Pathophysiology of Alzheimer's Disease

Alzheimer's disease (AD) is the most common cause of dementia in the elderly. The disease usually becomes clinically apparent as insidious impairment of higher intellectual function with alteration in mood and behavior. Later, progressive disorientation, memory loss, and aphasia become manifested, indicating severe cortical dysfunction. Eventually in 5-10 years, the affected individual becomes profoundly disabled, mute, and immobile. Patients rarely become symptomatic before 50 years of age, but the incidence of the disease rises with age and the prevalence roughly doubles every 5 years, starting from a level of 1% for the 60-64 years old population and reaching 40% or more for the 85-89 years old cohort. This progression increase in the incidence of the disease with age has given rise to major medical social and economic problems in countries with a growing number of elderly individuals. Most cases are sporadic, and although 5%-10% are familial, the study of such familial cases has provided important insight into the pathogenesis of the more common sporadic form. While pathogenic examination of the brain tissue remains necessary for the definitive diagnosis of Alzheimer's disease, the combination of clinical assessment and modern radiological methods allows accurate diagnosis in 80%-90% of cases.

The neuropathological hallmarks of AD include "positive" lesions such as amyloid plaques and cerebral amyloid angiopathy, neurofibrillary tangles and glial responses, and "negative" lesions such as neuronal and synaptic loss. Clinicopathological correlation studies have been crucial to generate hypotheses about the pathophysiology of the disease, by establishing that there is a continuum between "normal" aging and AD dementia, and that the amyloid plaque build-up occurs primarily before the onset of cognitive deficits, while neurofibrillary tangles, neuron loss, and
particularly synaptic loss, parallel the progression of cognitive decline.

Amyloid plaques: Extracellular protein deposit in the cortex of AD patients. The major protein in neuritic plaques is amyloid β-peptide (Aβ), which is a 40-42 amino acid peptide derived from a membrane protein, the β-amylloid precursor protein (APP) after sequential cleavage by enzymes. APP encoded by gene on chromosome 21. APP interact with extracellular matrix and supports the growth of neuritis in neuronal culture, Its physiological role is likely related to the modulation of synaptic activity although still controversial. Genetic evidence implicates Aβ in the pathogenesis implicated Aβ in the pathogenesis of Alzheimer's disease, Almost all patients with trisomy 21 (Down syndrome) develop pathologic changes indistinguishable from those seen in Alzheimer's disease, suggesting that having an increased copy of the APP gene increases the metabolism of APP to Aβ.

Neurofibrillary tangles (NFT): intraneuronal aggregates of hyperphosphorylated and misfolded tau that become extraneuronal ("ghost" tangles) when tangle- bearing neurone die. Tau protein is a microtube- associated protein normally located to the axon, where it physiologically facilitates the axonal transport by binding and stabilizing the microtubules. In Alzheimer's disease, tau is translocated to the somatodendritic compartment and undergoes hyperphosphoration, misfolding and aggregation giving rise to neurofibrillary tangles and neuropil threads
Figure 1. Photomicrographs of the core pathological lesions observed in Alzheimer and Lewy body diseases. (A) Plaque evident on routine H&E stained section of frontal cortex; (B) tangle in a hippocampal pyramidal neuron on routine H&E stained section; (C) silver stain highlights both a plaque and a tangle; (D) immunohistochemistry against Ab highlights plaques; (E) immunohistochemistry against tau highlights tangles; (F) a cortical Lewy body can be seen in a layer V neuron on a routine H&E stained section of frontal cortex.

References:


3. Serrano-Pozo, A. Frosch, M. Masliah and Hyman, B. 2011 Neuropathological Alterations in Alzheimer Diseasewww.perspectivesinmedicine.org