ALZHEIMER'S DISEASE
AND OTHER CAUSES OF DEMENTIA

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OUTLINE OF LECTURE

- History and Background
- Neuroanatomy and Pathophysiology
- Aetiology
- Epidemiology
- Clinical presentation
- Diagnosis and Workup
- **Differential diagnosis (Other causes of Dementia)**
- Treatment
- Prognosis, patient/family education and Counselling
- Approach to Dementia in a medical colleague

History and Background

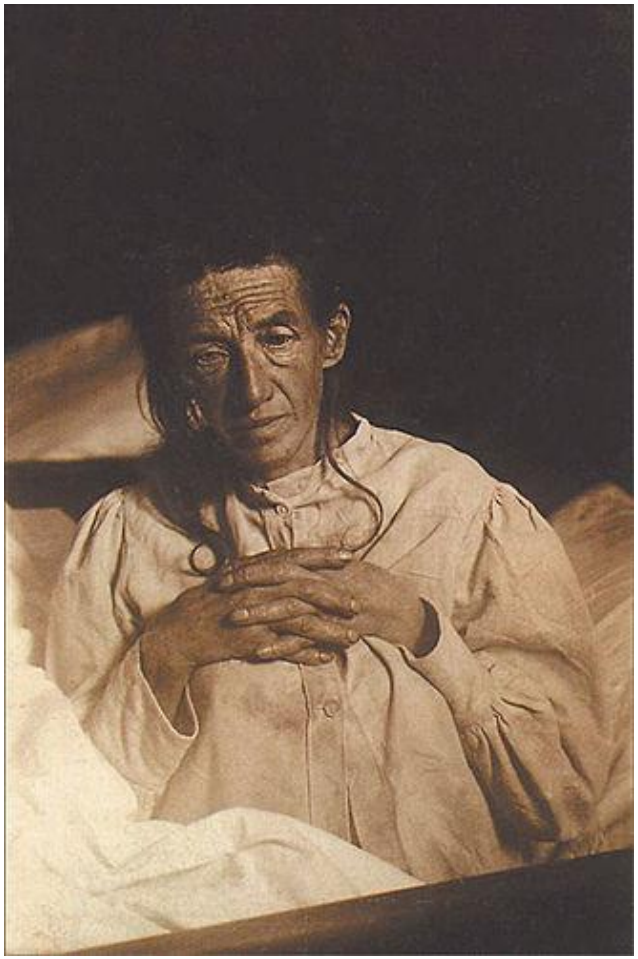
- DEFINITION OF DEMENTIA

Dementia is a broad category of brain diseases that cause long-term loss of the ability to think and reason clearly that is severe enough to affect a person's daily functioning.

History and Background

- Reference to Dementia has been from antiquity
- Pythagoras, (Physician/Mathematician) 7th century BC, made reference to dementia and delineated the ‘Senium’ as being from age 63years
- Aristotle, Plato, Cicero, Galen and Celsus all made observations about dementia in old age

Alzheimer’s patient, Auguste Deter in 1902



History and Background

- Dr Alzheimer gave a lecture on Nov 3 1906 where he described the clinical features and pathology of the condition which was then known as **PRE-SENILE DEMENTIA**, in distinction to **SENILE DEMENTIA** which was considered 'normal' at the time after age 65years.
- Alzheimer published his findings in 1907, and the rest is history!
- The disease was thereafter named after him
- In 1976, Neurologist Robert Katzman however argued that there should be no distinction between Pre-Senile and Senile Dementia, based on the identical pathology of both conditions, and that Dementia is never normal as was then accepted with Senile Dementia (over age 65years)

History and Background
ALZHEIMER'S DISEASE (AD)

- Alzheimer's disease is an acquired disorder of cognitive and behavioural impairment that markedly interferes with social and occupational functioning. It is an incurable disease with a long and progressive course.
- Most common cause of dementia, 75% of all dementias
- 1901, Dr Alois Alzheimer, German psychiatrist observed a 51 year old woman with short-term memory loss at a Frankfurt asylum. Patient died in 1906 and her brain was autopsied, which revealed AMYLOID PLAQUES and NEUROFIBRILLARY TANGLES

