Dementias in SSA: clinical diagnosis, pathology & therapeutics

9th RTC in Sub-Saharan Africa
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Newcastle Centre for Brain Ageing and Vitality
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 ataxias, Friedreich’s Ataxia

• HIV-related Neurocognitive Disorders; HAND, HAD, HIVE

• Motor Neurone Disorders; ALS, PLS, SMA with dementia
GBD 1990-2013: DALYs for all Causes

Tree Map of Low and Middle Income Countries:
All ages  70+ years and Both sexes

Murray et al, 2012; Whiteford et al, 2013
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: 28.28 million
- 2020: 32.30 million
- 2025: 38.72 million
- 2030: 46.74 million
- 2035: 56.16 million
- 2040: 66.45 million
- 2045: 77.63 million
- 2050: 89.28 million

High Income
Low and Middle Income

47 million

Wimo A et al 2015
What Are the Most Common causes of Degenerative Dementias?

- Alzheimer's disease: 55-70%
- Vascular dementia: 15-25%
- Other dementias: 10-30%
- Frontotemporal lobar dementias: 5-10%

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

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
Worldwide costs of dementia forecast?

![Graph showing projected global costs of dementia in billions of US dollars from 2015 to 2030. The costs are expected to increase significantly over the years, reaching 2 trillion US dollars by 2030. The graph highlights the projected costs reaching 1 trillion US dollars in 2025 and 2 trillion US dollars in 2030.]
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 (2014): 51 hospital-based studies case-control (10), cohort (6), cross-sectional (31)

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

Lekoobou A et al, BMC Public Health, 2014
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
Sub-Types of HIV and Cognitive Impairment

HIV Subtype D Is Associated with Dementia, Compared with Subtype A, in Immunosuppressed Individuals at Risk of Cognitive Impairment in Kampala, Uganda

Ned Sacktor,1 Noeline Nakasujja,2 Richard L. Skolasky,2 Mona Rezapour,4 Kevin Robertson,5 Seggane Musisi,7 Elly Katafira,2 Allan Ronald,9 David B. Clifford,6 Oliver Laeyendecker,2,4 and Thomas C. Quinn3,4

Departments of 1Neurology, 2Orthopedic Surgery, and 3Medicine, Johns Hopkins University School of Medicine, Baltimore, and 4Laboratory of Immune Regulation, Division of Intramural Research, National Institute of Allergy and Infectious Disease, National Institutes of Health, Bethesda, Maryland; 5Department of Neurology, University of North Carolina, Chapel Hill; 6Department of Neurology, Washington University, St. Louis, Missouri; Departments of 7Psychiatry and 8Medicine, Makerere University, Kampala, Uganda; and 9Department of Medicine, University of Manitoba, Winnipeg, Canada

Background. In the United States, clade B is the predominant human immunodeficiency virus (HIV) subtype, whereas in sub-Saharan Africa, clades A, C, and D are the predominant subtypes. HIV subtype may have an impact on HIV disease progression. The effect of HIV subtype on the risk of dementia has, to our knowledge, not been examined. The objective of this study was to examine the relationship between HIV subtype and the severity of HIV-associated cognitive impairment among individuals initiating antiretroviral therapy in Uganda.

Methods. Sixty antiretroviral-naive HIV-infected individuals with advanced immunosuppression who were at risk of HIV-associated cognitive impairment underwent neurological, neuropsychological, and functional assessments, and gag and gp41 regions were subtyped. Subtype assignments were generated by sequence analysis using a portion of the gag and gp41 regions.

Results. Thirty-three HIV-infected individuals were infected with subtype A, 2 with subtype C, 9 with subtype D, and 16 with A/D recombinants. Eight (89%) of 9 HIV-infected individuals with subtype D had dementia, compared with 7 (24%) of 33 HIV-infected individuals with subtype A (P = .004).

