Dementia: A Bird's Eye View

Dr. Joy D Desai MD DNB
Consultant Neurologist
The Jaslok Hospital & Sir HN Reliance Hospital
Mumbai

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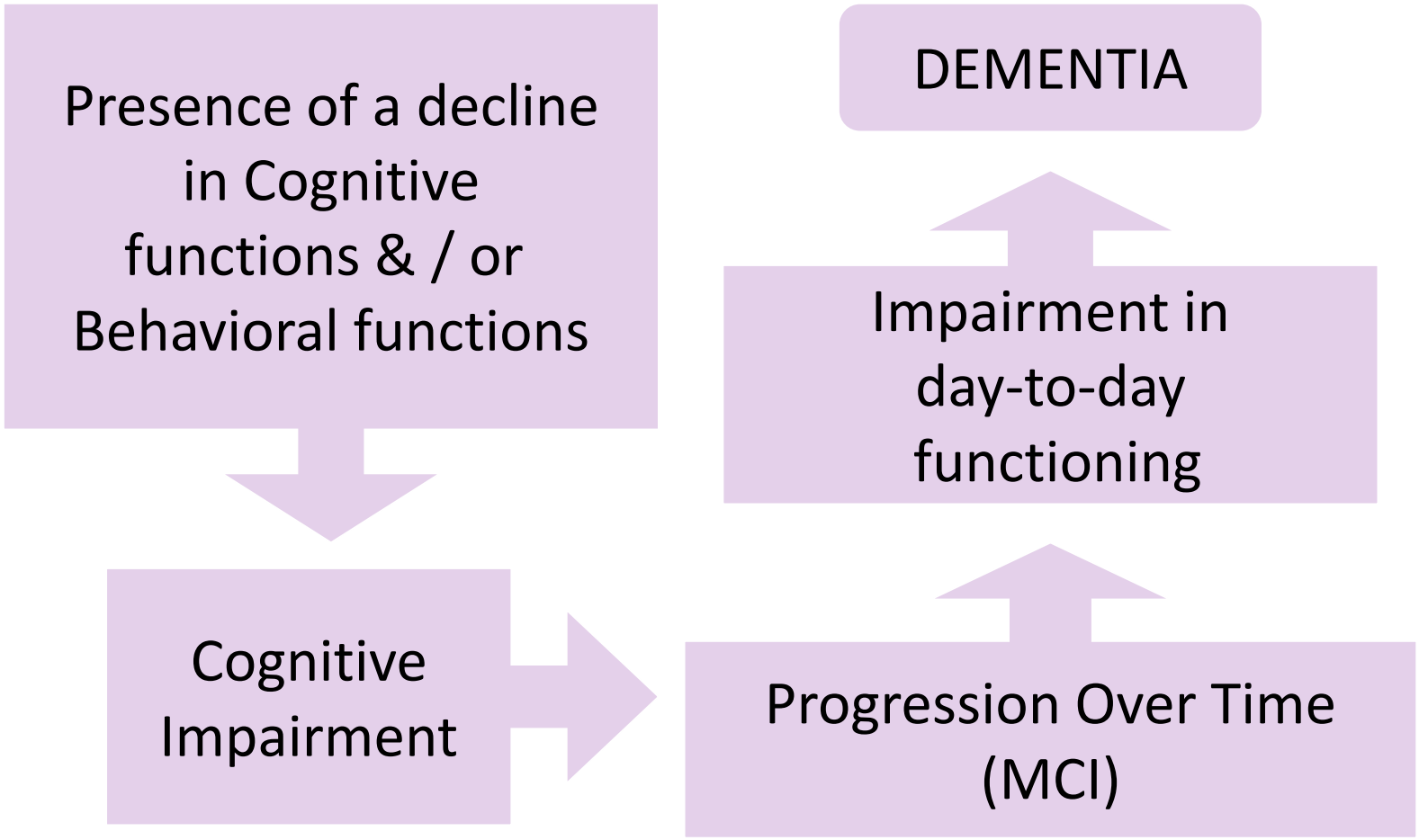
Dementia

- An acquired, progressive and often global impairment of memory, intellect and personality, without disturbance of consciousness
- A clinical syndrome caused by a wide range of diseases that affect the brain, either its structure or function

Definition of dementia

- Dementia: a progressive disorder characterized by cerebral dysfunction in three of six domains: memory, language, personality, praxis, visuospatial skills, and cognition (abstraction, judgement, executive function, etc.)
- Should affect quality of life

What is Dementia ?



Dementia

- Cortical dementias
  - Brain pathology predominantly affects the cortex
- Subcortical dementias
  - Brain pathology primarily involves the deeper brain structures
- Cortical and subcortical disturbances can coexist
  - The location and extent of damage to the brain usually explains the losses of function associated with dementia

History: Analytical approach

- Is this truly a dementia, reflecting a decline in at least three of the following six domains:
  - Personality
  - Behavior
  - Memory
  - Language
  - visuo-spatial skills
  - praxis

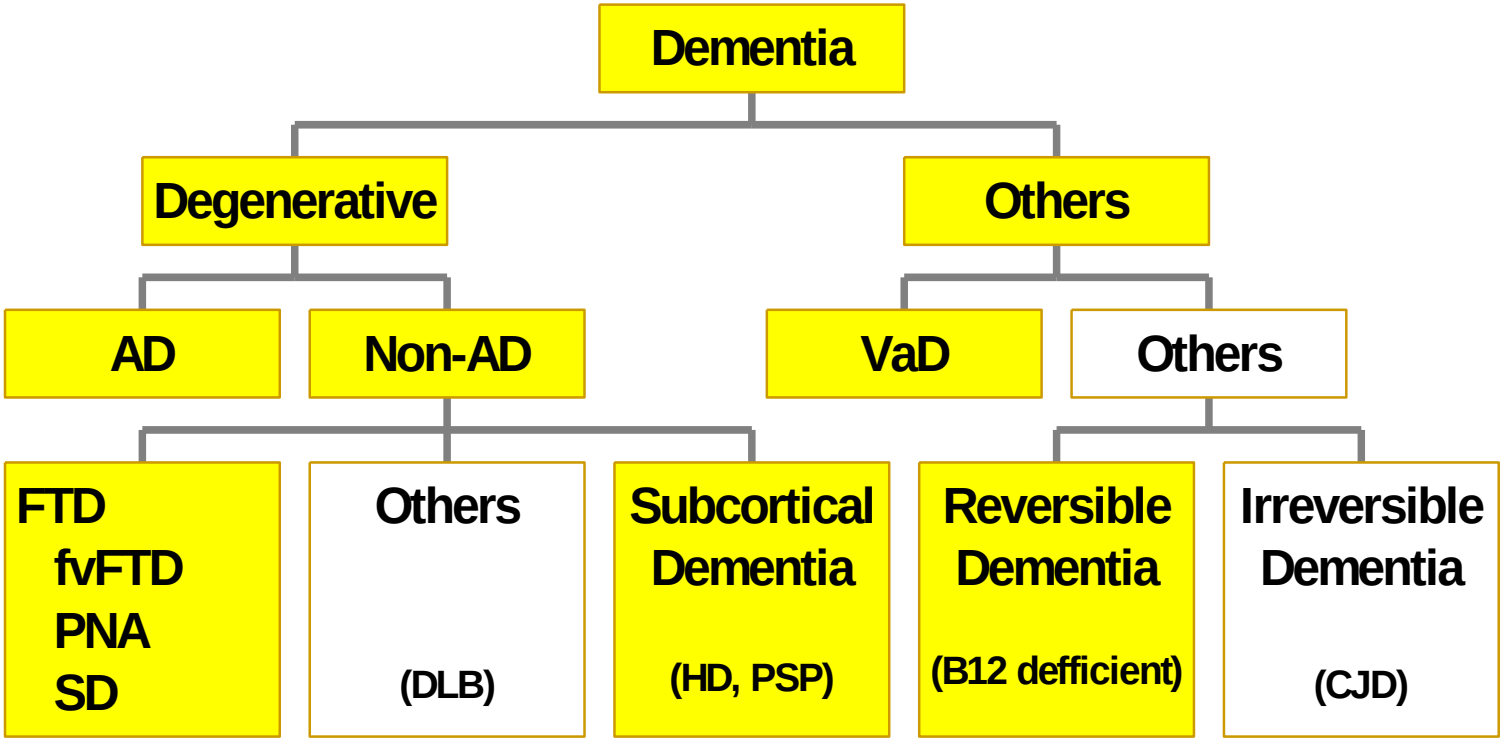
History

- Where is the lesion or lesions within the CNS? Cortex alone or is there a involvement of basal ganglia, cerebellum, spinal cord...
- What is the tempo of progression: Subacute, chronic, rapidly progressive, fluctuating ?

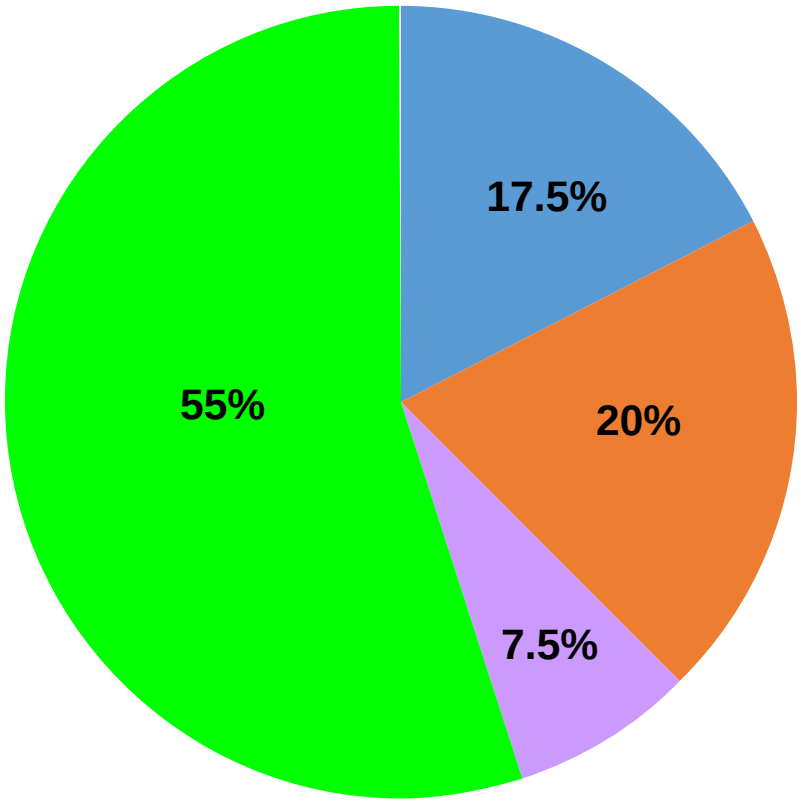
History

- What is the pathological basis of lesion/s?
- What is the present disability/QoL ?
- Is there an underlying systemic dysfunction producing the neurological symptoms ?

