Other Dementias

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DIFFUSE LEWY BODY DISEASE

PATHOGENESIS, PATHOPHYSIOLOGY, PATHOLOGY

Lewy bodies - intracytoplasmic, single or multiple, eosinophilic, round-elongated inclusions that have **dense core** surrounded by **pale halo**.

- composed of **fine 7-8 nm straight filaments** (densely packed in core but loose at rim); immunocytochemically - neurofilament antigens, α-synuclein, ubiquitin.

Dementing disorders associated with Lewy bodies can be categorized into three groups:

1) Parkinson disease without cortical Lewy bodies or AD changes (Lewy bodies only in substantia nigra)
2) Parkinson disease with ***cortical Lewy bodies*** (**diffuse Lewy bodies disease, DLBD**)
3) Alzheimer disease with ***cortical Lewy bodies*** (**Lewy body variant of AD, LBV** – 15-30% of all AD cases).

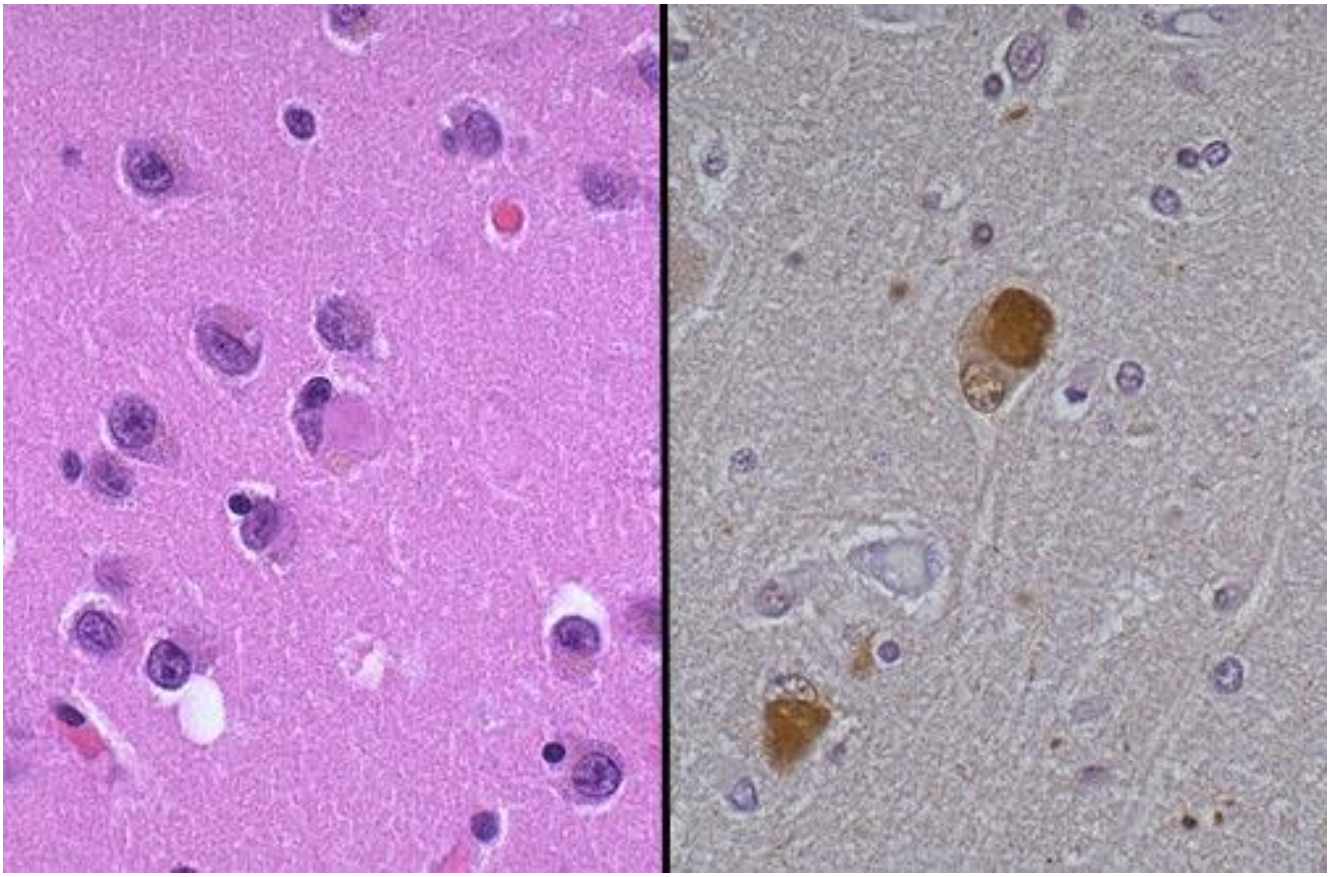
Lewy body-related pathology is the second most common dementia histopathology behind AD!

