Post-Stroke Cognitive Neurology in the SSA Context

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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
  ➢ Cognitive Function in SVD, Dementia: Medial Temporal Lobe Atrophy (Hippocampus) and Frontal Lobe atrophy
  ➢ Pathophysiology of Leukoencephalopathy, White matter changes
  ➢ Post-stroke and VaD in SSA
• Take home message

Newcastle Centre for Brain Ageing and Vitality
The VaD-AD pendulum

Willis Dementia Occurring Post-apoplexy

Binswanger, Alzheimer Arteriosclerotic Dementia, SAE

Kraepelin Arteriosclerotic Dementia

DSM-I Chronic Brain Syndrome

Hachinski Scale

DSM-III MID

DSM-IV Executive Dysfunction

Erkinjuntti Cortical vs. Subcortical

DSM IV-Executive Dysfunction

DSM V Executive Dysfunction

Newcastle Contributions


Katzman: AD is the Main Cause of Atrophy and Dementia

Pathological reports of Alzheimer's disease

NINDS-ADRDA Criteria for AD

Katzman: AD is the Main Cause of Atrophy and Dementia

NINDS-AIREN Criteria

Newcastle Contributions

Modified after S. Salloway, 2004; R Kalaria 2009

1st genetic form of VaD

CADASIL

1st genetic form of VaD

DSM V VCICSS/VCING NCVD

Modified after S. Salloway, 2004; R Kalaria 2009
Vascular Factors and Neurodegeneration

**Vascular disease risk factors**
- Hypertension, diabetes, dyslipidemia, obesity, atherosclerosis, CHD

**Cerebral Vessel wall changes**

**Other factors:**
- Genetic: APOE E4, eNOS
- Environmental

**Chronic Hypoperfusive State**
- (Oligaemia)
  - (SVD and microinfarcts)

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

**Progression over time**
- Strokes

**Mixed**
- Aβ, CAA, NFT-tau

**VaD (PSD)**

**AD**
Early Role of Vascular Dysregulation in Dementia and AD

Analysis of >7,700 brain images and tens of plasma and CSF biomarkers from ADNI;

Results suggest intra-brain vascular dysregulation is an early pathological event during disease development.

High abnormality levels also observed for specific proteins associated with the vascular system’s integrity.

Vascular Factors in Dementia: What is the epidemiological and clinical evidence?

- Vascular disease risk during mid-life associated with dementia and AD; 
  **hypertension** > dyslipidemia (high cholesterol) > diabetes > hyperhomocysteinaemia > atrial fibrillation...obesity, smoking

- Strokes increase w/ age and dementia risk; AD risk by 3-fold

- Carotid atherosclerosis increases risk of AD

- Vascular risk factors promote conversion of MCI to AD

- Cardiovascular medications delay functional or slow decline in AD; statins and anti-hypertensives (beta-blockers)

- Vascular factors predict rate of progression in AD; some factors such as high cholesterol, atrial fibrillation and angina

Evidence from longitudinal studies on Blood Pressure and Dementia

Previous high blood pressure

• The H70-study, Gothenburg, Sweden
  Skoog et al. Lancet 1996

• The Honolulu Asia Aging Study
  Launer et al. Neurobiol Aging 2000

• The Rotterdam Study
  Ruitenberg et al. Dissertation 2000

• The Kuopio Study, Finland
  Kivipelto et al. BMJ 2001

• Kungsholmen, Sweden
  Qiu et al. Arch Neurol 2003

• Chinese Study
  Wu et al. Life Science 2003

↑ Neuritic plaques
↑ Neurofibrillary Tangles
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).
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.
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.

*Pendlebury ST and Rothwell P, TLN, 2009*

**Pooled cumulative incidence of post-stroke dementia excluding pre-stroke dementia in hospital-based cohorts Pooled cumulative incidence of PSD excluding pre-stroke dementia in hospital-based cohorts of any stroke (first-ever or recurrent stroke)**

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

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
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 a 30 points score test. Mildly cognitively impaired subjects can have scores 26 to 21
Cognitive Function after Stroke

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.
Vascular Cognitive Impairment

Vascular = all causes of CVD
(cardiovascular also)
Cognitive Impairment = early to late
and severe forms of dementia
syndromes
(VaD and MCI)
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 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).
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*
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?