Dementia in a Clinic



Differential diagnosis of dementia



- Alzheimer's Disease
- – Multi-infarct dementia
  – Binswanger's disease
- – Parkinson's disease
  – diffuse DLB
  – Lewy body variant of AD
- Other dementias
  – frontal lobe dementia
  – Creutzfeldt-Jakob disease
  – corticobasal degeneration
  – progressive supranuclear palsy
  – potentially reversible dementias

Gersing et al., 1998; Cras, 1998

Symptomatic dementia

- Diagnosed when dementia occurs in specific geographical / historical setting
- Important to lay emphasis as always on the history and specific clinical setting of the occurrence of dementia e.g. in a patient seropositive for HIV I & II viruses

Symptomatic dementia

- Primary CNS vasculitis
- Lympangio-endotheliomatosis
- Primary CNS lymphoma
- Progressive multi-focal leuco-encephalopathy (PML)
- Vitamin B12 deficiency
- Hashimoto’s encephalopathy
- Whipple’s disease

ALGORITHM

- Age of onset
- Lesion localization/ lesions localized
- Tempo of progression
- Primarily CNS degenerative disorder vs. any effect of systemic dysfunction
- Input from investigations
- Options of therapy

The Primary Degenerative Dementias

- Alzheimer's Disease: variable age of onset, memory impairment, preserved insight, visuo-spatial dysfunction, personality change
- Fronto-temporal Dementia: earlier age of onset, often familial, dominated by behavioural change and impaired executive functioning, later language dysfunction, followed by memory impairment
- Diffuse Lewy Body Disease: Vivid visual hallucinations, fluctuating cognition, REM sleep behavioural dysfunction and parkinsonism

What Is Alzheimer's Disease?

- It is characterized by the progressive loss of cognitive functions: memory, personality, behaviour, language, visuo-spatial skills, and praxis
- This occurs due to neuronal degeneration and synaptic failure
- It results in patients loosing cognitive and hence livelihood abilities that are vital for independence in activites of daily living
- Pathological hallmarks: intra-neuronal accumulation of phosphorylated tau, extracellular deposition of abnormal beta pleated amyloid proteins (senile or neuritic plaques), and congophilic or amyloid angiopathy in brain vessels

Pathology: Amyloid plaques and Neurofibrillary tangles

Light micrographs of human brain in AD

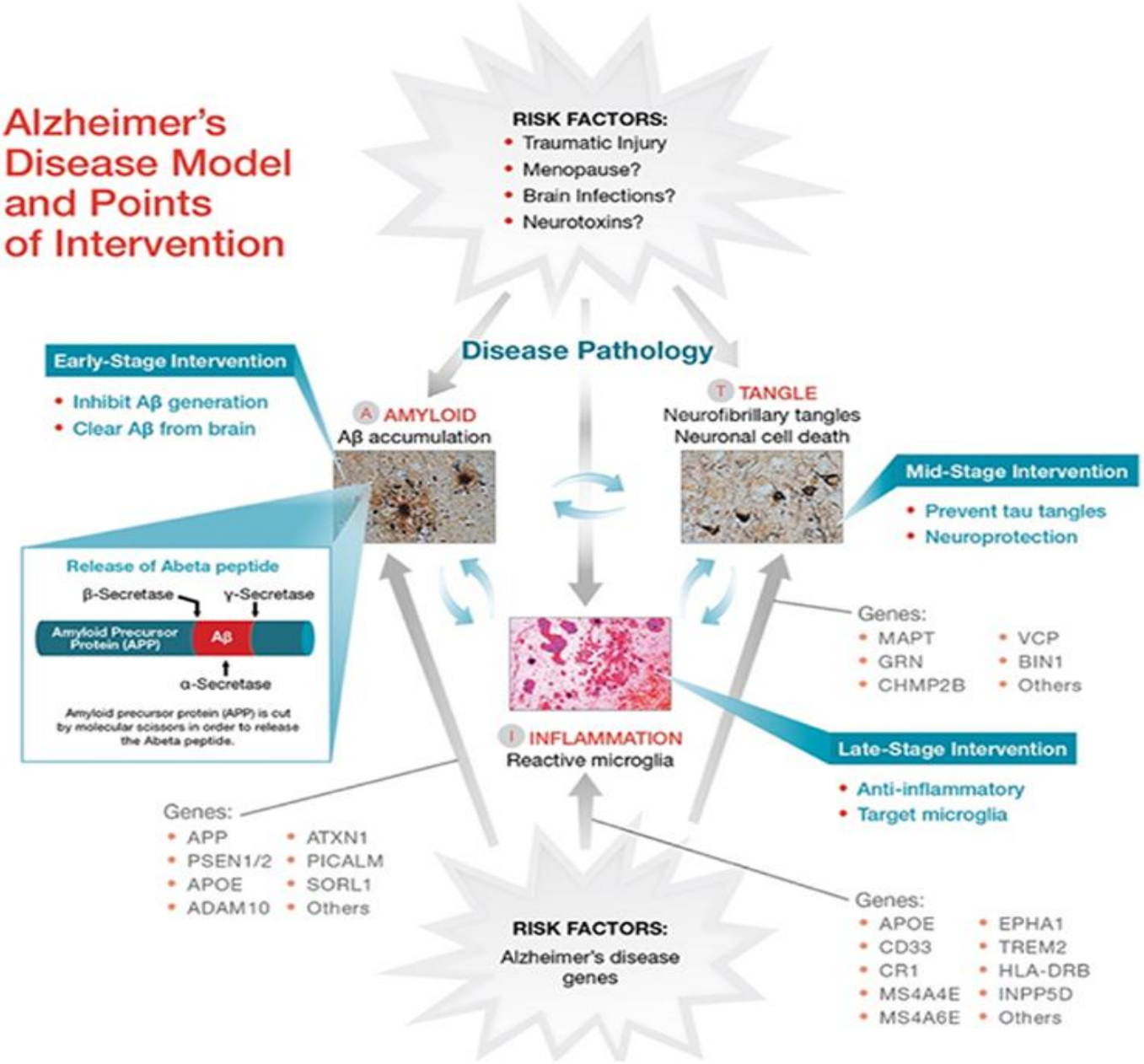
Neurons filled with neurofibrillary tangles

Plaque surrounding amyloid deposit

How/why does it start? How/why does it progress?

- In a nutshell Alzheimer's Disease manifestation requires:
  - Genetic predisposition: ApoE, Presenilin 1, Presenilin2, TREM2, SorL1, TOMM40 etc.
  - Lifestyle risk factors: metabolic syndrome, sedentariness, aberrant sleep hygiene, head trauma, alcoholism.
  - What is not clear is the physiology that initiates this process and drives its progression: hence all treatment trials till date have failed to halt or reverse the course of Alzheimer's disease.

Alzheimer's Disease Model and Points of Intervention



Central obesity and increased risk of dementia more than three decades later

Methods: A longitudinal analysis was conducted of 6,583 members of Kaiser Permanente of Northern California who had their sagittal abdominal diameter (SAD) measured in 1964 to 1973. Diagnoses of dementia were from medical records an average of 36 years later, January 1, 1994, to June 16, 2006. Cox proportional hazard models adjusted for age, sex, race, education, marital status, diabetes, hypertension, hyperlipidemia, stroke, heart disease, and medical utilization were conducted.

Results: A total of 1,049 participants (15.9%) were diagnosed with dementia. Compared with those in the lowest quintile of SAD, those in the highest had nearly a threefold increased risk of dementia (hazard ratio, 2.72; 95% CI, 2.33–3.33), and this was only mildly attenuated after adding body mass index (BMI) to the model (hazard ratio, 1.92; 95% CI, 1.58–2.35). Those with high SAD (>25 cm) and normal BMI had an increased risk (hazard ratio, 1.89; 95% CI, 0.98–3.81) vs those with low SAD (<25 cm) and normal BMI (18.5–24.9 kg/m^2), whereas those both obese (BMI >30 kg/m^2) and with high SAD had the highest risk of dementia (HR, 3.60; 95% CI, 2.85–4.55).

Conclusions: Central obesity in midlife increases risk of dementia independent of diabetes and cardiovascular comorbidities. Fifty percent of adults have central obesity; therefore, mechanisms linking central obesity to dementia need to be unveiled. ***Neurology*® 2008;71:1057–1064**

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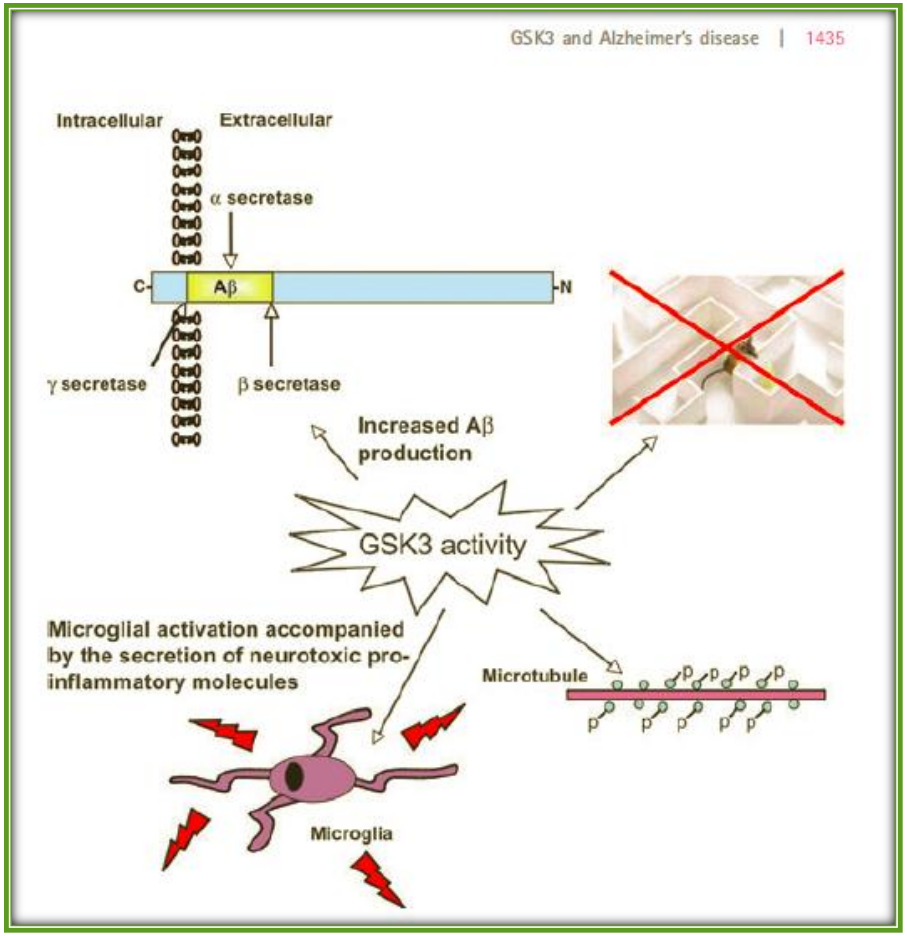
MINI-REVIEW

