

DEBATE: IS AD IS A HOMOGENEOUS NOSOLOGIC ENTITY: YES

P. Martinez-Martin

Alzheimer Disease Research Unit, CIEN Foundation, Carlos III Institute of Health, Alzheimer Centre Reina Sofia Foundation, Madrid, Spain

pmartinez@isciii.es

Variability is one of the most prominent characteristics of the Biology. Once this statement is kept in mind, it is easy to realize that all phenomena related to the biological processes are subjected to variability. Of course, diseases are a part of the life and, therefore, are manifested in a variable way. This fact is verified daily and is a customary part of the clinical practice. "There are not illnesses, but sick persons", as an old say stresses to highlight the diversity of mechanisms and circumstances that may be influencing each particular case.

Apparently, the debate could be solved against the homogeneity of the Alzheimer's disease (AD) after appealing to the variability of the disease, but the question in the heading includes an essential adjective for the discussion: "nosologic". Nosology is a branch of Medicine that deals with classification of diseases. In turn, classification of diseases may take into account the etiology, the pathogenesis, the symptoms or, alternatively, the organ system involved.

From this point of view and considering the abovementioned alternatives, we will examine the nosologic situation of AD, an illness that may be defined as a progressive cognitive deterioration with change in personality and behaviour associated to characteristic neuropathological features: senile plaques and neurofibrillary tangles (Alzheimer 1907).

Current knowledge about the etiology of AD is incomplete. Genetics play a decisive role in the familial forms of the disease and for predisposing background, but evidence shows that a relatively short proportion of cases (<10%) are related to this origin. For the sporadic form, the cause of the disease awaits to be identified. In the meanwhile, the disease is classified as a "neurodegenerative" one.

A great deal of knowledge exists about pathogenetic mechanisms involved in AD. Brain amyloid accumulation is a hallmark of the disease and amyloid beta peptide may be responsible for symptomatic synaptic dysfunction (in addition to the production of oligomers and fibrils). Secretases beta and gamma, presenilin-1 mutations, and nicastrin appear to be involved in the production of the beta amyloid peptide. Neurofibrillary tangles are composed of abnormal hyperphosphorylated filaments including microtubules, tau protein, and ubiquitin. From a biochemical perspective, AD consistently involves 3 and 4 tau isoforms, in a hyperphosphorylated state, and accumulation of amyloid beta. So, although the most intimate mechanisms for AD development remain unknown, some pathophysiological features are well established.

There are several clinical forms of AD related to, for example, the age of onset, predominant symptoms, and associated features, rate of progression and duration of disease. This is one of the most variable aspects of AD disease, requiring a broad differential diagnosis and even a level for relative uncertainty into the diagnostic criteria ("possible AD"). As previously mentioned, this is an expression of the variability linked to biology (for example, APOE, diabetes) and environmental factors (for example, education, trauma, stress) that produce a range of dementia variants or phenotypes.

Some abnormalities are described out of the brain (for example, in blood cells), but the organ massively and constantly involved is the brain. Dysfunctions observed in AD patients are related to neurotransmitter systems dysfunction, synaptic failure, neuronal loss, and halting or canceled neuronal circuits and networks. The relation between dementia and the typical AD lesions is determined by different criteria (CERAD, Braak, National Institute of Aging-Reagan Institute) that consider quantitative aspects, age-adjustment, and topographic distribution along the course of the disease. Neuritic plaques are the signature of the disease, in spite of their morphological variability. Their presence is necessary for a diagnosis of AD. The presence of tau pathology is also required although it may be expressed in a more variable way.

In the neocortex, a consistent neuronal loss occurs in pyramidal neurons in frontal and temporal lobes, in the hippocampus (CA1 area and subiculum), basolateral amygdale, nucleus basalis of Meynert and septal nuclei.

The conclusion is that AD is a homogeneous nosologic entity and this the reason why is considered "the prototypical dementia", a title bearing the meaning of a recognizable and conceptually stable model: "AD is a neurodegenerative disease settled in the brain, with beta amyloid accumulation and hyperphosphorylated tau, causing dementia, and with neuropathological changes characterized by neuritic plaques, neurofibrillary tangles, synaptic dysfunction and neuronal loss with a characteristic special distribution."