



Correlation of elements in control and Alzheimer-diseased brain parts

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Introduction: Despite of the now well-recognised importance of trace elements in medical field – it is established that several diseases of the central nervous system, like Alzheimer's disease are connected to alterations of trace elements levels – reliable data on their concentrations in normal and pathological human brain are still rare. Correlation studies are even more scarce in the literature, especially in case of Alzheimer's disease.

Patients and methods: Brain samples were obtained from the Institute of Neuropathology, University of Munich, where samples were pathologically classified and stored at $-70\text{ }^{\circ}\text{C}$ until required. Samples were lyophilised in a freeze-dryer until constant weight. Instruments used for collecting tissue, storage and transportation were of the same material in all cases (ceramic-, Ti-tools, high purity laboratory). The trace element analysis of tissues with high fat content by instrumental neutron activation analysis (INAA) introduces methodological problems. In our previous work an adequate INAA method has been developed and applied for the determination of Fe, Zn, Rb, Cs and Se in brain regions of control and Alzheimer's disease patients. One radiochemical neutron activation analysis (RNAA) method was applied for I analysis. Applicability of the INAA and the RNAA methods was checked by analysis of biological standard reference materials.

Results: Correlation was investigated for every possible combination of the six elements using the separate data for each individual and brain part. Control and Alzheimer's disease results correlated in case of two elements only: Fe and Rb. Correlation for Fe is highly significant ($p < 0,01\%$), which may underline the hypothesis of several investigators about the role of this element in progression of Alzheimer's disease. To a lesser extent, control and Alzheimer's disease Rb data showed correlation as well ($p = 2\%$). Investigating interelemental relationship the following observations can be made. First, a strong correlation was found between Rb and Cs concentrations in both groups, which is possible due to the nonselective accumulation of the two elements. However, it should be noted that although there is a highly significant correlation between Rb and Cs in both groups, and between control and Alzheimer's disease Rb data as well, but this is not true for control and Alzheimer's disease Cs data. This might signal slightly different biological behaviour despite their high degree of chemical similarity. An equally strong correlation was found in case of pairs Rb-Fe in the Alzheimer's disease group and Zn-Se in the control one. Weaker but still significant correlation could be observed between several elements.

Conclusions: Our data and the correlations found may help us understand better the role and interactions of the studied trace elements in the central nervous system.

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Amyloid precursor protein metabolism in high cholesterol diet ApoB transgenic mice

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Introduction: In the last few years several authors have investigated the possible role of dyslipidemias in the pathogenesis of Alzheimer's disease. Amyloid precursor protein plays a significant role in the development of Alzheimer's disease. The β -amyloid peptide ($A\beta$) being the main component of amyloid plaques, is derived by proteolytic cleavage from the amyloid precursor protein. Biochemical and epidemiologic data suggest a link between cholesterol, amyloid precursor protein processing, $A\beta$ and Alzheimer's disease. Cholesterol is transported by a very low density lipoprotein (VLD) that contains three apolipoprotein (E, C, B100) which are transformed to a low density lipoprotein (LDL) with mainly apolipoprotein B100 as their coat protein. Previous studies have shown that rabbits and rats fed with a cholesterol-rich diet have a tendency to accumulate $A\beta$ in the brain.

Methods: Our aim was to examine the possible role of cholesterol in the production of amyloid precursor protein, protein kinase-C (PKC) and BACE (β -secretase) in ApoB transgenic mice. The development of B6XCBAF1 line of mice expressing human ApoB100 transgene was used. The mice were maintained on a high-cholesterol diet (2% cholesterol) for 17 weeks. Changes in amyloid precursor protein, protein kinase-C and BACE protein levels were detected by Western blotting and mRNS of amyloid precursor protein by semiquantitative RT-PCR. Soluble and membrane-bound fractions of the cortical samples were separated by centrifugation.

Results: In the soluble and membrane-bound fraction of the cortical samples of ApoB transgenic fed with cholesterol-rich diet (K ApoB), the amyloid precursor protein levels increased (117.6%) compared with samples of non transgenic animals fed with cholesterol rich diet (Kk). In the K ApoB samples the protein kinase-C levels did not change in the soluble fraction, but in the membrane-fraction the Kk values decreased (87.5%). In the BACE protein levels no differences was observed. Surprisingly, no differences have been found in the mRNS of amyloid precursor protein levels in the studies group.

Discussion: These data suggested that cholesterol probable interferes with the amyloid precursor protein metabolism, but this influence might not be through the protein kinase-C signal transduction pathway.

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Please, help us to find a new Hungarian amyloid precursor protein mutation! Searching for deterministic genes in Hungarian Alzheimer families

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Alzheimer's disease is highly prevalent but etiologically complex disorder of the adult brain. Several highly penetrant genes have been cloned for rare, autosomal-dominant, early-onset forms of Alzheimer's disease. It is well-known that many mutations have been described within the amyloid precursor protein (APP), such as Swedish double (595/596; 670/671), Flemish (692), Dutch (693), Florida (717), London (717), Australian (723). Presenilin 1, presenilin 2 mutations have been reported as causative genes as well. Susceptibility genes polymorphism may modulate β -amyloid ($A\beta$) handling, like ApoE- ϵ 4, ApoE promoter (A491T), α 2-macroglobulin (exon 24 G), PON-2 (C311S), NOS-3 (C270T), cathepsin-D (A224V) etc.

The authors' purpose is searching for new, still not identified mutations and genes in Hungary.

With the help of the memory clinics, specialists and family doctors from the whole country the authors are going to screen potential Alzheimer's disease cases segregated in families. Affected individuals and their relatives are genotyped for reported mutations and demonstrated polymorphisms from DNA or RNA of lymphocytes. Their approach uses traditional genetic linkage methods combined with strategic search for SNP's in the potential "hot" areas around candidate genes in certain chromosomal intervals in order to map and clone genes bearing causative mutations. After genetic analysis a diagram of the pedigree can be drawn.

Knowledge of these novel genes can lead us to understand more about the pathomechanism of Alzheimer's disease and to design new therapeutic strategies in order to block $A\beta$ production, inhibit its assembly into toxic aggregates or accelerate its removal.

So if you do have a potential Alzheimer's disease family please call us!

Dementia or depression. What should be the first step?

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The prevalence of depression is 65% and 41% among the elderly who live at chronic departments and social welfare homes, respectively. Furthermore, over the age of 60, the prevalence estimates of the memory impairment is 5-15% and doubles annually in community samples.

Atypical appearance, the depression in elderly is fraught with danger. Cases with masked depression show apathy, hypo/abulia, depressed mood, fatigue, intense anxiety, somatization disorder (obstipation, psychomotor retardation, perceptive disturbances, physical complaints), pseudodementia. On the other hand, in dementia

the prevalence of apathy is 60-70%, depression is 50%, and anxiety is 50%. Predisposing factors are female gender, other psychiatric disorders, positive family history, social problems e.g widowed, divorced, personality, comorbidity, drugs, alcohol, stroke. The criteria of a novel diagnostic entity the vascular depression are subcortical and white matter deficits, apathy, low insight, relatively late-onset and vascular risk factors.

