high default rates
Advice for Patients and Carers

- Treatment of VRFs is likely to reduce risk of both VaD and AD
- Cholinesterase inhibitors may help DLB/AD and mixed VaD/AD but only if supervision/follow up available
- Cognitive stimulation therapy (psychosocial treatment likely to be beneficial (trialed in Tanzania and Nigeria) but not widely available
- Avoid antipsychotics if possible (stroke and mortality risk in dementia – especially in DLB)
- Carer support and assessment of psychiatric symptoms/difficulties such as refusing to eat usually most distressing for carers
Dementia prevalence can be modified by societal changes.....many factors increase dementia prevalence at specific ages (e.g. those associated with diabetes, survival after stroke, and vascular incidents),

Factors, which could decrease prevalence, such as improved prevention of vascular morbidity, higher levels of education, seem to have had a greater effect

“CFAS results suggest that prevention is possible and that we can have agency in this most complex of disorders.” Sube Banerjee, Editorial Lancet, 2013
Vascular Factors and Neurodegeneration

**Vascular disease risk factors**
Stroke, hypertension, diabetes, dyslipidemia, obesity, atherosclerosis,

**Chronic Hypoperfususive State**
(Oligaemia)
(SVD and microinfarcts)

**White matter lesions**
(demyelination /axonal changes)

**Other factors:**
Genetic -APOE E4/
Environmental

**Aβ, CAA, NFT-tau**

**AD**

**Mixed**

**VaD (PSD)**

**Progression over time**
Stroke: Time is Brain

Stroke - Act F.A.S.T

- Face: Has their face fallen on one side? Can they smile?
- Arms: Can they raise both arms and keep them there?
- Speech: Is their speech slurred?
- Time: Time to call 999 if you see any single one of these signs.

Face:
- Face Drooping. Look for an uneven smile.

Arms:
- Arm Weakness. Is one arm weak? Can you lift both arms?

Speech:
- Speech Difficulty. Listen for slurred speech. Do people understand your speech?

Time:
- Time is Brain! Go to the hospital immediately, preferably with an acute stroke unit!
Vascular Dementia in Africa

Knowledge and perception of stroke amongst hospital workers in an African community


“This study demonstrates gaps in the knowledge of hospital workers about stroke, and treatment choice is influenced by cultural and religious beliefs”

“Health education is still important, even, amongst health workers and stroke awareness campaigns may need to involve faith-based organizations.”
Summary: Post-stroke Cognitive Impairment and Dementia

- In tandem with ageing, stroke and dementia increased in LMICs
- Vascular risk factors associated with Dementia and Neurodegeneration; *Hypertension is foremost in most studies*; *control VRFs*
- Neuropsychometric assessment: MMSE, MoCA, CSI-D, IDEA
- ~30% Stroke survivors develop dementia (PSD): ~75% in form of VaD; similar trends in SSA; in SSA VaD prevalence is 2-3%
- Demographic transition suggests changing dementia trends in SSA: higher estimates of VCI and VaD than 10 years ago
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Collaborators: Ahmad Khundakar, Alan Thomas, John O’Brien (Camb), Paul Francis (KCL), Clive Ballard (KCL), Paul Ince (Sheff), RA Kenny (Dublin)
Asante Sana!
The IDEA study team

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• Adesola Ogunniyi
• Richard Walker