The Molecular Pathology of Alzheimer's Disease

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KEYWORDS

• Alzheimer's disease • Tau protein • Amyloid-β protein
• Neurofibrillary tangles • Plaques
• Protein aggregation disorders

List of Key Learning Points

- The pathologic hallmarks of Alzheimer's disease are the presence of both neurofibrillary tangles and senile plaques, first described in a patient with presenile dementia by Alois Alzheimer.
- Neurofibrillary pathology consists of intraneuronal fibrils present in tangles, and in neurites found both throughout the neuropil and in neuritic senile plaques.
- Neurofibrillary pathology in Alzheimer's disease consists of paired helical filaments comprising tau protein.
- Amyloid pathology occurs as the deposition of amyloid-β (Aβ) protein within senile plaques and in the form of diffuse deposits throughout the neuropil. In addition, it can be found as deposits around blood vessels.
- Aβ deposits derive from the processing of a transmembrane-spanning Aβ protein precursor (APP) to release an extracellular Aβ peptide of 40 to 43 amino acids in length; larger peptides form more insoluble Aβ deposits.
- Mutations in APP and the presenilin proteins 1 and 2 cause familial Alzheimer's disease and result in increased deposition of insoluble Aβ. Presenilin 1 possesses the catalytic sites of a tetrameric γ-secretase complex that cleaves APP, with the aid of β-secretase, to Aβ peptides.
- Tau mutations cause tauopathy in conditions other than Alzheimer's disease in the absence of amyloid pathology. These conditions include frontotemporal dementia syndromes, and indicate that amyloid is not essential to cause dementia.
- Tau pathology in Alzheimer's disease precedes amyloid pathology by 2 decades.
- Molecular imaging of amyloid in Alzheimer's disease using Pittsburgh B compound and the future development of selective tau ligands indicate that knowledge of the pathogenesis of Alzheimer's disease will be greatly improved by direct visualization of the pathology in humans.

The German psychiatrist Alois Alzheimer presented the original description for a 55-year-old patient who had suffered with presenile dementia and who had the unique combination of both senile plaques and neurofibrillary degeneration in her brain.[1] Alzheimer was prompted to consider this case as representing a specific disease process in which the neurofibrillary pathology made it particularly distinctive. In just 2 pages, Alzheimer had described the pathologic basis for the

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disease to be given his name. By 2010, more than 9000 articles related to Alzheimer's disease were published in a single year.

The pathologies that Alzheimer observed at autopsy can now be examined during life by molecular imaging techniques that allow an even greater insight into the pathogenesis of the disease and the means to assess therapeutic efficacy. This article focuses on the molecular pathology found in Alzheimer's disease, namely that of tau protein and amyloid-β (Aβ) protein (**Fig. 1**).

TAU PROTEIN PATHOLOGY IN ALZHEIMER'S DISEASE

Normal Tau Protein

Tau proteins are a family of microtubule-associated proteins. Tau proteins are predominantly expressed in neurons, where they play an important role in the assembly and stabilization of tubulin monomers into microtubules that constitute the neuronal cytoskeletal network. Microtubules are essential in morphogenesis, cell division, and intracellular trafficking of organelles. At physiologic concentrations tau proteins stabilize microtubules as tracks for intracellular transport, but in excess they interfere with transport down the axon. Tau also plays a role in signal transduction through its interaction with phospholipase C-γ, interacts with actin and the plasma membrane, is involved in anchoring of protein kinases and phosphatases, and is important in neurite outgrowth.[2]

Human tau protein in the central nervous system exists in 6 isoforms, ranging from 352 to 441 amino acids in length and derived by alternative mRNA splicing from a single gene (*MAPT*) located on