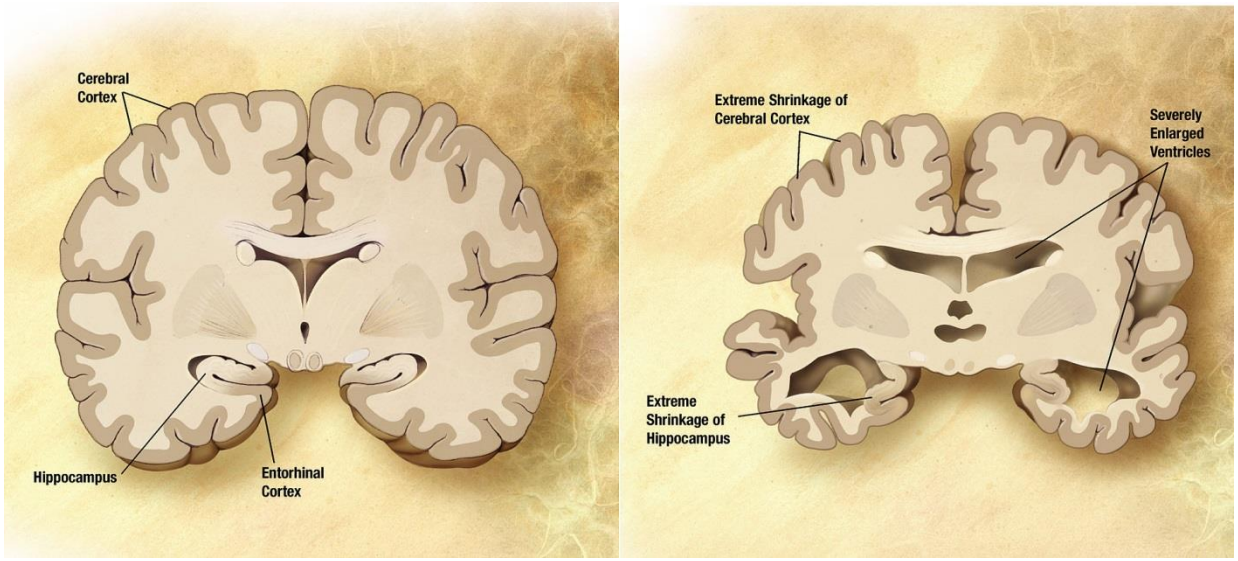
NEUROANATOMY

- Healthy neurons have an internal support structure made up of **microtubles.**
- A special protein called TAU binds the microtubles together.
- In AD, TAU is changed chemically, it pairs with other threads of tau which become tangled together. The microtubles then disintegrate collapsing the neuron transport system.
- The formation of these neurofibrillary tangles(NFTs) leads to cell communication malfunction and later death
- In addition to NFTs the anatomic pathology also includes senile plaques(SPs- also known as beta-amyloid plaques).
- The hippocampus and medial temporal lobe are the initial sites of tangle deposition and atrophy
- This atrophy can be seen on brain MRI early in AD and helps support a clinical diagnosis.

NEUROANATOMY

- SPs and NFTs were described by Alois Alzhemer in his original report on the disorder in 1907
- They are now universally accepted as the pathological hallmark of the disease.

Alzheimer's Disease Brain comparison



PATHOPHYSIOLOGY

- There is a continuum between the pathophysiology of normal ageing and that of AD
- Pathologic hallmarks of AD have been identified, (SPs and NFTs), however these features also occur in the brains of cognitively intact persons.
- AD affects 3 processes that keep neurons healthy: Communication, Metabolism, and Repair
- Certain nerve cells in the brain stop working, lose connections with other nerve cells, and finally die.
- The destruction and death of these cells cause the memory failure, personality changes and problems in carrying out activities of daily living.

