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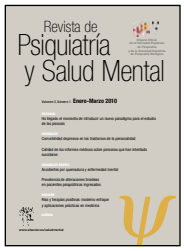

EDITORIAL

Very new developments in mild Cognitive impairment and Alzheimer's disease: Why should a psychiatrist care?

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In this editorial we would like to bring to the attention of the readership of Revista de Psiquiatria y Salud Mental some very recent developments in the field of Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI) that likely will have far reaching implications for the diagnosis and treatment of this neurodegenerative disorder. To further orient the reader, we noted this editorial will serve less like a scientific review (we will not go into the details of the individual studies), but rather as a set of guideposts that the interested reader can use to delve more deeply into this fast-moving area. We will try to be objective, but occasionally we will take a position on the developments that we address. There are several reasons why a psychiatrist should care about some of these recent developments in the field of AD and its prodrome. First, in terms of demographics, North America and Western Europe have aging populations. As such the prevalence of AD is increasing and thus it is likely that more such patients will require medical care. Second, AD may have translational lessons for psychiatric diseases, in the sense that it has a replicable genetic architecture, predictive biomarkers, a cellular phenotype, and animal models. Yet despite these advantages, problems in interpretation and drug development remain and may provide information not only about what to do, but what not to do.

Clinical trials

There have been several failed clinical trials in AD within the past year. In evaluation of dimebon (), a drug with a novel mechanism of action in that it stabilized mitochondrial pores, results were positive in a trial conducted in Russia. The drug was originally developed as an antihistamine and was then found to have cholinesterase inhibiting properties (hence the original interest in the drug for AD). However, when a pivotal trial (Pfizer) was conducted in Western Europe and South and North America, results were negative (see Alzforum.com). It is unclear why the two trials yielded such different results, but one might reasonably surmise that the drug was less neurobiologically active than it first appeared to be. Another possible lesson of this trial has less to do with clinical methodology or pharmacology than with an issue often remarked upon in the sociology of science, namely, the so-called "winner's curse" (loannidis et al). As such the first positive study in a field may result from chance factors or expectations and often goes unreplicated.

More recently still, a gamma secretase inhibitor, semagacestat (Lilly) appeared to worsen AD patients with

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mild to moderate dementia, resulting in early termination of the trial (see Alzforum.com). Even though cognitive changes in phase 2 were quite small, phase 3 proceeded on the basis of biomarker evidence. This trial raised questions about 1.) the timing of intervention (e.g., should trials be conducted at much earlier points in the disease process) and 2.) whether the amyloid hypothesis correct in terms of providing a treatment target (recall that cleavage of APP by the gamma secretase complex is thought to produce a toxic species of amyloid, namely Abeta1-42 under certain circumstances). For an interesting and more positive view of beta-amyloid as a treatment target, see Cummings (2010).

Biomarkers

Jack and colleagues (2009) have used findings from the ADNI study to propose a comprehensive mode of how different biomarkers (e.g., regional brain volumes, CSF Abeta and tau, cerebral glucose metabolism, etc) have different types of predictive value at different phases of the illness (e.g., preclinical, MCI, and neurodegeneration due to cell death in Alzheimer's disease itself). Irrespective of the details of the model, some of which are arguable, the model has proved to be heuristic. ADNI is a large multi site consortium (over 50 sites) in which large groups of older healthy controls, individuals with MCI, and individuals with mild AD are assessed longitudinal using cognitive assays, structural neuroimaging, PIB imaging, PET, FDG, and whole genome scans. All subjects receive systematic and uniform examinations every 6 to 12 months. Data are publically available at www.loni.ucla; data dumps are frequent. In this model, misprocessing of APP, resulting in abnormal aggregation of Abeta peptides in the form of plaques is the initiating event of AD. Biomarkers of this amyloid process include increased PIB tracer retention (PIB is a radioligand that binds to extracellular amyloid in brain) and reductions in CSF Abeta. Neuronal dysfunction and neurodegeneration then become dominant, as evidenced by increased levels of CSF tau and reductions in PET FDG, especially in parietotemporal areas. Cognitive impairments may become obvious, especially in episodic memory. Last, regional brain atrophy occurs and in AD itself, is most closely correlated with compromised cognition. What is key in this view is that the relevance and dynamics of biomarkers change over time (e.g., amyloid deposition plateaus early in the disease process; brain atrophy accelerates and is more informative later in the disease process). However our own analyses of the ADNI data and studies from our own lab (Gomar et al, submitted; Goldberg et al 2010) suggest that regional atrophy and neurocognitive impairments with consequent compromises in everyday function occur relatively early in MCI.