i.e. Lewy bodies are found in 15-25% degenerative dementias.

- Lewy bodies, if ***present in cortex***, are invariably also ***present in brain stem***:
  1) **Lewy bodies in brain stem** (easily seen on *hematoxylin-eosin* sections) - reside in substantia nigra, locus caeruleus, and raphe nuclei.
  2) **cortical Lewy bodies** often lack surrounding halo and are more difficult to visualize (unless *immunostains for ubiquitin* are used); maximal numbers in cingulate gyrus, insular cortex, parahippocampal gyrus.

Lewy bodies:
H & E stain

immunoperoxidase stain for ubiquitin



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- brain is normal ÷ slightly atrophic.
- neurotransmitter deficits mostly involve **cholinergic** and **dopaminergic** systems;
  nucleus basalis atrophy and cholinergic deficiency (LBV > DLBD) are more severe than in AD!

N.B. relationships among DLBD, AD, and Parkinson disease are debated because there is evidence to support all points of view.

CLINICAL FEATURES

- mean age of DLBD onset is 57 years.
- male to female ratio 1.7:1.
- death ensues after 10-15 years.

MIXED (CORTICAL-SUBCORTICAL) DEMENTIA

moderate÷severe **dementia** + mild÷moderate **parkinsonism**.

- literature is divided on whether parkinsonian or cognitive symptoms present first.
- **dementia**:
  - multifactorial nature (presence and frequency of ***cortical Lewy bodies*** may be contributor);
  - prominent visual hallucinations, paranoid delusions, illusions, and behavioral dyscontrol are characteristic clinical features;
  - frequent fluctuations of behavior, cognitive ability, and level of alertness (episodic confusion and lucid intervals suggesting delirium).
  - absence of severe aphasia, agnosia, apraxia.

- **parkinsonism** reflects ***basal ganglia*** & ***nigral degeneration***; subcortical degenerative changes → psychomotor slowing; i.e. bradykinesia > resting tremor.
  - repeated unexplained falls occur early!

MANAGEMENT

Whether treatment is necessary at all, and if so, what symptoms warrant treatment?

Treatment of dementia (may exacerbate parkinsonian syndrome!!!) – as in AD:

- *ACETYLCHOLINESTERASE INHIBITORS* serve as 1st-line therapy for neuropsychiatric as well as cognitive symptoms.
- patients are very sensitive to *NEUROLEPTIC* medications (exaggerated adverse responses to standard doses) - use most selective neuroleptics (RISPERIDONE, CLOZAPINE).

Treatment of parkinsonian syndrome (with LEVODOPA) may exacerbate neuropsychiatric disorder.

Nonpharmacological aspects of caregiving are similar to AD.

VASCULAR DEMENTIA

- 2nd most common dementia of elderly in USA (but No.1 in Asia!)

