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Dubravka CVETKOVIĆ-DOŽIĆ
Milica SKENDER-GAZIBARA
Slobodan DOŽIĆ

INSTITUTE OF PATHOLOGY, MEDICAL FACULTY,
UNIVERSITY OF BELGRADE, BELGRADE, YUGOSLAVIA

Neuropathological hallmarks of Alzheimer's disease

ABSTRACT

Alzheimer's disease (AD) is the most common neurodegenerative disease and the leading cause of dementia especially in the Western countries. The onset of disease is rarely before the age of 60 and after that period the incidence and prevalence rise with increasing age. AD is clinically manifested by progressive memory loss and a general decline in cognitive function. With progression of disease due to severe cortical disfunction, patient becomes demented, aphasic, desorientated, immobile and emaciated. Pneumonia or urinary infection are the common causes of death. AD is usually divided into the following clinical forms: sporadic form with late onset (most common, in 85-90% cases), familial AD with early or late onset, and AD associated with Down's syndrome.

KEYWORDS: Alzheimer disease; Neurofibrillary tangles; Brain Diseases + etiology + physiopathology

MORPHOLOGICAL CHANGES

There is cortical atrophy with narrowing of gyri, widening of sucli and hydrocephalus ex vacuo. Most severly affected are temporal lobes (hippocampus, parahippocampus, amygdala), than frontal and parietal lobes. Occipital lobes and motor cortex are usually spared. The disease is characterized by deposition of beta amyloid protein in cerbral cortex and dramatic loss of neurones and synapses, particularly in those regions associated with cognitive functions. A number of important neuropathological changes occur in the brains of AD.

NEUROFIBLLIRATORY CHANGES

NFT are considered to be a major pathological hallmark of Alzheimer's disease. Alois Alzheimer was the first who described the NFT (1907) in the soma of cortical neurons in a 51-years old women who had had a 5-years history of progressive dementia. NFT develop within the pyramidal neuronal soma as argentophilic filamentous inclusions which extend into the neuronal processes. They are flame or globoid in shape. After deterioration of the parent cell, the NFT persist in neuropile for a long time as an extraneuronal structures. NFT consist of highly insolubile and proteolysis-resistent paired helicial filaments (PHF) in addition to 15 nm wide straight filaments and amorphous material of unknown biochemical composition. PHF are composed of protofilaments containing proteins that are immunologically related to normal cytoskeletal proteins. PHF appear as left handed double helices with diameter of 20-24 nm and priodicity of 160 nm. The main subunits of PHF are altered forms of microtubule associated tau protein which undergo abnormal phosphorylation (Trojanowski, 1993). Abnormally phosphorylated tau protein is believed to be neurotoxic and can be the cause of neuronal death. Apart from perikaryal NFT, PHF are also found in dystrophic neurites assiciated with plaques formation and neuropil threads. Besides tau protein, the immunoreactivity for beta amyloid protein (beta A/4 protin) and ubiquitin can be found in NFT (Perry et al, 1992). In general, NFT show a rather striking predilection to affect particular areas of the AD brains. Their density is highest in the pyramidal neurones of the medial temporal lobe (amygdala, CA1 area of hippocampus, subiculum, layers II and IV of the entorhinal cortex) and moderate in the layers III and V of the association cortex of the frontal, temporal and parietal lobes (Terry et al, 1994). The major subcortical neurones affected by NFT are cholinergic neurones of the basal nucleus of Meynert, noradrenergic neurones of locus coeruleus and serotonergic neurones of raphe nuclei. The characteristic and laminar distribution of NFT support the hypothesis that pathological process in AD may spread along a sequence of cortico-cortical connections between the assiciation cortical areas and the hippocampal formation. The NFT occur in neuron clusters that give rise to the feed forward and feedback cortico-cortical projections that occur between cortical and subcortical regions (Armstrong, 1993). The loss of these systems leads to the disconnection between hippocampus and neocortex and between neocortical association areas resulting in the disintegration of intelectual functions. NFT can be also found in several other disorders (Down's syndrome, postencephalic parkinsonism, subacute sclerosing panencephalitis, amyotrophic lateral sclerosis, parkinson-dementia complex from Guam, and dementia pugilistica) as well as in normal aging brains of undemented individuals. Because NFT are characteristic but not specific finding of AD, the diagnosis of AD must be based on correlation between clinical features (dementia) and neuropathological findings (NFT density and characteristic distribution) Using H&E stains it is difficult to identify NFT in tissue sections. They can be visualized by various silver stains (von Brownmuhl, Bielschowski and modifications), using histochemical methods such as thioflavine S, immunohistochemically with anti tau antibody and by electronmicroscopical investigations.