Diagnosis of VaD

Vascular Dementia

- multi-infarct dementia
- Small artery lesions
- Hypoperfusion
- Brain hemorrhage

Strategic Lesions

- Thalamus
- ACA territory
- PCA territory
- Angular gyrus

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*
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%)
Heterogeneity of CVD Changes

Multi-infarct dementia (MID)

SVD - lacunar state

SVD - WMLs

CADASIL

Strategic thalamic infarcts
Large-vessel Disease

ACA territory
MCA territory
PCA territory

Small-vessel Disease

Lacunes
Leuko-araiosis
microbleeds
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
## 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 ischemic VaD</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

Hippocampus, basal forebrain

Gyrus angularis

Parietal lobe

Aphasia, apraxia, disinhibition, apathy

Amnesia

Constructional problems

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
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 impaiement features associated with frontal lobe function i.e. Executive Function tasks, processing speed, working memory are more eveident.
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
Secondary cortical neurodegeneration after subcortical ischemia (SVD) as a mechanism for brain atrophy

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
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

Time course

3 mths / 90 days

Baseline

Modified from K Nagata, 2007
Baseline Recruitment at 3 months:
COGFAST- first ever (overt) stroke
Original screen ~702 Non- demented elderly (>70 years) stroke survivors
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

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Neuroimaging in Elderly Stroke Survivors
How do the MRI features compare with AD?
MTA Predictor of survival to dementia

MTA associated with shorter time to dementia- a role for Alzheimer pathology in post-stroke dementia (PSD)?

Firbank MJ et al, 2011
Neuropathology in Elderly Stroke Survivors
Do the pathological findings compare with AD?
COGFAST study: Dementia, Vascular Risk Factors and Pathological Diagnosis of VaD

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

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

Staging and natural history of cerebrovascular pathology

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

- Arteriosclerosis
- Amyloid angiopathy
- Perivascular hemosiderin leakage
- Perivascular spaces dilatation
- Myelin loss

Score:
- Score I
- Score II
- Score III
- Score IV
- Score V
- Score VI
# Inheritance of Cerebrovascular disease

<table>
<thead>
<tr>
<th>Group</th>
<th>Specific types</th>
<th>Genetics (gene /Chr.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke(s)</td>
<td>CADASIL, CARASIL, RVCL (HERNS, CRV, HRV)</td>
<td>NOTCH 3 (Chr 19), HTRA1</td>
</tr>
<tr>
<td>Hypertensive angiopathies</td>
<td>Familial Binswanger’s/Leukoencephalopathies</td>
<td>unknown</td>
</tr>
<tr>
<td>Amyloid angiopathies</td>
<td>Icelandic, Dutch, Flemish, Prion, Finnish, Hungarian, British, Danish, Others</td>
<td>Cystatin C, AβPP, PrP, Gelsolin, TTR, BRI</td>
</tr>
<tr>
<td>Other angiopathies</td>
<td>Moyamoya disease</td>
<td>Gene unknown/ Chr 3</td>
</tr>
<tr>
<td>Aneurysms</td>
<td>Sacular (berry), large aneurysms</td>
<td>Genes unknown (also congenital forms)</td>
</tr>
<tr>
<td>Vascular malformations</td>
<td>Cavernous angiomas</td>
<td>KRIT1 and other genes</td>
</tr>
<tr>
<td></td>
<td>Cavernous malformations</td>
<td>loci on Chr 7 and 3</td>
</tr>
</tbody>
</table>
Familial SVDs of the Brain causing VCI: CADASIL is the most common