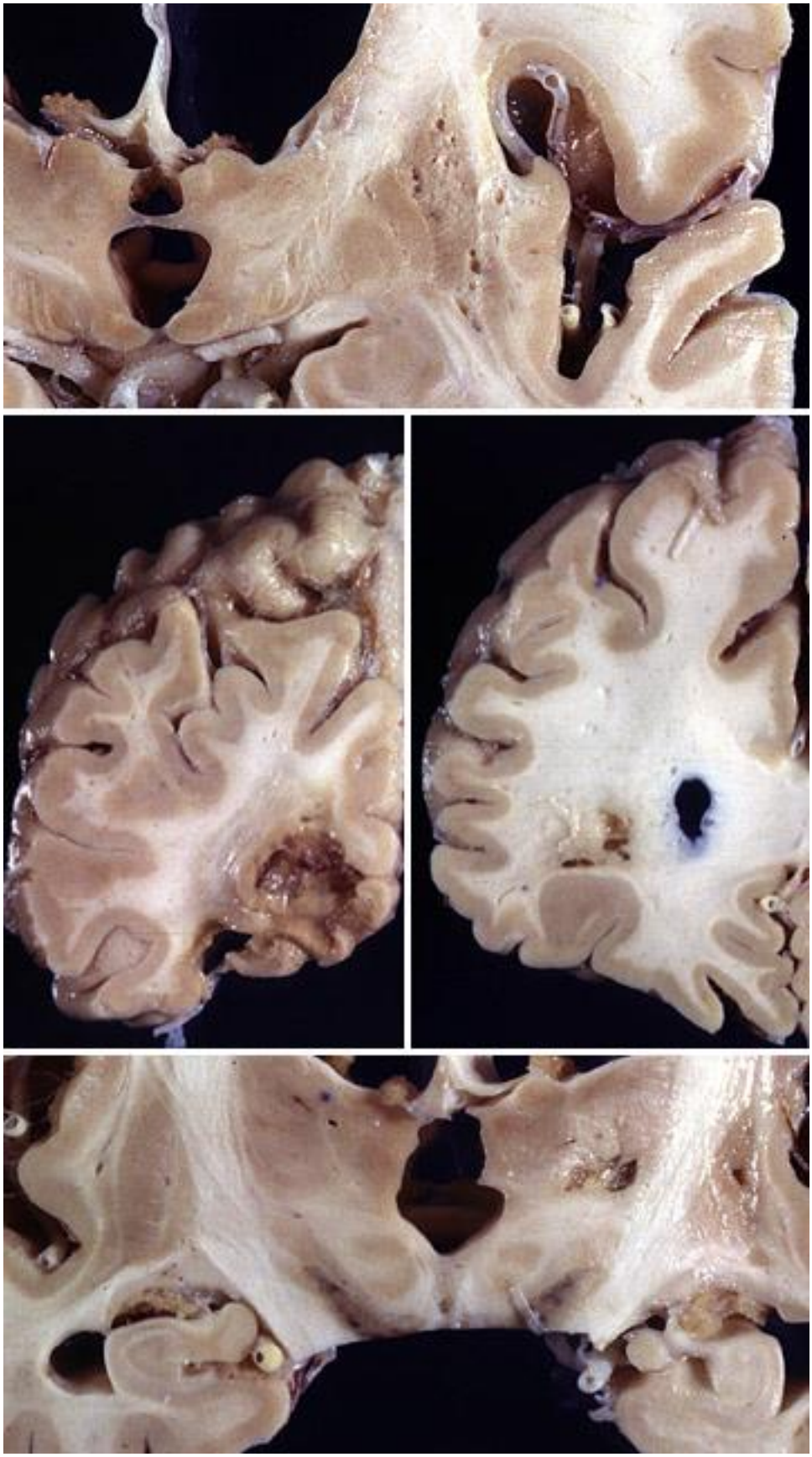
CAUSES AND TYPES

- brain injury from cerebrovascular disease:

a) **MULTIPLE CORTICAL INFARCTS** (multiple ischemic lesions in cerebral cortex* cumulatively result in loss of enough neurons** to produce dementia) - ***multi-infarct dementia***
   *not necessarily in eloquent locations
   **usually destroying at least 100 ml of brain volume
   N.B. many use "multi-infarct dementia" interchangeably with "vascular dementia".
b) occlusive disease of small penetrating cerebral arterioles [microangiopathy] → **MULTIPLE BILATERAL LACUNAR INFARCTS** (small infarctions in deep hemispheric white matter**)** resulting in *état lacunaire* (***Binswanger disease, s. subcortical arteriosclerotic encephalopathy***)
c) strategically placed **SINGLE INFARCT** (may cause specific cognitive deficit, aphasia, amnesia, but rarely causes dementia)
d) cerebral **hypoperfusion** (chronic, reversible) - most experts reject such mechanism.
e) ***amyloid angiopathy*** (not associated with dementia, but predisposes older persons to hemorrhagic lobar stroke).

