observed in the frontal, temporal, parietal cortex and the striatum in comparison to controls (Klunk et al. Ann Neurol. 2004). The cortical ^{11}C-PIB retention correlated inversely with cerebral glucose metabolism. We are presently study a group of MCI patients with respect to ^{11}C-PIB retention and cerebral glucose metabolism in brain. The patients are also undergoing neuropsychology testings as well as sampling of cerebrospinal fluid (CSF) for measurement of total tau, phospho-tau and Aβ 1–42 levels. Earlier studies have shown that PET studies of cerebral glucose metabolism may predict converters to AD. The ^{11}C-PIB studies will show the possibility to early detect amyloid deposition in brain. The availability of an in vivo amyloid imaging technology would fill the urgent need for an early accurate diagnostic tool of AD which also will allow early start of drug therapy and evaluation of treatment effects especially of anti-amyloid drugs.

24

Future treatment of early dementia: cholinesterase inhibitors or immunization?

E. Giacobini

Department of Rehabilitation and Geriatrics,
University of Geneva Medical School, Geneva, Switzerland

Various forms of pharmacological treatment are being tested clinically in an effort to slow down or block the conversion of MCI (Mild Cognitive Impairment) to AD (Alzheimer Disease). Experimental and clinical data suggest that ChEI (cholinesterase inhibitors) in addition to symptomatic benefit might have a delaying effect on AD progress (Giacobini, 2000).

Most advanced are two studies with the ChEI rivastigmine and galantamine including together 1800 patients for a duration of 3 yrs. A smaller (270 pats., MMSE > 24, CDR 0,5) 24-week, multicenter, randomized, double-blind, placebo-controlled study with donepezil has been completed. Results are indicative of cognitive benefit.

Other approaches being investigated include anti-inflammatories (rofecoxib, 1200 pats., 3 yrs), anti-oxidants (vit. E) + ChEI (donepezil) (769 pats., 3 yrs), nootropics (piracetam, 675 pats., 1 yr), AMPA receptor agonists (ampakine, 160 pats., 4 wk).

Data from the recent vaccination study (Nitsch et al., 2003; Hock et al., 2003) with pre-aggregated A-beta-42 shows that patients who generated amyloid plaque immunoreactivity over one year period, showed significantly slower rate of decline of cognitive functions and improvement in activities of daily living. These preliminary results suggest that targeting A-beta with immunization could be of benefit to early cases of AD.

25

Non-steroid antiinflammatory agents (nsaids): are they a valid approach to Alzheimer's disease prevention?

G. Pepeu, A. Bellucci, C. Prosperi, M. G. Giovannini, and **F. Casamenti**

Department of Pharmacology, University of Florence,
Florence, Italy

Neuroinflammation occurs in vulnerable regions of the Alzheimer's disease (AD) brain where β-amyloid (Aβ) peptide deposits, neurofibrillary tangles and damaged neurons and neurites provide stimuli for an inflammatory reaction. A similar inflammatory response, involving p38MAPK pathway activation, develops around the Aβ deposits in the brain of transgenic mice expressing APP (amyloid precursor protein) gene mutations, and surrounds Aβ plaques formed by intracerebral injections of Aβ peptides. The role of neuroinflammation in AD pathogenesis has not yet been fully defined but it is assumed that the observed increase in NO and glutamate levels, and the expression of neurotoxic cytokines may contribute to the neurodegenerative process.

In the rat model, administration of NSAIDs, including NO-flurbiprofen and selective COX2 inhibitors, for three weeks, strongly attenuates the inflammatory reaction and the neurodegenerative process, and prevents the disappearance of forebrain cholinergic neurons. In transgenic mice, it has been shown that NSAIDs administration reduces the inflammatory responses and the brain Aβ load. However, there are indications that the Aβ lowering effect may depend on a direct action on APP processing pathways. The animal and *in vitro* results lend a rational basis to the repeated observational studies demonstrating that NSAIDs give some protection against the development of AD. However, in AD patients, the therapeutic trials with different NSAIDs have so far generated negative or dubious results. The reasons of the discrepancy between preclinical and clinical findings, including duration of the treatment, time of its initiation, and drug dosage, need to be clarified.

26

Cholesterol and statins: to be or not to be relevant

P. Riederer[1] and **S. Hoyer**[2]

[1] Klinische Neurochemie, Klinik und Poliklinik für Psychiatrie und Psychotherapie, Universität Würzburg, and
[2] Pathochemie und Allgemeine Neurochemie,
Universität Heidelberg, Deutschland

Cerebral cholesterin (CH) is based nearly exclusively by in situ biosynthesis in an energy dependent process. It's metabolite 24S-Hydroxycholesterin can be detected in the CSF. CH is found mainly in the caveolae of membranes, which also contain insulin receptors, insulinreceptor-substrate-1 and proteinkinases, all being necessary requisites for signal transduction. CH is not only important for the stability and fluidity of membranes but plays also a decisive role in the build up of synapses. Age-dependent loss of acetyl-CoA leads to reduced synthesis of intracellular CH, which is further enhanced by increased membranal CH-turnover. Reduced CSF-CH and increase in CSF-24-S-hydroxy-CH reflects this fact. This process is even pronounced in Alzheimer's disease (AD). Lipophile lovastatin and simvastatin pass the blood-brain barrier and reduce free CH. This effect is directly correlated to facilitation of tau-hyperphosphorylation. In addition βA4 is able to destruction of cell membranal fluidity. And APO-E4 facilitates CH in the exofacial membrane. Therefore, there is an age-dependent and AD pronounced change in the ratio of cytofacial and exofacial CH in favour of the latter.