After general psychiatric interview, physical examination and brain imaging, Geriatric Depression Scale, Shortened Beck Depression Inventory, Mini-Mental State Examination, Clock Drawing Test could be useful distinction. The antidepressive therapy non-responder cases can direct the attention to dementia. As a first choice, one should always consider organic brain disorder after the age of 65.

The authors present a case which is a differential diagnostic problem. At first sight this case made an impression of depression.

Cognitive impairment-neuropsychiatric hospitalisation 2004

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Background: Disorders with cognitive impairment are becoming more and more serious health, social and economic problems. One of them is hospitalisation, which varies according to region, specialisation and costume. Course of the illness and hospitalisation as well largely depends on the health care system, which is undergoing changes. The purpose of the present study was to explore the features of inpatients with cognitive impairment, in order to improve the medical management in the future.

Method: Retrospective data evaluation of 60 consecutive cognitive impairment inpatients, who were admitted from 1. January 2004 in our neuropsychiatric unit.

Results: 39 female and 21 male were involved, average age was 75.2 (30-95 years). The cause of hospitalisation was BPSD in all cases. The aetiology of cognitive impairment was different: eight patients with probable Alzheimer's disease according to the NINCDS-ADRA, 23 patients with vascular disease, four patients with Lewy-body disease, 16 patients with vascular and Alzheimer's disease, three patients with pseudodementia, one patients with Huntington disease, five patients with unknown disease. Acute hospitalisation was higher in the vascular group with delirium.

The distribution of acute (A) and planned (P) hospitalisation proved to be A:25/P:35. The average hospitalisation days (HD) were 21 in case of A group and 12 in case of P group. Further we examined certain parameters from where patients were referred: special care, outpatient clinic, primary care, without medical care. The main samples are presented below. Duration of hospitalisation was: 11 days/special care, 20 days/outpatient clinic, 21 days/primary care, 12 days/without medical care, but the outcome

was significant seriously in the without medical care group, in spite of the same level of dementia.

Conclusion: Appropriate hospitalisation made in proper time could be advantageous. Special care is beneficial from several points of view. As even in progressive disorders potential reversible psychosyndrome may occur, therefore active neuropsychiatric treatment can prevent serious progression.

Cholinergic amplification and calcitonin gene-related peptide in the maintenance of Meynert's basal nucleus

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Nucleus basalis of Meynert comprises a large group of cholinergic nerve cells in the basal forebrain of primates. Number of cholinergic principal cells is 512 ± 25.3 per cubic mm of the nucleus in young adult *Macaca fascicularis* monkeys; it decreases to 160.4 ± 21.6 per cubic mm in old (>30 years) animals. Principal nerve cells of Meynert's basal nucleus exert intense choline acetyltransferase (ChAT) immunocytochemical reactivity throughout perikarya, dendrites and axon. Cholinergic axons of vicinal principal cells as well as cholinergic axons of cortical origin terminate in Meynert's basal nucleus and establish synapses with dendrites and somata of cholinergic principal cells. Such cholinergic-to-cholinergic circuits are regarded as one of the amplification systems in Meynert's basal nucleus. Another not less important afferent system originates from the parabrachial nucleus. Calcitonin gene-related peptide (CGRP) immunoreactive axons of CGRP-immunoreactive neurons of the parabrachial nucleus innervate the ipsilateral basal nucleus. CGRP-immunoreactive axons establish axo-somatic synapses on principal cells and axo-dendritic synapses in the neuropil. As a rule, CGRP-immunopositive axons also take part in the establishment of the glomerular units characterizing the neuropil of Meynert's basal nucleus. In such glomeruli or rather cartridges, the centrally located dendrite of the principal cell is surrounded by axons of various origin; these establish a number of axo-dendritic synapses on the central dendrite. Destruction of the parabrachial nucleus by means of electrolytic lesion results in degeneration of CGRP-immunopositive axons, followed by complete disappearance of the CGRP-immunoreactive innervation of Meynert's basal nucleus. Principal cholinergic neurons deprived of their CGRP-ergic input undergo considerable shrinkage. Nicotinic acetylcholine receptors (nAChR) are present in large numbers in Meynert's basal nucleus. These

receptors are invariably presynaptic and, as such, supposedly take part in the regulation of acetylcholine release like in other parts of the central nervous system. The combined activity of the various systems involved in the maintenance of acetylcholine output seems to be responsible for the supply of cholinergic innervation of the prefrontal cortex, which is critical in cognitive and mnemonic functions. Failure of these systems to ensure sufficient cholinergic input to the cerebral cortex might be one of the major factors responsible for the cardinal features of Alzheimer's disease: dementia, desorientation, dysphoria, depression, sleep disorders and memory loss. Since CGRP-ergic pathways are critical in the maintenance of cholinergic neurons in the basal nucleus, in conclusion it is hypothesized that relatively small and water-soluble portions of the large (37 AA) CGRP molecule, e.g. 1-8 AA (Ala-Cys-Asp-Thr-Ala-Thr-Cys-Val in human, Ser-Cys-Asn-Thr-Ala-Thr-Cys-Val in the rat) might be potential supplements for the missing CGRP in the sense proposed a few years.

Possible in vitro mechanism of fibrillar A β 1-42 toxicity in different cell cultures

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Alzheimer's disease is a neurodegenerative process, characterized by the amplification of the β -amyloid (A β) peptides and the neurofibrillary tangles. In vitro experiments different cell cultures (differentiated SH-SY5Y neuroblastoma cells, rat cortical neuroglia co-cultures and hippocampal neurons) and various methods (MTT assay, neutral red assay, immunocytochemistry and fluorescence microscopy) were used to investigate the mechanism of action of fibrillar A β 1-42. The fibrillar form of this peptide (1 or 10 μ M) induced irreversible changes in the cell viability and morphology. A β 1-42 caused: neurite degeneration, calcium signals, lipid peroxidation, τ hyperphosphorylation, membrane hypopolarization; decreased intracellular redox activity and membrane active uptake. The immobilized and non-fibrillar form of A β 1-42 were not toxic.

Our results suggest that the in vitro toxicity of A β 1-42 is more structural and molecular dependent than cell type dependent.

Quantitative SPECT in depression and dementia before and after acetazolamide provocation

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Recently, a pathogenetic relationship has been hypothesized between depression and dementia. It is frequently observed clinically that depression may precede the development of dementia. However, only a few functional neuroimaging studies have verified the neurobiological relationship between depression and dementia. In dementia, a decreased cerebral blood flow (CBF) and decreased cerebrovascular reserve capacity were found. A lower CBF was found in depression too, but the CBF normalized after improvement of the symptoms. The objective of this current study was to measure the reserve capacity of CBF in depression, and to compare it to that in dementia.

Fourteen patients (F/M=13/1; age: 52–78 years) with major depression and eight patients with Alzheimer dementia (F/M=6/2; age: 60–85 years) participated in the study. Regional cerebral blood flow (rCBF) was measured by ^{99m}Tc-MMPAO in a resting state and after acetazolamide injection.

