

Neuropathologic Changes of Alzheimer Disease: A Case Study

Mark Vincent C. Olorvida MHS, PA Student, Mentors: Christos D. Katsetos, M.D., Ph.D., FRCPath, Ahmed Abdulrahman, M.D., Drexel University College of Medicine, Philadelphia, PA

Background Information:

A 66-year-old Caucasian woman presented with a history of depression, anxiety, and dementia for about 2 years. She demonstrated multiple cognitive difficulties including memory deficit, and she later became more confused, agitated, and at times, delusional. She was employed at a bank, but lost her ability to do simple mathematics. For the last year of her life, her skills with a variety of motor functions declined. Her walk became unsteady and she started to have frequent falls and gait dysfunction. She frequently experienced right-sided headaches and her behavior progressively changed with psychotic symptoms.

The patient was admitted to the hospital after being found on her house floor due to a fall. She continued to have episodes of severe agitations requiring sedation, neurologic and psychiatric evaluations. Laboratory tests were unremarkable. An MRI revealed no evidence of acute stroke but showed severe volume loss and mild chronic ischemic white matter disease. An EEG demonstrated right temporal slowing, suggesting a small structural abnormality, but without any seizure activity. Cranial nerve exam revealed significant facial asymmetry, with left-sided drift at the corner of the mouth. She had increased tone in all limbs with occasional myoclonic light jerks in the left upper and lower extremities. The right plantar reflex was flexor, and left was extensor. The patient was transferred to a skilled nursing facility. Her condition rapidly worsened and she was transferred to hospice care. She passed away a couple of weeks after.

Methods:

The brain had diffuse cortical atrophy without lobar predilection. The hemispheres were symmetrical without externally discernible evidence of cerebral infarct, parenchymal hemorrhage, trauma, brain abscess, swelling, midline shift, or subfalcine herniation. Basal view of the brain was unremarkable, and the brainstem and cerebellum show no gross abnormality. Serial coronal sections of the cerebrum revealed diminution in bulk of white matter and diffuse thinning of the cortical mantle but with preservation of cortical white matter demarcation throughout the cortical ribbons in all lobes. There was moderate to pronounced bilateral dilatation of the lateral ventricles and third ventricle, with rounding of the lateral ventricular angles (Fig. 1E). Axial sections of the midbrain revealed pallor of the right substantia nigra (Fig. 1D) when compared to the left, as well as dilatation of the cerebral aqueduct. Remaining sections of the brainstem and cerebellum were unremarkable, with no grossly overt abnormalities.

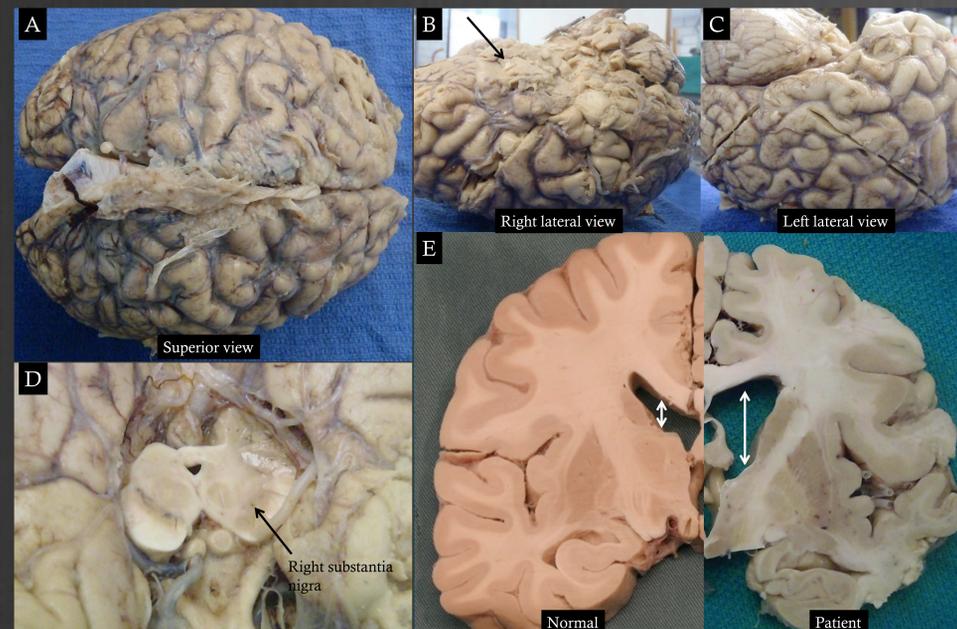


Figure 1. Gross photos. A, Superior view of the brain. B and C, Lateral views of the brain, showing pronounced cortical atrophy in the right mesiotemporal region (arrow). D, Pallor of the right substantia nigra compared to the left (arrow). E, Comparison of patient to normal, showing dilatation of lateral ventricles (arrows) with rounding of lateral ventricular angles and diminution in bulk of white matter.