Conclusions. These results suggest that, in untreated HIV-infected individuals with advanced immunosuppression who are at risk of developing HIV-associated cognitive impairment, HIV dementia may be more common among patients infected with subtype D virus than among those infected with subtype A virus. These findings provide the first evidence, to our knowledge, to demonstrate that HIV subtypes may have a pathogenetic factor with respect to their capacity to cause cognitive impairment. Additional studies are needed to confirm this observation and to define the mechanism by which subtype D leads to an increased risk of neuropahtogenesis.
Pathogenesis and Cellular Mechanisms

Note: This figure was modified from Jones G. & Power C. Neurobiology of Disease, 2006; 1 – 17
M/MΦ: monocytes/macrophages
Mechanisms in HAND with Age

Mechanisms leading to HAND are exacerbated in >50 yr olds with years of chronic neuroinflammation. Neurotoxins, inflammation and OS combined with normal aging processes increase HAND burden in ageing HIV patients.

*Fields J et al, 2014*
Rapidly Progressing Dementia

Cognitive/behavioral 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
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

- Failure rates to detect dementia: Clinicians fail to detect in 21%-72% of patients

- Definitive diagnosis by neuropathological examination
  - presence of amyloid plaques and neurofibrillary pathology
Age and Illiteracy are the strongest risks

Kalaria RN et al, 2008; 2012

Alzheimer’s disease (common dementia)
- Age
- Family history
- Down’s syndrome
- Head injury
- Apolipoprotein E-ε4
- Vascular factors
- Smoking
- Female gender
Diagnosis of Alzheimer’s Disease: NINCDS-ADRDA Criteria

Dementia
- Impaired memory
- ≥ 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 Dementia

Criteria (NINCDS-ADRDA, 1984; ICD-10, 1993; APA, 1994; 2011)

Development of multiple cognitive deficits manifested by both:

- **Memory impairment** (impaired ability to learn new information or to recall previously learned information)

- One (or more) of the following cognitive disturbances: a. **Aphasia** (language disturbances); b. **Apraxia** (impaired ability to carry out motor activities despite intact motor function); c. **Agnosia** (failure to recognize or identify objects despite intact sensory function); d. **Disturbance in executive functioning** (i.e., planning, organizing, sequencing, abstracting)

- Cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning
## AD Versus VaD: “Classical” Clinical Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>AD</th>
<th>VaD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of vascular conditions and risk factors</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Onset and progression</td>
<td>Insidious and gradual</td>
<td>Abrupt and stepwise</td>
</tr>
<tr>
<td>Neuroimaging positive for CVD</td>
<td>X</td>
<td>✓</td>
</tr>
<tr>
<td>Psychiatric comorbidity</td>
<td>May be present</td>
<td>Frequent</td>
</tr>
<tr>
<td>Executive dysfunction</td>
<td>None or mild</td>
<td>✓</td>
</tr>
<tr>
<td>Focal neurological signs and symptoms</td>
<td>X</td>
<td>✓</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>✓</td>
<td>May not be prominent</td>
</tr>
<tr>
<td>Gait disturbances</td>
<td>X</td>
<td>✓</td>
</tr>
<tr>
<td>Emotional lability</td>
<td>X</td>
<td>✓</td>
</tr>
<tr>
<td>Increased urinary frequency</td>
<td>X</td>
<td>✓</td>
</tr>
<tr>
<td>Diagnostic criteria</td>
<td>DSM-IV, NINCDS-ADRD AIREN</td>
<td>DSM-IV, NINDS-ADRD</td>
</tr>
</tbody>
</table>
Cross-section Through a Memory Clinic

Data from the Geriatric Dept., Huddinge University Hospital, Jönhagen & Wahlund, 2001

SMCI--subjective memory impairment
MCI--mild cognitive impairment
AD--Alzheimer’s disease
VaD--vascular dementia
MIX--”mixed” dementia
FTD--frontal lobe dementia
PPA--primary progressive aphasia
UNS--dementia of unspecified origin
Diagnostic issues in AD (2)

**Early and Late-onset**

**EOAD (<65 years; usually familial)**
Relatively rapid onset and progression; memory impairment; aphasia; agraphia; alexia; acalculia or apraxia (presence of temporal, parietal and frontal lobe involvement)

**LOAD (>65 years)**
1. Evidence of very slow gradual onset and progression (may only be obvious retrospectively)
2. Predominance of memory impairment (a. over intellectual impairment or b. meet general criteria for 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.
Cognitive Ageing related thresholds leading to Alzheimer’s Disease

