

Other Dementias

Last updated: September 5, 2017

DIFFUSE LEWY BODY DISEASE	1
PATHOGENESIS, PATHOPHYSIOLOGY, PATHOLOGY	1
CLINICAL FEATURES	2
MANAGEMENT	3
VASCULAR DEMENTIA	3
CAUSES AND TYPES	3
PATHOLOGY	3
CLINICAL FEATURES	4
DIAGNOSIS	5
TREATMENT	6

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).

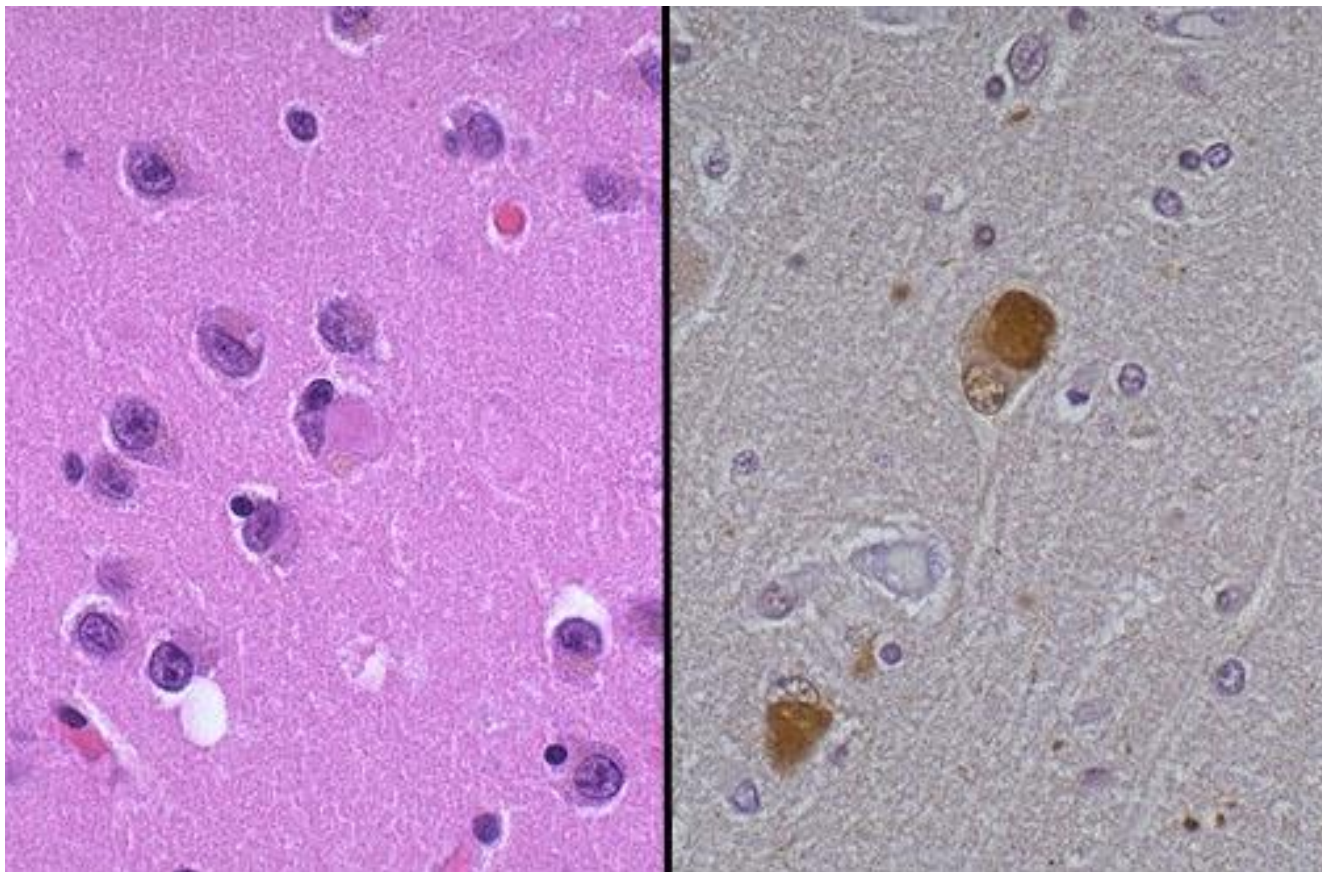
Lewy body-related pathology is the second most common dementia histopathology behind AD!