A global decrease in CBF was measured in depression. A significant correlation was found between the severity of depression and the decrease in CBF. The cerebral reserve capacity was normal, but decreased with age.

Our conclusion is that a measurement of the level of the cerebral reserve capacity can help in differentiating between depression and dementia.

An exploration into the ethical issues that surround cases of mental dementia

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The majority of patients who are diagnosed as suffering from mental dementia in Hungary are placed either in a government, private, or church institutions. The first section of this lecture presents the most relevant statistical data concerning elderly patients cared for in all three types of institution. Once this data has been presented, I investigate the deeper ethical issues that override the current governmental regulations, as well as the teachings of the various Christian churches regarding not only elderly patients suffering from mental dementia but also at those responsible for their care and those who do research into the illness. Under these headings, I explore more theoretical ethical questions of human individuality, the respect for life, and the quality of life, as well as procedures of research.

Misinterpretation in the psychiatric diagnosis (Case report)

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The path to a correct psychiatric diagnosis is a very bumpy road. Due to a lack of classical nosological entities the phenomenological classification systems help define the common language in psychiatry. The diagnostic procedures regarding organic mental disorders would seem to be easier due to their similarities to other medical disorders. All the same the psychiatrist may fall into a trap.

A 68-year-old female was suspected of having Alzheimer's disease. Her psychiatric history contained a brief psychotic episode and organic hallucinosis. She was partially disoriented in auto- and allopsychic orientation and completely disoriented in time and space. Her behavior was bizarre and communication with her was difficult, as she did not use understandable words. The vigilance and tenacity of her attention was decreased. Her Mini Mental State Examination (MMSE) score was 0. Her somatic and neurological condition was good. Structural imaging (CT) was normal, although functional imaging (SPECT) showed bitemporal hypoperfusion, and FDG-PET proved global cerebrocortical hypometabolism. She was treated with AChEI and memantine, a low dose of an atypical antipsychotics, speech therapy, and creative therapy. After six months, her mental state improved. Her MMSE increased to 12, and the PET results showed improved metabolism in the brain. After ten months her MMSE increased again to 28 and her behavior is appropriate, her communication skills are good, and her speech is fluent with mild difficulties in finding words.

Consequently, cognitive impairment is reversible after long periods of cerebral hypoperfusion and hypometabolism and vice versa. Such a case proves that besides observation of clinical symptoms and neuropsychological testing, structural and functional neuroimaging techniques, as well as the course of the disorder are essential.

Dementia: a social answer?

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In the presentation based on practical aspects the authors are going to outline the possibilities and obstacles of social work in a general hospital.

“The ornament of the elderly is the grandchildren, and the ornament of the sons is the fathers.” (Bible, Parables 17:6.)

– The essence of dementia through social “lens”. (The question of independence.)

– How does a social worker working in a hospital come into contact with dementia patients? (Family-social relations.)

– The obligatory assistance based on the Social law [66. § (1), 68. § (4)]

Social assistance in reality. (The possibility of the arrangement of home assistance. Profit oriented institutions. Local government institutions.)

– Case studies.

– Suggestions: The increase of wage for home assistance, extensive information for family members and for the assisting members, the establishment of both inpatient and outpatient facilities specified for dementia patients.

It would be crucial that the social supplying network facilitated an environment so that “fathers” could receive a treatment that they deserve and in the process the “grandchildren” would not have to exhaust themselves physically, emotionally or financially, rather the fathers and grandchildren could be each other’s ornaments.

Loving care and quality

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The presentation will focus on the importance of loving care for Alzheimer or dementia patients in relation to maximizing quality of life. We have this experience in our Dementia Program of Nursing Home of Catholic Diaconial Services in Dabas. Loving care means an attitude of carer(s) toward the patients.

Peter Ashley – diagnosed with Lewy-body dementia – on the 14th Conference of Alzheimer, Europe, in Prague emphasized the importance of care partner (the importance of the relationship between the patient and care partner) in his quality of life. He used the analogy that dementia is like a three legged stool: only one leg represents the drug therapy the other two are the relationship and self help. We found in Dabas in our practice that in the life of our residents in late-stage dementia, self help is highly compromised. We, carers, have to fill up what is lacking in our residents’ ability.

The relationships of residents have a great impact on their quality of life. Using drugs alone does not improve the quality of life. Moreover, using psychotropic drugs decrease the patients’ quality of life.

In our program in Dabas we regard all our residents as persons in every stage of their illness. Our quality relationship with them improves their wellbeing. It is difficult to find physicians who share the same value we have.

Using CNS Vital Signs in detection of early dementia and mild cognitive impairment

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The Dementia Center established at the Psychiatric Department of Szent János Hospital, Budapest, considers the early diagnosis of mental decline one of its main objectives. In many cases, if a mild cognitive disorder is detected, the progression of dementia can be slowed down or even stopped with modern forms of treatment. Most of the tests used in everyday practice for dementia-screening are simple, paper-and-pencil (MMS, Clock-test etc.), which are not sensitive enough to “pre-dementia”.

CNS Vital Signs is a computer-operated neuro-cognitive test battery, developed in the US. Its Hungarian translation has been completed by the psychological team at the Psychiatric Department of Szent János Hospital and it has been included in the original test-battery by the authors, so it is now applicable in our everyday work. The sub-tasks of the test battery assess memory functions (verbal and visual), attention, psychomotor speed, reaction time, and cognitive flexibility. The following tasks constitute the test-battery:

Tasks assessing verbal and visual memory functions: in case of patients showing a poor or deteriorating performance in these tests the possibility of Alzheimer’s disease should be considered.

Tasks assessing attentional and executive functions: deficits in these functions may be the early signs of subcortical or vascular dementia. The following tests should be considered here: Symbol Digit Coding, Stroop Test, Shifting Attention Test (the two latter indicating fronto-temporal dementia) and the Continuous Performance Test.

It is very important to analyse the pattern of performance in different tasks, as such a differentiation should be the basis of diagnostic assumptions. However, CNS Vital Signs is not a diagnostic instrument, but a dementia-screening tool, therefore a patient showing a good performance in the tasks can be regarded as having no dementia.

In our presentation we would like to report the findings of a pilot study about the application of CNS Vital Signs for dementia-screening in cases when other paper and pencil tests did not give any or sufficient information about the presence of dementia. According to our experiences, this test-battery is capable of detecting mild cognitive disorders which remain unnoticed when assessed by “traditional” dementia-screening instruments. If dementia is detected in an early phase, treatment can begin in time which may improve the patient’s future opportunities for a better quality of life.

β-amyloid-induced changes of synaptic plasticity in cortical neuronal networks: novel perspectives of Alzheimer’s disease therapy?

