Clinical Needs for Dementia and AD: Revising the Criteria

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The rapid growth of knowledge around the potential pathogenic mechanisms of AD including the amyloidopathy and tauopathy has spawned numerous experimental therapeutic approaches to enter into clinical trials. The neurobiological advantage of earlier intervention within pathological cascade of AD is clear and disease modifying therapies are now being investigated. Early intervention is likely to be more effective when there is a lower burden of amyloid and hyperphosphorylated tau and may truncate the ill effects of secondary events due to inflammation, oxidation, excitotoxicity…

As a consequence, there is today a debate about the better moment and duration for drug trials. The debate is directly related to the definition of Alzheimer's disease. What is AD? Should it be clinically defined by a reference to dementia? Should it be recognized earlier in the symptomatic phase, before threshold of the dementia syndrome, in case of specific cognitive changes? Can it be biologically defined by the evidence of specific biomarkers -today available in vivo – in the absence of any clinical symptoms? As we treat patients and not only lesions, we think that AD should remain defined as a disease with a clinical expression. But it should encompass the full spectrum of the clinical expression, including both the predementia and dementia phases. Indeed, there is no fundamental reason to link the diagnosis of a disease (AD) to a certain threshold of severity and to exclude *ipso facto* from diagnosis and treatment perspective a large number of patients who have already expressed the diagnosis clinically. The classical definition of AD, restricted to the concept of dementia, was mainly justified by the fact that the diagnosis was more difficult to make in the early, predementia phase in the last decades: and this was the reason of considering a stage of MCI (3). However, the emerging literature on MCI has emphasized an intrinsic etiological heterogeneity and a diversity of outcomes within research studies. Efforts to address these issues have not succeeded and the limitations of MCI are apparent. The risk of intervening on an etiologically heterogeneous sample of MCI subjects will include running the risk of "diluting" a significant treatment effect (4). The unprecedented growth of the scientific knowledge with the description of distinctive and reliable biomarkers of AD that are now available through structural MRI, molecular neuroimaging with PET, and cerebrospinal fluid analysis together with a better definition of a clinical profile of the amnestic disorders that occurs very early in the course of the disease makes possible to identify with a high accuracy AD at a symptomatic predementia stage (6). Interestingly, the high specificity of the new criteria was recently confirmed by two studies showing: 1) that it is possible to identify AD patients 2 years before dementia with a specificity of 92% as long as a specific verbal memory test is chosen, using cues for the control of encoding and the facilitation of retrieval (7); and 2) that a specificity of 100% can be reached if MRI and CSF studies are added to memory investigation (8). Therefore, these ongoing evidence suggest that it is possible to diagnose AD before the occurrence of a full blown dementia and give credit to the recent research criteria for AD which propose a diagnostic algorithm that includes the predementia phase of the disease. They are centered around a clinical core of early and significant episodic memory impairment (major criterion). They stipulate in addition the presence of at least one or more abnormal biomarkers (minor criterion) amongst structural neuroimaging with MRI, molecular neuroimaging with PET and CSF analysis of amyloid β/tau proteins. These new criteria (1 major + 1 or more minor criterion) are highly specific because they take advantage of the specific markers of the disease: the memory pattern is specify and is characteristic of a medial temporal lobe damage; the neuroimaging is not only used to exclude the other causes of brain diseases (vascular, tumor…) but to identify specific structural and functional arguments in favor of AD and CSF is proposed not for the exclusion of a meningitis but for evidence of specific changes of AD.

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