The GSK3 hypothesis of Alzheimer's disease

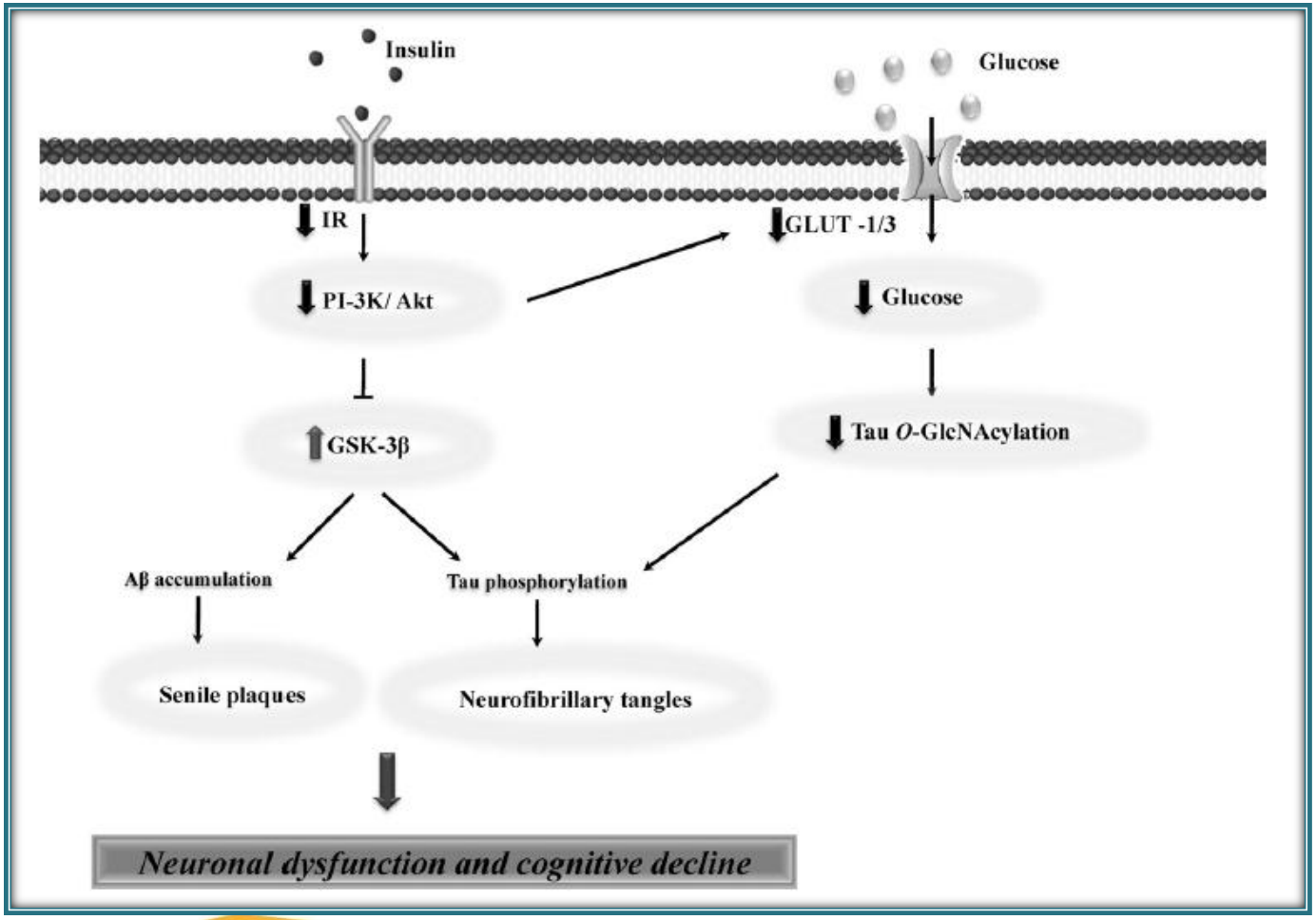
Claudie Hooper, Richard Killick and Simon Lovestone



Review

Insulin-resistant brain state: The culprit in sporadic Alzheimer's disease?

Sónia C. Correia[a,b], Renato X. Santos[a,b], George Perry[c,d], Xiongwei Zhu[c,1], Paula I. Moreira[a,e,*], Mark A. Smith[c,**]



Glymphatic Insights In A Nutshell

- Unidirectional flow of CSF mediated by the glymphatics occurs only in sleep and it abates on arousal (mediated by adrenergic tone)
- Supine and lateral sleeping postures optimize glymphatic function and prone sleeping reduces efficiency by 40%
- Voluntary exercise and low dose alcohol enhance glymphatic efficiency
- Head injury, diabetes mellitus, strokes (especially lacunar), and obstructive sleep apnoea impair glymphatic efficiency
- Glymphatic function excretes beta-amyloid and tau in normal asymptomatic individuals

Poor sleep is associated with CSF biomarkers of amyloid pathology in cognitively normal adults

Results: Worse subjective sleep quality, more sleep problems, and daytime somnolence were associated with greater AD pathology, indicated by lower CSF Aβ42/Aβ40 and higher t-tau/Aβ42, p-tau/Aβ42, MCP-1/Aβ42, and YKL-40/Aβ42. There were no significant associations between sleep and NFL or neurogranin.

Conclusions: Self-report of poor sleep was associated with greater AD-related pathology in cognitively healthy adults at risk for AD. Effective strategies exist for improving sleep; therefore sleep health may be a tractable target for early intervention to attenuate AD pathogenesis.
Neurology® 2017;89:1–9

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Review

Sleep Disturbance as a Potential Modifiable Risk Factor for Alzheimer's Disease

Eiko N. Minakawa [1,*], Keiji Wada [1] and Yoshitaka Nagai [1,2,*]

AASM American Academy of SLEEP MEDICINE™

Health Advisory: Sleep and Alzheimer's Disease

More research is needed to clarify the role of insufficient sleep, poor sleep, and obstructive sleep apnea in the development of Alzheimer's disease and related dementias. Research is also needed on the impact of sleep disorders treatment on Alzheimer's disease risk. This research should be prioritized by the National Institutes of Health (NIH), including the National Institute on Aging (NIA), and by other federal and private funding agencies.

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ORIGINAL ARTICLE

Obstructive Sleep Apnea is Associated With Early but Possibly Modifiable Alzheimer's Disease Biomarkers Changes

Claudio Liguori, MD[1]; Nicola Biagio Mercuri, MD[1,2,3]; Francesca Izzi, PhD[1]; Andrea Romigi, PhD[4]; Alberto Cordella, MD[2]; Giuseppe Sancesario, MD[3]; Fabio Placidi, PhD[1]

Study Objectives: Obstructive sleep apnea (OSA) is a common sleep disorder. The, literature lacks studies examining sleep, cognition, and Alzheimer's Disease (AD) cerebrospinal fluid (CSF) biomarkers in OSA patients. Therefore, we first studied cognitive performances, polysomnographic sleep, and CSF β-amyloid$_{42}$, tau proteins, and lactate levels in patients affected by subjective cognitive impairment (SCI) divided in three groups: OSA patients (showing an Apnea–Hypopnea Index [AHI] ≥15/hr), controls (showing an AHI < 15/hr), and patients with OSA treated by continuous positive airway pressure (CPAP).
Methods: We compared results among 25 OSA, 10 OSA-CPAP, and 15 controls who underwent a protocol counting neuropsychological testing in the morning, 48-hr polysomnography followed by CSF analysis.
Results: OSA patients showed lower CSF Aβ$_{42}$ concentrations, higher CSF lactate levels, and higher t-tau/Aβ$_{42}$ ratio compared to controls and OSA-CPAP patients. OSA patients also showed reduced sleep quality and continuity and lower performances at memory, intelligence, and executive tests than controls and OSA-CPAP patients. We found significant relationships among higher CSF tau proteins levels, sleep impairment, and increased CSF lactate levels in the OSA group. Moreover, lower CSF Aβ$_{42}$ levels correlate with memory impairment and nocturnal oxygen saturation parameters in OSA patients.
Conclusions: We hypothesize that OSA reducing sleep quality and producing intermittent hypoxia lowers CSF Aβ$_{42}$ levels, increases CSF lactate levels, and alters cognitive performances in SCI patients, thus inducing early AD clinical and neuropathological biomarkers changes. Notably, controls as well as OSA-CPAP SCI patients did not show clinical and biochemical AD markers. Therefore, OSA may induce early but possibly CPAP-modifiable AD biomarkers changes.
Keywords: obstructive sleep apnea, β-amyloid, lactate, continuous positive airway pressure, subjective cognitive decline.

Cerebrospinal fluid levels of Alzheimer's disease biomarkers in middle-aged type 1 diabetes patients

Article *in* Diabetologia · June 2014

Aims/hypothesis: Type 1 diabetes associates with moderate cognitive decline and cerebral alterations, and may lead to an increased risk of dementia, including Alzheimer's disease. This study aimed to investigate the levels of risk markers for Alzheimer's disease in middle-aged type 1 diabetes patients and controls, and their potential associations with cognitive and cerebral measures.

Conclusions/interpretation: CSF-levels of biomarkers for Alzheimer's disease are altered in patients with type 1 diabetes versus controls, but the observed profile does not match the profile characterizing pre-Alzheimer's disease patients.

