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SCIENCE DIRECT
European Psychiatry 20 (2005) S1–S14
EUROPEAN PSYCHIATRY
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Dementia

Sunday, April 3, 2005

S-16. Symposium: Recent advances in the development of biomarkers in Alzheimer's disease

Chairperson(s): Harald Hampel (München, Germany), Markus J. Schwarz (Munich, Germany)
16.15 - 17.45, Gasteig - Room 0.131

S-16-01

Evaluation of phosphorylated-tau protein as a core biomarker of Alzheimer's disease

H. Hampel, *München, Germany*

Objective: A biomarker of Alzheimer's disease (AD) could be established by CSF analysis of neurofibrillary tangle related pathology. Microtubule associated protein tau is abnormally phosphorylated (p-tau) in AD and aggregates as paired helical filaments in neurofibrillary tangles.

Methods: Recently, immunoassays have been developed detecting tau at specific phosphorylated epitopes in CSF as a potential biological marker for AD.

Results: CSF p-tau was highly increased in AD compared to healthy controls and other neurological disorders and further differentiated AD from its most relevant differential diagnoses including fronto-temporal dementia and major depression. P-tau 231 levels declined with disease progression, correlating with cognitive performance at baseline. Mild cognitively impaired patients showed elevated p-tau231 baseline level, correlating with rate of cognitive decline compared to healthy controls. In a comparative study, p-tau reached specificity levels under 75 percent between AD and the combined non-AD group when sensitivity was set at 85 percent.

Conclusion: Cumulative data indicates that quantification of CSF p-tau improves early detection, differntial diagnosis and tracking of disease progression during the pre-dementia and clinical stages of AD. The NIA biological markers working group recommends p-tau as a feasible, core biomarker candidate for large-scale validation studies, as well as clinical drug studies.

S-16-02

Proteome analysis of potential protein markers for Alzheimer's disease

K. Blennow. *Goteborg, Sweden*

S-16-03

Peptide Screening in Cerebrospinal Fluid

H. Selle. *Hannover, Germany*

The composition of cerebrospinal fluid (CSF) reflects blood brain barrier function as well as brain cell metabolism. The screening of peptides from CSF is a tool for the identification of biomarkers, that indicate significant events or conditions of the CNS, e. g. the occurrence and the extend of damage to neuronal cells or the brain barriers. Such markers can

(1) provide a deeper understanding of neurological and psychiatric diseases by elucidating aspects of pathophysiology

(2) correlate with disease-related events allowing diagnostic or even prognostic statements.

We present examples for the comprehensive CSF peptide analysis using the differential peptide display (DPD) approach that combines chromatographic procedures with a mass-spectrometric analysis. Peptides of interest are identified by amino acid sequencing, allowing the investigation of the relation between the peptide(s) and the underlying pathology. Degenerative diseases like Alzheimer's disease are characterised and the effect of a brain barrier disruption on the peptide content of CSF is demonstrated.

S-16-04

Antibodies against amyloid-beta peptide

R. Dodel. *Bonn, Germany*

S-16-05

Kynurenine metabolites in pathophysiology and diagnosis of Alzheimer's dementia

M. J. Schwarz, K. Bürger, J. Teipel, J. Zach, H. Hampel. *Psychiatric Hospital, LMU Muni, Munich, Germany*

Although the accumulation of hyperphosphorylated tau protein as neurofibrillary tangles and the aggregation of abnormal amyloid 1-42 as plaques are well known histopathological hallmarks, the exact mechanism of the neurodegenerative process of the Dementia of the Alzheimer type (DAT) is still not understood. A metabolic pathway of tryptophan, the so-called kynurenine (KYN) pathway, leads to neuroactive metabolites like kynurenic acid (KYN-A) and 3-hydroxy-kynurenine (OH-KYN). While KYN-A acts as an antagonist at the glutamate receptor of the NMDA-type and exerts neuroprotective potency, OH-KYN and its further metabolite quinolinic acid induce neurodegeneration through induction of neurotoxic radicals and agonism at the NMDA receptor. We therefore hypothesized

https://doi.org/10.1016/S0924-9338(05)80002-1 Published online by Cambridge University Press

an increased production of the neurotoxic OH-KYN in patients suffering from DAT. Since the key enzymes of the KYN metabolism are ubiquitously expressed and since a peripheral marker for DAT would be extremely helpful for early diagnosis, we investigated serum levels of TRP, 5-HIAA, KYN, KYN-a, and OH-KYN in 20 patients with DAT, 20 patients with late-onset major depression, and 20 healthy persons. We established a gradient high-performance liquid chromatographic (HPLC) method with UV and fluorescence detection. DAT patients showed slightly decreased TRP levels as compared to healthy control persons. The serum levels of 5-HIAA, KYN, and KYN-A were not different between the groups. DAT patients, however, showed markedly higher serum OH-KYN levels than patients with major depression and healthy controls ($p<.0001$). Our data strongly indicate an increased production of the neurotoxic TRP metabolite 3-hydroxy-kynurenine in DAT. Peripheral KYN metabolites are known to penetrate the blood-brain barrier and to correspond with the central nervous levels. Elevated OH-KYN levels could contribute to the neurodegenerative process in DAT. Moreover, an increased degradation of TRP via the KYN pathway could explain the reduced levels of serotonin and its metabolites, as TRP availability has a key role in the control of serotonin production. Finally, serum OH-KYN levels may serve as a peripheral marker for DAT, after further studies have confirmed the herein presented result.

