Dementias: clinical diagnosis, pathology & therapeutics

13th RTC in Sub-Saharan Africa
CAN, Douala, Cameroon
20th October 2022

Raj Kalaria
Translational and Clinical Research Institute, Newcastle University
Newcastle upon Tyne NE4 5PL, UK;
University of Nairobi, Kenya
Email: raj.kalaria@newcastle.ac.uk
How do we Define Dementia?

- Memory problems in the healthy elderly do not mean they have dementia
- Dementia is more than forgetfulness or a subjectively poor memory
- Impairment in any of these:
  - memory
  - language
  - visual processing and orientation
  - mood, personality, and social skills
  - frontal executive function, including planning and problem solving
- Causes inability to function independently
Global Burden of Dementia

Doubling of Prevalence between 1990 and 2016


I in 3 Dementia or Stroke

Lancet Neurol 2019; 18: 88–106
Prevalence of Dementia Worldwide

Dementia is a clinical syndrome caused by neurodegeneration. Alzheimer’s disease (AD) is the most common type followed by vascular dementia (VaD), dementia with Lewy bodies (DLB) and frontotemporal dementia (FTD).

Prince M et al, 2010
Numbers of People with Dementia

The growth in numbers of people with dementia (millions) in high income (HIC) and low and middle income countries (LMIC)

- 2015: High Income = 19.50, Low and Middle Income = 28.28
- 2020: High Income = 21.97, Low and Middle Income = 32.30
- 2025: High Income = 24.73, Low and Middle Income = 38.72
- 2030: High Income = 27.95, Low and Middle Income = 46.74
- 2035: High Income = 31.72, Low and Middle Income = 56.16
- 2040: High Income = 35.71, Low and Middle Income = 66.45
- 2045: High Income = 39.14, Low and Middle Income = 77.63
- 2050: High Income = 42.18, Low and Middle Income = 89.28

47 million

Wimo A et al 2015
Global Burden of DALYS and Deaths

Figure 2: Contribution of various neurological disorders to the overall burden from neurological disorders in 2015. Estimates are for (A) disability-adjusted life-years and (B) deaths.
What Are the Most Common causes of Degenerative Dementias?

- **Alzheimer's disease**: 55-70%
- **Vascular dementia**: 15-25%
- **Other dementias**: 10-30% (eg, Lewy body dementia, Parkinson's dementia, Frontotemporal lobar dementias)


Rarer dementias not shown but do not amount to >15 of total.
Ageing-related Brain Disorders and Dementias

- Alzheimer’s Disease
- Parkinson’s Disease
- Dementia with Lewy Bodies
- Frontotemporal Dementias
- Prion Diseases
- Vascular Dementia
What is Alzheimer’s Disease?

A progressive degenerative brain disorder and the most common cause of dementia
Alzheimer's Disease: Main features

• Alzheimer type of dementia: 55%-60% of all dementia cases

• AD ~doubles after age 65 yrs:
  – >65 yrs 5% (3%-11%); >75 yrs: 10% (7%-15%); >85 yrs: 20%...

• Majority of AD late-onset: Slow gradual onset and progression;
  – Predominance of memory impairment (a. over intellectual impairment or b. meet general criteria for dementia)
  – 5% estimated to be of familial form: autosomal dominant inheritance
  – Mild cognitive impairment (‘early stage’ of AD) 63%-80% will progress to AD

• Diagnosis of exclusion: no evidence of CVD, HIV, PD, HD, NPH

• Definitive diagnosis by neuropathological examination
  – presence of amyloid plaques and neurofibrillary pathology
Age and illiteracy are the strongest risks

Alzheimer’s disease (common dementia)
- Age
- Family history
- Down’s syndrome
- Head injury
- Apolipoprotein E-ε4
- Vascular factors
- Smoking
- Female gender