Neuritic plaques (NP)

Neuritic (amyloid, senile) plaques are foci of enlarged axons, synaptic terminals and dendrites, associated with extracellular beta/A4 amyloid. They appear as spherical areas of 10-15 nm in diameter with amyloid-positive core surrounded by argentopholic material. NP are generally confined to the cerebral cortex but they may be also seen in subcortical gray matter. The sites of predilection are amygdala, CA1 area of hippocampus, subiculum and layers II, III and V of the entorhinal cortex (Mc Kee et al, 1991). There are several plaques subtypes. The two most prominent are diffuse and classic plaques. Diffuse or immature plaque consists of beta/A4 in a non-aggregated form, free of any neuritic involvement. This form should be aggregated at some stage of the disease. It was shown that beta/A4 deposits promote neuritic interactions that result in neurite dystrophy (Porbst et al 1987). Classic plaque consists of fibrilis of aggregated beta/A4 core surrounded by clear halo with dystrophic neurites (DN), activated microglia and reactive astrocytes at the periphery. DN within plaque consists of distended axons, dendrites and synaptic terminals. DN exibit immunoreactivity for amyloid precursor protein, growth associated protein (GAP43), tau, ubiquitin and neurofilaments. Histologic and immunohistochemical methods used to demostrate NP

Address correspondence to:
Dr Dubravka Cvetković-Dožić, Institute of Pathology, Medical Faculty, University of Belgrade, 11000 Belgrade, Yugoslavia

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include congo red, thioflavine S, silver stains and immunohistochemical stains that can demonstrate various biochemical components of the plaques. It is difficult to see NP in ordinary H&E preparations.

Neuropil threads (NT)

NT appear as argentophilic network of fragmented and twisted fibers in the neuropil. They are formed within axons, dendrites and presynaptic terminals. NP are often associated with NFT, but are independent of NP. Ultrastructurally, NT are composed of PHF. Immunohistochemical techniques revealed that they contain tau and ubiquitin (Braak et al, 1986).

Hirano's bodies (HB)

HB are eosinophilic rod-like intraneural structures, most often found in the hippocampal pyramidal neurones. They are best seen in H&E preparations. Ultrastructurally HB consistes of crystalloid arrays of interlacing filaments displaying either a lattice-like or herringbone configuration (Hirano et al, I968).

Granulovacuolar bodies (GVB)

GVB appear as round vacuoles (3-4 microns) with a dense core which stains blue in H&E and are argentophilic. They are confined to the soma of hippocampal pyramidal neurones. The significance of HB and GVB is unknown.

Cerebral amyloid (congophilic) angiopathy (CAA)

CAA appear as accumulation of beta/A4 amyloid filaments within walls of small arteries and arterioles of the leptomeninges and cerebral cortex. Beta/A4 can be also deposited within cerebral cortical capillaries when it usually make a spike-like projections into the brain parenchyma. CAA is rarely demonstrable in the white matter and brainstem. CAA may be the cause of small cortical infarcts and hemorrhage (Okasaki et al, 1979). The methods used to demonstrate CAA are congo red, thioflavine S, silver stains and immunoperoxidase staining with antibody to beta/A4 protein.

ETHIOLOGY AND PATHOGENESIS

In attempt to elucidate the causes of AD, only two factors stand out as having a major influence on the occurence of AD. These are age and genetics. The association with age is not complitely understood, but is likely to involve both environmental and genetic factors. Other possible risk factors are: family history, maternal age, head injury, socioeconomic status (level of education and occupation), environmental exposures (electromagnetic fields or aluminium in drinking water). Treatable diseases such as cardiac arrhythmias and diabetes have recently been reported to increase the risk for AD, while long-term use of oestrogen replacement therapy in post menopausal women may act as protective factor (Amaducci, 1997).