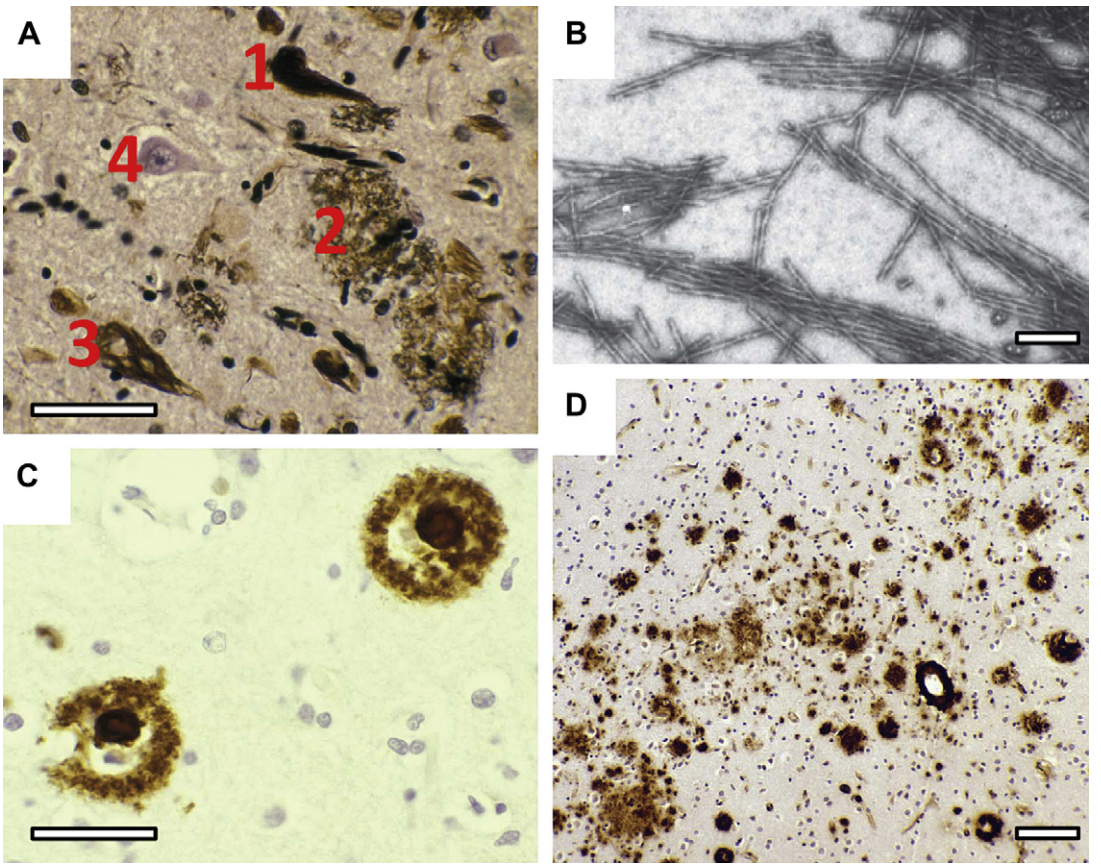

Fig. 1. Neuropathology of Alzheimer's disease is characterized by tau and amyloid-β (Aβ) pathologies. (*A*) Tau pathology involves intracellular accumulations of fibrous tau in neurofibrillary tangles within pyramidal neurons (**1**) and in the neurites of plaques (**2**), and throughout the neuropil. The NFTs eventually become extracellular ghost tangles (**3**) once the cytoplasmic membrane has burst. An unaffected neuron is also seen (**4**). (*B*) Paired helical filaments (PHFs) extracted from Alzheimer's disease brain tissue. (*C*, *D*) Aβ pathology in Alzheimer's disease showing plaques with cores (*C*); diffuse cortical amyloid staining and amyloid angiopathy surrounding a blood vessel (*D*). (*A*, *C*, *D*) Tau and amyloid pathology visualized using monoclonal anti-tau and polyclonal anti-Aβ; scale bars, 50 μm. (*B*) Electron microscopy of negative-stained PHF preparations; scale bar, 250 nm.