S-16-06

CSF phosphorylated tau protein correlates with protein expression in brain as well with neocortical neurofibillary tangles in Alzheimer's disease

C. Bürger, K. Buerger, S. J. Teipel, H.-J. Möller, P. Davies, H. Hampel, R. Zinkowski, J. De Bernardis, D. Kerkman, T. Pirttilä, I. Alafuzoff, H. Soininen. *ZI für Seelische Gesundheit Genetische Epidemiologie, Mannheim, Germany*

Objective: Neurofibrillary tangles (NFT), consisting mainly of phosphorylated tau protein (p-tau), and deposition of plaques are a major histopathological hallmarks of Alzheimer's disease (AD). Deposition of neuritic plaques can be considered as a feature of NFT pathology as well. P-tau phosphorylated at threonine 231 (p-tau231) and at threonine 181 (p-tau181) in cerebrospinal fluid (CSF) have been suggested as useful biomarkers of AD. To determine whether p-tau proteins in CSF correlate with counts of tangles and neuritic plaques in brain. For p-tau231, the correlation with protein expression in brain homogenates was investigated in the same set of patients as well.

Methods: Memory clinic-based autopsy-confirmation study. Participants: 27 clinically diagnosed, severely demented subjects with AD who later came to autopsy. Main outcome measures: Levels of p-tau231 and p-tau181 in CSF; scores of NFT and neuritic plaques in frontal, temporal, parietal cortex, and in CA1 region of the hippocampus; p-tau231 levels in brain homogenates from frontal cortex.

Results: P-tau231: Mean levels of CSF p-tau231 correlated with p-tau231 in brain homogenates ($p < 0.01$), as well as with tangle counts in frontal, temporal, and parietal cortex ($p < 0.01$), but not in CA1 ($p = 0.34$). To counts of neuritic plaques, CSF p-tau231 was correlated in frontal ($p = 0.02$) and temporal ($p = 0.03$) cortex. Levels of p-tau231 in brain homogenates from frontal cortex were correlated with counts of NFTs and neuritic plaques in frontal, temporal, parietal cortex, and in CA1 region of the hippocampus (p from < 0.001 to 0.04). P-tau181: Levels of p-tau181 were not correlated to counts of NFTs and neuritic plaques in either of the regions studied.

Conclusion: Concentrations of p-tau231 in the CSF are likely to reflect key neuropathological features of AD.

Monday, April 4, 2005

SS-07. Section Symposium: The European Network on Old Age Psychiatry (ENOAP) - Results and perspectives for nations and WHO

Chairperson(s): Nicoleta Tataru (Romania), Raimundo Mateos (Santiago de Compostela, Spain)
08.30 - 10.00, Gasteig - Room 0.131

SS-07-01

The European network on old age psychiatry - resulting challenges for the EAGP

R. Ihl. *Düsseldorf, Germany*

Objective: Following the definition of the WHO, 52 nations belong to Europe. Concerning structures in Geriatric Psychiatry, the variety of cultures leads to a wide spectrum of quantitiy and quality of care. Most of the structures are unknown between nations and in most nations even within the nation. When a future structure of Geriatric Psychiatry shall be developed, this will be the first puzzle to be solved. Making services visible via the internet. might be a solution of this problem. Secondly, concerning healthy aging and treatment and care in Geriatric Psychiatry, the knowledge is poor leading to insufficient results and, moreover, to stigma. However, the knowledge for a solution exists. The challenge will be to transfer it to professionals in this field and to the public. Again, an internet based knowledge platform could be a first right move. It could for instance also include possibilities for training, teaching or mediating teachers. The first two steps will be the precondition for the third: determining tasks for research and quality asscurance. To improve care in Geriateric Psychiatry, the EAGP will have to communicate this three-step model to the population, the professionals working in the field and to european and national governments.

SS-07-02

Skill-based objectives for specialist training in old age psychiatry

R. Mateos. *Psychogeriatric Unit of the CHUS University Hospital, Santiago de Compostela, Spain*

The four Technical Consensus Statements on Psychiatry of the Elderly produced at meetings organized by WHO and WPA since 1996 are the general background of this document. This consensus curriculum on Skill-Based Objectives in Old Age Psychiatry (OAP) is the result of a process initiated by the European Association of Geriatric Psychiatry (EAGP), and jointly organized with the World Health Organization (WHO) and by the World Psychiatric Association (WPA) Section of Psychiatry of the Elderly. It was developed at the meeting 'Development of Strategies, Policies and Actions in Education and Training in Old Age Psychiatry in Europe' (Prilly/Lausanne, 8–11 June 2002) and published in 2003 after a thorough consultation process with multidisciplinary experts

https://doi.org/10.1016/S0924-9338(05)80002-1 Published online by Cambridge University Press