PATHOLOGY

Multiple remote cystic infarcts in various locations over several years:



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CLINICAL FEATURES

Clinical features vary, but few generalizations are applicable (when compared with Alzheimer's disease):

1) **men** > women
2) often have **risk factors** (hypertension, diabetes, hyperlipidemia, cigarette smoking).
3) history of **transient ischemic attacks**
4) ***earlier age*** of onset (< 75 yrs)
5) onset may be ***abrupt***
6) **stepwise deterioration!!!** (episodes of sudden neurologic deterioration)
7) **focal neurologic signs** (limb rigidity, spasticity, hyperreflexia, extensor plantar responses, gait disturbance)
8) **pseudobulbar palsy** (emotional lability, dysarthria, dysphagia).
9) ***memory disturbance is of RETRIEVAL type*** - able to register information but difficulty spontaneously recalling it - categorical clues or multiple choices help.
10) ***shorter*** survival (after mental status changes onset).

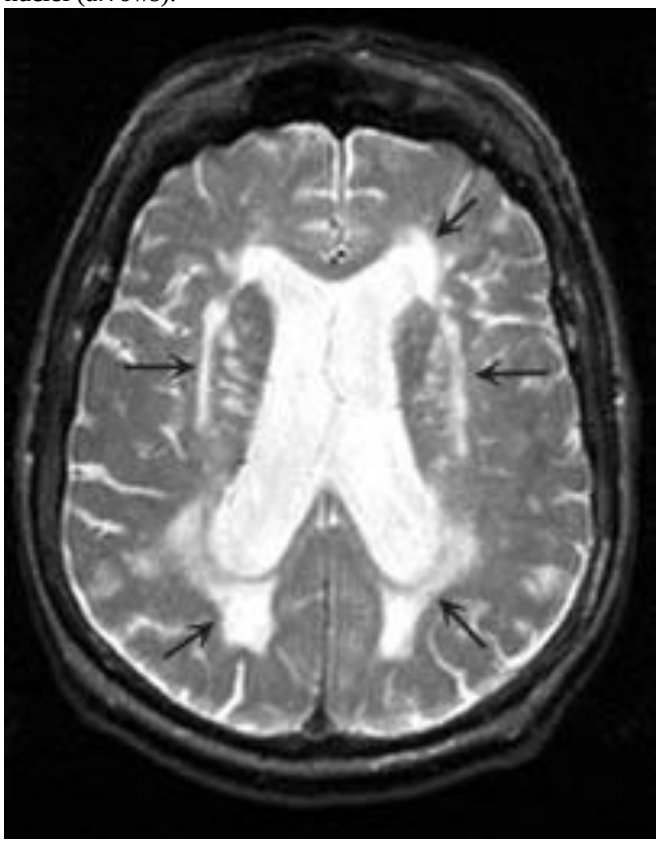
CLINICAL SUBTYPES:

Cortical syndrome (***multi-infarct dementia***) - abrupt onset of cognitive failure, focal sensorimotor signs, severe aphasia (when present).

Subcortical syndrome (***Binswanger disease***):

1) dementia of subtle onset and slow progression (vs. multi-infarct dementia)
2) bilateral pyramidal signs (lateralizing motor signs are uncommon).
3) gait imbalance (with *marche a petit pas*)
4) "frontal" abulic behavior, mildly impaired memory.
5) pseudobulbar signs, urinary incontinence.
6) associated (but not always) with severe hypertension and systemic vascular disease.

multiple areas of abnormal high signal intensity in periventricular white matter, corona radiata and lentiform nuclei (*arrows*).



DIAGNOSIS

- BRAIN IMAGING (provides supporting, but not diagnostic, evidence):
  a) focal infarctions in **strategic cortical locations**.
  b) ***Binswanger disease*** - ischemic periventricular **white matter** changes, sparing cortex and basal nuclei.

TREATMENT

- by **stroke prevention strategies**:
    1) antihypertensives
    2) cigarette cessation
    3) blood cholesterol reduction
    4) anticoagulants / antiplatelet therapy (ASPIRIN, CLOPIDOGREL, TICLOPIDINE).

BIBLIOGRAPHY see p. S11