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Within cortical neuronal networks, information processing occurs via the activity of interacting pyramidal cells that are controlled by local inhibitory interneurons, and subcortical, e.g., cholinergic and endocannabinergic afferents. Alzheimer’s disease, a progressive neurodegenerative disorder, is characterized by the dysfunction of cortical neuronal circuitries controlling attention, learning and memory. The most accepted theory of Alzheimer’s disease pathogenesis implicates the release of potentially neurotoxic β-amyloid peptides (Aβ) from

damaged neurons and activated glial cells. De novo synthesized A β in neurons first accumulates in vesicular elements of axons and synapses.

Recent data from our laboratories indicate that induction of spike-timing-dependent long-term depression (tLTD) and potentiation (tLTP) at unitary connections between pyramidal cells in layer 2/3 of the neocortex is regulated by dynamic changes in Ca²⁺ concentrations in dendritic spines. tLTP, but not tLTD, exhibited a pre-synaptic origin and dependence on NMDA receptor activation. We have also shown that neocortical pyramids can simultaneously utilize at least two (type 1 cannabinoid receptor [CB1R] dependent or independent) retrograde synaptic signaling mechanisms to tune the efficacy of input synapses.

When exposed to low (≤ 500 nM) concentrations of synthetic A β , both tLTD and tLTP induction were abolished in neocortical pyramidal cells. AMPA and NMDA current recordings in patches excised from pyramidal cells showed that A β did not change the gating kinetics of either channel. However, A β significantly reduced the AMPA/NMDA current ratio by affecting AMPA, but not NMDA receptors. Rapid rearrangement of AMPA receptor subunits was not detected. Ca²⁺ imaging experiments indicated anomalies of Ca²⁺ signaling in dendrites of neocortical pyramids affected by A β . Data from APP/PS1 mice verified the above findings, and established synaptic dysfunction prior to the development of massive A β plaque formation.

Recently, we have also shown simultaneous afferentation of neocortical pyramids by cholinergic and CB1R-containing projections. Activation of postsynaptic muscarinic acetylcholine receptors induced endocannabinoid release, and suppressed perisomatic inhibition on pyramidal cells. Therefore, pharmacological modulation of endocannabinoid release and/or CB1R activity in the neocortex may relieve remnant pyramidal cell activity and improve information processing in LNNs in Alzheimer's disease.

Alzheimer's disease: changes in the enzyme activity of kynurenine aminotransferase and kynurenic acid in the blood related to genetic risk factors

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Introduction: Alzheimer's disease is the most common cause of dementia in the population aged 65 and above. Alzheimer's disease leads to a progressive and irreversible loss of memory and cognitive function. Excitatory amino acid receptors (EAAR) are involved in the physiology of the brain, and are critically involved in the

long term potentiation, learning and memory. Overstimulation of these receptors and excitotoxicity leads to nerve cell death and may play a role in the pathogenesis of Alzheimer's disease. Kynurenic acid, a tryptophan metabolite, is the only known endogenous EAAR antagonist. It shows neuroprotective and anticonvulsive activities. Kynurenic acid is synthesized from tryptophan via kynurenine by its biosynthetic enzyme, kynurenine aminotransferase (KAT I and KAT II). As kynurenic acid is an endogenous neuroprotective compound, changes in the concentration may play a role in Alzheimer's disease.

Methods: Kynurenine and kynurenic acid concentration from plasma of 28 Alzheimer's disease patients and 14 age matched controls were detected by HPLC. KAT I and KAT II enzyme activities were measured spectrophotometrically by the modified method of Mason.

Results: Kynurenic acid in the plasma of Alzheimer's disease patients was significantly decreased. The kynurenine and the activity of the KATs revealed no significant changes.

Discussion: Kynurenic acid is a broad spectrum EAAR antagonist and a neuroprotective agent. It is synthesized both in the brain and in the blood, interaction of the compartments is well known. Significantly increased KAT I and KAT II activity and kynurenic acid content was demonstrated (H. Baran et al, 1999) in the caudate nucleus and putamen of Alzheimer's disease patients. Significantly decreased plasma kynurenic acid in our results may demonstrate that compensatory neuroprotective mechanisms are consumed in the brain regions. Kynurenic acid analogues that show neuroprotective activity and have no cognitive side effect may be therapeutic agents.

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Dynamic EEG protocol in Alzheimer's disease

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Purpose: Conventional and quantitative electroencephalography gives important help in the assessment of neuropsychiatric patients. However these methods provide little information about mental functioning itself. Our team tried to find a task related electrophysiological model, easily to perform in all of this patient population. The aim of the present study was to test our dynamic electrophysiological model in patients with Alzheimer's disease.

Method: Eleven patients with mild and moderate Alzheimer's disease participated in the study, ten healthy subjects served as control population. Mental calculation (reverse counting) was used as mental task. Differences of power spectra computed from pre-task and post-task EEG sections were analysed between patient groups by visual evaluation of spectral maps and statistical analysis.

Results: Differences in the absolute power between pre-task and post task periods were similar in the two groups, a frontal increase was observable in the lower frequencies after performing the cognitive test. This was followed by definite power reduction in Alzheimer group in all other localisations and frequency bands. Statistical comparison of peak and mean frequencies and interhemispherical coherence also showed similar trends in the two groups. Performing the task resulted in an increase of α peak frequency in Alzheimer group bitemporally and a frontal decrease in control group, and topographical distribution of increase of peak frequency in β band was also different.

Widespread increase was observed in interhemispherical coherence in both groups in all frequency bands after performing cognitive task. Most important differences in the two groups were observed temporally, as less intensive changes were presented in Alzheimer group in α and θ bands.

Conclusions: Our method seems to provide consistent findings in both patient populations, reflecting changes during the task, whereas differences were found in qualitative electroencephalographic data of the two groups.

Psychosis of patients with dementia – the caregiver’s point of view

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Psychotic symptoms, such as delusions and hallucinations, are common in dementia. Longitudinal studies suggest that psychosis occurs in as many as 50% of patients with dementia. Nearly one in four of us will experience psychotic symptoms at some point in later life.

In the presentation the various concepts of psychosis, resulting in its “narrow” and “broad” definitions, are addressed and the differences pointed out. The presenter commits himself to the narrow definition. The importance of early recognition of psychotic symptoms is stressed. The arguments are mainly from the caregiver’s point of view, emphasising that the adequate therapy of symptoms greatly relieves the suffering of the patient and eases the burdens of the caregiver.

β -amyloid precursor protein accumulates within less than 60 minutes after axonal damage – Is it relevant in the pathogenesis of Alzheimer’s disease?

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Introduction: Traumatic brain injury is a well-known epigenetic risk factor for the development of Alzheimer’s disease. Traumatic brain injury is frequently associated with axonal injury, which results in accumulation of β -amyloid precursor protein (APP) in the damaged axons. APP and β -amyloid has been shown to co-localise in damaged axons and close to the

APP immunoreactivities β -amyloid positivities were found in the neuropil, in forms of plaques and diffuse staining.

APP immunohistochemistry is a reliable and sensitive marker of axonal injury of mild to severe degree and is considered as an important evidence to prove traumatic brain injury and comment on estimated survival time. According to the literature data APP immunoreactivity has been demonstrated by standard methods earliest 90 minutes after traumatic brain injury. We present three cases (victims of assault or accident) with well-documented post-traumatic brain injury survival times of 35–60 minutes, showing APP immunoreactivities following antigen retrieval.

