S31. Alzheimer's Disease: from molecular biology to clinical therapy

Chairs: F Müller-Spahn (CH), C Haass (D)

S31-1
EPIDEMIOLOGY AND RISK FACTORS FOR ALZHEIMER'S DISEASE

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This presentation addresses the possibilities of prevention of Alzheimer's disease by prevention of vascular diseases and by treatment of risk factors for vascular diseases. The evidence for a causal link between vascular factors and Alzheimer's disease will be presented. As an example data obtained in the Rotterdam Study will be shown. Vascular factors to be discussed include blood pressure and smoking. Atherosclerosis and thrombogenesis will be addressed, as well as vascular diseases, including stroke and co-morbid vascular diseases, including diabetes mellitus and atrial fibrillation. For each of these factors the individual attributable risk (etiologic fraction) for Alzheimer's disease will be assessed. In addition, the overall population's attributable risk of vascular factors and diseases for Alzheimer's disease will be estimated. This presentation will, finally, address the potential for prevention of Alzheimer's disease and associated neurologic diseases by intervention of vascular factors and vascular disease.

S31-2
THE PATHOLOGICAL FUNCTION OF PRESENILIN AND βAPP IN ALZHEIMER'S DISEASE

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Alzheimer's disease (AD) associated mutations have been identified in three genes. Point mutations within the βAPP gene are located close to the cleavage sites of the three secretases and influence their activity in a pathological manner by overproducing the highly neurotoxic 42 residue Aβ (Aβ42). Mutations in the Presenilin genes (PS-1 and PS-2) are the most common cause of early onset familial AD. PS proteins undergo proteolytic processing. The fragments generated occur as a heterodimer which binds to another unknown protein to form a 100–150 kDa complex. Besides this major processing pathway two additional proteolytic mechanisms involving the proteasome and caspases are utilized to degrade PS proteins in highly regulated manner. Presenilin mutations are known to cause the enhanced production of Aβ42 by a so far unknown mechanism. We will present data demonstrating that Aβ40 and Aβ42 are generated by two distinct cellular mechanisms. PS genes are homologous to the sel-12 gene of Caenorhabditis elegans which has been postulated to function in the facilitated signaling by lin-12 and gpl-1. We introduced the human PS-1 cDNA into sel-12 mutant animals and found that human PS-1 fully complements the sel-12 phenotype. Moreover, we demonstrate that two AD mutations, C410Y and A246E exhibit a strongly reduced rescuing activity.

S31-3
EARLY DIAGNOSIS AND BIOLOGICAL MARKERS IN ALZHEIMER'S DISEAE (AD) PATIENTS

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Several biochemical measures showed significant alterations in AD patients versus controls, such as cerebrospinal fluid (CSF) levels of amyloid precursor protein (APPs), amyloid β-peptide $(A\beta)_{1-42}$, and Tau protein, intracellular calcium level regulation by potassium channels in blood cells, and serum p97 levels. Some of these measures may change with progression of the disease (total Aβ, Tau protein). Although some of these measures were significantly altered in AD when mean levels were compared to levels in control groups, there was still substantial overlap so that these measures were not considered to be sensitive enough to serve as a biological marker. However, if the assumption is true that the specific histopathology precedes the clinical manifestation of AD for years, or even decades, then a significant portion of the age-matched controls might be preclinical AD patients. Therefore, considerable overlap of a potential marker between AD patients and *age-matched* controls does not definitely exclude that the measure might be a sensitive and specific tool. New research designs for a biological marker of sporadic AD have to be developed that include not only healthy age-matched controls, but cover the whole age-range of healthy subjects in order to differentiate age-effects from effects of a beginning AD pathology (sensitivity). Further control groups should include other neurodegenerative, neurological and psychiatric disorders (e.g. major depression) (specificity).

S31-4
ALZHEIMER'S DISEASE: POTENTIAL OF IMAGING AND SPECTROSCOPIC TECHNIQUES: PET, SPECT, DCS-MRI, MRI, MRS AND FMRI. AN OVERVIEW

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Reduced Cerebral blood flow, Neural loss, Brain atrophies, abnormalities of membrane phospholipds and metabolic variations are involved in the pathophysiology of Alzheimer's disease (AD). Imaging Techniques such as PET SPECT use radioactive water to evaluate deficits in regional cerebral blood flow (rCBF). An alternative can be Dynamic Susceptibility Contrast MR Imaging which uses contrast agents instead of radionuclides to evaluate rCBF. MRI has been largely applied to determine the extent of global and regional brain atrophy. Magnetic Resonance Spectroscopy (Proton-, Phosphorus-, Carbon-MRS) provides, in a noninvasive way, insights into in vivo brain metabolism for a number of metabolites. Proton MRS (1H) provides information mainly on N-acetyl-containing molecules with N-acetylaspartate as the major contributor, choline containing compounds (glycerophosphocholine and phosphocholine), creatine and phosphocreatine, inositol, glucose, glutamate and glutamine. Phosphorus-MRS provides information on phospholipid metabolism (phosphomonoesters and phosphodiseters) and on energy metabolism (ATP, phosphocreatine, inorganic phosphate). Carbon-MRS, with specifically 13C labelled precursor such as glucose, highlights the Krebs Cycle trunover. Significant but heterogeneous metabolic variations are reported by different groups worldwide in patients with mild to moderate AD. Based on our experience these data will be presented and discussed. These studies can also be correlated with neurocognitive rates. FMRI, which provides activation maps reflecting significant regional cere-

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