Microscopic evaluation revealed extensive neurodegenerative changes in the cerebral cortex involving the frontal, lateral temporal, parietal and occipital areas and in the cortical white matter junction. These changes were characterized by profusion of phosphorylated tau positive neurofibrillary tangles, pretangle neurons, neuropil threads, dystrophic neurites in the context of neuritic plaques, and dense and diffuse accumulation of A β deposits. Multiple sections of the hippocampus and the basal ganglia also revealed the same extensive neurodegenerative changes.

The cerebral cortex exhibited moderate gliosis without disruption of the cortical architecture. There was no evidence of laminar necrosis, infarct, or microvascular intercortical lesions. No Lewy bodies were present, substantiated by negative alpha-synuclein immunohistochemical stain. Both sections of the substantia nigra exhibited, for the most part, preservation of neuromelanin bearing neurons, even the right side, which grossly showed pallor when compared to the left.

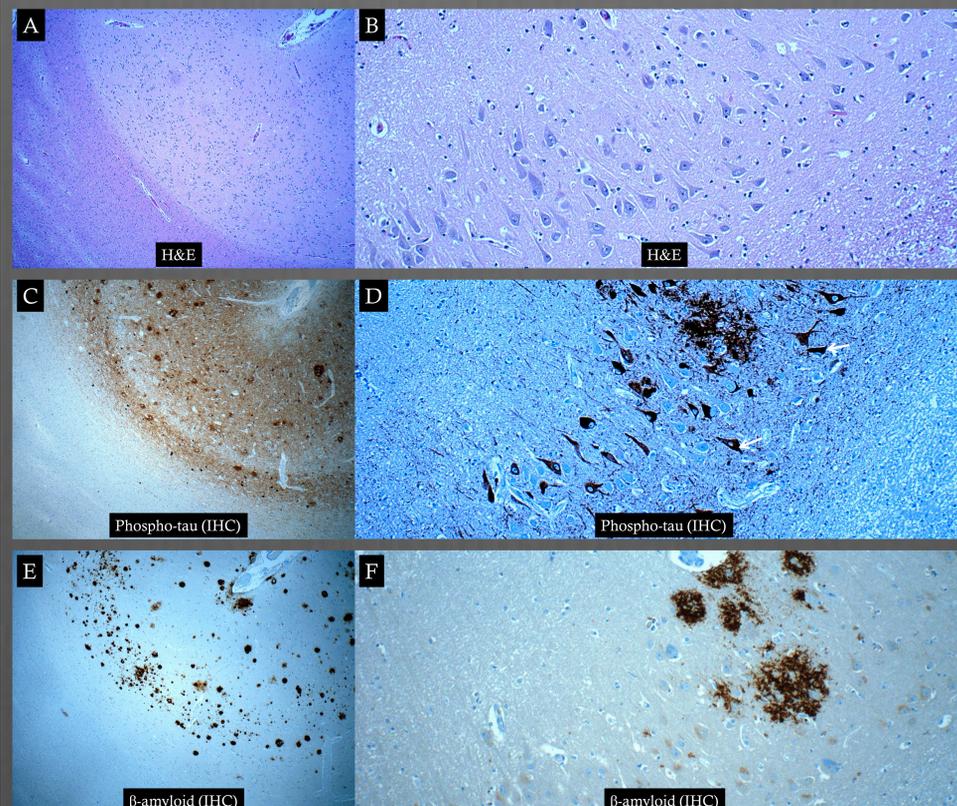


Figure 2. Left Posterior Hippocampus and Entorhinal complex. A and B, H&E. C and D, Phospho-tau IHC stain, revealing numerous neurofibrillary tangles (D, arrows) as well as neuritic plaques with dystrophic neurites. E and F, β -amyloid IHC stain, revealing A β plaques (E) present throughout the cortex and senile plaques of the diffuse type (F).

Results:

Final gross impression included prominent diffuse cortical atrophy suggestive of a neurodegenerative process. There was no evidence of stroke, brain abscess, infection, tumor, demyelinating disease or traumatic brain injury. There was absence of hippocampal sclerosis. No developmental brain abnormalities or abnormalities of neuronal cortical migration were identified.

Microscopic evaluation confirmed severe neurodegenerative changes affecting the neocortex, mesolimbic region, and basal ganglia, consistent with hypermobility Alzheimer disease (AD). There was no evidence of frontotemporal dementia, diffuse Lewy body disease, vascular dementia or other neuropathologic processes associated with dementia. The final neuropathologic diagnosis was Alzheimer disease, high, with an ABC score of A3, B3, and C3.