Material and methods: Post-mortem delay were less than 24 hours. Brains were fixed in 4% paraformaldehyde for 30 days. Blocks were sampled extensively for paraffin embedding. Slides were stained with H&E and processed for APP (Chemicon, clone 22C11; 1:10000) immunohistochemistry using citrate buffer and microwave as antigen retrieval technique.

Results: Sections revealed APP immunoreactivity predominantly in forms of small globules or granules and occasionally as thin and short filamentous deposits. They were detectable in the pons, corpus callosum, internal capsule and cerebral white matter with some variation in localisation and intensity. Many of the neuronal somata were labelled in the cortex and brainstem. A focal faint neuropil staining was also noted. β -amyloid precursor protein was not found in areas frequently affected in Alzheimer’s disease.

Conclusions: APP can be detected by immunohistochemistry as early as 34 minutes after traumatic brain injury using antigen retrieval technique. These results may have implication in consideration of minimal survival time after injury. It also indicates that APP accumulation is an early event following brain trauma, detectable in neurons, damaged axons and the neuropil. Further studies are needed to elucidate its potential relevance in the pathogenesis of Alzheimer’s disease.

Blood markers in Alzheimer’s disease: altered distribution of acetylcholinesterase molecular forms in lymphocytes and platelets

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Background: Alzheimer’s disease is a progressive neurodegenerative disorder characterized by an irreversible memory loss and cognitive deterioration. Cholinergic dysfunction in the central nervous system is the most prominent neurochemical abnormality in patients with Alzheimer’s disease. Peripheral tissues may be suitable for exploring the above-mentioned pathophysiological hypotheses.

Objectives: In order to promote the diagnosis of

Alzheimer's disease and when investigating the effects of drugs that affect the cholinergic neurons in the central nervous system, the aim of this study was to determine the activities of acetylcholinesterase (AChE) and its molecular forms in the erythrocytes, the lymphocytes and the platelets, in normal elderly subjects and in probable Alzheimer's disease patients.

Methods: Apolipoprotein E (ApoE) genotyping and the butyrylcholinesterase K (BuChE-K) variant were analyzed by using the polymerase chain reaction on blood samples from the controls and the Alzheimer's disease patients. The lymphocytes and platelets were separated by differential centrifugation. The lymphocytes were further purified on a Ficoll-iodamide gradient. The acetylcholinesterase activity was measured by spectrophotometry, and those of its molecular forms by radiometric assay. The acetylcholinesterase molecular forms were separated by means of 5-20% sucrose density gradients.

Results: Three acetylcholinesterase molecular forms exist in the blood cells: the dimeric globular (G2), tetrameric globular (G4) and asymmetric (A12) forms. Interestingly, no globular monomeric (G1) form was found in human blood cells. In both lymphocytes and platelets, the major acetylcholinesterase molecular form was G2 (approximately 80%), with the G4 and A12 forms nearly equally distributed. There were no significant differences in acetylcholinesterase activities between the normal and Alzheimer's disease samples (from patients with mild and moderately severe cognitive deficiencies). However, significant differences were found between the control and Alzheimer's disease samples as concerns the molecular form distributions in the lymphocytes and the platelets. Namely, the amount of the A12 form in the Alzheimer's disease samples was increased (to 142% and 153% in the lymphocytes and the platelets, respectively) as compared with the controls. The Alzheimer's disease patients were found to carry the apolipoprotein E4 allele at a significantly higher frequency than in the control group, whereas there were no significant differences between the groups as regards the occurrence of the butyrylcholinesterase K variant.

Conclusions: Besides routine memory tests and advanced imaging methods assessment of the distribution of the acetylcholinesterase molecular forms in the lymphocyte and platelets may provide a suitable marker for the Alzheimer's disease.

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Cholesterol and Alzheimer's disease

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Increasing evidence suggests a link between Alzheimer's disease, vascular risk factors and atherosclerosis. Alterations of cholesterol homeostasis can have pronounced consequences on cell structure and function and may be

both a cause and casualty of Alzheimer's disease. Cholesterol is known to be an essential modulator of physicochemical state and functional activity in physiological membranes and thus plays an essential role in the regulation of synaptic function and cell plasticity. In vitro and in vivo modulation of membrane cholesterol levels affect different cholesterol pools within the plasma membrane bilayer that are differentially sensitive to amyloid β -peptide's ($A\beta$) disrupting effects. An especially important aspect of this association is the relationship between $A\beta$ and cholesterol that can be described as a reciprocal process. It would appear that cholesterol levels modulate $A\beta$ levels and in turn $A\beta$ acts on cholesterol homeostasis. Membrane acyl-chains in the hydrocarbon core are most susceptible to $A\beta$. In this membrane region, cholesterol attenuates the membrane disordering effects of $A\beta$. On the other hand, statin treatment in vivo depletes a cholesterol pool in a membrane area, which is much less susceptible to $A\beta$'s membrane-disrupting effects. Niemann-Pick Type C (NPC) is an inherited neurodegenerative disease of childhood and adolescence that develops from a failure of cholesterol trafficking within the endosomal-lysosomal pathway. Although NPC differs in major respects from Alzheimer's disease, intriguing parallels exist in the cellular pathology of these two diseases, including neurofibrillary tangle formation, prominent lysosome system dysfunction and influences of apolipoprotein E $\epsilon 4$ genotype. Added to these similarities are new findings that some neuronal populations develop abnormalities of endosomes resembling those seen at the earliest stages of Alzheimer's disease and also accumulate β -cleaved amyloid precursor protein (APP) and $A\beta$ peptides within endosomes. My presentation gives a brief overview of $A\beta$ peptide effects on cellular cholesterol trafficking and potential mechanisms of those effects. I report data about the relationship of vascular risk factors (APOE genotypes, serum cholesterol and triglycerides levels) and altered serum butyrylcholinesterase activity in type IIb hiperlipidaemic subjects, and how these parameters correlate with APOE genotypes of which APOE-4/4 carriers represent the Alzheimer's disease population with the highest cerebrovascular risk. Our data indicate that certain dyslipidaemias even affecting the activity of enzymes involved in acetylcholine metabolism. In this regard lipid abnormalities should be considered as a potential therapeutic target in dementia.

First experiences of the function of an outpatient memory clinic in the Department of Psychiatry of Pécs University

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Background: The outpatient memory clinic is new unit of the Department of Psychiatry of Pécs University in Hungary since the November 2003. That outpatient setting was established for the standardized programme for diagnosing and treating memory disorders especially

dementias. The general practitioners and psychiatric ambulatory services of the surrounding were informed about the diagnosing and therapeutic supplies of the outpatient clinic. This presentation is a summary about the first experiences of a new ambulatory setting for patients with cognitive impairment.

Methods: The authors analysed all the patients who have appeared in the outpatient memory clinic since its foundation. Standardized neuropsychological and imaging methods were used in that unit.