<table>
<thead>
<tr>
<th>Factor</th>
<th>Developed regions (North America, Europe, Japan)</th>
<th>Asia (China, Guam, India, South Korea, Taiwan*)</th>
<th>Africa (Egypt, Nigeria, Kenya, South Africa)</th>
<th>Latin America (Argentina, Brazil, Venezuela)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing age</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
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<tr>
<td>Female sex</td>
<td>Positive</td>
<td>Positive</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Family history</td>
<td>Positive</td>
<td>Positive</td>
<td>..</td>
<td>Positive</td>
</tr>
<tr>
<td>Head injury</td>
<td>Positive</td>
<td>..</td>
<td>..</td>
<td>Positive</td>
</tr>
<tr>
<td>Genes (APOE ε4 allele)</td>
<td>Positive</td>
<td>Positive</td>
<td>No risk</td>
<td>Unclear</td>
</tr>
<tr>
<td>Illiteracy or lack of education</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>MCI or cognitive impairment without dementia</td>
<td>Positive</td>
<td>Positive</td>
<td>..</td>
<td>Positive</td>
</tr>
<tr>
<td>Urban living</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Low socioeconomic status or poverty</td>
<td>Unclear</td>
<td>Positive</td>
<td>..</td>
<td>Positive</td>
</tr>
<tr>
<td>Occupation as housewife</td>
<td>Negative</td>
<td>Positive</td>
<td>Unclear</td>
<td>Positive</td>
</tr>
<tr>
<td>Depressive illness</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Vascular disease†</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Unclear</td>
</tr>
<tr>
<td>Low fibre diet</td>
<td>Unclear</td>
<td>Positive</td>
<td>Positive</td>
<td>..</td>
</tr>
<tr>
<td>Smoking</td>
<td>Positive</td>
<td>Positive</td>
<td>..</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

Kalaria RN et al, TLN 2008; 2012
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
Dementia in sub-Saharan Africa
Challenges and opportunities

Dominant and Modifiable Risk Factors for Dementia in Sub-Saharan Africa: A Systematic Review and Meta-Analysis

Akin Ojagbeni 1*, Akinkunmi Paul Okekunle 2,3 and Opayemi Babatunde 4

1 Department of Psychiatry, College of Medicine, University of Ibadan, Ibadan, Nigeria, 2 Department of Epidemiology and Medical Statistics, College of Medicine, University of Ibadan, Ibadan, Nigeria, 3 Department of Food and Nutrition, College of Human Ecology, Seoul National University, Seoul, South Korea, 4 School of Medicine Primary Care Center Versus Arthritis Kele University, Staffordshire, United Kingdom

Background: Sub-Saharan Africa (SSA) is projected to have a rapid increase in the number of people living with dementia by 2050. Yet, there is currently no robust evidence on the risk factors for dementia in the sub-region that could inform context specific interventions.

Methods: We conducted a systematic review and meta-analysis of observational studies to determine the dominant and modifiable risk factors for dementia in SSA. We searched MEDLINE, EMBASE, PsychINFO, and African Journals Online using keywords for dementia and Alzheimer's disease as well as the mp operator for all 47 SSA countries.
Cognitive Ageing related thresholds leading to Alzheimer’s Disease (AD)

- Memory
- Language
- Spatial ability
- Aggressiveness
- Apathy
- Personality changes
- ADL (Activities of Daily Living)
- Social ability
- Dementia
### Presentation of AD Neuropsychiatric Inventory (NPI)

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Percentage</th>
<th>Associated Behavior</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apathy</td>
<td>72%</td>
<td>Appetite</td>
<td>31%</td>
</tr>
<tr>
<td>Agitation</td>
<td>60%</td>
<td>Disinhibition</td>
<td>30%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>45%</td>
<td>Night-time</td>
<td>24%</td>
</tr>
<tr>
<td>Irritability</td>
<td>42%</td>
<td>Delusions</td>
<td>22%</td>
</tr>
<tr>
<td>Depression</td>
<td>38%</td>
<td>Hallucinations</td>
<td>10%</td>
</tr>
<tr>
<td>Motor behaviour</td>
<td>38%</td>
<td>Euphoria</td>
<td>2%</td>
</tr>
</tbody>
</table>

*J Cummings, 2010*
Diagnosis of Alzheimer’s Disease: NINCDS-NIA-AA Criteria

Dementia
- Impaired memory
- \( \geq 1 \) other cognitive domain impaired
- Clinical examination
- Neuropsychological tests

Probable/Possible diagnosis
- Progressive worsening
- Absence of other disorders that could account for deficits

Definitive diagnosis by autopsy

Diagnosis of AD

A, T, N (V) criteria

• Mean annualized rate of hippocampal volume loss ~1.6% ± 1.4%/year
• Rates were greater in AD patients: hippocampus ~4.0% ± 1.9%/year
• Rates approximately 2 x times greater in AD than in age and gender matched controls.