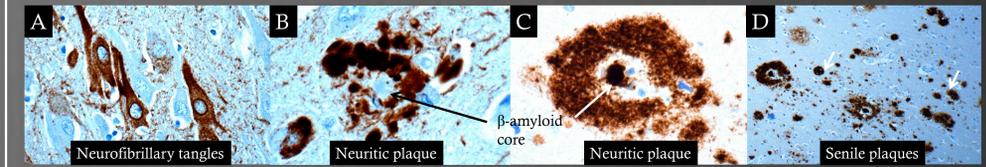


Fig 3. A, close-up view of a neurofibrillary tangle (Phospho-tau IHC). B and C, close-up view of a neuritic plaque stained with Phospho-tau IHC (B) and β -amyloid IHC (C) to highlight the β -amyloid core. D, close-up view showing senile plaques (arrows) and neuritic plaques.

Conclusion:

The three main components related to assessment of AD neuropathologic changes are collectively termed the ABC score: A for Amyloid, refers to parenchymal A β deposition, B for Braak and Braak, refers to neurofibrillary tangles, C for CERAD, refers to neuritic plaques. Each component is assessed and assigned with 1 of 4 scores (0, 1, 2, 3); the scores are combined and cases are identified as having high, intermediate, or low level of AD neuropathologic change. These levels are correlated with clinicopathologic changes as well as the presence/absence and extent of other contributing disease.

AD can exist in 'pure form,' but it commonly coexists with pathologic changes of other diseases that can contribute to cognitive impairment. Therefore, it is important to assess non-AD brain lesions and to document the type and extent of comorbidity in brains of individuals with AD neuropathologic change because they can potentially contribute to the patient's cognitive impairment or dementia.

Macroscopic examination of the brain with AD will show variable degrees of cortical atrophy, resulting in a widening of the cerebral sulci that is most pronounced in the frontal, temporal, and parietal lobes. With significant atrophy there is compensatory ventricular enlargement (hydrocephalus ex vacuo) secondary to loss of brain parenchyma.

Microscopically, neurofibrillary tangles are a major component of AD neuropathologic changes. These are bundles of paired helical filaments primarily composed of abnormally phosphorylated tau protein that displace or encircle the nucleus. The tangles can be visualized with a variety of histochemical stains or with immunohistochemistry directed against tau or phospho-tau epitopes. Senile plaques, the other major component of AD neuropathologic changes, are extracellular deposits of β -amyloid proteins, which are morphologically diverse and follow a distinct sequence of spatial involvement of the medial temporal lobe. A subset of senile plaques are neuritic plaques, which are focal, spherical collections of dilated, tortuous, dystrophic neurites, often around a central β -amyloid core. Senile plaques and cores of neuritic plaques can be visualized by histochemical and immunohistochemistry directed against β -amyloid epitope.

Other features of AD neuropathologic changes include granulovacuolar degeneration, Lewy bodies, Hirano bodies, and cerebral amyloid angiopathy, but these are less straightforward to assess. Moreover, the timing of any of these pathologic changes relative to functional changes is difficult to assess with certainty in autopsy samples. It is important to recognize that the recommended use of neurofibrillary tangles, parenchymal A β deposits, and neuritic plaques as the defining histopathologic lesions of AD neuropathologic change does not preclude the possibility that other processes or lesions that may be critical contributors to the pathophysiology of AD.

References:

- Kumar V, Abbas A, Fausto N, Aster J. *Robbins and Cotran's Pathologic Basis of Disease 8th Edition*. Philadelphia, PA: Elsevier Saunders; 2010.
- The Alzheimer's Association. 2014 Alzheimer's Disease Facts and Figures. Alzheimer's Association. http://www.alz.org/alzheimers_disease_facts_and_figures.asp. Published March 2014. Accessed March 27, 2014.
- Hyman B, Phelps C, Beach T, Bigio E, et al. National Institute of Aging--Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. *Alzheimer's & Dementia*. 2012; 8(1-13). doi: 10.1016/j.jalz.2011.10.007
- Thal D, Rub U, Orantes M, Braak H. Phases of A β -deposition in the human brain and its relevance for the development of AD. *Neurology*. 2002; 58(1791-1800).
- Kovacs G, Gelpi E. Clinical Neuropathology Practice News 3-2012; the "ABC" in AD--revised and updated guidelines for the neuropathologic assessment of Alzheimer's disease. *Clinical Neuropathology*. 2012; 31(116-118).
- Montine T, Phelps C, Beach T, Bigio E, et al. National Institute on Aging--Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. *Neuropathology*. 2012; 123(1-11). doi 10.1007/s00401-011-0910-3.
- Alzheimer's Society. Factsheet: What is Frontotemporal Dementia. Alzheimer's Society. http://www.alzheimers.org.uk/site/scripts/documents_info.php?documentID=167. Published April 2013; Accessed March 27, 2014.