Results: Of the 55 patients who were examined in this unit, 42 had dementia, five had a secondary memory impairment (pseudodementia) and seven had mild cognitive impairment. Of the 42 patients with dementia 35 had Alzheimer's disease, four had vascular dementia and three had frontotemporal dementia. Only 30% of demented patients were in mild stage at the first appointment. All the patients with pseudodementia suffered from depression. Depression was observed frequently in the demented group, too. Agitation, delirium and paranoid delusions were also found in high proportion of patients with severe dementia. Antidementia agents were used in all cases.

Conclusions: The demand on examination and up-to-date pharmacotherapy of dementias is on the increase in Hungary. The authors are opinion of that the proper informations for primary care physicians about the potentialities of an outpatient memory clinic determinate the successful function of that ambulatory setting. The psychiatric assessment of patients with memory complaints should not be restricted to the diagnosis of dementia.

The appearance of Ekbom-symptom in dementias

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Background: Delusion of infestation is a part of monosymptomatic hypochondriacal psychosis, although reports do exist on the appearance of these delusions in other mental disorders, eg. schizophrenia, depression and dementias. The psychosis of parasitosis is mostly induced by tactile hallucinations. Ekbom-symptom can indicate the initial stage of cognitive decline in older age.

Method: We analysed all the cases with Ekbom-symptom observed in one year duration in our clinical practice. The level of cognitive impairment was measured by the MMSE. We also considered the type of dementias, based on clinical examination.

Results: Four cases were found: three males (cases 1, 2, 3, ages: 56, 63, 67 years) and one female (case 4, age: 76). The MMSE-scores were found 26 in the cases 1, 2 and 3. That score was found 23 in case 4. FTD and ALS were diagnosed in case 1, probable Alzheimer's disease in case 2, dementia associated with Parkinson disease in case 3 and combined Alzheimer and vascular dementia in case 4. The delusions of infestation were resulted from tactile hallucinations in cases 1 and 3, tactile and visual hallucinations in cases 2 and 4. The Ekbom-symptom disappeared completely in cases 1, 2 and 3, when

antipsychotic (risperidone) medication has been started. The psychosis of infestation had a chronic outcome in case 4. A half year long follow up period revealed that cognitive decline were progressive in cases 1 and 3. The MMSE score decreased with 2 points in that cases.

Conclusions: Mild stage of different types of dementias were found in the cases hospitalized with Ekbom-symptom. Antipsychotics proved to be effective in the treatment of Ekbom-symptom associated with dementia.

Utilization: Psychosis of infestation can be the first symptom of a hidden dementia. Psychiatrists as well as primary care physicians should consider the presence of dementia when Ekbom-symptom occurs. Not only biological but psychological factors (loss of existential defension) are important in the understanding of Ekbom-symptom.

An integrativ approach to dementia. Report about the dementia center of Szent János Hospital, Psychiatric Department

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The Dementia Center of the Szent János Hospital's Psychiatry Department has been operating since 2003. The adequate professional and social implementation, which takes into consideration effects of dementia on health, society, family and culture, is an essential part of the functioning of the dementia center. The backgrounds of the symptoms group and its satisfactory treatment are both complex and therefore require the co-operation of various professionals. In the catchment area to Szent János Hospital's Psychiatry Department (approximately 350 000 people), the dementia is quite frequent and its treatment is a complex process. In the Dementia Center of the Psychiatry Department, the diagnosis and treatment of dementia are based on the protocol of Collegium of Psychiatry, in which the diagnosis and the therapeutic approach are done in a multidisciplinary way. In 2003 and in 2004 to June 30 in the department we diagnosed and treated 145 inpatients as well we registered 38 outpatients, with dementia symptoms.

Since the availability of dementia registration forms in 2003, their usage is mandatory. Into the early and preventive screening the CNS Vital Signs computer based screening test was introduced, and our findings of them we will present in an other presentation. In pharmacotherapy, we have access to the latest and most effective medications.

The essence of the integrationist approach as it is practiced in the Szent János Hospital's family centered psychiatry department, is that it is not solely the dementia patient who is being treated rather the patient is treated together with his or her family and with the other assistances of the patient. The other essential part of our approach is the systematic organization and running of the patient's social environment and social

assistance, but this is also more thoroughly discussed in an other presentation, too. In our preventive work, two of our colleagues participate in an educational program organized by a Hungarian patient organization (FEHT – Family members of people with memory loss Association).

We also put a great emphasis on ethical issues. Based on our own experience we would like to call attention to the shortcomings of the Hungarian medical and social supplier system, which can be seen with the process of diagnosing the capabilities of dementia patients who are not in psychiatry departments.

The up to date treatment of dementia is impossible without a multidisciplinary team that does the research and therapy in collaboration.

In the presentation we are going to talk about our experiences that are supported by actual facts and findings.

Brain-specific nutrition. Can memory be saved?

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Aims: In Hungary 12–15% of the population – meaning 200–300 thousand people – have some kind of dementia, 50–70% of which is Alzheimer's disease. The occurrence is 5–10% in case of people above 65. As the world population gets older, the number of people diagnosed with dementia increases. Several people either consider dementia as a natural part of old age or are ashamed of their declining mental abilities.

Methods: Research revealed that therapies without medicine also exist with the help of which memory can be saved and the quick decline can be slowed. Vitamins, antioxidants, minerals, flavonoids etc. taken in during nutrition belong here. Meanwhile, nonprescription memory enhancers are more and more widespread although their efficiency is questionable.

Results: The author, analyzing the international literature, summarizes the impact of the different nutrients and food supplements on memory diseases. The diet that limits the ageing of the brain is described in details: antioxidants, enzymes, fluid intake, micronutrients of natural origin and the major mistakes in nutrition and medicines that lead to memory-decline.

It should also be taken into consideration that the patient's appetite often decreases, he/she starts to lose weight serving as a catalyst for further processes.

Applicability: Of course, no one should think that he/she can save his/her memory or cure the disease with only a good diet but the elongation of the independent life worthy of being human becomes possible. As a summary, it can be concluded that the listed brain-specific nutrients or those mentioned in the literature showed only slight results, mainly in the memory tests.

