

the dementia is fully expressed clinically and the pathology may be irreversible. Hopefully studies underway with the γ -secretase LY-450139 and the passive immunotherapy agent bapineuzumab will be positive, but we should plan ahead for interventions in the pre-dementia stages of AD, using the proposed NINCDS-ADRDA modified diagnostic criteria. Furthermore the mixed pathology (amyloid oligomers and deposition, tau hyperphosphorylation, inflammation, microvascular changes, Lewy Body formation) in most patients with AD over age 75 will require combination of treatments to significantly modify disease progression. Alternatively we could assess the relative weight of each pathology for older patients with AD, using brain imaging (FDG-PIB, MRI, SPECT DAT-scan) and CSF in order to build relatively homogenous groups of patients for targeted monotherapy, and treat young patients with AD carrying relatively pure amyloid pathology. Pharmacogenomics will likely play in major role in studying responder profiles and may help select the best disease-modifying drug class for individual patients.

28 WHY SO FEW DRUGS FOR AD? THE ANSWER

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The period 2007–2009 marked the set back of three major approaches and several extensive clinical trials directed to prevent aggregation or accumulation of beta-amyloid in the brain by means of anti-aggregants of various types, gamma-secretase modulation or passive immunization. None of these attempts showed a significant clinical effect.

On the other hand, preventive therapy with anti-oxidants, anti-inflammatories and lipid-lowering drugs have been equally negative. Why so many drugs for Alzheimer's disease have failed in development? We need to rethink the amyloid hypothesis in new terms, change the clinical approach and the target, and rethink the trials. We proposed that the realities of Alzheimer's disease, especially the progression of the neuropathology prior to the onset of clinical symptoms, require to privilege early targets such as beta-amyloid oligomers or early tau and their biomarkers (Giacobini and Becker, 2007) and distinguish signs capable of differentiating individuals at risk as surrogate targets for preventive treatment, testing and use in clinical trials (Becker et al., 2008).

Keywords: Alzheimer's disease; Beta-amyloid; Oligomers; Tau; Biomarkers

References

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29 THE CONTRIBUTION OF TAU-RELATED PATHOLOGY IN ALZHEIMER DISEASE: WHAT WE REALLY KNOW?

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Objectives: In last years, clinicopathological studies applying stereological principles permitted to define reliably the cognitive impact of Alzheimer disease (AD) lesions in the human brain. Unlike fibrillar amyloid deposits that are poorly or not related to the dementia severity, neuronal pathology and synaptic loss explain more than 50% of global dementia severity. Although interesting, these results are not sufficiently informative for the clinician who seeks to establish correlations between the loss of specific cognitive functions and damage of neocortical association areas.

Methods: We obtained estimates of total neuron numbers, NFT and A beta volume in the anterior cingulate cortex of 15 autopsy cases aged over 80. Prospective neuropsychological assessment of attention, memory and executive functions was available.

Results: Attention deficit was associated with decreased total neuron (13.6%, OR = 0.92, $p < 0.05$) but not NFT numbers in this area. This was also the case for verbal episodic (35.2%, OR = 0.79, $p < 0.01$) and semantic memory (36.9%, OR = 0.74, $p < 0.01$) deficits. Total NFT and neuron numbers were significantly associated with the presence of procedural memory deficits and explained 35.1% (OR = 1.23, $p < 0.01$) and 21.9% (OR = 0.89, $p < 0.01$) of its presence respectively. When both variables were entered in multiple regression models, only total NFT numbers remained significant predictors of the cognitive outcome (39.2%, $p < 0.05$). Importantly, the relationship between NFT numbers in anterior cingulate cortex and these deficits persisted when adjusting for Braak NFT staging. No significant relationship was found between executive functions and anterior cingulate cortex pathology.

Conclusions: In the course of brain aging, it is possible to establish fine relationships between the performance in neuropsychological testing and development of tau-related pathology in neocortical areas.