Molecular changes in the AD prodrome

AD is a neurodegenerative condition characterized histopathologically by neuritic plaques and neurofibrillary tangles. To identify both neurosusceptibility *and* intrinsic neuroprotective factors at the molecular level, not confounded by the downstream consequences of pathology, thus heading us into prevention, we studied expression in over 26000 genes using microarray technology in post-mortem cortical tissue from 28 cases who were non-APOE4 carriers (called the APOE3 group) and 13 cases who were APOE4 carriers (Conejero-Goldberg et al 2010). Because APOE genotype is the major genetic risk factor for late onset AD with an odds ratio of 3.8 for the APOE4 variant, the former group was at low risk for development of the disease and latter group was at high risk for the disease. Mean age at death was 42 years and none of the brains had histopathology diagnostic of AD at time of death. We identified 70 transcripts that differed significantly between the groups using a novel 'double subtraction" method. Group separation was significant (fig. 1). We also found that multiple Kyoto biological pathways were disrupted in the APOE4 group, including those involved in mitochondrial function (genes were consistently downregulated), calcium regulation, and cell-cycle re-entry. Using more sophisticated pathway analyses we then found that these molecules comprised a network with multiple connections with each other and with APP and MAPT. Overall, our results yielded three primary findings:

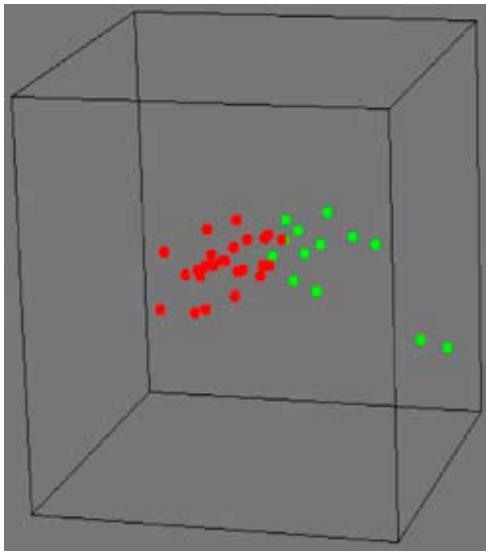

Figure 1 Using a Euclidean distance Multi Dimensional Scaling statistics on data from the microarrays, group differences in the APOE3 and APOE4 "clouds" were significant. (Classes: E3 red and E4 green).

1) The earliest impetus for pathogenic processes in E4 individuals may come from a variety of abnormalities in signaling cascades and biologic processes that involve calcium regulation, mitochondrial function, cell cycle regulation abnormalities, apoptosis, and wnt signaling. Several of these have been at the periphery of discussions about the pathogenesis of Alzheimer's disease; in our study they were found to be central. Conspicuous by its absence at this early stage of the disease process

was the canonical amyloid pathway, suggesting that the latter may be a cascade within a cascade.
2) There may be active protective processes as well as pathological processes.
3) Our data suggest that there is a long prodromal period prior to the onset of clinical Alzheimer's disease, given that mean age at death of our sample was 42 years.

In summary, the importance of this study is that the findings appear to be antecedents of amyloid-beta deposition and expression of phospho-tau (i.e., observed in neurofibrillary tangles). Since the current Alzheimer's disease pathogenesis debate focuses on whether amyloid-beta abnormalities precede tau fibrillization or vice versa, this study contributes by pointing to important mechanisms that may precede either, and thus may be a causative link in the long molecular cascade or cascades that results in APOE4-driven clinical AD. Given that the study was leveraged on APOE genotype, this study provides some of the best insights yet available into the early gene expression changes that accompany APOE4-related Alzheimer's disease. Nevertheless, we note that there is no consensus on the precise molecular mechanisms by which APOE4 ultimately causes neurodegeneration.

This short review can be read as a cautionary tale. To improve psychiatric treatments, especially in schizophrenia, the field has begun wide ranging searches for replicable genetic findings, biomarkers, and animal models. However, as results from the AD literature make clear, even with these translational advantages, coming up with an effective treatment is far from automatic.

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