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# S34. Alzheimer's disease

## AGE-ASSOCIATED MEMORY IMPAIRMENT AND THE DIAGNOSIS OF EARLY ALZHEIMER'S DISEASE

H.Förstl, C. Geiger-Kabisch, H. Sattel, C. Besthorn, F. Hentschel, R. Zerfaß, C. Czech, U. Mönning, K. Beyreuther
Central Institute of Mental Health, J 5, 68159 Mannheim, Germany

A reliable and early identification of patients developing Alzheimer's disease (AD) is one of the obligatory requirements for a timely and potentially successful therapeutic intervention. We examined the potential diagnostic significance of mild cognitive impairment and subjective memory complaints. 32 patients with age-associated memory impairment (AIM) and 79 patients with AD were examined prospectively and their subjective complaints, cognitive performance and neuroimaging findings were compared with findings in 53 healthy elderly controls. Both, memory complaints and depressive disturbances had high loadings on one underlying principal component in the patient groups. There was no statistical correlation between a global score of cognitive performance and subjective complaints in the patients, but the correlation between performance and brain atrophy was statistically significant. The degree of brain atrophy, but not subjective complaints (or the diagnostic distinction between AIM and AD) were associated with the severity of cognitive deterioration during a 2-year follow-up period. This, and the observation of an increased frequency of the apolipoprotein E allele 4 in the AD and AAMI groups, suggests that biological susceptibility markers will be of greater significance for the early identification of patients with AD than the patients' subjective complaints.

## CEREBROSPINAL FLUID MARKERS OF ALZHEIMER'S DISEASE

C.G. Gottfries, K. Blennow, A. Wallin
University of Göteborg, Department of Clinical Neuroscience, Section of Psychiatry and Neurochemistry, Mölndal Hospital, S-431 80 Mölndal, Sweden

In a clinical neurochemical approach to Alzheimer's disease (AD), several cerebrospinal fluid (CSF) biochemical markers are used. CSF markers may reflect the underlying pathological process in AD. However, it is also possible to make use of 'negative markers', intended to reflect pathological processes that are unrelated to AD. The list of potential positive CSF biochemical markers includes beta-A4-protein for amyloid deposition, hyperphosphorylated tau-proteins for neurofibrillary tangles, neuron-specific enolase and ganglioside GM1 for neuronal degeneration, and chromogranin A and synaptotagmin for synaptic degeneration. Markers for non-AD-related degenerative diseases are sulfatide for white matter lesions and the CFS serum albumin ratio for intracerebral small blood-vessel disorders.

## DECREASED ß-AMYLOID SENSITIVITY IN ALZHEIMER'S DISEASE

A. Eckert, H. Förstl, H.Hartmann, W.E. Müller
Central Institute of Mental Health, Departments of Psychopharmacology and Psychiatry, J 5, D-68159 Mannheim, Germany

Since several years it is assumed that changes of free intracellular calcium concentration ($[Ca^{2+}]_i$) occur in central neurons during aging and Alzheimer's disease (AD). Moreover, the role of ß-amyloid in AD and its cellular mechanism of action on neurons are still unclear. Presently, there is growing evidence that ß-amyloid or its fragment 25-35 (ßA25-35) influence neuronal $Ca^{2+}$ regulation and render neurons more sensitive to stimuli, which elevate intracellular free $Ca^{2+}$ levels. We previously demonstrated that the mitogen-induced $Ca^{2+}$ response of circulating human lymphocytes of healthy volunteers is affected by ßA25-35 in a manner similar to its effects on central neurons. In the present study, we investigated intracellular $Ca^{2+}$ regulation and ß-amyloid's effects on $Ca^{2+}$ signalling in lymphocytes of AD-patients. Basal $Ca^{2+}$levels and $Ca^{2+}$ responses after stimulation with phytohemagglutinin (PHA, 15 and 100 $\mu$g/ml) were unaltered in lymphocytes of AD-patients compared to normal controls (n=32). In addition, we used freshly prepared human lymphocytes to examine the $Ca^{2+}$-amplifying effect of ß-amyloid, the main component of senile plaques in AD. Preincubation of lymphocytes of young healthy controls with ßA25-35 (1$\mu$mol/1) for 60sec significantly enhanced the mitogen induced $Ca^{2+}$ rise by about 20nmol/1 (n=20). This amplifying effect of ß-amyloid on calcium signalling was not altered in lymphocytes of nondemented, elderly controls (n=20). Surprisingly, the ß-amyloid sensitivity was strongly reduced ($p<0.01$) in the AD group (n=20), confirming our preliminary study. Only few elderly controls showed a $Ca^{2+}$ response to ßA25-35 of 11nmol/1 or less, the maximum response seen in the AD group (except one patient). Our findings indicate that the sensitivity of the lymphocyte for ß-amyloid's effects is reduced in a high percentage of patients with probable AD. This is not merely an effect of aging, since non-demented elderly patients exhibit ß-amyloid responses similar to young healthy volunteers.

ß-Amyloid's effect in AD is unexpected. ß-Amyloid's effect on $Ca^{2+}$ regulation in lymphocytes certainly represents a promising candidate for a peripheral marker of AD. Further studies on the mechanisms of the reduced response to ß-amyloid might give important insights in the molecular pathology of AD.

## CALCIUM MEASUREMENTS IN T-LYMPHOCYTES OF PATIENTS WITH ALZHEIMER'S DISEASE, OLD AND YOUNG CONTROLS

J.B. Aldenhoff, C. Dumais-Huber
Central Institute of Mental Health, J 5, D-68159 Mannheim, Germany

Calcium (Ca) plays a central role in cellular models of aging. Theories generated from animal data postulated an increased Ca-concentration as the major pathogenic factor of age-related changes in brain biology. The investigation of this hypothesis on humans is complicated be the choice of the cell type. We choose T-lymphocytes because of their similarities to neurons in respect to Ca-channels and Ca-dependent processes. We investigated the intracellular Ca-concentration in T-lymphocytes from 10 patients with Alzheimer's disease, 10 older and 10 young controls. Ca was measured by the Ca-sensitive dye fura2 before and after stimulation with the mitogen PHA.

Baseline levels showed no differences between these groups. After stimulation with PHA, in all groups oscillating responses of intracellular Ca-concentration were observed which showed different kinetics between the groups but no significant differences.

Thus, the postulated increase of the Ca-concentration could not be proven in normal aged people nor in patients with Alzheimer's disease. Further considerations concerning the different kinetics will be presented in the discussion.

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