Alcoholic dementias

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Ten percent of dementias had alcoholic etiology in the USA. Thirtyseven homeless patients with alcoholic dementias without cerebrovascular and traumatic brain lesions were investigated in the Crisis Intervention Department at the Budapest Social Center between 1998–2004. Detailed medical, neurological and psychiatric investigations, ratings on Mini Mental State Examination Scale (MMSES) were carried out, Zung's and Beck's Depression and Anxiety Self-Rating Scales were also used in many cases. Cerebrovascular and brain traumatic lesions were excluded mainly with computer tomography made in different hospitals. Dementia was diagnosed, if the total score of MMSES did not reach the value of 24. The woman-man ratio was 1:2.7. Alcoholic dementias were associated with pellagra in one case, with hepatic insufficiency in one case, with polyneuropathic muscular weaknesses in three cases, with coordination disturbance in one case and with moderate chronic delirium in two cases. Patients were under 40 years of age in 13%, between 40–49 years in 11%, between 50–59 years in 51% and above 60 years of age in 25%. Mild dementias (MMSES total scores between 23–18) in 78%, moderate dementias (MMSES total scores between 17–10) in 16% and severe dementias (MMSES total scores under 10) in 6% were found. Desorientations in time and space occurred in 68% and 49% of the cases, respectively. Decreased working, long- and short-term, biographical memories were diagnosed in 92%, 77%, 50% and 42%, respectively. Memory interference was found in 64% of the cases. In general, different emotional disturbances appeared in 78% of the cases. Depression in 35%, apathy in 30%, irritability in 20% of the cases were found and the patients had rarely anxiety, euphoria, somatisation, agitation, negativism. Patients could not differentiate between similar terms in 77% and they could not interpret the proverbs in 79% of the cases. In general, other thinking disturbances occurred in 41% of the cases. Incoherent speech in 16% and confabulation in 8% of the cases were found, rarely the patients had rigid thinking, hesitation, paralogia, or inhibited thinking. In summary, alcoholic dementias developed mainly after 50 years of age, which reflected that perhaps age-dependent brain changes contributed to the pathogenesis. On the other hand, alcoholic dementias could be hardly differentiated from the Alzheimer's type of dementias with chronic alcoholisms by using routine diagnostic psychiatric methods.

Delusional jealousy, a “double” and Alzheimer-dementia – A particular psychopathology and the possible balances in the therapy

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Background: Alzheimer-dementia is frequently characterized – beside the common syndromes of dementia – by different psychotic and affective, as well as somatic and neurological symptoms which need to be correctly diagnosed and treated along with the dementia.

Method: The case presentation was about an elderly

female patient suffering from Alzheimer-dementia (proven by MRI, tests and clinical outcome) that was characterized by delusional psychotic symptomatology (a particular "double" symptom formation and delusional jealousy) and somatic comorbidity. The highly educated patient was followed up and treated – after a short hospitalization period – on outpatient basis for more than three years.

Discussion of results: Differential diagnostic difficulties of the Alzheimer-syndrome itself, the mixed psychopathology, the role of co-morbidity and the side effects of anti-psychotic and anti-demential agents, as well as the somatic illnesses were discussed. The delusional psychotic jealousy and the "double" psychopathology were connected to an Alzheimer type dementia with a particular familial relationship that could also be interpreted psycho-dynamically on the basis of her life-history. A familial essential tremor vs. the extra-pyramidal side effects of anti-psychotics and a temporary delirium were also problems of differential diagnosis in a period of treatment. (Cholinesterase and NMDA receptor blocking agents, atypical anti-psychotics, anti-Parkinson drugs, nootropics and drugs for treatment of the essential familial tremor of the patient were given.) A supportive therapy served to gain trust and compliance of the patient and her "high status" family (many doctors, pharmacists within), that tried even medically to "control" the care and therapy.

Conclusion: During a longitudinal clinical follow up period the possible balance and fine-tuning of therapy as well as relations to particular psychopathology were highlighted and discussed within the clinical background of the relatively well stabilized Alzheimer-syndrome.

Hallucination? Delusion? Reality?

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A patient (64-year-old, female) had to be taken up urgently by the psychiatry as she was referred to us by her GP (general practitioner) because of her changed, inadequate behaviour. She accepts being taken up, she does not show any resistance, objection. Her spontaneous complaints are: she feels very tired because "her son-in-law wants to make away with her".

Asking her in a direct way: it turns out, her son-in-law has been threatening her (for about two months) (even through the wall), he poisons her meals, steals her possession, his aim is: to make away with her to cancel her usufruct on their detached house.

Case history: Special lung processes in her young adulthood, abdominal operations (gall bladder stone, hernia). Antecedents of the psychiatric case are positive. In the year before her taking up she came several times to our clinic. We treated her with depression and anxiety with little result. She has not been here in the past two months.

Heteroanamnesis from her daughter (their relationship is harmonic): Her premorbid personality was char-

acterized by resoluteness, activity, diligence, unconditioned trust to people, selflessness and caring. She has been feeling her to be depressed, not interested, easily tired and forgetful. She has had a feeling of guilt because of some undone work. She said her life had no sense, but she did not tell about suicide thoughts.

They did not recognize any rise in her mood when she was taking her medicine. She was postponing the clinical treatment offered by her doctor. About two months ago her behaviour changed: she got not well concentrated, forgetful, she has been looking for her things – thinking they are lost, she did not do housework, she did not spend time on her look, she was not interested in her favourite TV programmes any more, she did not speak much, she got hostile. She had no confidence to her son-in-law at all. She accused him of stealing her things several times and poisoning her meals. When taking her up: she looks ordinarily.

Internal state: negative. Neurologically: liberation reflexes (palmomental and holding reflexes), lack of explaining a proverb or explaining a term, poor motivation, difficulties in saying words. Psychological state: along a psychopathological symptom building. Marked psychotic syndrome, acoustic hallucinations, persecutive doxasma, thinking being stolen and poisoned, paranoid way of life, global cognitive deficit syndrome, concentration gets tired easily, not able to concentrate distributively, deconcentration, disturbance of quantitative memory (especially for short term), disturbance of fresh remembering memory.

Protein crosslinking and ubiquitylation in neurodegenerative diseases

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Previous research from our laboratories indicated that different histological types of neurodegenerative dementias are associated with elevated concentrations of protein-bound Nε(γ-glutamyl)lysine isopeptide crosslinks in brain cortex and free and free isodipeptide in the CSF. By mass sequence analysis, we showed that the bulk of the isopeptide crosslinks is confined to the insoluble, highly ubiquitylated protein fraction of Alzheimer's diseased brain tissue and located these crosslinks to three lysine and three glutamine residues of ubiquitin, HSP27, α-synuclein and parkin proteins.

Here we analyzed brain tissue specimen from hippocampus, basal ganglia and pons from autopsy specimens of five patients with Lewy-body dementia (LBD) and five not demented patients with Parkinson's disease

(PD) by α -synuclein immunoaffinity separation of chaotrope-insoluble brain proteins. Proteins were fragmented by trypsin and peptides were resolved by HPLC. Crosslinked peptide mass peaks having two N-termini were identified by MALDI-TOF and further sequenced by tandem mass spectrometry.

Our results showed that the N ϵ (γ -glutamyl)lysine crosslinks of Lewy-bodies from DLB and PD patients are identical to those sequenced from Alzheimer's patients. However, the abundance of α -synuclein ubiquitin and parkin-HSP27 crosslinks is significantly higher than in Alzheimer's disease.

These data indicate a common pathway for generating intraneuronal protein aggregates in neurodegenerative diseases associated with Lewy-body as well as neurofibrillary pathologies. Therefore, transglutamination-mediated crosslinking of ubiquitinated neuronal proteins may be a generic mechanism for protein aggregate stabilization.

