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EDITORIAL

Alzheimer's disease: a challenge for modern neuropathobiology

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The clinical entity known as Alzheimer's disease (AD) clearly existed before 1907, when Alois Alzheimer described the clinical course and changes in the brain of a 55-year-old woman dying after a 4-year history of progressive dementia [2, 4]. In his report of Auguste D, he demonstrated neurofibrillary tangles (NFT) using the newly developed Bielschowsky silver impregnation method, and observed cortical "miliary foci" of senile plaques (SP), described by Blocq and Marinesco [7] 15 years before. Examination of the histologic slides of Auguste D's brain recovered 1992 in Munich revealed numerous NFTs and amyloid plaques in the upper parts of cerebral cortex, but no hippocampus was available. The genotype was determined ApoE ε3/3 [14]. In the second case, Johann F, a male aged 56 years [3], numerous amyloid plaques but no NFTs were found in the neocortex, and DNA extraction revealed ApoE ε3/3 without APP mutations [13]. Later studies suggested a familial form of the "plaque only type" of AD [19]. The case of Auguste D marks the beginning of research in Alzheimer's disease (term introduced by Kraepelin in 1910 [20]), now recognized as the most common cause of dementia in the elderly—the disease/epidemy of the twenty-first century, and the focus of intensive research during the past three centuries [17, 23].

Recently revised research and consensus criteria for the diagnosis of the major dementing disorders, in combination with modern (neuroimaging and cerebrospinal fluid) biomarkers improved the clinical diagnostic accuracy of AD from 65 to 92–96% [10]. Neuropathologic studies using immunohistochemistry, modern molecular biologic and genetic methods can achieve a diagnosis/classification, based on homogenous definitions, harmonized interlaboratory methods and standards for the assessment of nervous system lesions, in about 99%, without, however, being able to clarify the causes/etiology of most of these disorders, including AD. The current algorithms for the neuropathologic diagnosis of AD, based on (semi-) quantitative and topographic assessment of plaques and tangles, despite reasonable interrater agreements, only consider the classical "plaque and tangle" phenotype of AD, but do not recognize other subtypes, e.g. "plaque only", "tangle predominant" and AD with amygdala Lewy bodies (see [12, 18]). Furthermore, according to recent studies of the BNE consortium, good agreement was reached only when the lesions are substantial, while it was poorer for mild lesions [1]. Specific problems further arise from a frequent lack of correlation between clinical and morphologic findings, co-morbidity in advanced age with frequent coincidence of various pathologies (AD-like, Lewy and vascular pathologies, hippocampal sclerosis, argyrophilic grains, etc.; see [12]), considerable differences between genetic/familial and sporadic AD [22, 26], and between young and oldest-old demented patients [15], who often do not meet the diagnostic criteria of AD [11]. Although correlations between cognitive deficits and the severity and extension of tau pathology and/or the β-amyloid load have been found, the distinction between "physiologic" (in non-demented subjects) and pathologic aging (often but not consistently associated with cognitive decline) is often difficult. Furthermore, the suggestion that plaques and NFTs, the morphologic markers of AD, may "cause" this disorder is oversimplified and wrong, since accumulating evidence suggests that AD pathology represents effect rather than cause or at least a host response to injury, equaling adaptative or neuroprotective reaction [8, 9]. Although modern

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molecular genetics, biochemistry and animal models, at least in part reproducing the morphology of human AD and related disorders, have produced a large and convincing body of data on the pathogenesis and pathophysiology of the disease, showing a complex cascade of events leading from preclinical to fully developed neurodegeneration, both their molecular backgrounds, basic etiologic factors, pathogenic interrelations and impact for the manifestation of AD are not yet fully understood.

The present AD cluster is intended, in addition to review the current classification and basic pathology of AD, its subtypes/variants and coincidental lesions [12] and the variations in the neuropathology of genetic/familial forms of AD including the pathogenic mechanisms underlying the differences to "sporadic" AD [22], to discuss a number of heterogenous problems concerning the genetics, molecular pathogenesis, proteomics and other important mechanisms in human AD and related animal models. Misfolded tau protein and disease modifying pathways in transgenic rodent models of human tauopathies, including AD, provide an up-to-date account on the complex neurodegenerative cascade with special emphasis on the evolution of NFTs, neuronal death pathways and neuroinflammation [28], while the multifactorial and heterogenous mechanisms of tau-induced neurodegeneration and its regulatory mechanisms are presented by Iqbal et al. [16]. A major cause of cerebral dysfunction in AD and related disorders is caused by degeneration/disconnection of synapses and disturbed synaptic plasticity due to APP mismetabolism and related to cell cycle disorders and neuronal death [5]. Neurovascular mechanisms and blood–brain barrier disorders in AD and their role in contributing to both, onset and progression of AD are critically reviewed [6]. The importance of genetics and molecular pathogenesis of sporadic and hereditary cerebral amyloid angiopathies (CAA) and their transgenic animal models [21] are closely related to microvascular changes in AD and their potential impact on therapy with special impact on a possible improvement of immunotherapy for AD [25]. With regard to the pathogenesis of neurodegeneration, oxidatively modified proteins, identified by modern proteomics in human AD and animal models, and oxidative stress induced by β-amyloid are considered to be a driving force in AD pathogenesis [24]. Modern combinations of proteomics with approaches at the level of the genome, transcription and proteomics-driven biomarker search represent progress in our understanding of dementia-related pathogenesis and may allow diagnosis in early disease stages, monitor its progression and assess treatment responses [27].

As editor, I am grateful to all the authors who have given their time and efforts to produce, what is hoped, an informative and well-accepted series of reviews. These articles may not only provide information about currently important problems in dementia and AD, but also should promote present and future research efforts in order to help to clarify the large number of secrets and unanswered questions about the neuropathobiology of these deleterious disorders. More than hundred years after its first description, AD has become the most frequent and frightening neurodegenerative and dementing disease worldwide in our times that needs new strategies for early and accurate diagnosis, better genetic and molecular biologic description as well as deeper insights into their pathogenic cascade. All these efforts will depend on international networking and close cooperation between clinicians, neuroscientists, public health institutions, caregivers, and sponsors. What is presently puzzling and unclear will undoubtedly be unveiled by future neurobiological research in order to overcome the increasing burden of neurodegenerative and dementing disorders, and to promote effective preventive and treatment strategies. As previously emphasized, there will be a long and difficult way out of the swamp of our presently limited or even misunderstanding [18]. This AD-review cluster may help to find it in the near future.

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