- Memory
- Language
- Spatial ability
- Aggressiveness
- Apathy
- Personality changes

Dementia

ADL (Activities of Daily Living)
Social ability
Signs of Dementia vs Age-Related Changes

- **Memory loss that disrupts daily life**: forgetting recently learned information
- **Challenges in planning or solving problems**: changes in their previous abilities and concentrating
- **Difficulty completing familiar tasks**: difficulties in daily tasks in familiar environments
- **Confusion with time and place**: lose track of dates, seasons and passage of time
- **Trouble understanding visual images and spatial relationships**: difficulty reading, judging distance, colour, contrast
- **New problems with words in speaking or writing**: difficulty following/joining conversation, vocabulary problems
- **Misplacing things and losing ability to retrace steps**: losing things and the way
- **Decreased or poor judgement**: experience changes in decision-making
- **Withdrawal from work or social activities**: cannot keep up with social activities, hobbies, work projects, sports etc.
- **Changes in mood and personality**: become confused, suspicious, aggressive, fearful, anxious, easily upset

Terminal stages of AD

How can we tell?

• Limited vocabulary (six words or less)
• Absence of smiling
• Inability to walk without substantial assistance
• Inability to sit up independently
• Difficulty eating or swallowing
• Recent weight loss
• Decreased consciousness or coma
• Bowel or urinary incontinence
• Recurrent respiratory or urinary infections
• Inability to hold up the head or track objects with the eyes
Objectives for Neuropsychometry screening

• 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; Others Montreal Cognitive Assessment (MoCA)

• 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
Alzheimer’s Disease (AD)

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

Dementia with Lewy Bodies (DLB)

- 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
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
Tests of Cognition in Dementia (1)

ADAS-Cog is used to test several features of cognition in subjects suspected with dementia

1. First 10 min conversation- travel, weather, exercise, other
2. Word recall task –words shown on card
3. Naming fingers and objects – asked to name
4. Command –make a fist, point ceiling etc
5. Delayed word-recall task –recall previous words
6. Constructional praxis –ability to copy geometric forms
7. Ideational praxis –do something (fold letter)
8. Orientation – person, day, month, year
9. Word-Recognition task
Accumulation of Different Types of Brain Pathology during Ageing
Key Pathological Hallmarks of AD

Accumulation of Brain Pathology with Age

- Amyloid or Neuritic plaques (NP)
- Neurofibrillary tangles (NFT)
Amyloid Plaques (Aβ protein deposits)

Aβ in neocortex and hippocampal formation. EM shows fibrillar amyloid
Brain amyloid plaques with Ageing

Cortical accumulation of NPs

Nelson PT et al, JNEN, 2012
Key Pathological Hallmarks of AD

Accumulation of Brain Pathology with Age

- Amyloid or Neuritic plaques (NP)
- Neurofibrillary tangles (NFT)
Neurofibrillary tangles
(Hyperphosphorylated tau protein)

NFT in neocortex and hippocampal formation. EM shows neurofibrillar twisted fillaments (tangles)
Topographic distribution of NFT and NP in AD

Thirty-nine cytoarchitectural fields were assessed on a 0-4+ scale for the presence of NFT or NP in 17 hemispheres. A consistent hierarchical distribution was observed.
Correlation of AD Neuropathological Changes With Cognitive Status

- Correlations between antemortem cognitive status (MMSE), and counted neocortical NFTs (A) and neuritic β-amyloid plaques (NPs; B)
- Correlation between final MMSE scores and neocortical NFT counts is stronger than that between MMSE scores and NP counts

Nelson PT et al, 2012
Cognition and Brain Pathology during Ageing

Progressive accumulation of brain pathology increases damage and decreases cognitive functions
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.
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
Patterns of Atrophy in Dementia

- Pattern of atrophy is different between types of dementia

Loss of brain tissue in these regions predicts poor performance on tests of memory.
Screening, Diagnosis and Risk Factors for Dementia in SSA

Arms of Newcastle Longitudinal studies
Extensions of Newcastle Dementia Studies in SSA