Jack et al, 1998
• Hippocampal sparing and limbic-predominant AD subtypes account for ~25% of cases

• Supports hypothesis that AD has distinct clinicopathological subtypes

• Implications for designing clinical, genetic, biomarker, and treatment studies
Hippocampal and cortical NFT densities by AD subtype

- Hippocampus: average NFT count per 0.125 mm² for the CA1 and subiculum regions.

- Cortex: average NFT count per 0.125 mm² for the superior temporal, middle frontal, and inferior parietal regions

- Box plots: median (IQR) and error bars represent 10–90th percentile
Neuroimaging correlates of pathologically defined subtypes of Alzheimer’s disease: a case-control study

Jennifer L Whitwell, Dennis W Dickson, Melissa E Murray, Stephen D Weigand, Nirubol Tosakulwong, Matthew L Senjem, David S Knopman, Bradley F Boeve, Joseph E Parisi, Ronald C Petersen, Clifford R Jack Jr, Keith A Josephs

- Patterns of atrophy on MRI differ across the pathological subtypes of AD
- MRI regional volumetric analysis can reliably track the distribution of NFT pathology and can predict pathological subtype of AD at autopsy
Progression of Dementia

Genetics of AD: how much of AD is explained by autosomal dominant or recessive patterns?

Sporadic AD 90-95%;
Familial AD ~5-10%

*Current estimates from ~500 families world-wide
Genes and Molecular Genetics of AD

Manhattan plot of stage 1 for genome-wide association with Alzheimer’s disease (17,008 cases and 37,154 controls). Red line- The threshold for genome-wide significance ($P < 5 \times 10^{-8}$). Newly associated genes (Red) and previously identified genes (Black) are shown. Red diamonds represent SNPs with the smallest $P$ values in the overall analysis.
Neuropsychometric Test and Screening*

• Cognitive function tests have been used and developed over several years, many translated in local languages

• First stop: **Mini-Mental State Examination (MMSE)**-widely used; Others Montreal Cognitive Assessment (MoCA)

• Neuropsychometric Batteries/Tools contain several components to test different cognitive abilities, e.g. CANTAB, CAMCOG, ADAS-Cog, CASI, **IDEA** etc.

• Value of informant questionnaires; IQCODE

*Most tools widely available online; main obstacles availability of trained staff*
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
Alzheimer’s Disease (AD)  Dementia with Lewy Bodies (DLB)

**MMSE 18/30**
Orientation 5/10
Short term memory 0/3

**MMSE 20/30**
Orientation 8/10
Short term memory 2/3
Alzheimer’s disease

Dementia with Lewy Bodies

**MMSE 18/30**
Orientation 5/10
Short term memory 0/3

**MMSE 20/30**
Orientation 8/10
Short term memory 2/3
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.

Observe examples of stick design in 4 impaired subjects.
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
Progressive accumulation of brain pathology increases damage and decreases cognitive functions; MCI, mild cognitive impairment
Why focus on MCI?

- Mild cognitive impairment (MCI) is an intermediate between normal ageing and dementia
- *Area of intervention to prevent or delay progression of dementia*
- Earlier treatment will lead to better prognosis
- Caregiver support and planning (Wills etc.)

*Stephan, Minett, Pagett et al. BMJ Open 2013;3:e001909*
MCI patients at higher risk for AD

- Older age (but not older than 85 yrs)
- Lower education
- Lower physical activity
- Recurrent depression
- Uncontrolled vascular risk factors (DM2, HTN, AF)
- Use of inappropriate medications
- MRI hippocampal atrophy
- CSF and PET indicating amyloid accumulation
Medications for MCI and AD

1. Memory enhancers:
   Acetylcholinesterase inhibitors (AChEIs):
   a. Donepezil (‘Aricept’) 5-10mg at night
   b. Rivastigmine (‘Exelon’) 3-6mg twice daily
   c. Galantamine (‘Reminyl’) 16-24mg daily