<table>
<thead>
<tr>
<th>Type</th>
<th>Gene</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>CADASIL</td>
<td><em>NOTCH3</em></td>
<td>Notch3</td>
</tr>
<tr>
<td>CARASIL (Maeda syndrome)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>intervertebral disc herniations, kyphosis,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ossification, alopecia</td>
<td><em>HTRA1</em></td>
<td>Htra1</td>
</tr>
<tr>
<td>AD Retinal Cerebral Vasculopathy with</td>
<td><em>TREX1</em></td>
<td>DNA ex</td>
</tr>
<tr>
<td>Leukodystrophy (RVCL)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial SVD- Portuguese-French type</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Familial Multi-infarct dementia-Swedish type</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Subcortical angiopathic encephalopathy</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>(SAE/PADMAL)</td>
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</tbody>
</table>

* Described in Japanese, Chinese-American and Mutations also reported in American, French, and Dutch families
Key Features in CADASIL

- Worldwide occurrence of CADASIL (>600 families)
- Variable clinical phenotypic features contributed by epigenetic and/or genetic factors.
- Commonly misdiagnosed as MS, cerebral vasculitis, Binswanger’s disease, leukoencephalopathy of undetermined cause or AD.
- Mis-sense mutations in NOTCH3
- General absence of hypertension or hypercholesterolemia. Exceptions—some data on ↑ homocysteine and Type 2 diabetes
Cognition, Dementia and CADASIL

After Dichgans et al, 1998
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: PIs 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></td>
<td>Modified Tokens Test (IU Token Test)</td>
</tr>
<tr>
<td>General Cognitive Functioning</td>
<td>Community Screening Instrument</td>
</tr>
<tr>
<td></td>
<td>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; Unverzagt 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 Alcohol use</td>
<td>1.253 (0.51 – 3.10)</td>
<td>1.19 (0.47 -3.00)</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_
Neuroimaging in Nigerian Older Stroke Survivors

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.

**MTLA vs WMH score showed positive correlation ($r=0.461$, $p=0.002$) supporting a vascular basis for MTLA.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal vs vCIND</th>
<th>OR</th>
<th>95% CI</th>
<th>*p value</th>
<th>vCIND vs PSD</th>
<th>OR</th>
<th>95% CI</th>
<th>p value</th>
<th>Normal vs (vCIND + PSD)</th>
<th>OR</th>
<th>95% CI</th>
<th>*p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTLA rating</td>
<td></td>
<td>2.02</td>
<td>1.05 – 3.87</td>
<td>0.035</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.25</td>
<td>1.16 – 4.35</td>
<td>0.016</td>
</tr>
<tr>
<td>Log _ TBV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
<td>0.00 – 1996.50</td>
<td>0.260</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>

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**

**Participants screened: n = 449**

- No dementia on screening: n = 352
  - Randomly selected for follow-up clinical DSM-IV dementia assessment: n = 43
  - Follow-up clinical DSM-IV dementia assessment: n = 87

- Probable or possible dementia on screening: n = 97
  - Not followed up: n = 5 (5.4%)
    - Error calculating cognitive screening score: 4
    - Unable to trace: 1

- Not fully screened: n = 6 (1.3%)
  - Left before screening completed: 4
  - Unable to speak or communicate: 1
  - Became acutely unwell: 1
IDEA Study Screening Tools

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
Vascular Factors and Neurodegeneration

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

- Other factors: Genetic -APOE E4/
- Environmental

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

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

Aβ, CAA, NFT-tau

- AD
- Mixed
- VaD (PSD)

Progression over time
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*
- Neuropsychometric assessment: MMSE, MoCA, CSI-D, CAMCOG-VCI
- ~30% Stroke survivors develop dementia (PSD): ~75% in form of VaD; similar trends in SSA
- Medial Temporal and Frontal lobe atrophy caused by vascular disease irrespective of AD pathology; *Brain atrophy is an important target*
- Demographic transition suggests changing dementia trends in SSA: higher estimates of VCI and VaD than 10 years ago
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.”
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Asante Sana!
The IDEA study team

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