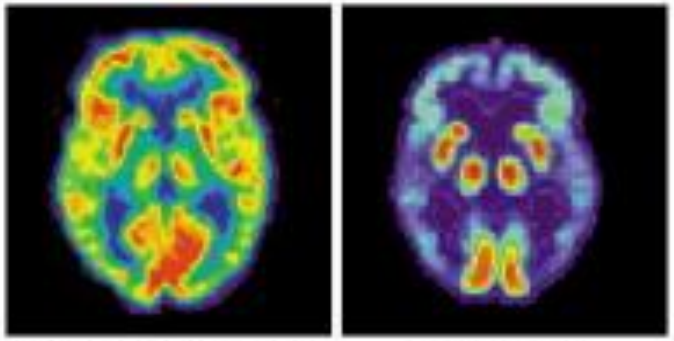
PATHOPHYSIOLOGY

- Since the time of Alzheimer, efforts have been made to elucidate the composition of SPs and NFTs
- SPs have always been known to contain a starch-like substance ,**Amyloid** (Greek: Amylon-starch) usually in the centre of these lesions
- This amyloid protein has been characterised and its amino acid sequence recorded, and the gene responsible for encoding it’s precursor protein has been located on chromosome 21

PATHOPHYSIOLOGY

- Several hypotheses have been proposed for the development of SPs and NFTs, including the AMYLOID CASCADE HYPOTHESIS and the MITOCHONDRIAL CASCADE HYPOTHESIS
- Although NFTs and SPs are characteristic of AD they are not pathognomonic, as they are found in other neuro-degenerative disorders, including Progressive supra-nuclear palsy and Dementia Pugilistica (Chronic Traumatic Encephlopathy-CTE)
- SPs may, of course, occur in normal aging
- Therefore, the mere presence of these lesions is not sufficient to support the diagnosis of AD. They must be present in sufficient numbers and in a characteristic topographic distribution to fulfil the current histo-pathologic criteria of AD diagnosis.
- Evidence has shown that abnormal Amyloid metabolism plays a key role in NFT formation and beta amyloid is capable of damaging TAU protein

PET Scan of Alzheimer Brain



PET Scan of Normal Brain

PET Scan of Alzheimer's Disease Brain

AETIOLOGY

- The cause of AD is unknown!
- Several investigators now believe that a combination of environmental and genetic risk factors trigger a pathophysiologic cascade that over decades, lead to Alzheimer pathology and dementia

AETIOLOGY

RISK FACTORS

- Advancing age
- Family history – Most cases of AD are sporadic, but up to 5% may be familial and Autosomal dominant
- Mutations – APP (amyloid precursor protein), PS1 and PS2 genes on Chromosome 21, 14 and 1 respectively- lead typically to autosomal dominant early-onset AD
- APOE E4 Genotype (apolipoprotein E, E2-4 alleles), on chromosome 19
- Obesity
- Smoking
- Insulin resistance
- Vascular factors
- Dyslipidaemia
- Hypertension
- Down syndrome
- Traumatic brain injury(TBI)
- Infection (Treponema, Borrelia burgdorferi, HSV1)
- Depression

EPIDEMIOLOGY

- Prevalence of Dementia worldwide in persons 65years of age and older is 6-10%, with AD accounting for 75% of cases
- Between 60-69years prevalence of AD <1%, In 75year-olds it's 5-10%, but in persons 90-95years old it's 40-50%!
- World prevalence of AD is currently put at about 30 million, projected to hit 106 million by 2050!
- Note that there is no age at which AD's prevalence is 100%. Therefore it is not an inevitable accompaniment of old age!
- In Nigeria the prevalence reported is somewhat lower than this, but this may just reflect our lower life expectancy in the third world!
- AD affects men and women equally, but increase life expectancy in women may skew the prevalence to them.
- AD and other dementias are more common in African Americans than whites in USA (Ratio 2:1), but incidence is similar all over the world without a racial bias.