Impairment of the glymphatic system after diabetes

Determinants of Shortened, Disrupted, and Mistimed Sleep and Associated Metabolic Health Consequences in Healthy Humans

Diabetes 2015;64:1073–1080 | DOI: 10.2337/db14-1475

Oral Systemic Linkages

Periodontitis and Alzheimer's disease

HEALTH AND MEDICINE

Porphyromonas gingivalis in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors

Porphyromonas gingivalis, the keystone pathogen in chronic periodontitis, was identified in the brain of Alzheimer's disease patients. Toxic proteases from the bacterium called gingipains were also identified in the brain of Alzheimer's patients, and levels correlated with tau and ubiquitin pathology. Oral *P. gingivalis* infection in mice resulted in brain colonization and increased production of $A\beta_{1-42}$, a component of amyloid plaques. Further, gingipains were neurotoxic in vivo and in vitro, exerting detrimental effects on tau, a protein needed for normal neuronal function. To block this neurotoxicity, we designed and synthesized small-molecule inhibitors targeting gingipains. Gingipain inhibition reduced the bacterial load of an established *P. gingivalis* brain infection, blocked $A\beta_{1-42}$ production, reduced neuroinflammation, and rescued neurons in the hippocampus. These data suggest that gingipain inhibitors could be valuable for treating *P. gingivalis* brain colonization and neurodegeneration in Alzheimer's disease.

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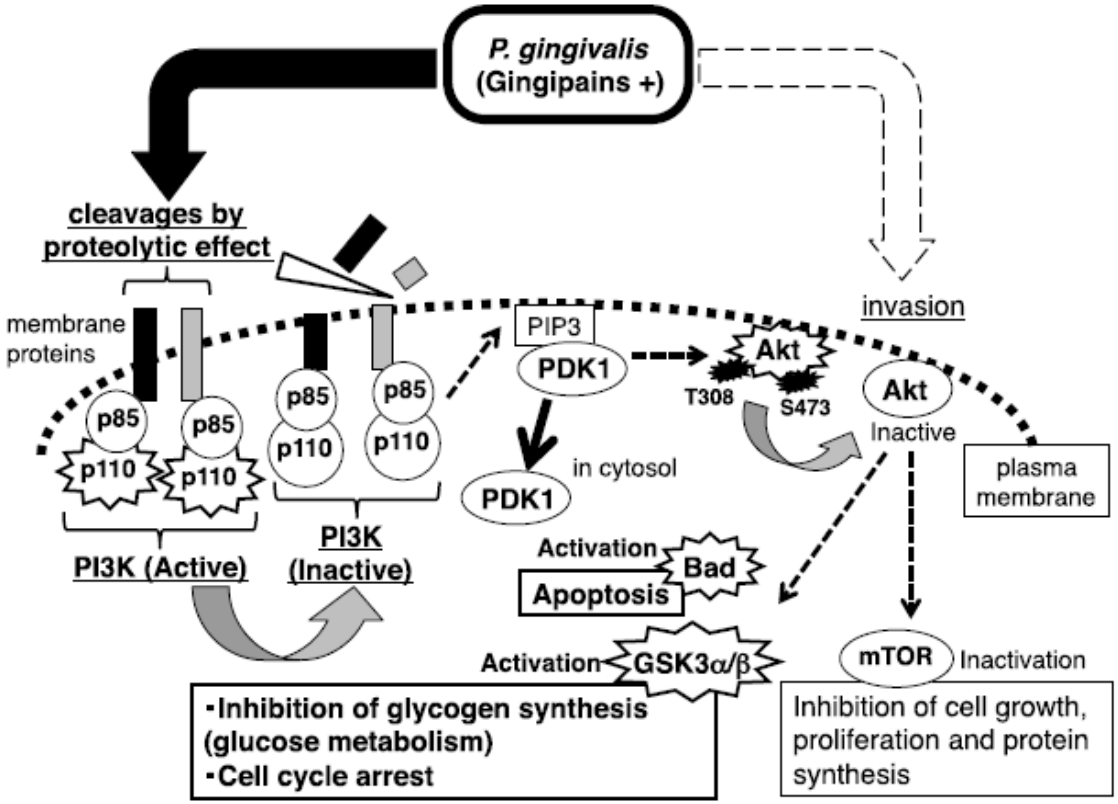
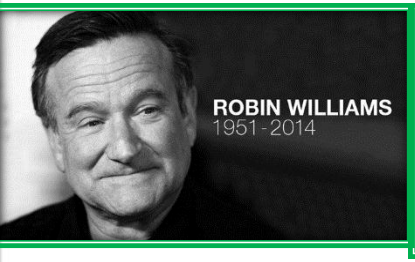
Molecular mechanisms of *Porphyromonas gingivalis*-host cell interaction on periodontal diseases

Masaaki Nakayama [a,b,*], Naoya Ohara [a,b]



Why is DLBD of relevance to psychiatrists & neurologists?

- It is the second commonest degenerative dementia after AD.
- The largest risk factor is age with most cases being clinically manifest by ages of 70 to 85 years; Men are at higher risk
- Amongst patients with dementia undergoing autopsy after death, Lewy body pathology is found in 20 to 25% of brains.
- In an Indian nuclear medicine study on FDG-PET scanning in patients with cognitive dysfunction from New Delhi, 13 out of 117 patients had typical occipital hypoperfusion patterns consistent with DLBD.
- It is widely perceived around the globe that DLBD is under-recognized and under-reported due to diagnostic difficulties.



SPECIAL EDITORIAL

The terrorist inside my husband's brain

The colors were changing and the air was crisp; it was already late October of 2013 and our second wedding anniversary. Robin had been under his doctors' care. He had been struggling with symptoms that seemed unrelated: constipation, urinary difficulty, heartburn, sleeplessness and insomnia, and a poor sense of smell—and lots of stress. He also had a slight tremor in his left hand that would come and go. For the time being, that was attributed to a previous shoulder injury.

Robin was growing weary. The parkinsonian mask was ever present and his voice was weakened. His left hand tremor was continuous now and he had a slow, shuffling gait. He hated that he could not find the words he wanted in conversations. He would thrash at night and still had terrible insomnia. At times, he would find himself stuck in a frozen stance, unable to move, and frustrated when he came out of it. He was beginning to have trouble with visual and spatial abilities in the way of judging distance and depth. His loss of basic reasoning just added to his growing confusion.

Susan Schneider Williams Sep 2016

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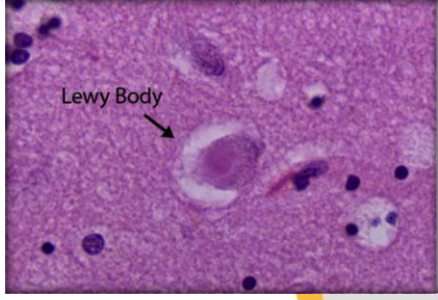
What are Lewy Bodies?



- Lewy bodies are spherical, intra-cytoplasmic, eosinophilic, neural inclusions: they have a dense hyaline core and a halo of radiating filaments composed of abnormally truncated and phosphorylated intermediate neurofilament proteins that include ubiquitin and associated enzymes.
- Alpha-synuclein antibodies have been shown to label purified Lewy bodies, and the alpha-synuclein antibodies PER1 and PER2 strongly stain Lewy bodies and Lewy neurites.
- Clinical presentation varies according to the site of Lewy body formation and secondary axon loss.

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TABLE 91.1. PRIMARY LEWY BODY DISORDERS

Region Primarily Affected	Clinical Syndrome	Classification
Substantia nigra	Extrapyramidal movement disorder	Parkinson disease
Limbic cerebral cortex	Cognitive decline and neuropsychiatric symptoms	Dementia with Lewy bodies
Sympathetic neurons in spinal cord	Autonomic failure	Primary autonomic failure
Dorsal vagal nuclei	Dysphagia	Lewy body dysphagia
Pedunculopontine nucleus[a]	Sleep disturbance	REM sleep behavior disorder

REM, rapid eye movement.
[a]Precise clinicopathologic correlate for this is yet to be established, although involvement of the pedunculopontine nucleus is highly probable from current data.
Adapted from Lowe JS, Mayer RJ, Landon M, Pathological significance of Lewy bodies in dementia; In: Perry R, McKeith I, Perry E, eds. *Dementia with Lewy bodies*. New York: Cambridge University Press, 1996:195–203.

Research report

TIGAR inclusion pathology is specific for Lewy body diseases

Karla L. Robles López, Julie E. Simpson, Lisa C Watson, Heather Mortiboys, Guillaume M. Hautbergue, Oliver Bandmann[1], J. Robin Highley[*,1]

Sheffield Institute for Translational Neuroscience, University of Sheffield, Sheffield, UK

Background: We previously reported up-regulation of *tigarb* (the zebrafish orthologue of human TIGAR, TP53 – Induced Glycolysis and Apoptosis Regulator) in a zebrafish *pink1*$^{-/-}$ model of Parkinson's disease (PD). Genetic *inactivation* of *tigarb* led to the rescue of dopaminergic neurons and mitochondrial function in *pink*$^{-/-}$ zebrafish. The aim of this study was to determine the relevance of TIGAR for human PD, investigate its disease specificity and identify relevant upstream and downstream mechanisms.

Results: TIGAR was detected in Lewy bodies and Lewy neurites in the substantia nigra of sporadic PD and Dementia with Lewy bodies (DLB) patients. Staining of adjacent sections and double staining confirmed the presence of TIGAR alongside alpha-synuclein in these LB and neurites. In contrast, TIGAR-positive aggregates were not seen in cortical Lewy bodies. TIGAR protein was also absent in both TDP-43-positive inclusions in MND and glial cytoplasmic inclusions in MSA. Subsequent investigation of the TIGAR-upstream regulator p53 and the downstream targets HK-I and HK-II in PD brains suggested a possible mild increase in HK-I.

Conclusions: TIGAR protein, is present in SN Lewy bodies of both sporadic PD and DLB. The absence of TIGAR protein in the pathological inclusions of MND or MSA suggests disease specificity and further raises the possibility that TIGAR may be involved in PD pathogenesis.