Longitudinal studies in Dementia in Africa (Ibadan, Nigeria, Nairobi, Kenya and Hai District Tanzania: PIs R Kalaria, A Ogunniyi, M Owolabi, R Akinyemi, R Walker
Community Validation, Hai Dementia screening Study

**COMMUNITY VALIDATION**
- Attended screening: n = 455
- Participants screened: n = 449

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

**Cut-off of ≤ 7**

- No dementia on screening: n = 352
- Probable or possible dementia on screening: n = 97
  - Randomly selected for follow-up clinical DSM-IV dementia assessment: n = 43
  - Follow-up clinical DSM-IV dementia assessment: n = 87
  - Not followed up: n = 5 (5.4%)
    - Error calculating cognitive screening score: 4
    - Unable to trace: 1

**Cut-off of ≤ 8**

<table>
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<tr>
<th>Parameter</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>60.0%</td>
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<tr>
<td>Specificity</td>
<td>84.2%</td>
</tr>
<tr>
<td>LR</td>
<td>3.80</td>
</tr>
<tr>
<td>Cut-off of ≤ 8</td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>88.6%</td>
</tr>
<tr>
<td>Specificity</td>
<td>64.2%</td>
</tr>
<tr>
<td>AUROC curve</td>
<td>0.846 (95%CI 0.776 - 0.915)</td>
</tr>
<tr>
<td>Educational level no association</td>
<td></td>
</tr>
</tbody>
</table>
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.

Observe examples of stick design in 4 impaired subjects.
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
## Prevalence Estimates of Dementia in sub-Saharan Africa (~2.1 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 Brazaville</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, Ibadan</td>
<td>65+</td>
<td>CSI-D</td>
<td>2.29% (age-adjusted)</td>
</tr>
<tr>
<td>Gureje, 2006</td>
<td>Nigeria, Ibadan</td>
<td></td>
<td>10 word learning list</td>
<td>‘Probable Dem’ 10.1%</td>
</tr>
</tbody>
</table>
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*

**Profound NFT pathology**
Progression of Dementia

Progressive accumulation of brain pathology increases damage and decreases cognitive functions.
Progression of Dementia

Mathis et al., Nucl Med Biol 2007;34(7);809-22

Amyloid Deposition precedes Clinical Dementia by Years
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.)

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, HPT, AF)
- Use of inappropriate medications
- MRI hippocampal atrophy
- CSF and PET indicating amyloid accumulation
## Presentation of AD Neuropsychiatric Inventory (NPI)

<table>
<thead>
<tr>
<th>Item</th>
<th>Percentage</th>
<th>Item</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>

*Cummings, 2010*
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
<table>
<thead>
<tr>
<th>Side Effects of ACHEIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild sedation (initially)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
</tr>
<tr>
<td>Anorexia, nausea, vomiting</td>
</tr>
<tr>
<td>Diarrhoea</td>
</tr>
</tbody>
</table>
Maladies Neurodégénératives dans Afrique

- **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
- 12 studies describing genetics of PD in Africa
- 2 studied inheritance patterns of familial PD
- 10 focused on one of Parkin, PINK 1 and LRRK2 genes in familial PD
- All studies were from North Africa, mostly powered by the French PD Genetics Study Group (Lesage et al)
- Most sig. finding was very high freq. of LRRK2 mutation (41%)
- Parkin and PINK 1 mutations were also documented

After Akinyemi R, 2009
Dementia with Lewy Bodies in Africa

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

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

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

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

Arnold Pick
1854-1924
Clinical Syndromes in FTD

- Frontotemporal dementia (frontal variant; FTD; bvFTD)
- Semantic dementia (SD)
- Progressive non-fluent aphasia (PNFA)
Frontotemporal Dementias in Africa

• 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

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

**FTLD-Tau**

- 3R Tau+  
- MAPT mutation
- 4R Tau+
- 3R & 4R Tau+

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

**FTLD-TDP / -FUS / -UPS**

- TDP-43 +; NF or INA -
- NF or INA +; TDP-43 -ve
- NF or INA -; TDP-43 -

- TDP43- Sporadic; GRN, C9ROF72 expansion, TARDP, VCP mutations
- aFTLD-U NIFID*
- 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

