



# Rethinking Alzheimer's disease

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Alzheimer's disease (AD) is a neurodegenerative disorder with insidious onset and progressive course, which prevalence increases with the age. It is characterized by neuronal degeneration and death, related to the deposition in the brain of the amyloid  $\beta_{1-42}$  peptide and the hyperphosphorylated tau protein, and initially affects brain areas, namely the hippocampus and other medial temporal lobe structures, which are important for memory processes (Blennow et al., 2006). As a consequence of the aging of the population, the number of patients with AD and other dementias, as well as the number of elderly people who, although not demented, suffer from significant cognitive decline, is growing worrisomely (Alzheimer's Disease International, 2009).

Alzheimer's disease is the most frequent cause for dementia. Indeed, the presence of dementia is presently required for the diagnosis of AD according to established diagnostic criteria, like the *International Classification of Diseases* (World Health Organization, 1992), *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 1994), or those proposed by the *National Institute of Neurological and Communicative Disorders and Stroke* (McKhann et al., 1984), that is to say, the patient must have deficits in memory and other cognitive domains, representing a decline in relation to a previous level, and interfering significantly with the social and professional life.

However, AD begins insidiously, usually with memory difficulties, many years before the patient has a cognitive and functional decline compatible with the diagnosis of dementia. Furthermore, it is often difficult to appreciate the memory complaints in the initial phase of AD, because healthy people frequently report an unfavorable opinion about their own memory, and there is a slight decline in objective memory performance in the aging process (Mendes et al., 2008).

Several nosologic concepts were proposed, in the last decades, to describe the patients who have cognitive deficits

but are not demented. Of these, the one that became more popular was mild cognitive impairment (MCI), as established by Petersen et al. (1999), and subsequently refined (Portet et al., 2006).

Certainly, clinicians interested in memory disorders have been in the last few years consulting younger patients and patients with more subtle complaints. The nosologic concept of MCI has been very useful to establish the probability of progression to dementia and promote an adequate follow-up in these patients. However, the concept of MCI has important limitations. First of all, it represents a stage of cognitive decline between normality and dementia, rather than a disease (Gauthier et al., 2006). In second place, some patients with MCI are intriguingly stable and do not progress to dementia after many years (Petersen et al., 2001). In third place, some patients with cognitive complaints who have no alterations in the neuropsychological testing, and thus do not fulfill MCI criteria, do nevertheless progress to dementia (Nunes et al., 2010). We must thus recognize that the concept of MCI is unsatisfactory both from a diagnostic and prognostic point of view.

However, and very importantly, the studies performed in patients with the diagnosis of MCI allowed a better understanding of the initial phases of AD, and lead to the proposal of new AD criteria that can diagnose the disease at initial stages, before the patient is demented (Dubois et al., 2007; Albert et al., 2011). These criteria are still considered mainly appropriate for clinical research, but their use is certainly spreading to specialized practice. The new criteria are based on the identification of pathological alterations in the brain typical of AD, or biomarkers, namely: (1) decline in episodic memory, confirmed by neuropsychological testing, (2) atrophy of the hippocampus and other medial temporal lobe structures shown by magnetic resonance imaging using volumetric techniques, (3) detection of abnormal CSF biomarkers, namely low amyloid  $\beta_{1-42}$  concentrations,

increased total tau concentrations, or increased phosphorylated tau concentrations, (4) reduced glucose metabolism in bilateral temporal parietal regions by positron emission tomography. In familial cases, the finding of a causative mutation in the genes responsible for autosomal dominant forms of the disease may establish the definite diagnosis of AD. Other genetic and biochemical biomarkers, as well as neuroimaging using radioligand compounds with affinity for the amyloid  $\beta_{1-42}$  peptide, are presently being developed.

We still do not know the combination of biomarkers most sensitive and specific for the early diagnosis of AD. Large multicentric studies are being conducted to answer this important question, but so far the follow-up times have been generally limited. In the large *Alzheimer's Disease Neuroimaging Initiative* (ADNI) cohort, the use of neuropsychological, brain imaging, and CSF neurochemical biomarkers could only reach a predictive accuracy for MCI conversion to dementia of 64% (Ewers et al., 2010). This is not surprising, since the average follow-up was 2.3 years, and presumably many converters just had not the time to progress to dementia. Longer follow-up times will decisively be needed to find the best combination of biomarkers for an accurate early diagnosis of AD.

In conclusion, the reliable identification of patients with memory complaints who already have Alzheimer's disease opens new frontiers in the management of the disease, since it will allow these patients to undergo interventions that might involve manipulation of risk and protection environmental factors, cognitive rehabilitation procedures, and clinical trials with putative neuroprotective drugs.

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