The Core Clinical Features In DLBD

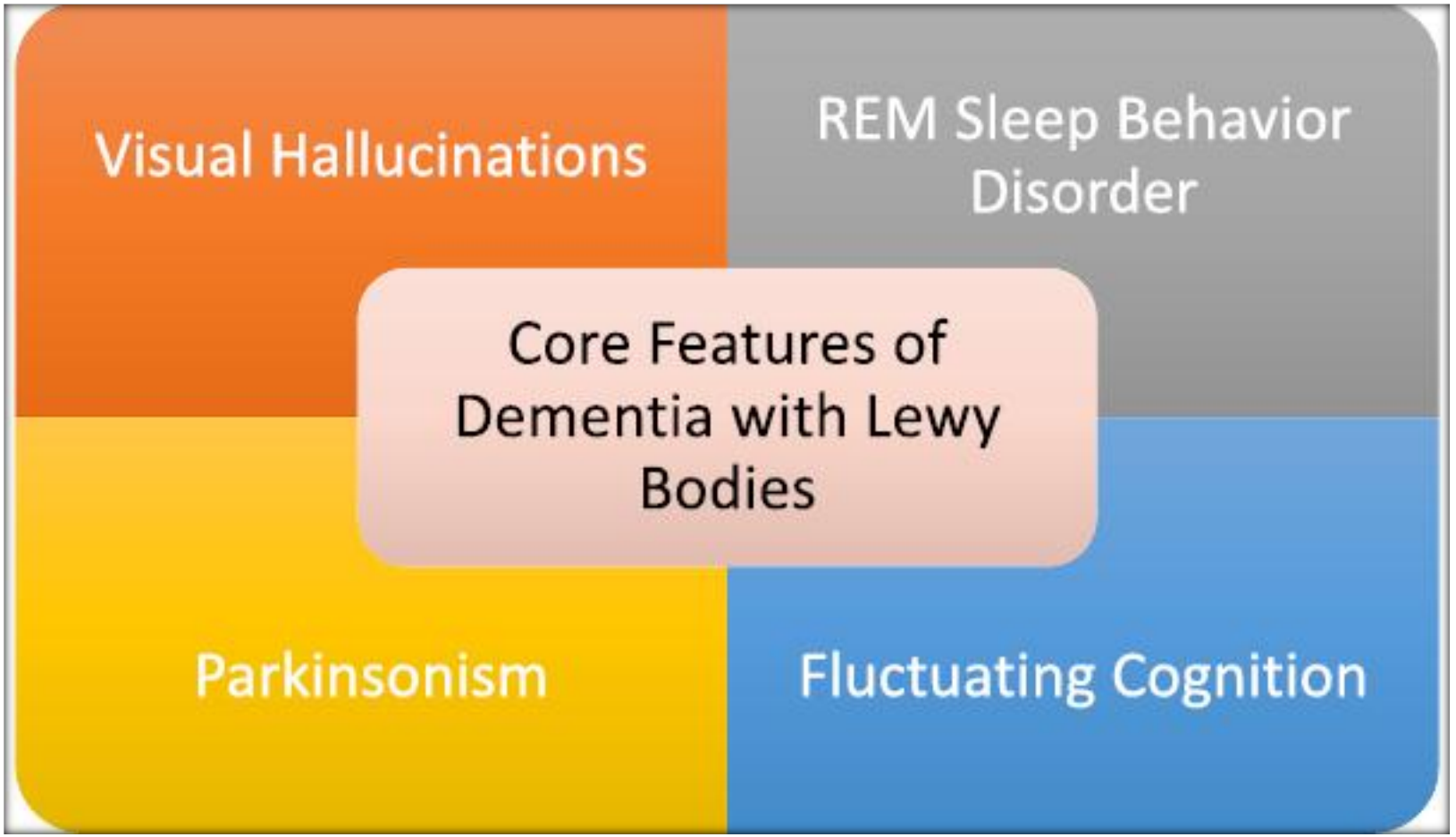


TABLE 4-1 **Diagnostic Criteria for the Clinical Diagnosis of Dementia With Lewy Bodies**[a]

- **Central Feature (Essential for diagnosis of possible or probable dementia with Lewy bodies [DLB])**

  Dementia with progressive cognitive decline of sufficient magnitude to interfere with social or occupational function. Memory impairment may not necessarily occur early but usually develops with progression. Deficits on tests of attention, executive function, and visual-spatial ability may be prominent.

- **Core Features (Two core features are sufficient for a diagnosis of probable DLB, one for possible DLB)**

  Fluctuating cognition, pronounced variation in attention and alertness

  Recurrent visual hallucinations, typically well formed and detailed

  Spontaneous motor manifestations of parkinsonism

- **Suggestive Features (If one or more of these is present, along with one or more core features, a diagnosis of probable DLB can be made. In the absence of any core features, one or more suggestive features are sufficient for possible DLB. Probable DLB should not be diagnosed on the basis of suggestive features alone.)**

  Rapid eye movement (REM) sleep behavior disorder

  Severe neuroleptic sensitivity

  Single-photon emission computed tomography (SPECT) or positron emission tomography (PET) imaging evidence of low dopamine transporter concentration in the basal ganglia

- **Supportive Features**
  - Reduced metaiodobenzylguanidine (MIBG) myocardial scintigraphy
  - SPECT perfusion with reduced occipital activity
  - Relatively preserved medial temporal lobe structures on CT/MRI
  - Repeated falls and syncope
  - Transient, unexplained loss of consciousness
  - Autonomic dysfunction
  - Other types of hallucinations
  - Systematized delusions
  - Depression
  - Prominent slow-wave activity on EEG, with temporal lobe transient sharp waves

Some defining features of cognitive impairment in DLBD

- Dementia is usually but not always the presenting feature of DLBD; a minority present with psychosis, some with psychosis and mood disorder, others with orthostatic hypotension and falls.
- Fluctuations occur in half to three-fourths, visual hallucinations are present in half to one third of patients. Depression is commoner in DLBD than in AD.
- Shimomura reported disproportionately more severe visuo-perceptual, visuo-constructive, and visuo-spatial dysfunction with disproportionately milder impairment in memory.
- Ballard reported a better preserved recent memory and more impaired visuospatial praxis.

‘Fluctuations’ in cognitive function & awareness in DLBD

The third core feature often present in DLB is fluctuating mental status. Fluctuation in alertness, attention, and cognition is frequently difficult to elicit in clinical history taking, but may manifest as staring spells similar to absence seizures, periods of decreased attention and awareness, frequent daytime napping, and periods of seemingly unprovoked confusion. Some liken this fluctuation to “low-grade” delirium and it is thought to be secondary to cholinergic deficits caused by Lewy body deposition in cholinergic-rich neuronal foci.[19]

REM Sleep Behaviour Disorder

The final core diagnostic feature in DLB is RBD. With RBD, those afflicted physically act out their dreams because of lack of muscle paralysis (loss of muscle atonia) during REM sleep. Bed partners of patients with RBD often report that the patient will thrash about the bed, kicking, punching, screaming, and/or grunting. The frequency of these episodes varies greatly, possibly occurring several times per night or every few months.[27] In one study, patients with "idiopathic" RBD were followed for nearly 4 years and 45% went on to develop disease processes meeting the criteria for PD and DLB. Of the 45% developing neurodegenerative processes, 55% developed PD and 44% developed DLB; 93% of those who progressed into DLB had cognitive impairment at baseline compared with only 42% of those who went on to develop PD.[28] The etiology of RBD is suspected to be from the formation of Lewy bodies in various nuclei in the reticular activating system in the brainstem. This can often occur in the very early stages of DLB with symptoms of RBD manifesting years before the disease is clinically diagnosed. When RBD is suspected, an overnight

Heiko Braak (1937), University Of Ulm, Germany

In DLB, a consistent gradient of LB density has been noted, as follows: substantia nigra > entorhinal cortex > cingulate gyrus > insula > frontal cortex > hippocampus > occipital cortex. Paralimbic and neocortical LB densities are highly correlated with each other but not with nigral pathology, which suggests that DLB should not be considered merely a severe form of PD (74). One study of pathologic burden versus clinical severity examined correlations between two simple measures of cognitive ability and a range of lesion counts and neurochemical measures in the midfrontal cortex of DLB cases (75). Severity of dementia was significantly correlated with LB density, plaque density, and severity of cholinergic deficit, but not with neurofibrillary tangle density or synaptophysin levels. In contrast, in AD cases, tangle