CLINICAL PRESENTATION
Alzheimer's Disease

- Insidiously progressive memory loss
- Behavioural changes
- Language disorders (eg, Anomia)
- Impairment of visuospatial skills
- Impairment of executive functions
- Inability to calculate is profound

CLINICAL PRESENTATION

- Always remember to get a history from a close relation who knows patient very well.
- Also ask about family history of AD and other dementias

CLINICAL PRESENTATION

- When does a person cross the line from being just absent-minded and forgetful, to being **DEMENTED?**

CLINICAL EXAMINATION

- Complete physical examination
- Detailed neurologic examination
- **Mental status examination**

Above to be done to evaluate disease stage and rule out co-morbid conditions

CLINICAL EXAMINATION

- The initial Mental Status Examination should include evaluation of the following:-

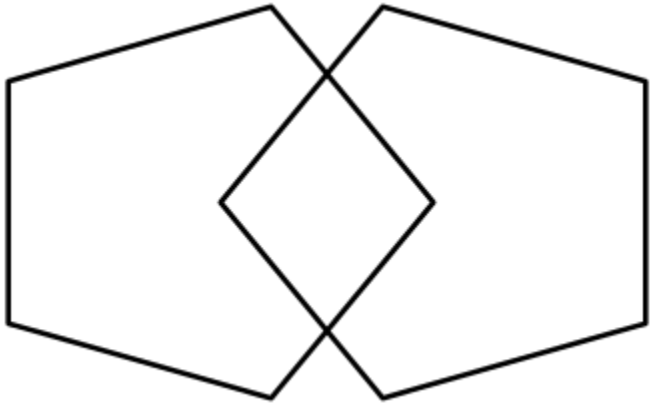
- Attention and concentration
- Recent and remote memory
- Language
- Praxis (ie, ability to perform motor skills without nonverbal prompting)
- Executive function
- Visuospatial function

CLINICAL EXAMINATION

STANDARDISED EXAMINATIONS

- Mini-Mental Status Examination (MMSE)
- MoCA (Montreal Cognitive Assessment)
- SLUMS (St Louis University Mental Status) Examination