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



Source of picture: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD) >>

- 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

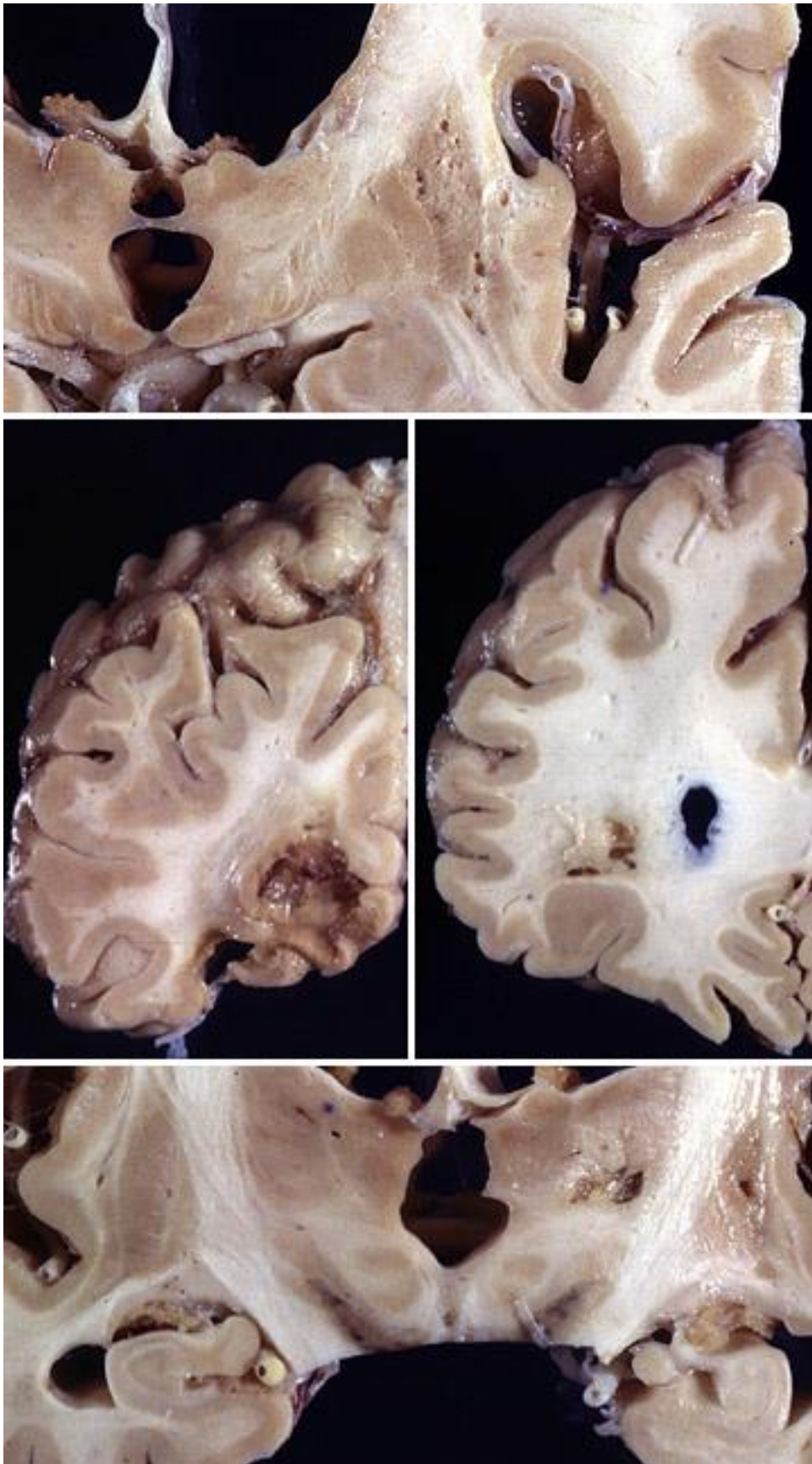
- brain injury from cerebrovascular disease:

- 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".
- 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*)
- strategically placed **SINGLE INFARCT** (may cause specific cognitive deficit, aphasia, amnesia, but rarely causes dementia)
- cerebral **hypoperfusion** (chronic, reversible) - most experts reject such mechanism.
- 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:



Source of picture: "WebPath - The Internet Pathology Laboratory for Medical Education" (by Edward C. Klatt, MD) >>

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).

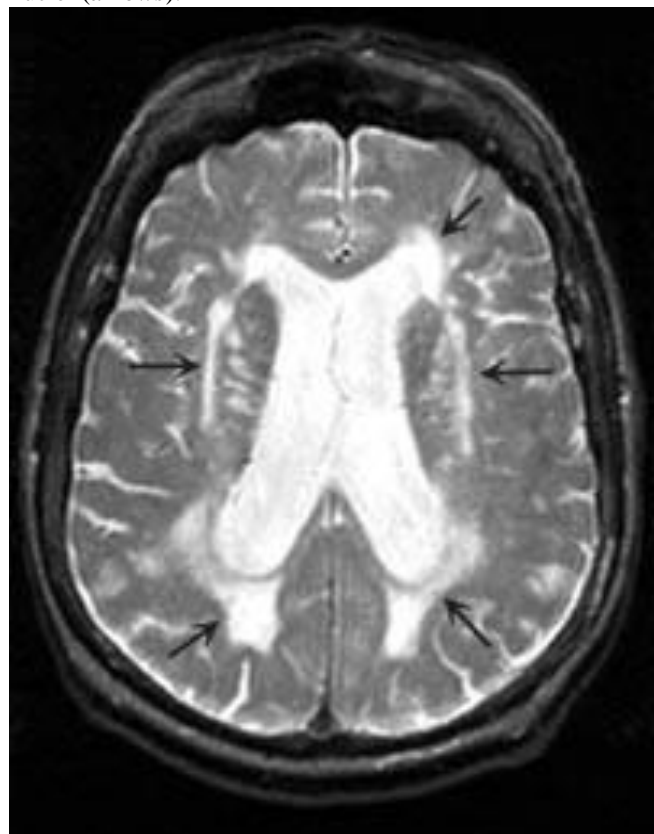
CLINICAL SUBTYPES:

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