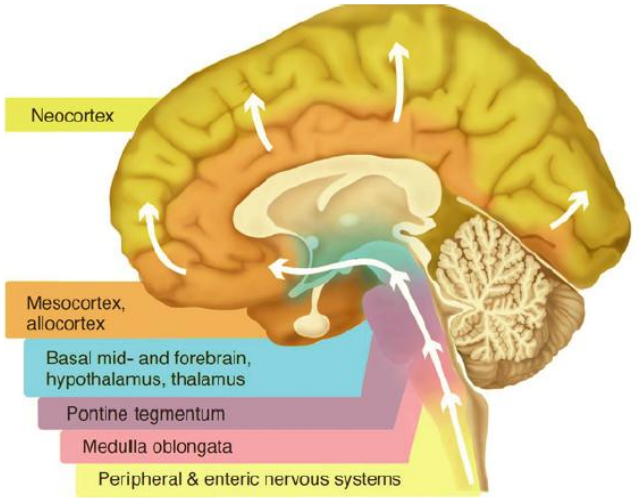
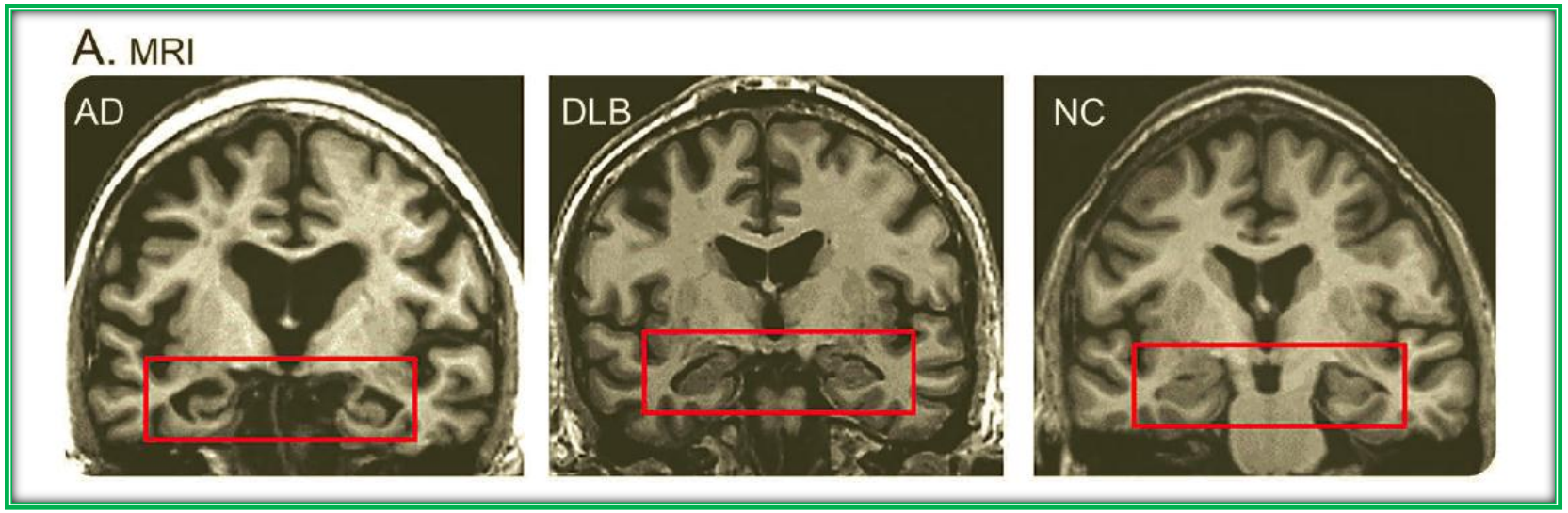
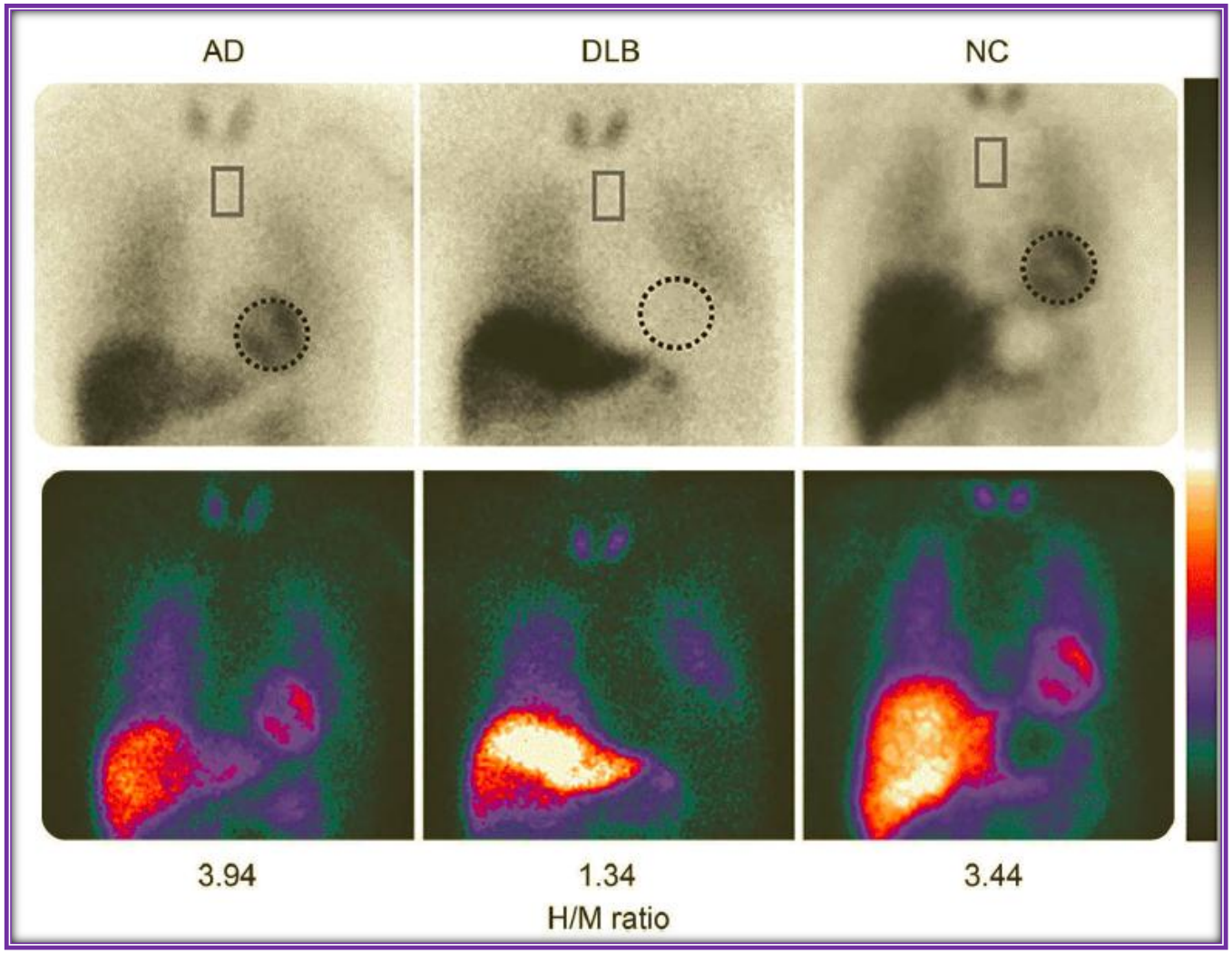


Fig 4: Staging of Lewy pathology according to the Braak model

On MRI medial temporal structures are better preserved in DLBD compared to AD



^{123} I-MIBG Cardiac Scintigraphy in DLBD

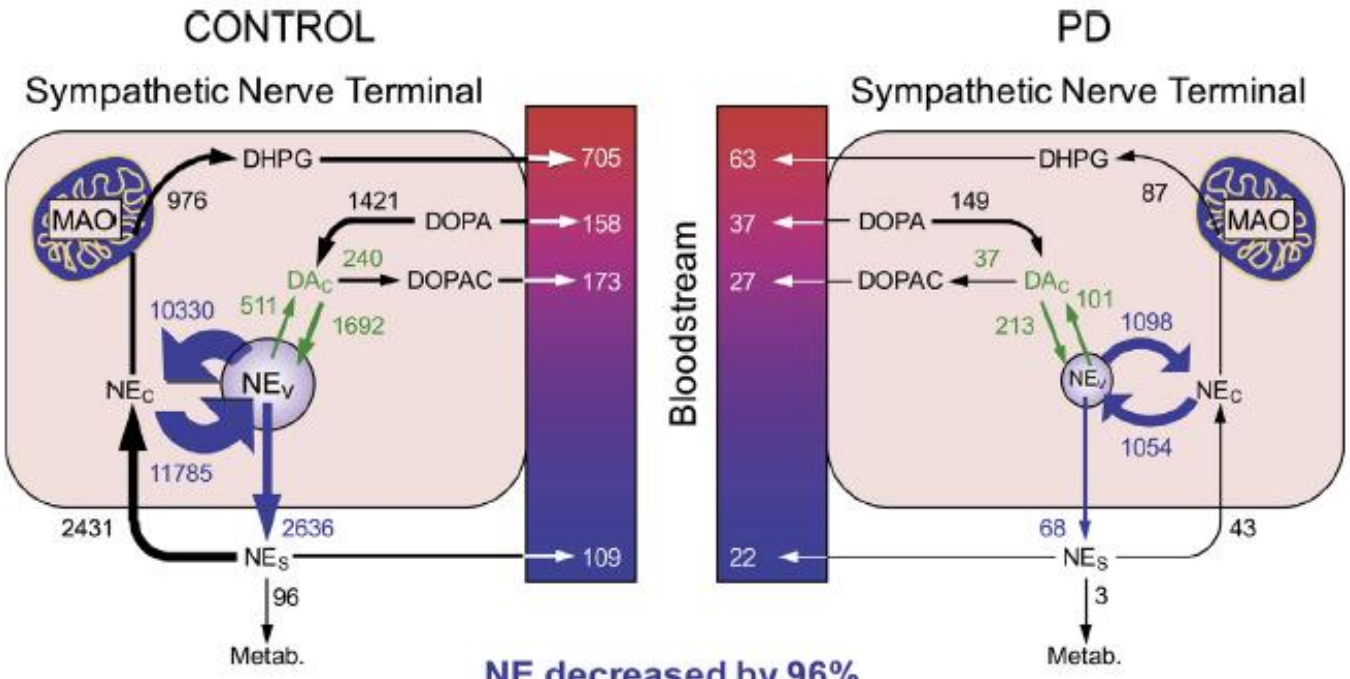


Research report

The heart of PD: Lewy body diseases as neurocardiologic disorders

David S. Goldstein [a,*], Yehonatan Sharabi [b]

[a] Clinical Neurocardiology Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892-1620, United States
[b] Chaim Sheba Medical Center and Tel Aviv University Sackler Faculty of Medicine, Israel



NE decreased by 96%

Innervation (DOPA production) decreased by 88%

∴ NE synthesis / vesicular storage decreased by 67%

^{18}F-FDG-PET scanning in DLBD

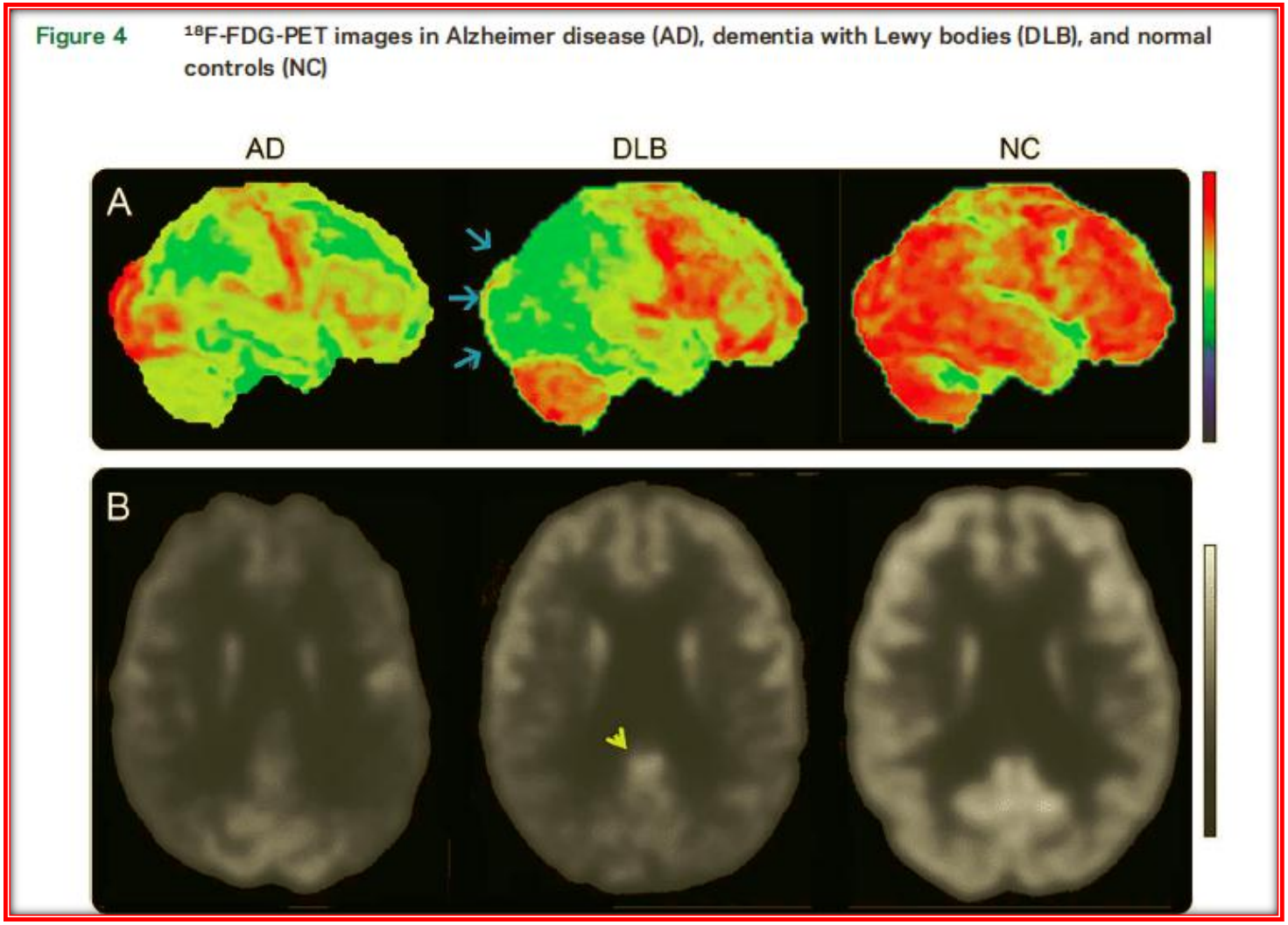
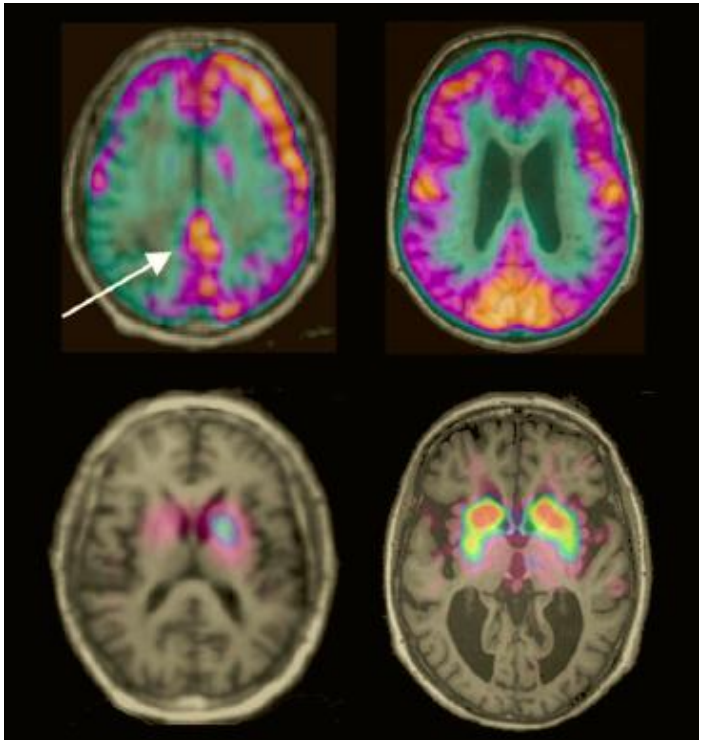