Drawing of Interlocking Pentagons



CLINICAL EXAMINATION

STAGES OF ALZHEIMER'S DISEASE

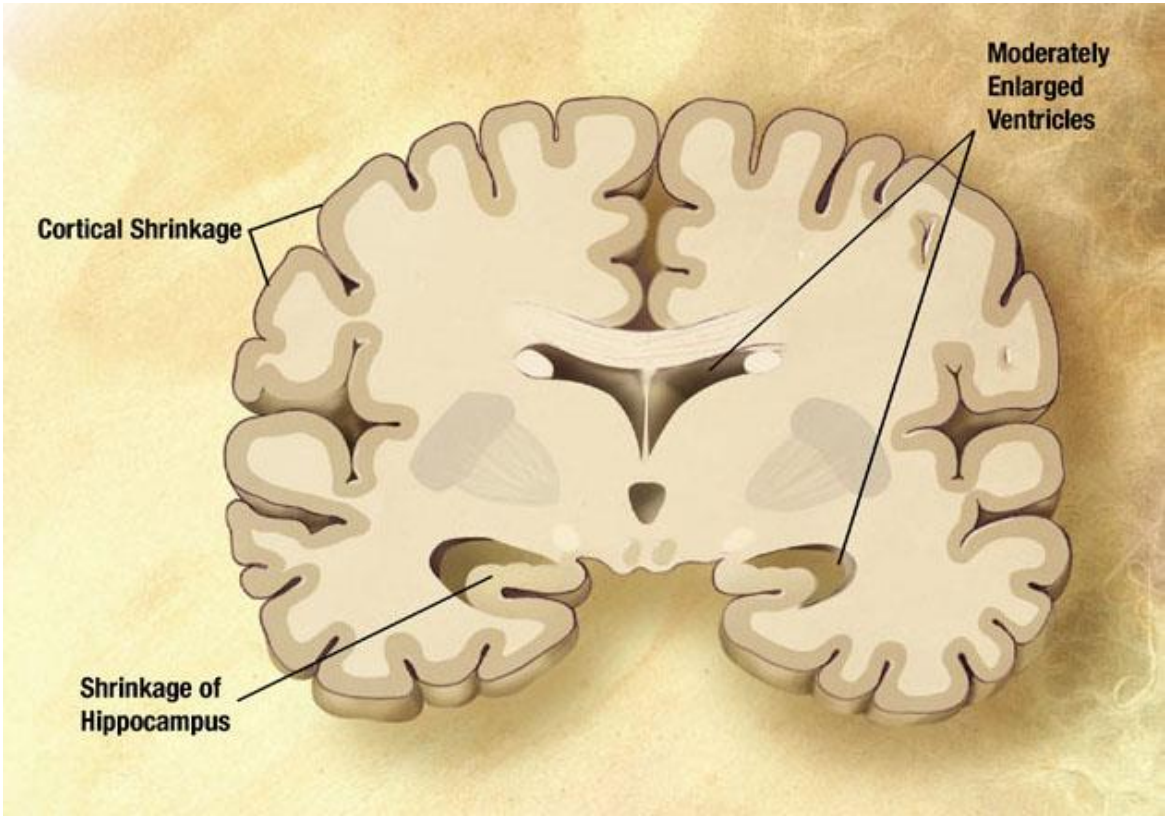
- Preclinical
- Mild
- Moderate
- Severe

STAGES OF ALZHEMER'S DISEASE

PRE-CLINICAL

Memory loss, is the first visible sign, and is the main feature of Mild Cognitive Impairment (MCI), which is considered by many scientists and clinicians as the transitional clinical phase between normal brain aging and AD.

Pre-clinical Alzheimers's Disease



STAGES OF ALZHEIMER'S DISEASE

MILD

- Memory loss
- Confusion about the location of familiar places (getting lost begins to occur)
- Taking longer to accomplish normal daily tasks
- Trouble handling money and paying bills
- Compromised judgement often leading to bad decisions
- Loss of spontaneity and sense of initiative
- Mood and personality changes; increased anxiety