   NMDA-receptor antagonist:
   d. Memantine (‘Ebixa’) 10mg twice daily

2. Psychotropic agents for residual symptoms (BPSDs) i.e. mood (depression & irritability) and behavioural disturbances (restlessness, agitation, psychotic symptoms, insomnia)-
   **antidepressants, neuroleptics, anticonvulsants**

3. Control of cardiovascular risk factors e.g. HTN

4. Aβ lowering vaccines: aducanumab (June 2021); lecanamab (Sept 2022)
Ageing-related Brain Disorders and Dementias

• Alzheimer’s Disease
• Parkinson’s Disease
• Dementia with Lewy Bodies
• Frontotemporal Dementias
• Prion Diseases
• Vascular Dementia
Dementia with Lewy Bodies (DLB) (PDD-AD continuum)

- Dementia syndrome (early neuropsychiatric features)
- Mild Parkinsonism
- Visual hallucinations and fluctuations in conscious level
- Cortical Lewy Bodies
- Relatively little tangle burden
- Marked cholinergic deficits but preserved M1 receptors
Diagnostic Criteria for DLB

McKeith et al, Neurology, 2005; 2017

• Cognitive decline & reduced social/occupational function
  • Attentional, executive and visuo-spatial dysfunction prominent

• CORE features
  • Fluctuation
  • Recurrent visual hallucinations
  • Spontaneous parkinsonism

  At least one core + one suggestive or 2 core features for Probable DLB

• Suggestive features:
  • REM sleep behaviour disorder
  • Neuroleptic sensitivity
  • Dopaminergic abnormalities in basal ganglia on SPECT/PET

  One core or suggestive feature sufficient for Possible DLB
Dementia with Lewy Bodies

• ~15% of all dementia cases have Lewy body pathology at autopsy
  – Lewy body variant of Alzheimer’s disease
  – Lewy body dementia
  – Diffuse Lewy body disease

• Most are not recognised clinically during life
  – Diagnosed as Alzheimer’s or vascular dementia
AD-DLB-PDD continuum

• Lewy bodies and Lewy neurites seen in ~ 15% of all autopsy cases of dementia

• One in seven cases of dementia is due to DLB

• One case of DLB for every 4 of AD and 2 of PD

McKeith I et al, 2017
What Are the Most Common causes of Degenerative Dementias?

- Alzheimer's disease: 55-70%
- Vascular dementia: 15-25%
- Other dementias: e.g., Lewy body dementia, Parkinson's dementia, Frontotemporal lobar dementias: 10-30%

Rarer dementias not shown but do not amount to >15 of total.

Frontotemporal Dementias (FTD)

- Pick (1892) and bilateral frontal lobe atrophy
- FTD is a focal degenerative disorder (cause FTLD)
- Alteration in personality, social conduct and executive function
- Non-Alzheimer pathology disorder
- Related FTD syndromes – Semantic dementia, Primary Progressive non-fluent Aphasia,
- FTLDs are tauopathies which include:
  - FTLD with Pick bodies, Corticobasal Degeneration (CBD), Progressive Supranuclear Palsy (PSP), Sporadic multiple system tauopathy, Argyrophilic Grain Disease (AGD), NFT dementia, FTDP-17
Clinical Syndromes in FTD

- **Behavioural-variant of FTD** - associated with early behavioural and executive deficits

- **Semantic dementia (SD)** - with progressive deficits in speech, grammar, and word output

- **Progressive non-fluent aphasia (PNFA)** - progressive disorder of semantic knowledge and naming

*Bang J et al, 2015*
Frontotemporal Lobar Degeneration

**Frontal and temporal lobe atrophy**

Neurofibrillary pathology; tau or ubiquitin (Ub) positive structures

Regions of Interest: frontal and temporal lobes, hippocampus, cingulate gyrus

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### FTLD-Tau

- **3R Tau+**
  - MAPT mutation
  - FTLD with Pick bodies
  - FTLD with MAPT mutation: 3R+; 4R+
  - CBD, PSP, AGD, MSTD, other tauopathy
  - Neurofibrillary tangle dementia

### FTLD-TDP / -FUS / -UPS

- **3R & 4R Tau+**
  - TDP-43 +; NF or INA -
  - TDP43- Sporadic; GRN, C9ROF72 expansion, TARDP, VCP mutations
  - aFTLD-U NIFID* BIBD*