Therapy with statins in AD have not yet proven significance to improve the disease and its progress. Any such therapy if proven successful has to be monitored carefully by regular control of CH-dependent plasma and CSF markers to avoid any patients harm due to reduction of membrane CH beyond the point of induction of cell death.

27

Ethics in dementia treatment

F. Gerstenbrand[1], **H. Baumgartner**[2], and **W. Struhal**[1]

[1] Department of Neurology, University of Vienna, Vienna, and
[2] Department of Neurology, University of Innsbruck, Innsbruck, Austria

As we know, dementia has different roots. In the very last time free to the intention that every patient with symptoms of dementia is an Alzheimer disease, the vascular dementia finds back to its right place. The mixed dementia (Korczyn) is an incoming

diagnostic decision.

Drug treatment of dementia remains a problem. Different drugs against Alzheimer disease are used without impressive success. A new treatment trend for so-called "hypertension-vascular dementia" is spreading. Supported by cardiology various medications against hypertension are used for blood pressure higher than 120 to 80 mm HG independent of the age of a patient, because increased blood pressure leads to stroke and dementia. But it is evident, that a number of patients with a long low blood pressure are developing vascular dementia or stroke.

Another ethical problem in dementia is the uncertainty of the diagnoses of Alzheimer's disease. Many patients being informed to suffer from this incurable illness, react with a shock, a depression is the frequent consequence. Some of the patients develop suicidal ideas. The patients, relatives as well as the responsible doctors are responding with a therapeutical nihilism as a consequence of knowing the diagnosis. On the other hand better therapeutical results can be achieved in vascular dementia or dementia caused by intoxication, after brain trauma etc. With special treatment programs a prolongation of life with good quality is possible in non-Alzheimer dementia.

Important ethical problems for all forms of dementia are the decision about the right point in time using for the transferring the patient to a nursing home and the reduction of therapeutical program using expensive drugs.

The discussion about end of life decision in patients with Alzheimer's disease and other severe state of dementia is controversial. "Passive euthanasia" is illegal in most European countries, only renunciation of maximal therapy is accepted.

EARLY DEMENTIA DIAGNOSIS AND TREATMENT (Room A)

Chairmen: **M. EMRE (Ankara, Turkey)**
E. GIACOBINI (Geneva, Switzerland)
P. RIEDERER (Würzburg, Germany)

09.00	M. EMRE (Ankara, Turkey)	Diagnosis and differential diagnosis of dementia
09.20	C. CALTAGIRONE (Roma, Italy)	Mild cognitive impairment: evidence of an Alzheimer diseases's preclinical phase
09.40	A. NORDBERG (Huddinge, Sweden)	Diagnosis of early dementia with A-beta visualization with PET
10.00	E. GIACOBINI (Geneva, Switzerland)	Future treatment of early dementia: cholinesterase inhibitors or immunization?
10.20	Coffee break	
10.40	G. PEPEU (Pisa, Italy)	Non-steroid anti-inflammatories agents (NSAIDs): are they a valid approach to Alzheimer's disease prevention?
11.00	P. RIEDERER (Würzburg, Germany)	Cholesterol and statins: to be or not to be relevant?
11.20	F. GERSTENBRAND (Wien, Austria)	Ethics in Dementia treatment
11.40	General Discussion	
12.00	End of the Session	

12.00 **Special Lecture**

Chairmen: **L. VECSEI (Budapest. Hungaly)**
F. PICCOLI (Palermo, Italy)

A. LATHA (New York, USA) and E.S. VIZI (Budapest, Hungary)
Role of sympathetic nervous system in neuroimmune diseases

Journal of Neural Transmission

GENERAL INFORMATION
springeronline.com
ELECTRONIC CONTENT
springerlink.com

Contents Vol. 111 No. 5 May 2004

ISSN 0300-9564 JNTRF3 111 (5) 575–640, I–XLVII (2004)

Alzheimer's Disease and Related Disorders

Biological Psychiatry

Abstracted/Indexed in:
Current Contents, SCI, ASCA, and ISI/BIOMED, Biosis, Elsevier BIOBASE/Current Awareness in Biological Sciences, Reference Update, Index Medicus/MEDLINE, EMBASE/Excerpta Medica

Published May 3, 2004

Printed on acid-free and chlorine-free bleached paper