STAGES OF ALZHEIMER'S DISEASE

MODERATE

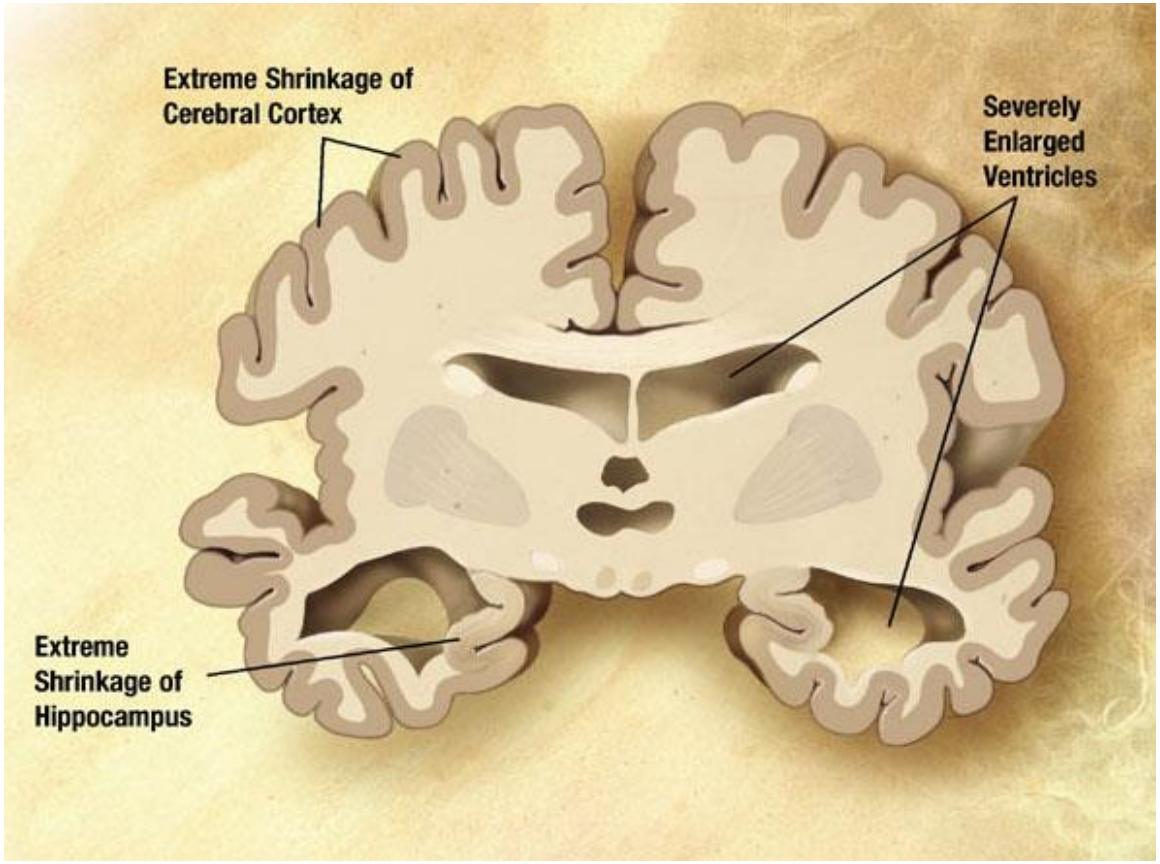
- Increased memory loss and confusion
- Shortened attention span
- Problems recognizing friends and family members
- Difficulty with language; problems with reading, writing, working with numbers
- Difficulty organizing thoughts and thinking logically
- Inability to learn new things or to cope with new unexpected situations
- Restlessness, agitation, anxiety, tearfulness, wandering, especially in the late afternoon and night
- Repetitive statements or movements, occasional muscle twitching
- Hallucinations, delusions, suspiciousness or paranoia, irritability
- Loss of impulse control (undressing in public, vulgar language)
- Perceptual-motor problems (eg, inability to get out of a chair or setting a table)

STAGES OF ALZHEIMER'S DISEASE

SEVERE

- Weight loss
- Seizures
- Groaning , moaning or grunting
- Increased sleeping
- Patient can no longer recognize family and loved ones
- Can no longer communicate in any way
- Lack of bladder and bowel control
- In end-stage AD, patients are in bed all the time and death is often (mercifully) the result of other illnesses, frequently aspiration pneumonia.

Severe Alzheimer's Disease



DIAGNOSIS AND WORKUP

Clinical Guideline for Diagnosis

- The **NIH-ADRDA (Alzheimer's Association)**(USA)criteria for diagnosis of AD require the finding of a slowly progressive memory loss of insidious onset in a fully conscious patient.
- AD cannot be diagnosed in patients with clouded consciousness or delirium. Toxic metabolic conditions and brain neoplasms must also be excluded as potential causes of the patient's dementia.
- AD is therefore a diagnosis of exclusion. All other known causes of dementia must be excluded to arrive at AD diagnosis.
- Brain biopsy would be useful, but for obvious reasons cannot be used in routine clinical practice. Autopsy of course is only of benefit to researchers and medical science but not the patient!

