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Essentials of Anatomy as Related to Alzheimers disease: A Review

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Abstract

Alzheimer disease (AD) is the sixth leading cause of death, presently in America. AD is the centre of preoccupation of not only the scientific community, but also of the intelligentsia. lzheimer disease (AD) is a neurodegenerative disorder marked by cognitive and behavioral impairment that significantly interferes with social and occupational functioning. It is an incurable disease with a long preclinical period and progressive course. In AD, plaques develop in the hippocampus, a structure deep in the brain that helps to encode memories, and in other areas of the cerebral cortex that are involved in thinking and making decisions.

For clinical research, the classification of AD has recently been divided into 3 phases . First is a presymptomatic phase during which people are cognitively normal but with evidence of amyloid deposition with or without other neuropathological changes. Second is a symptomatic prodromal phase characterized by mild cognitive impairment (MCI) with amyloid deposition and more diverse evidence of neurodegeneration. In Individuals with MCI due to AD or prodromal AD experience a progressive cognitive decline greater than expected for their age and education level but without obvious signs of impaired function. The third phase occurs when cognitive impairment worsens and interferes with activities of daily living. The patient is then diagnosed with dementia and has a full repertoire of molecular and neurodegenerative changes.

AD is a progressive disorder with interrelated molecular, physiological, anatomical, and clinical changes. This review describes these domains and the progression of biological changes (genetic, molecular, and cellular) that underlie AD and their correlation with the clinical syndrome.

The study of various structures of the brain, their connections and the pathways involved (anatomy), their normal functioning (physiology) and how this is subverted, leading to AD (pathology and pathogenesis), is vital to understanding comprehensively the complete gamut of clinical features of the Alzheimer disease. The anatomical structures, their connections and interplay, as implicated as having a role in AD, are briefly reviewed in this article. The functional significance with AD, of each structure is highlighted. The most common risk genes associated with AD susceptibility have roles in lipid processing, immune function, endocytosis, or synaptic integrity . Many genetic risk factors are associated with late-onset AD (after 65 years of age or older). Apolipoprotein E is the most well-known risk factor gene. APOE is involved in cholesterol transport in CSF and in binding and clearance of beta-amyloid (Aβ) in the brain . Of its 3 major alleles, the APOE ε4 allele confers the greatest risk for developing late-onset familial and sporadic AD, most likely by reducing cholesterol efflux from neuronal cells and astrocytes, and by binding and depositing Aβ. The prevalence of this allele is approximately 15% in the general population and approximately 40%in patients with AD . The ε2 allele appears to play a protective role against AD. In addition to APOE, risk genes associated with lipid processing include ABCA7, clusterin and sortilin-related receptor L (SORL1). ABCA7 encodes an adenosine triphosphate (ATP)-binding cassette transporter and plays multiple roles including substrate transport across cell membranes, regulation of amyloid precursor protein (APP) processing, and inhibition of Aβ secretion . CLU, a major brain apolipoprotein that reversibly and specifically binds Aβ and appears to act as a molecular chaperone, influences Aβ aggregation, deposition, conformation, and toxicity . SORL1 is involved in vesicle trafficking from the cell surface to the Golgi-endoplasmic reticulum. It directs APP to endocytic pathways for recycling and plays an important role in Aβ generation .

Phosphatidylinositol-binding clathrin assembly protein (PICALM) gene and bridging integrator 1 are implicated in cell-cell communication and transduction of molecules across the membrane. CD33 is a member of the sialic-acid-binding immunoglobulin-like lectins (Siglec) family which is thought to promote cell-cell interactions and regulate functions of cells in the innate and adaptive immune systems . The gene TREM2 has a role in modulating risk for late-onset AD and heterozygous rare variants are associated with a significant increase in the risk of AD . TREM2 is an innate immune receptor expressed on the cell surface of microglia, macrophages, osteoclasts, and immature dendritic cells; it triggers the activation of immune responses. CD2-associated protein is a scaffold/adaptor protein that associates with proteins involved in receptor-mediated endocytosis. EPHA1 is a member of the ephrin receptor subfamily and a membrane-bound protein that plays a role in cell and axon guidance, cell morphology and motility,

and apoptosis and inflammation. Membrane-spanning 4A gene cluster, which encodes the beta subunit of high-affinity IgE receptors and complement receptor 1 (CR1), also plays a role in immune response.

The time course and levels of AD pathology highlight the connections between the molecular, physiological, anatomical, and cognitive changes. Dementia associated with AD is related to the aberrant processing and clearance of Aβ and tau. Feedback mechanisms associated with inflammatory responses and oxidative stress set in motion a cascade of pathological events. Cellular-level events lead to synaptic dysfunction and neurodegeneration in the brain. In particular, AD appears to follow the default-mode network, associated with resting state episodic memory. Biomarkers for Aβ plaque, neurofibrillary tangles, and brain atrophy serve as the limited window on biology available to the clinician.

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