Figure 4 ^{18}F-FDG-PET images in Alzheimer disease (AD), dementia with Lewy bodies (DLB), and normal controls (NC)

The ^{18}F-FDG PET Cingulate Island Sign and Comparison to ^{123}I-β-CIT SPECT for Diagnosis of Dementia with Lewy Bodies

Seok Ming Lim[1], Andrew Katsifis[2], Victor L. Villemagne[1,3], Rene Best[1], Gareth Jones[1], Michael Saling[4], Jennifer Bradshaw[4], John Merory[5], Michael Woodward[5], Malcolm Hopwood[6], and Christopher C. Rowe[1,3]



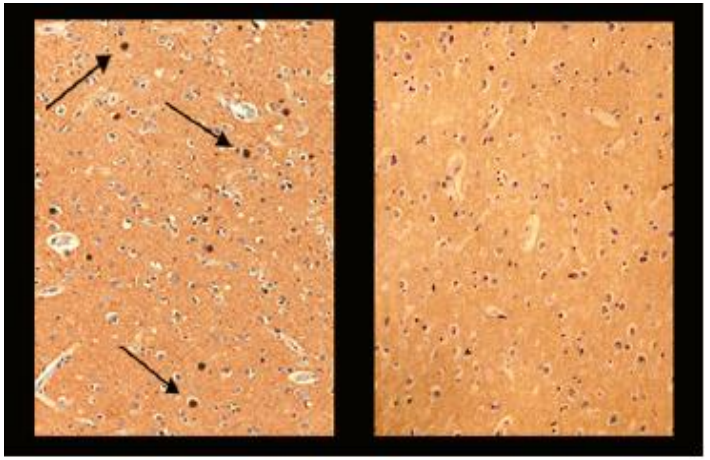


FIGURE 3. ^{18}F-FDG PET (top row) and β-CIT SPECT images (middle row) overlaid on MRI in patient with DLB (left column) and patient with AD (right column) who had diagnosis confirmed at autopsy. Immunohistochemical stain for α-synuclein demonstrates frequent Lewy bodies in DLB patient (black arrows) but none in AD patient. White arrow points to posterior cingulate cortex on ^{18}F-FDG PET study, demonstrating cingulate island sign of DLB.

Genetics In DLBD

- Though most cases of DLBD are sporadic some families have been described. Most data that exists on genetic influences comes from assessment of susceptibility genes in sporadic cases.
- The epsilon 4 subtype of ApoE is more represented in both AD and DLBD.
- The allelic distribution of a penta-nucleotide within the promoter region of the nitric-oxide synthase gene (NOS2A) occurs more frequently in autopsy proven DLBD compared to controls.

The New Mutation, E46K, of α-Synuclein Causes Parkinson and Lewy Body Dementia

Juan J. Zarranz, MD, PhD,[1] Javier Alegre, MD,[2] Juan C. Gómez-Esteban, MD,[1] Elena Lezcano, PhD,[1]

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JAMA Neurology | Original Investigation

High Frequency of *GBA* Gene Mutations in Dementia With Lewy Bodies Among Ashkenazi Jews

Tamara Shiner, MBChB, PhD; Anat Mirelman, PhD; Mali Gana Weisz, PhD; Anat Bar-Shira, PhD; Elissa Ash, MD, PhD; Ron Cialic, MD, PhD; Naomi Nevler, MD; Tanya Gurevich, MD; Noa Bregman, MD; Avi Orr-Urtreger, MD, PhD; Nir Giladi, MD

Glucocerebrosidase mutations in diffuse Lewy body disease☆

Kenya Nishioka[a], **Owen A. Ross**[a], **Carles Vilariño-Güell**[a,h], **Stephanie A. Cobb**[a], **Jennifer M. Kachergus**[a], **David M.A. Mann**[b], **Julie Snowden**[b], **Anna M.T. Richardson**[b], **David Neary**[b], **Christopher A. Robinson**[c], **Alex Rajput**[c,d], **Spiridon Papapetropoulos**[e], **Deborah C. Mash**[e], **Rajesh Pahwa**[f], **Kelly E. Lyons**[f], **Zbigniew K. Wszolek**[g], **Dennis W. Dickson**[a], and **Matthew J. Farrer**[a,h,*]

[a]Department of Neuroscience, Mayo Clinic, Jacksonville, FL, USA

[b]Neurodegeneration and Mental Health Research Group, School of Community Based Medicine, University of Manchester, Hope Hospital, Salford, M6 8HD, UK

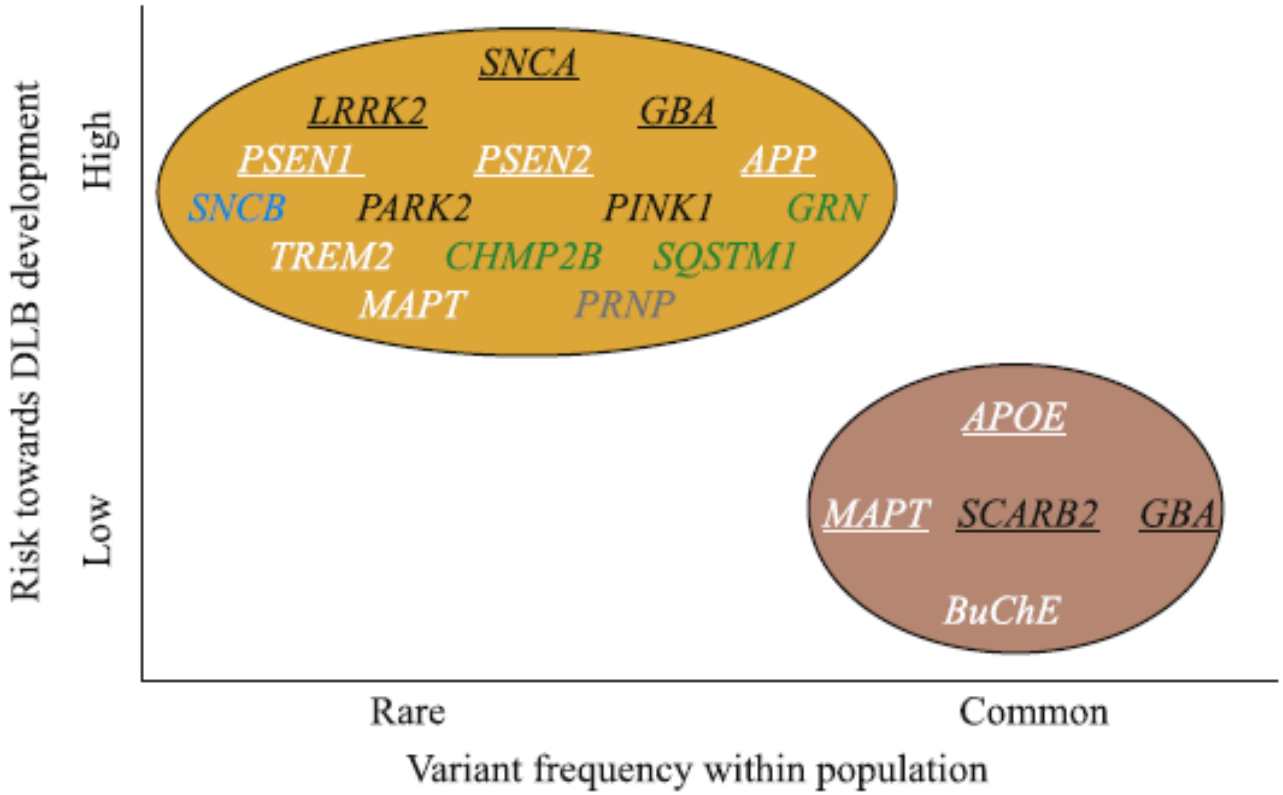

Fig. 2. Variant risk versus variant frequency for DLB. Genes previously associated with PD, AD, FTD and Creutzfeldt-Jacob Disease and no other neurodegenerative disease are depicted in black, white, green, grey and blue respectively. Evidence for the association between genes and DLB is stronger for those genes that are underlined than not underlined. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The Challenges In Managing DLBD

- The most troublesome symptoms are vivid visual hallucinations. In one study that assessed quetiapine 33% of patients withdrew due to orthostatic hypotension and sedation (Takahashi H et al; Prog Neuropsycholpharmacol Biol Psychiatry 2003)
- A RCT using risperidone actually showed a deterioration in cognition, worsening psychiatric symptoms, and a withdrawal rate of 65% (Workman R et al; J Neuropsychiatry Clin Neurosci 1997)
- Studies using olanzapine have shown conflicting results and it is not recommended for use in DLBD.
- Pimavanserin, a selective 5HT-2A inverse agonist has been approved for management of psychosis in synuceinopathies.