DIFFERENTIAL DIAGNOSIS

- Depression
- Chronic Traumatic Encephalopathy (CTE, Dementia Pugillistica)
- Cortical Basal Ganglionic Degeneration (“Alien limb”, multiple deficits)
- Dementia in Motor Neuron Disease (Usually mild)
- Dementia with Lewy Bodies (DLB) (Hallucinations,Parkinsonism)
- Frontotemporal Lobe Dementia (FTD) (Personality changes, Language difficulties)
- Huntington’s Disease Dementia (Chorea, Autosomal dominant inheritance)
- Normal Pressure Hydrocephalus (Triad of Dementia, Gait imbalance, Incontinence)
- Neurosyphylis (GPI, now rare)
- Parkinson’s Disease (Mild dementia in late stages)
- Parkinson-Plus Syndromes (Atypical Parkinsonism, Progressive Supranuclear palsy)
- Lyme disease (Spirochaete – Borrelia burgdorferi, Chronic encephalopathy/fatigue)
- Prion-Related Diseases (Creutzfeldt-Jakob disease)
- Thyroid Disease (Hypothyroidism and even Thyrotoxicosis)
- Vascular Dementia (Advanced CVD in HTN and DM)
- Wilson’s Disease (Hepatolenticular degeneration, Autosomal recessive gene)

DIFFERENTIAL DIAGNOSIS

Other Disorders to consider in the Differential diagnosis of AD include:-

- Age associated memory loss
- Alcohol and drug abuse
- Vitamin B12 deficiency
- Hearing and Visual Impairment
- Hypernatremia
- Hypoglycaemia
- Polypharmacy
- Volume depletion

WORKUP
(Investigations)

ALZHEMER'S DISEASE IS A CLINICAL DIAGNOSIS

- **CT SCAN OF BRAIN**
- **MRI OF BRAIN**
- **SPECT** (Single Photon Emission Computerised Tomography)
- **PET** (Positron Emission Tomography)
- **Other Laboratory Tests**

These tests help exclude other possible causes of dementia like **CVD**, **CSDH**, **NPH**, Vit B12 deficiency, syphylis and thyroid disease**.**

WORKUP

- In patients with AD, Brain CTs and MRIs can show diffuse cortical and/or cerebral atrophy, but these findings are not diagnostic of AD.
- Atrophy of the Hippocampi on coronal MRI is considered a valid biomarker of AD neuropathology in clinical research studies, but this is not routinely measured in clinical care.
- PET scans with the injection of an agent which attaches to beta amyloid (Florbetaben F18, approved March 2014 by FDA) has been shown to improve the diagnostic yield for AD by revealing the AMYLOID BURDEN of the brain.
- It also has a predictive value in patients with MCI and others with positive FH of AD to determine their risk of developing AD in future.
- It is now likely we may diagnose AD with these augmented PET scans before symptoms actually develop!
- This of course has great promise in the field of therapeutics and drug trials.

WORKUP

- **EEG** (in ?CJD –Creutzfeldt-Jakob disease, other Prion-related diseases, Pseudodementia)
- **Lumbar puncture**, ?Normal Pressure Hydrocephalus (NPH), Raised TAU protein in AD and low Amyloid – Research tool
- **Genotyping**, - Research tool, for Alleles of APOE to predict AD risk
- **Smell Test** - University of Pennsylvania Smell Identification Test (UPSIT)- Alzheimer's Association International conference (AAIC), Copenhagen, Denmark, July 2014
- **Eye Test** – Fluorescent agent used to determine Beta Amyloid burden of the brain from retinal Amyloid burden (AAIC July 2014)

TREATMENT

THERE IS NO CURE FOR ALZHEIMER'S DISEASE!

- Only symptomatic treatments are available
- All drugs approved and available for treatment of AD modulate NEUROTRANSMITTERS, either ACETYLCHOLINE or GLUTAMATE in the brain.
- The standard medical treatment for AD includes Cholinesterase inhibitors (ChEIs) and a partial N-methyl-D-aspartate(NMDA) antagonist

TREATMENT contd

SECONDARY SYMPTOMS OF AD (eg, depression, aggression, agitation, hallucinations, delusions, sleep disorders) can be problematic.

