CLINICOPATHOLOGICAL STUDY OF SPECTRUM OF AGEING AND DEMENTIA

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AIM

❖ To study the clinicopathological spectrum of dementia compared with age-matched individuals without overt cognitive impairment.

Objectives:

❖ To assess morphology, regional involvement, and severity of various abnormal
proteins in the aging brain and neurodegenerative disease.
❖ To assess the clinical severity of dementia and associated pathological burden in the
brain.
❖ To determine contribution of vascular pathology to dementia and normal ageing.

Justification of study

- Dementia is biologically heterogeneous, so clinical syndromes alone can mislead diagnosis and treatment selection
- In the therapeutic era, accurate clinicopathological correlation (with standardized scoring/biomarkers) is essential to target the right pathways
- India lacks robust clinico-path data; this study fills that gap to improve diagnostic precision and guide pathology-based

METHODS

-**Design:** Single-center **ambispective** study (retrospective + prospective), Dept. of Neurology, **NIMHANS**; ethics approval → **May 2025**.

-**Cohort:** Pathology-confirmed neurodegenerative cases (retrospective autopsies; prospective brain donations) and age-matched comparators without overt impairment.

-**Clinical phenotyping:** DSM-5/ICD-10 diagnosis; **CDR** (global & sum-of-boxes) and domain scores; **IQCODE** for retrospective arm; demographics and comorbidities.

-**Tissue & IHC: FFPE**; **H&E 3 µm** morphology (plaques; **CAA/SVD**; infarcts; edema; neuronal loss; gliosis; Lewy/pale bodies; inflammation/hemorrhage). **IHC 4 µm** with H_2O_2 quench, citrate retrieval (pH 6), **DAB**, hematoxylin, **DPX**; batch positive controls.

-Antibodies: **Tau AT8** , **β-amyloid**, **α-synuclein** .

-**Sampling:** Medial temporal (amygdala, hippocampus at LGN level, parahippocampal gyrus); neocortex (superior/middle frontal; superior/middle/inferior temporal; inferior parietal; striate); subcortex (basal ganglia, thalamus, basal forebrain—nucleus accumbens, nucleus basalis of Meynert); brainstem (midbrain, pons—LC level, medulla).

-**Scoring: Thal Aβ 1–5; Braak NFTs I–VI; CERAD C0–C3 → ABC/ADNC** (low/intermediate/high); **Lewy** patterns; **LATE–TDP-43**; **HS 0–4; AGD 0–3; ARTAG** presence.

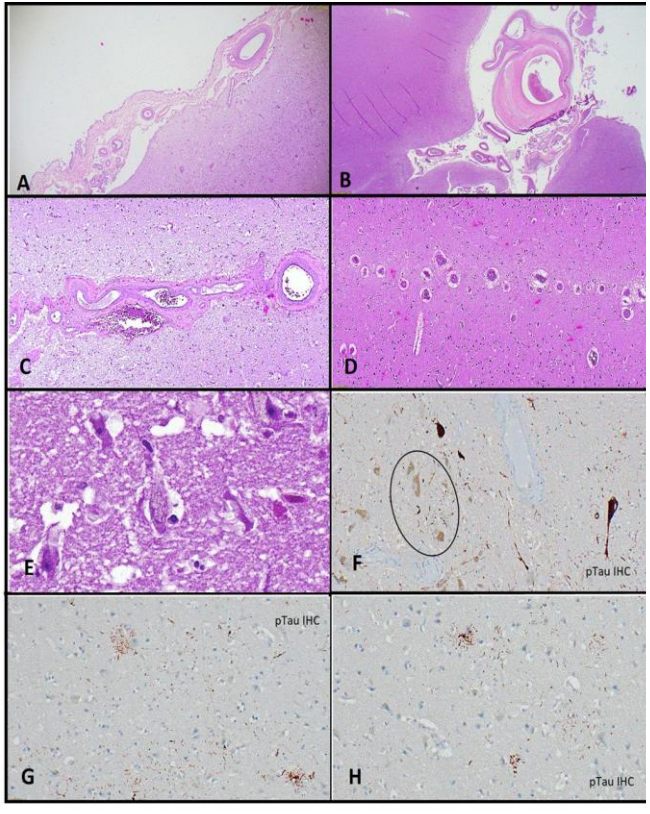

Fig : B399. VASCULAR DEMENTIA.
A: Markedly thickened leptomeningeal arteries and arterioles .
B: Meningeal medium sized artery with medial sclerosis and atherosclerotic changes
C: Deep white matter vessels with marked arteriosclerotic changes. Prominent perivascular edema and early ischemic changes seen
D: Linear of of transversely sectioned arteriosclerotic vessels wih perivascular changes.
E: Intracellular tangle seen on HE
F, G,H: Neurofibrillary tau pathology seen in the midbrain, cingulate and superior frontal gyri. The pigmented nigral neurons are circled in F.
(Original magnification: A,B,C,D 40x E 400x; F,G,H 200x