Neurotransmitter abnormalities

There is a dramatic decline in activity of cortical choline acetyltransferase (ChAT) with depletion of cortical acetylcholine in AD brains. The cholinergic neurones in the nucleus basalis of Meynert are markedly affected. Other neurotransmitters such as serotinin, noradrenaline dopamine and glutamate are less affected (Plaitakis, I997).

Cytochrom oxidase abnormalities

It was postulated that defect in the key mitochondrial electron transport chain enzyme cytochrome oxidase (CO) may be the fundamental cause of AD (11). This notion is prticularly attractive as in vitro data indicate that a CO defect could alter processing of the beta-amyloid precursor protein. Proteins levels of mitochondrial- and nuclear-encoded CO subunits are moderately reduced in temporal and pariteal cortex, but not in relatively spared brain areas in AD. The decreased CO in brain areas having reduced neuronal activity may be the secondary event consequent to the primary neurodegenerative process (12).

Molecular pathogenesis

An increasing number of genetic loci are determined on different chromosomes: AD1 (chromosome 21), AD2 (chromosome 19), AD3 (chromosome 14) and AD4 (chromosome 1). Molecular analysis of beta amyloid of AD reveals that it is derived from a large mulecule termed amyloid precursor protein (APP). APP is a integral membrane glycoprotein, which is expressed in almost all tissues and cell lines, with gene locus AD1 on chromosome 21. Under the normal APP processing there is the formation of solubile APP molecule which appear to have a function on neuronal regulation. The normal regulation of APP processing is controlled by a positive feedback system from cholinergic neurones. As a result of abnormal APP processing arises beta-pleated sheet configuration of amyloid, also known as beta/A4 amyloid. There are some convincing evidence that beta/A4 is directly neurotoxic by disrupting the function of membrane proteins involved in the neuron's calcium homeostasis. It seems that the mutations at the APP gene are clustered within and around the amyloidogenic region and increase the amount of beta/A4 amyloid formations by various mechanisms. These mutations accounts for the early-onset familial AD. Recently it was shown that many other early-onset familial AD were linked to a locus AD3 on chromosome 14. The mutant gen encode a protein designated presenilin-1 (PS-1) that is predicted to be an integral membrane protein. In addition, a few Italian and Volga German families with early-onset familial AD were linked to locus AD4 on chromosome 1. The mutant gene encode a protein presenilin-2 (PS-2). How these proteins participate in the pathogenesis of AD is unknown. Preliminary data suggest that these mutations act through the APP/betaA4 final common pathway. Many other genetic risk factor are now being evaluated. These include genes encoding ApoE, alpha 1-anti-chymotripsin and mitochondrial proteins. It was described that ApoE familiy of lipoproteins with gene locus AD2 on chromosome 19 are associated with the most common forms of AD starting after 60-years of age (late-onset sporadic AD and late-onset familial AD). Apolipoproteins are lipid carrier molecules which play a significant role in the regulation of lipid metabolism in the CNS. Apo E is the major lipoprotein expressed in the CNS. It occurs in three isoforms (E4, E3, E2). A possible role of ApoE-4 in pathogenesis od AD consists of increasing the rate of deposition of beta /A4 and plaque fomation. It also may facilitate hyperphosphorylation of tau protein with formation of PHF. In the 3% of the population who are homozygous for ApoE-4 the risk for developing AD is approximately 90%. Following this investigations ApoE-4 was firmly established among major risk factors for AD.

TREATMENT

There is no definitive treatment for AD. The most advanced treatment strategy is the use of cholinomimetic agents which can enhance the cognition and slow down neurodegeneration by inhibiting abnormal APP processing. Other potential therapeutic manipulations include the use of oestrogen, antipsychotic agents, antioxidant compounds, etc. The possibility of modifying the risk for AD by controlling some of these factors is a challenge for researchers in this field.

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