- **4R Tau+**
  - NF or INA +; TDP-43 -ve
  - aFTLD-U NIFID* BIBD*

- **TDP-43 -; TDP-43 -**
  - CHMP2B mutation

* BIBD, basophilic inclusion body disease; NIFID, neuronal intermediate filament inclusion disease; TDP-43 transactivation response DNA binding protein with M(r) 43 kD; PGRN, progranulin; VCP, Valosin-containing protein
FTD linked Parkinsonism- Chr 17

- Features of Parkinsonian tremor
- Progressive cerebral atrophy
- Increased hypometabolism
- Tau-IR deposits in neocortex as well as white matter (oligos)

G389R mutation  A→B 3 yrs
Huntington’s Disease (HD)

- HD is an autosomal dominant disorder; prevalence 3-10 per 100,000.
- HD phenotype = chorea (brief, irregular contractions that appear to flow between muscles), psychiatric abnormalities and cognitive decline
- Linked to *Huntingtin* gene on chromosome 4
- “Mutation” involves expansion of CAG repeats (>36) normal up to 26). HD is most common polyglutamine (PG) disorder.
- Expansion of PG tract (N-terminal) confers “gain of toxic function” in full-length huntingtin product
Huntington’s Disease- pathology

- HD patients exhibit severe caudate and considerable putaminal atrophy due to loss of medium spiny neurones.
- Anti-ubiquitin staining reveals abnormal cortical neurites in wide distribution.
Causes of Dementia: clues from neurological features and cognitive decline

Clinical and pathological presentations and possible diagnosis of dementia

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Diagnostic considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia with myoclonus</td>
<td>Prion disease</td>
</tr>
<tr>
<td></td>
<td>Autosomal dominant AD</td>
</tr>
<tr>
<td>Dementia with ataxia</td>
<td>Inherited forms of ataxia including SCA2, SCA3, SCA17, DPRLA</td>
</tr>
<tr>
<td>Dementia with chorea</td>
<td>Huntington’s disease</td>
</tr>
<tr>
<td></td>
<td>SCA3, SCA17, DPRLA, neuroferritinopathy, neuroacanthocytosis</td>
</tr>
<tr>
<td>Dementia with dystonia</td>
<td>Wilson’s disease</td>
</tr>
<tr>
<td></td>
<td>Niemann–Pick disease (NPC1 and NPC2)</td>
</tr>
<tr>
<td>Dementia with progressive myoclonic epilepsy</td>
<td>Mitochondrial disease, Lafora body disease, Neuronal ceroid lipofuscinosis</td>
</tr>
</tbody>
</table>
Screening, Diagnosis and Risk Factors for Dementia in SSA

Arms of Newcastle Longitudinal studies
Variation in Dementia Prevalence estimates in Africa

Akinyemi R et al, Alz & Dementia, 2021
Meta-Analysis of SSA dementia epidemiological datasets

Guerchet et al 2017
- Prevalence
  ✓ (All Studies) : 5.5%
  ✓ (DSM criteria) = 6.38%

Incidence : 1.3%

Ojagbemi et al 2021
- Prevalence
  ✓ Hospital-based studies : 3% (CI 1% - 5%)
  ✓ Community (clinically diagnosed) : 5% (CI 2%-7%)
  ✓ Community (rating scales): 9% (CI 6% - 11%)
- Incidence : 2% (CI 1% - 4%)

Guerchet et al, ADI Technical Report, 2017
Ojagbemi et al, Frontiers Neurology, 2021
Subtypes of Dementias in Africa

- **Alzheimer’s disease**: Several countries
- **Parkinson’s disease**: Several countries
- **Dementia with LBs**: Nigeria, Tunisia
- **Frontotemporal Dementias**: Nigeria, South Africa
- **Huntington’s disease LBs**: Tunisia, Senegal, South Africa
- **Prion diseases**: Tunisia, South Africa
- **Ataxias (SCAs) and MNDs**: North Africa, West, Central & East Africa
Proportions of AD as a Dementia Subtype in Africa (Community and Hospital-based Studies)