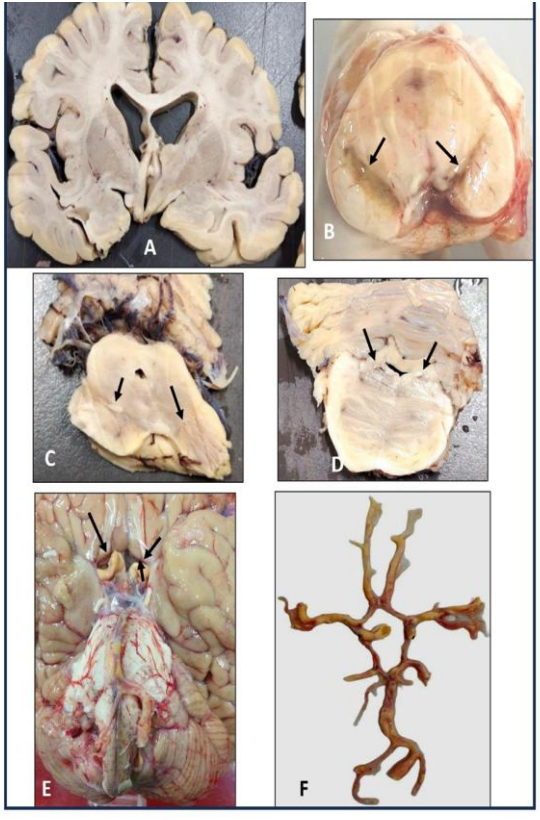

Fig : Gross images
A: Frontotemporal dementia: Coronal slice of brain at the level of the mamillary bodies showing gross cerebral cortical atrophy (frontal and temporal) and ex vacuo hydrocephalus.
B: Normal midbrain at the level of 3rd cranial nerve exit, showing preserved nigral pigmentation (arrows)
C: Midbrain showing loss of substantia nigral pigmentation in Progressive Supranuclar palsy. (arrows)
D: Lower pons with depigmentation of the Locus ceruleus (arrows) in PSP
E: Vascular Dementia: Base of the brain with rigid, thick walled, yellow ICAs indicating atherosclerotic changes (arrows).
F: Extensive atherosclerotic changes evident in the dissected Circle of Willis.