- Antidepressants
- Anxiolitics
- Antiparkinsonian agents
- Beta blockers
- Anticonvulsants (for control of seizures and for their effects on behaviour)
- Neuroleptics (Quetiapine)

TREATMENT contd

HOSPITALISATION

- May be needed to treat comorbidities
- To protect patient if posing a danger to himself/herself or others.
- To help relieve care-giver fatigue, stress or burnout.

“WHO CARES FOR THE CAREGIVER???”

TREATMENT contd

- Evidence suggests that cholinergic systems that modulate information processing in the Hippocampus and neocortex are impaired early in the course of AD.
- Centrally acting ChEIs prevent the breakdown of acetylcholine
- Four such agents have so far been approved for the treatment of Mild to Moderate AD:-

  A. TACRINE

  B. DONEPEZIL (Aricept)

  C. RIVASTIGMINE (Exelon)

  D. GALANTAMINE (Razadyne)

TREATMENT contd

- Treatment of Moderate to severe AD requires the use of (N-methyl-D-aspartate)NMDA antagonist MEMANTINE (Namenda)
- Mental activity to support cognition
- Experimental Therapies, eg, amyloid immunisation, IVIG containing amyloid-binding antibodies, Vit E therapy, etc.
- Physical Activity

PREVENTION OF ALZHEIMER'S DISEASE

- There is no proven modality for preventing AD
- However epidemiologic evidence suggests that a healthy lifestyle can reduce the risk of AD
- Physical activity, exercise, and cardiorespiratory fitness may be protective
- The Mediterranean diet may also be protective
- Light to moderate alcohol drinking may reduce the risk of AD
- It has also been suggested that engaging in regular intellectual and brain-tasking activities may help to reduce the risk of developing AD

Intellectual activities like playing chess can help reduce Alzheimer's risk

PROGNOSIS, PATIENT/FAMILY EDUCATION AND COUNSELLING

- Alzheimer's disease is relentlessly progressive and universally fatal, with a huge financial and emotional burden on caregivers and the society
- Mean life expectancy from diagnosis is 7 years, and less than 3% of patients live longer than 14 years
- Efforts must be made to educate spouse and other family members about what to expect and prepare for, concerning AD
- A power of attorney may need to be obtained from the patient before he or she becomes too ill to give consent for his/her affairs to be managed by a nominated 3rd party or parties.

Alzheimer's Disease respects no one!

Actor Charlton Heston and President Ronald Reagan, in the White House!

DEMENTIA IN A COLLEAGUE

WHAT DO YOU DO IF YOU SUSPECT DEMENTIA IN A COLLEAGUE?

ALZHEIMER'S DISEASE
TAKE-HOME POINTS

1. Alzheimer's Disease is an acquired neurodegenerative disorder of unknown cause, with no effective treatment or cure.
2. Affects mainly people over 65years of age, some familial types may present before age 60years
3. Prevalence is still low in Nigeria compared to advanced western nations because of our short life expectancy
4. Diagnosis of AD is always clinical, and unless a brain biopsy (or autopsy) is done, is a diagnosis of exclusion

ALZHEIMER'S DISEASE
TAKE-HOME POINTS

5. Always look for treatable causes of dementia like Chronic subdural haematoma, Thyroid diseases, Normal pressure hydrocephalus and Neurosyphilis. Brain Imaging (MRI) helps in differential diagnosis.
6. The caregiver may be suffering more than the patient and may need more attention
7. The medications used in the treatment of AD only control the symptoms and do not affect the course of the disease
8. Do not ignore symptoms of Dementia in a colleague
9. Regular exercise in middle age (age 50-65yrs) can help prevent cognitive decline and development of MCI or AD.

(Alzheimer's Association International Conference (AAIC), Copenhagen, Denmark 2014. Presented July 14, 2014)

ALZHEIMER'S DISEASE
TAKE-HOME POINTS

10. TO AVOID DEMENTIA,

ALWAYS USE YOUR BRAIN!

I THANK YOU FOR YOUR ATTENTION!