<table>
<thead>
<tr>
<th>Country, Location; Type of sample</th>
<th>Sample size, Age (yrs)</th>
<th>Dementia Prevalence (%)</th>
<th>Alzheimer’s Disease (%)</th>
<th>VaD (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa, 10 countries; Community</td>
<td>10,413; &gt; 65 yrs</td>
<td>2.4%</td>
<td>57%</td>
<td>27%</td>
<td>(George-Carey et al., 2012)</td>
</tr>
<tr>
<td>SSA, 5 countries (Benin, Botswana, CAR, Congo, Nigeria); Community/hospital</td>
<td>10,413; &gt; 65 yrs</td>
<td>0–10%</td>
<td>54–83%</td>
<td>8–31%</td>
<td>(Mavrodaris et al., 2013)</td>
</tr>
<tr>
<td>Nigeria, Abeokuta/Ibadan; Hospital/clinic</td>
<td>240,294;</td>
<td>0.05%</td>
<td>57%</td>
<td>17%</td>
<td>(Amoo et al., 2011)</td>
</tr>
<tr>
<td>Egypt, Al Kharga District; Community</td>
<td>8173; &gt; 50 yrs</td>
<td>2.3%</td>
<td>51%</td>
<td>29%</td>
<td>(El Tallawy et al., 2012)</td>
</tr>
<tr>
<td>South Africa, Durban; Hospital</td>
<td>140; &gt; 60 yrs</td>
<td>8%</td>
<td>–</td>
<td>40%</td>
<td>(Ramllal et al., 2013)</td>
</tr>
<tr>
<td>Egypt, Al-Quseir city,</td>
<td>2222; &gt; 60 yrs</td>
<td>3.8%</td>
<td>48%</td>
<td>37% (1.4%)</td>
<td>(El Tallawy et al., 2014)</td>
</tr>
<tr>
<td>Tanzania, Hai District; Community</td>
<td>1198; &gt; 60 yrs</td>
<td>6.4%</td>
<td>48%</td>
<td>41% (2.6%)</td>
<td>(Paddick et al., 2013),(Paddick et al., 2014)</td>
</tr>
<tr>
<td>Egypt, Quena/Aswan; Community</td>
<td>691; &gt; 60 yrs</td>
<td>5.1%</td>
<td>–</td>
<td>–</td>
<td>(Khedr et al., 2015)</td>
</tr>
<tr>
<td>Congo, Brazzaville, Bangui, CAR; Community</td>
<td>910;</td>
<td>6.1%</td>
<td>69%, 83%</td>
<td>31%, 18%</td>
<td>(Samba et al., 2016)</td>
</tr>
</tbody>
</table>

Longdon AR et al, 2013; Akinyemi et al. BRB 2019
Brain AD lesions in East Africans

• Comparable to a US sample, ~18% of elderly East Africans exhibit Aβ(42) deposits (9/50 cases)

• Severe CAA was evident in brains of two subjects

• Typical τ +ve NFT pathology was evident in the hippocampus and neocortex

• These findings suggest that elderly East Africans are unlikely to escape AD (even if incidence is low)

(Ogeng’o J et al, 1996)
Hereditary AD in a large Xhosa Family, SA

*Heckmann J et al, 2004*

*Missense (I143M) mutation in Presenilin 1*
Dementia with Lewy Bodies in Africa

Dementia With Lewy Bodies in a Nigerian: A Case Report

Adesola Ogguniyi, Effiong E. U. Akang, Oye Gureje, Masaki Takao, Pedro Piccardo, Olusegun Baiyewu, Kathleen S. Hall, Bernardino Ghetti, and Hugh C. Hendrie

- Isolated cases of DLB may exist with PD
- Full spectrum of DLB-PDD likely exist in Africa
Frontotemporal Dementias in Africa

Frontotemporal dementia in a Nigerian woman: case report and brief review of the literature.

RO Akinyemi¹⁴, MO Owolabi¹, VA Makanjuola², AO Ogunseyinde³ and A Ogunniyi¹.