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Pimavanserin for Parkinson's Disease Psychosis: Effects Stratified by Baseline Cognition and Use of Cognitive-Enhancing Medications

Alberto J. Espay, MD, MSc,[1*] Michael T. Guskey, PharmD, MBA,[2] James C. Norton, PhD,[2] Bruce Coate, MPH,[2] Joaquin A. Vizcarra, MD,[1] Clive Ballard, MBChB, MRCPsych,[3] Stewart A. Factor, DO,[4] Joseph H. Friedman, MD,[5,6] Anthony E. Lang, MD, FRCPC,[7] Niccole J. Larsen, PhD,[2] Candace Andersson, PhD,[2] Doral Fredericks, PharmD, MBA[2] and Daniel Weintraub, MD[8,9]

Conclusions: The antipsychotic effect of pimavanserin is robust in PD patients with cognitive impairment and may be enhanced by concomitant cognitive-enhancing medication use. Future prospective studies are needed to confirm these preliminary findings.

Case one - a

- M/mid-50s; loss of memory, irritability, bouts of confusion, episodes of irrelevant talking, two instances of inappropriate social behavior, one instance of riding out on motorcycle and being unable to find the way home.
- Three instances of sudden lip-smacking and unresponsiveness for 40-60 secs.

Case one - b

- Wife notices that he is frequently unsteady and walks as if drunk.
- Patient says he also has headaches.
- Though fluctuating, the problem progresses over 6-8 months/ Alcoholic
- Prior to admission confused and babbling with weakness of left hand/leg that recovers in six hours.

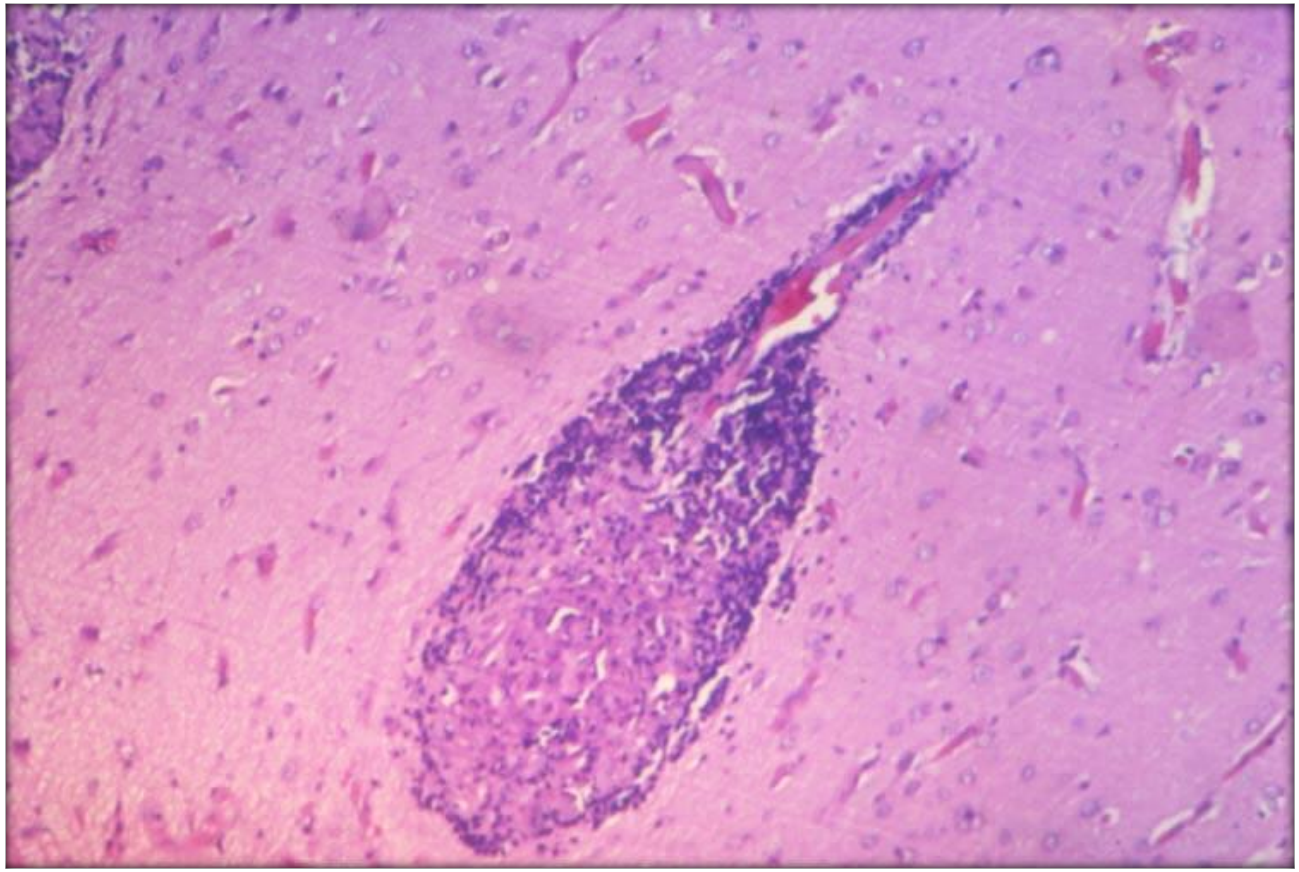
Case one - c

- O/E confused disoriented, unable to perform well on any cognitive task, nystagmus, limb ataxia, and one extensor plantar response.
- General exam normal.
- Elevated ESR, normal biochemistry and hematology, B12 moderately low, vasculitic work-up negative.

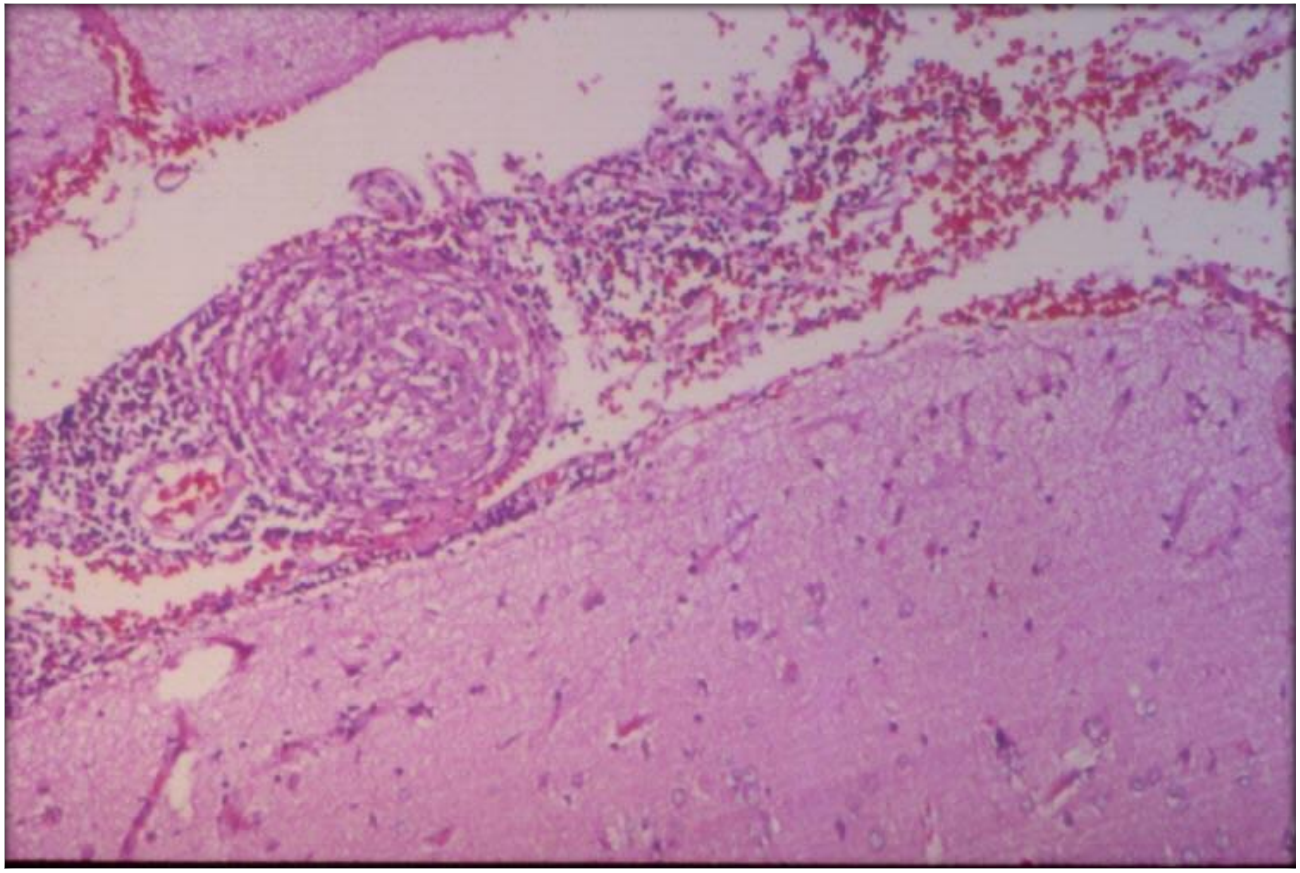
Case one- d

- CSF: 89 cells; predominant lymphocytes
- Elevated CSF protein but normal CSF sugar
- MRI brain: Small T2W hyper intensities within cerebral white matter.
- 4 vessel DSA normal
- Diagnostic conundrum

Brain biopsy from right frontal lobe and adjacent meninges



Brain biopsy from right frontal lobe and adjacent meninges



Take Home Messages

- Dementia is an acquired, progressive, global, disabling cerebral disorder.
- Its manifestations are varied and dependent on numerous: causative, pathophysiological, and time of assessment related factors.
- It requires a broad based knowledge and meticulous approach for its correct designation and therapy.