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DIFFERENTIAL DIAGNOSIS OF ALZHEIMER'S DISEASE: NEUROPATHOLOGICAL ASPECTS

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Alzheimer's disease (AD) is characterized neuropathologically by the presence in the cerebral cortex of severe neuronal and synapse loss as well as neurofibrillary tangle (NFT) formation and a variable degree of amyloid deposition. While these markers are used routinely for the neuropathological diagnosis of AD, they are not specific to AD and are observed in many related neurodegenerative conditions. The review of a large series of post-mortem materials permitted the elaboration of criteria for the differential diagnosis of such dementing illnesses based on the regional and laminar distribution of the lesions in the cerebral cortex. We have in particular analyzed brains from patients with progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Pick's Disease, post-encephalitic parkinsonism (PEP), dementia pugilistica, and Guamanian amyotrophic lateral sclerosis/parkinsonism-dementia complex. Quantitative analysis of lesion distribution reveals that AD differs strikingly from all other disorders in terms of laminar distribution of NFT, in that NFT are located in layers V and III of neocortical areas in AD, whereas in the other illnesses they predominate in layers II and VI. Also AD shows variable levels of amyloid deposition throughout the cerebral cortex, but the other diseases are characterised by a relative paucity of amyloid deposition. In all disorders, the hippocampus and entorhinal cortex are severely affected already at early stages. Molecular analyses of lesions have shown that these diseases can be further differentiated on the basis of biochemical profile of NFT components. Depending on the disease, NFT contain different levels of hyperphosphorylated tau protein isoforms, with AD, PEP and Guamanian cases characterized by a tau 55, 64, 69 triplet, while tau doublets are seen in PSP and CBD (tau 64, 69) and Pick's Disease (tau 55, 64). These data demonstrate that approaches combining quantitative anatomic and molecular methods permit the clear differentiating of several neurodegenerative diseases that may be difficult to distinguish based solely on clinical data.

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GENOTYPE AND AGE OF ONSET OF ALZHEIMER'S DISEASE

M.C. Chartier-Harlin

Neurofibrillary tangles and b-amyloid depositions are the two hallmarks required to confirm Alzheimer's disease (AD) diagnosis. AD is a genetically complex disorder, which mainly occurs sporadically, but can segregate as an autosomal dominant disorder in some families (FAD). Moreover, the age of onset led to the distinction of early and late onset cases. Our studies aim to dertemine the genetic factors involved in AD.

Linkage analyses and association studies were performed on early-onset FAD kindred and sporadic AD cases, respectively. Classical Methods of Molecular Biology are used (DNA/RNA amplifications, sequencing .).

To date 3 genes are involved in early-onset FAD, APP (5 to 10%), PS1[1] (50 to 70%) and PS2[2] (2%) genes: each leading to different genotype-phenotype relationships - around 20% of EO-FAD remains unexplained. These genes are involved in the same neuropathological cascade which demonstrates the crucial role the APP metabolism playsin development of AD.

A fourth gene (apolipoprotein E[4]) is a susceptibility gene for 40 to 60% of AD cases We demonstrated that the different apo E alleles act either as risk or protective factors[3]. They also modulate the development of other neurodegenerative disorders sharing AD hallmarks[4].

Elucidation of the different genotypes of AD may lead to adapted treatments.

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DEMENTIA SPECTRUM OF DEPRESSION: NEW BIOLOGICAL APPROACHES TO DIFFERENTIAL DIAGNOSIS

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Dementia and depression are the most frequent psychiatric disorders in the elderly. Recent studies suggest that depression, cognitive impairment and degenerative dementia should be considered as an interesting continuum. Since up to 30-40% of patients with dementia also show signs of depression, which can be a very early sign of dementia, differentiating dementia with depression from depressive dementia is of utmost importance. The formation of brain amyloid and neurofibrillary tangles in Alzheimer's disease can precede the onset of clinical signs by many years. Thus, the improvement of early differential diagnosis is mandatory. Recent psychogeriatric biological research has raised a set of biological measures that may contribute to the differential diagnosis of depressive and degenerative dementia. The most promising approach may combine various neuroimaging and biochemical procedures, including structural and functional neuroimaging, as well as enzyme-linked immunosorbent assay (ELISA) quantification of proteins related to the specific histopathology in Alzheimer's disease. The latter includes amyloid percursor protein and tau protein derivatives in blood and cerebrospinal fluid. Structural neuroimaging includes MRI and MRI-morphometry, functional neuroimaging includes EEG, complemented bz mapping and sleep polygraphy, SPECT, PET and a new non-invasive optical method, near infrared spectroscopy (NIRS(. Future prospective studies will clarify the sensitivity, specificity and diagnostic usefulness of the proposed neurobiological markers.

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PHARMACOTHERAPY OF ALZHEIMER'S DISEASE: DOES IT WORK?

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Major advances in cholinergic therapy have been achieved with the development of a second generation cholinesterase inhibitors (ChEI), with long term action and low toxicity. More selective muscarinic (M1 and M3) and nictotinic (aplha4-beta 2 and alpha 7) agonists are also being tested. Bifunctional molecules are being designed and combination therapies (e.g. ChEI and MI agonist) are started. The main question emerging from the recent results of medium term (6-12 months) clinical trials with five different ChEI (tacrine, E2020, ENA-713, Metrifonate and Eptastigmine) is whether or not the clinical effect seen with all these compounds is directed towards symptomatic improvement, or to slow deterioriation. Recent analysis of clinical data suggests that for at least some compounds, the most salient effect is a stabilisation of the patient cognitive function (ADAS-Cog and MMSE), and global measures of activity (CIBIC-plus) as compared to placebo-treated. These clinical results suggest that some ChEI maz have other pharmacological effects in addition to ChE inhibition. The most likelz explanation based on experimental data is an effect on APP metabolism and secretion (Mori et al, 1995 and Giacobini, 1996). In addition to ChEI, other important lines of development are a. antiooxidants, b. estrogens and c. anti-inflammatory drugs, which are being clinically explored in the USA.

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