Departments of Medicine¹, Psychiatry² and Radiology³, University College Hospital, Ibadan and Department of Medicine⁴, Federal Medical Centre, Abeokuta, Nigeria

• Isolated cases of FTD described in North Africa

• Unknown if full spectrum of FTDs exist in Africa
SA family with history of dementia (FTD)

Family Tree

- Seven siblings
- 1 x died, childless, aged 45 years
- Six siblings developed dementia in late 40's to early 50's
- Oldest child of oldest sibling dementing (at 54)

Family tree has been disguised to preserve individual patient identity. Family tree x 300 years genealogical Institute of South Africa (Dr Leon Endeman)
Dementia in Infectious Disease

• Factors include viral, bacterial, fungal, and parasitic organisms

  *HIV is the most common cause*

• Presence of fever, peripheral leukocytosis, or CSF pleocytosis should prompt investigation for an infectious agent

• Consequences on behavioural and cognitive function most frequent in immunocompromised patients
HIV-related Neurocognitive Impairment in SSA

14 countries: South Africa (14), Uganda (8), Nigeria (6), Zambia (4), Kenya (4), Cameroon (3) DRC (3), Ethiopia (2), Malawi (2), CAR (1), Botswana (1), Guinea Bissau (1), Tanzania (1), Zimbabwe (1)

Diagnostic tools: variable. International HIV Dementia Scale (IHDS) 21-80%; Sloan Memorial Kettering scale frequently used

Total reports (2020): 51 hospital-based studies case-control (10), cohort (7), cross-sectional (31)

Absolute participants with HAND 0-396; prevalence 0%-80%

Frequency of HIV Meningoencephalitis

- ~50% HAND- HIV-associated neurocognitive disorders
- ~20% HAD- HIV associated dementia
- ~2% HAD with ART treatment
- >50% HIVE- HIV encephalitis as less severe HAND
  - Persistent immune activation, inflammation, viral escape / blipping in treated subjects,
  - comorbid conditions show HIV disease progression and ↑ HAND risk
Pathogenesis and Cellular Mechanisms

HIV-1-infected M/MΦ

Endothelial cell

Increased BBB permeability

Blood

Brain

Macrophages

Microglia/Macrophages

Virions & Viral proteins

Neurotoxic factors

Inflammatory factors

Eicosanoids

Free Radicals

MMPs

Inflammation

Up-regulation of Bax and Down-regulation of Bcl-2/Bcl-x

Excitotoxicity

Increased secretion

Decreased uptake

Glutamate

Astrocytes

Endothelial cell

Restricted infection

Restricted infection

Productive infection

Restricted infection

Neuron

Neuronal apoptosis

Note: This figure was modified from Jones G. & Power C. Neurobiology of Disease, 2006; 1 – 17
M/MΦ: monocytes/macrophages
Rapidly Progressing Dementia

Cognitive/behavioural symptoms and neuropsychological profile were compatible with diagnosis of AD (DSM IV-TR).

MRI scan medial temporal lobe atrophy (MTA) = highest atrophy rating scale

*Treponema pallidum* hemagglutination and VDRL in CSF +

*Treated w/ 0.15 · 106 IU/kg benzylpenicillin for 2 wks. 6 months later, MMSE 27/30 slight improvement of language-related skills, but little improvement in memory*
**Prion Disorders**

- Fatal degenerative conditions; transmissible spongiform encephalopathies (TSEs)
- Sporadic (85%) and familial types; CJD, FFI, GSS, Kuru, BSE, Scrapie
- Rapid insidious onset; duration of illness 6-9 months
- Neurological features: myoclonus, seizures, motor involvement, ataxia
- Progressive dementia
- Definitive diagnosis at autopsy

The normal (left) and disease-carrying forms of human prion protein with beta-strands in blue and alpha-helices in green

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Stanley Prusiner, Born 1942
"for his discovery of Prions - a new biological principle of infection"

Carlton Gajdusek, Nobel Prize in 1976- Kuru Studies
Neuropathology of Prion Disorders

- Cruetzfeldt-Jacob Disease (CJD), Fatal Familial Insomnia (FFI), Gerstmann Sträussler Scheinker syndrome (GSS), nvCJD, Bovine Spongiform Encephalopathy (BSE) as Prion disorders;

- Severe atrophy may involve all lobes; Spongiform change; Florid prion plaques (with angiopathy). Sometimes restricted regional pathology
Neurodegenerative Dementias

(specific molecular pathologies causing dementia)