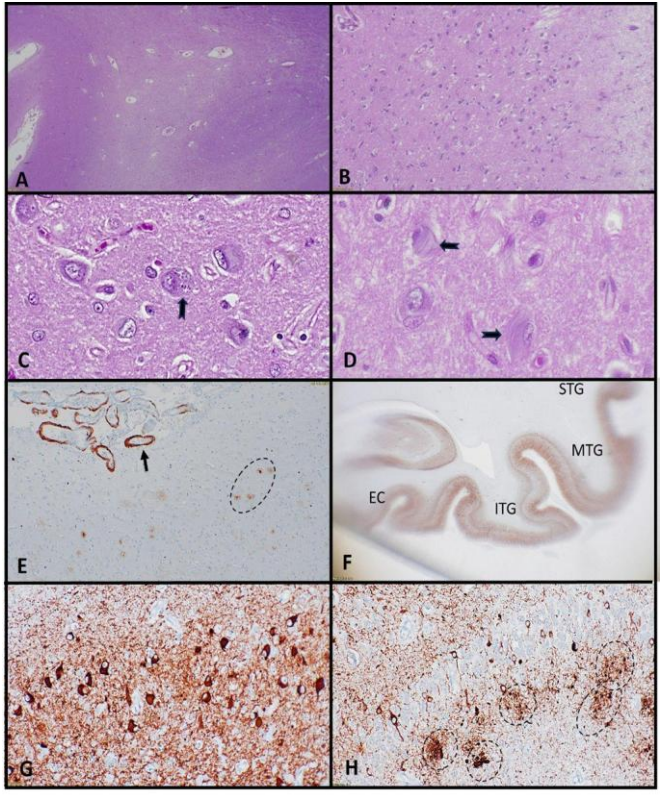

Fig : B271.16. ALZHEIMER'S DISEASE.
A: Cortical Atrophy and white matter pallor.
B: Loose neuropil and reactive astrogliosis due to neuronal loss.
C: Granulovacuolar degeneration in a hippocampal pyramidal neuron (arrow).
D:Neurofillary tangle in pyramidal neurons occasionally discernible on HE stain.
E: Several beta amyloid plaques (circled) in the cerebral cortex. Cerebral amyloid angiopathy of the leptomeningeal vessels (arrow).
F:Dense phospho-Tau immunostaining in the hippocampus, EC, ITG, MTG and part of STG
G: Numerous pTau immunopositive NFT on a background of abundant NTs.
H: Several pTau positive Neuritic plaques (circled).
(A-D- HE stain; E,F: Beta amyloid immunostain; G,H: pTau Immunostain
Original Magnification- A,E 40x; B,G,H 100x; C,D 200x; F whole mount.

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RESULTS:

Cohort n=13 consecutive brains; age 69.2 ± 13.1 y (46–92), median 67 (IQR 57–78); **57% female**; **early-onset <60 y: 31% (4/13)** NPMI 7.1 ± 2.8 h (median 6.5; all ≤12 h). Brain weight (n=10): 1,164 ± 93 g; no sex difference (p=0.43).

Clinical spectrum : AD-spectrum 38% (5/13); **FTD-spectrum 46% (6/13)**; **vascular/mixed 15% (2/13)**. Median illness duration **5.3 y**; AD trended longest (6.8 ± 3.4 y), ns (p=0.41).

Imaging MRI/CT in **9/13**: AD: temporo-parietal + hippocampal loss; bvFTD: fronto-insular atrophy (L>R in 2, R>L in 1, symmetric in 1). WMH (ARWMC ≥ 2) **4/9**, correlating with macro-atherosclerosis at autopsy.
Neuropsych (10 donors): median **MMSE 13/30**; FTD showed executive–language asymmetry (verbal fluency lower vs AD, p=0.075); AD episodic memory **≈ –1.9 SD**.

Macroscopic pathology (n=13) : Frontal atrophy 100%; temporal 69.2%; parietal 23.1%; occipital 7.7%. **Ventricular dilation 61.5%** (ex-vacuo); hippocampal shrinkage 46.2%. .
Atherosclerosis 38.5%; large chronic infarct/hemorrhage 30.8%.

Functional domains (n=13) Executive dysfunction 100%; **social-behavioural change 100%**.
Memory 92.3%; language 84.6%; gait/balance 76.9%; perceptual-motor 69.2%.
Parkinsonism 38.5%; autonomic 30.8%; mood 30.8%; attention fluctuation 23.1%; hallucinations/psychosis 23.1%.

Clinicopathological correlation (subset n=8 with full clinico-path data): Concordant 62.5% (5/8): AD (A3B3C2; A2B3C2; intermediate), vascular SVD/microinfarcts, and **PSP** (4R tauopathy).
Discordant 37.5% (3/8): amnestic AD→**FTLD-tau (tangle-only)**; amnestic AD→**PART** (Thal 0, CERAD 0, Braak ≤ IV); bvFTD→**non-specific dementia** (no definitive lesion).

CONCLUSIONS

Dementia in mid- and late-life is **predominantly mixed**, with converging amyloid–tau, α-synuclein, TDP-43 and **vascular** injuries shaping phenotype on a frontotemporal scaffold.

Universal **frontal atrophy** explains the dysexecutive/behavioural core; additional temporal/hippocampal loss loads memory–language deficits.

ADNC remains foundational, but ~70% show **co-pathology** (CAA/SVD, ARTAG/LATE), driving clinical heterogeneity and faster decline.

Vascular burden (≈⅔ of brains) is age-linked and synergistic with neurodegeneration, reinforcing the need for **biology-driven** diagnosis and management.

Clinicopathological **concordance 62.5%** (subset) exposes diagnostic blind-spots; **multiplex biomarkers (AT[N])** are essential for in-vivo detection of co-pathology.

Autopsy continues to be the gold standard, crucial for refining criteria and India-specific biomarker cut-offs; **scaling the brain-donation pipeline** is a priority for powered, population-relevant studies.