Images showing brain scans and histological sections.
Corticobasal Degeneration

- Slowly progressive dementia
- Asymmetric lesions (Apraxia)
- Frontal and Parietal atrophy
- Corpus Callosum thining
- Heterogeneity of neuronal inclusions
- Balloned neurones (H&E)
- Neuronal vacuolation
Progressive Supranuclear Palsy

• S-R-O Syndrome; Midbrain (SN) degeneration; Neuronal Inclusions (\textit{Tau})
Pick’s Disease

“knife-like” atrophy
# Tauopathies - CBD, PSP and Pick's

<table>
<thead>
<tr>
<th>Feature</th>
<th>CBD</th>
<th>PSP</th>
<th>Picks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical atrophy</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>WM pathology</td>
<td>Frontal</td>
<td>Cerebral</td>
<td>Frontal lobe</td>
</tr>
<tr>
<td>Basal Ganglia changes</td>
<td>Caudate</td>
<td>Pallidus</td>
<td>Caudate</td>
</tr>
<tr>
<td></td>
<td>atrophy</td>
<td>pigmented</td>
<td>atrophy</td>
</tr>
<tr>
<td>Cortical changes</td>
<td>superior</td>
<td>middle +</td>
<td>severe</td>
</tr>
<tr>
<td>Tau reactivity</td>
<td>++</td>
<td>++ (NFT)</td>
<td>Pick bodies</td>
</tr>
<tr>
<td>Threads</td>
<td>+++</td>
<td>+</td>
<td>Variable</td>
</tr>
<tr>
<td>Astrogliosis</td>
<td>+++</td>
<td>+++</td>
<td>Variable</td>
</tr>
<tr>
<td>Microgliosis</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Oligodendrocytes</td>
<td>+++</td>
<td>++</td>
<td>Variable</td>
</tr>
</tbody>
</table>
Frontotemporal Lobar Degeneration

FTLD: Tau –ve

- Originally all as Pick’s disease
- 10-15% of all dementias
- Clinical presentation FTD, semantic dementia, primary aphasia, corticobasal-like syndrome
- Subtypes: FTLD, FTLD-U, FTLD-MND
- Marked frontotemporal atrophy
- Neuronal loss and astrogliosis
- Progranulin (PGRN) cases +ve for TDP-43

“Progranulin”
Most mutations null alleles, FTD results from PGRN haploinsufficiency

PGRN (FL) many functions: trophic and anti-inflammatory activity,
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
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.
HD and Polyglutamine (PG) pathogenesis

PG domains lead to cytoplasmic inclusions. Huntingtin has many roles- protein trafficking, vesicle transport, postsynaptic signaling, transcriptional regulation, and apoptosis-multiple intracellular pathways are disrupted.

- Inverse correlation between age of onset and CAG repeat numbers.
### 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>
</table>
| Dementia with myoclonus               | Prion disease  
Autosomal dominant AD                                                              |
| Dementia with ataxia                  | Inherited forms of ataxia including SCA2, SCA3, SCA17, DPRLA                             |
| Dementia with chorea                  | Huntington’s disease  
SCA3, SCA17, DPRLA, neuroferritinopathy, neuroacanthocytosis                          |
| Dementia with dystonia                | Wilson’s disease  
Niemann–Pick disease (NPC1 and NPC2)                                                   |
| Dementia with progressive myoclonic epilepsy | Mitochondrial disease, Lafora body disease, Neuronal ceroid lipofuscinosis               |
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 Nobel Prize in Physiology or Medicine 1997
Carlton Gajdusek, Nobel Prize in 1976- Kuru Studies

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

The normal (left) and disease-carrying forms of human prion protein with beta-strands in blue and alpha-helices in green
CJD, FFI and nvCJD as Prion disorders; Severe atrophy may involve all lobes; Spongiform change; Florid prion plaques (with angiopathy). Sometimes restricted regional pathology.
# 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)
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

DEMENTIA
Learning Objectives

Overview of Neuropathology of Dementia

• Ageing related decline 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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