• Alzheimer’s disease and age-related disorders
• Dementia with Lewy bodies (DLB); Parkinson disease with dementia (PDD) - The synucleinopathies
• Frontotemporal dementia (+tau) / Tauopathies
  – FTD and Parkinsonism Chr. 17, CBD, PSP, Pick’s disease
  – Argyrophilic grain disease (AGD) and Tangle only dementia
• Frontotemporal dementias (-tau)
  – FTDs with ubiquitin, progranulin and TDP-43 inclusions
• Prion diseases
  – Creutzfeldt-Jakob disease, Fatal familial insomnia, GSS, Kuru
• Trinucleotide Repeat disorders (polyglutamine diseases)
  – Huntington’s disease (HD), Spinocerebellar ataxies, Friedreich’s Ataxia
• HIV-related Neurocognitive Disorders; HAND, HAD, HIVE
• Motor Neurone Disorders; ALS, PLS, SMA with dementia
Pathological Expression of Disease: Disorders of protein accumulation or proteinopathies

- Alzheimer disease - Aβ plaques, tau
- Parkinson’s/ DLB - LBs (α-synuclein)
- FTD I: FTDP-17/ Pick’s CBD, PSP - Tau+, Pick bodies (3R and 4R tau)
- FTDs II: - Tau-, ubiquitin, PGRN, TDP-43
- Prion diseases - PrP plaques, tau, CAA
- Multiple System Atrophy - Glial synuclein inclusions
- Polyglutamine diseases - HD and Spinocerebellar Ataxias

(as extracellular deposits or intracellular inclusions; insoluble (or protein misfolding) products that form aggregate by “seeding” mechanism)
Accumulation of Different Types of Brain Pathology during Ageing
Propagation of Neurodegenerative Pathologies in Common Dementias

- Highest stages are diagnostic for the dementia type

Goedert M et al, 2015
Vascular Dementia (VaD)

The conventional definition of VaD is deficient as stroke may produce a spectrum of cognitive changes but not necessarily prominent memory loss as in Alzheimer’s Disease (AD)
Vascular Dementia

Main Types:  
I Multi-infarct Dementia,  
II Subcortical Ischaemic Vascular Dementia,  
III Strategic infarct dementia

Causes:
- Large infarcts (Atherothromboembolism)
- Lacunar infarcts
- Small vessel disease (SVD) (arteriolesclerosis)
- Multiple microinfarcts
- White matter changes (lesions)

Worldwide prevalence 10-15%  
(as high as~35%)
Vascular Cognitive Impairment

Vascular = all causes of CVD
(cardiovascular also)
Cognitive Impairment = early to late and severe forms of dementia syndromes
(VaD and MCI)
Progress towards standardised diagnosis of VCI guidelines from VICCCS

**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)

- 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*

O Skrobot et al, 2017. 2018
Processes influencing clinical expression of dementia

Additional opportunities for interventions

- Ageing related decline
- Environmental risk factors
- Comorbidity
- Genetically determined disease process
- Neuronal repair and compensation mechanisms
Overview of Neurology/Neuropathology of Dementia

- Ageing related decline, atrophy and neuronal attrition
- AD as most common form of neurodegenerative dementia
  - Amyloid, Tau and other factors in AD
- Parkinson’s disease, Dementia with Lewy bodies
- FTDs (tau + /tau –), Huntington’s disease and Prion diseases
- HAND, HAD, HIVE common in some parts of SSA
- Overlap between degenerative disorders, e.g. AD, DLB, VaD
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- Godfrey Mbowe
- Sarah Mkenda
- John Kisima
- Olaide Olakehinde
- Bingileki Lwezuala
- Laura Ternent
- Catherine Dotchin
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- Declare Mushi
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BRAIN AGEING AND DEMENTIA IN LMICs 2022

Themes: Epidemiology, Genetics, Risk Factors, Pathophysiology, Prevention, Care

This in-person conference will provide a forum to discuss risk factors and increasing burden of vascular and neurodegenerative diseases including HIV Dementias in the context of incidence and prevention in cross-cultural populations in Low and Middle Income Countries compared to Europe, North America and Japan.

Grants and Policy Workshop 5th December
Symposium 6-9 December, 2022
(Safari Park Hotel, Nairobi, Kenya)

Registration:
Email: advascular@ncl.ac.uk
Website: https://conferences.ncl.ac.uk/advascular/