The ageing mind – successful ageing

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Using cultural-historical data, the author provides an overview of the past up to present day, that is, the XXI century. This century will undoubtedly become the century of old age and ageing. An ageing population is the biggest challenge our world has to face, but at the same time has enormous inherent possibilities as well. 2000 years ago Hypocrites, in the quest for finding the answer to successful ageing, claimed that the kind of old age we can expect results from the life-style we had as a young person. Certainly, structural analysis of personality can provide vital information for the life-prospects of a person.

Unfortunately, nowadays it is the negative features of old age that are mostly considered. The positive aspects such as wisdom, certain behavioural patterns, successful performance, play no role at all in our ideal in life.

The author's research into how young age relates to old age, is not focused on the finite nature of life. It examines the personality and performance of people who have aged successfully and how these factors affect long life.

Drawing upon the fields of natural and social sciences plus art, the writer highlights the characteristics of prominent historical personalities who lived to a successful old age.

Aunt Bori is back again – The revolving-door psychiatry

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Background: Medical, social and ethical questions are examined in cases of health provision of old people with severe dementia. That patients are unable to take care of themselves often get into contact with the health-

care system only when their condition is in serious state. The frequent getting back of the old patients induce inter- and intrapsychic conflicts among staff having the obligation of providing medical attendance. The arising emotions of them indicate some questions of moral issues, which have an influence on the decision-making concerning professional points. The returning demented patients might cause the development of burn-out in the staff.

Methods: The question is elaborated through the demonstration of the case study of an 85-years-old female patient suffering from vascular dementia admitted several occasions to the department of psychiatry.

Results: The patient suffers from severe dementia, her MMSE score was 10 at the last treatment. The patient is childless. She lives with her alcohol-dependent husband who often assaults his wife. Patient was placed in the charge of a guardian excluding power of disposal during the examined period. She has received medical attendance exceedingly many occasions since April, 2003. She was admitted to the psychiatric ward six, to the ambulatory setting seven times. She was an inpatient in the traumatologic ward one time, and an outpatient 12 times. She was admitted to the neurologic ward one time, to the ambulatory setting seven times. Neurosurgical ambulatory examinations were provided two times. She was an outpatient in the department of internal medicine five times. Altogether, eight hospital and 33 ambulatory admissions had been registered in a one-year period. We found out that on same days the patient was treated in numerous hospitals.

Conclusions: The authors revealed that the treatment of the old patients with dementia who are not able to look after themselves does not end up with institutional medical attendance, but it demands follow-up contribution among the medical and social caretakers and systems of authorities. Communicative and competency problems can arise in the margin zones, which interfere with the patient's quality of life. Therefore the collaboration between the home-care system, the GP and the family is exceedingly important.

Concentration of Al, Mg and P in control and Alzheimer-diseased brain parts

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Introduction: Dementia of the of Alzheimer-type (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS) are the most frequent age-related human neurodegenerative diseases. The occurrence of amyotrophic lateral sclerosis-Parkinson's disease in all incidence disease foci coupled with the absence of demonstrable heritable or transmissible factors had led to focus the research on non-transmissible environmental factors. Metal analysis of the central nervous system tissues from the cases showed high level of Al and Mn. It was hypothesized that Ca and Mg dietary deficiencies might increase the neurotoxicity of metals.

Patients and methods: The samples were collected from three control patients. All subjects taken into consideration were diseased for reasons not involving the nervous system. Three Alzheimer's disease subjects were also followed. The pathological signs of Alzheimer's disease were demonstrated both by biochemical and electronmicroscopic methods. The digested samples were analysed for Al, Mg and P by inductively coupled plasma atomic emission spectroscopy (ICP-AES). The dried samples were measured by instrumental neutron activation analysis (INAA) for Mg and Al. The INAA determination of human brain Al levels is complicated by the interfering reaction of P. We have worked out an analytical method which can eliminate this interference. The accuracy of the data was investigated by the analysis of biological standard reference materials.

Results: The control values of Mg and P obtained in this study are in good agreement with literature data, although data available regarding elemental levels in human brain are rather scarce. Significantly higher Al and lower Mg and P values were found in some Alzheimer's disease brain parts compared to the controls. The decline in P with Alzheimer's disease may reflect a loss of myelin phospholipids over time. It has been previously shown that high Al intake decreases P absorption and increases P excretion suggesting that they are antagonistic. Low level of Mg overexcites the brain's neurons and results in less coherence. It has been suggested that Alzheimer's disease involves a defective transport process characterized by both an abnormally low Mg incorporation and an abnormally high Al incorporation in brain neurons. The origin of this disturbance rests on an alteration of serum albumin, forming a species which has greater affinity for Al than for Mg, in contrast to the normal protein which binds Mg better than Al. The altered albumin crosses the blood-brain barrier more efficiently than the normal protein and competes with it in binding to brain neurons. Binding of altered albumin to the neurons would both impede Mg uptake and facilitate Al uptake.

Conclusions: Our results suggest the possibility of a multielement involvement in Alzheimer's disease.

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New trends in drug discovery for treatment of Alzheimer's disease

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Introduction: β -amyloid ($A\beta$) peptides are in the center of drug design for treatment of Alzheimer's disease. $A\beta$ peptides have neurotoxic (synaptotoxic) effect and simultaneously $A\beta$ -fibrils can activate microglial cells. Toxic microglial products can damage and kill neurons.

Our aim was to design and synthesize peptides that prevent any interaction of $A\beta$ peptides with neuronal and glial cells.

Methods: In vitro neuroprotective activity of our novel peptides was measured with MTT-assay in differentiated SH-SY5Y cells and primary neuron culture. Brain slices were used for in vitro electrophysiology experiments. Transmission electron microscopy was used for studying $A\beta$ -aggregation to fibrils. In vivo electrophysiology experiments were performed in rat using microiontophoretic administration of $A\beta$ and other peptides in the hippocampus. Mice and human microglial cell cultures were used for microglia activation studies.

Results and discussion: A series of pentapeptides derived from $A\beta$ 1-42 proved to be neuroprotective both in vitro and in vivo. Two of these pentapeptides (Arg-Ile-Ile-Gly-Leu and Arg-Val-Val-Ile-Ala) are slightly modified peptide sequences from the C-terminal part of $A\beta$ 1-42. Our studies with radioactive labelled compounds proved that these novel pentapeptides tightly bind to the surface of $A\beta$ fibrils. We suppose that this binding prevents the interaction of $A\beta$ fibrils with neuronal membrane proteins.

Interestingly, the same peptides prevent also the interaction of fibrillar $A\beta$ 1-42 with microglial cells inhibiting microglia activation. These findings can give a solid base for further preclinical studies. Our pentapeptides are putative drugs in treatment of Alzheimer's disease.

Treatment of agitation in old-age patients

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The importance of research regarding agitation occurring in elderly patients lies in the high incidence of the condition. The number of elderly people in the world is rising steeply, there is an ever growing number of dementia patients treated in inpatient units and agitation is one of the most frequent behavioral symptoms of dementia. Although there is clearly a relationship between agitation and the degree of cognitive impairment, dementia per se does not fully explain agitation, we need to consider psychological and environmental factors, the possibility of concomitant somatic diseases, psychiatric conditions, the problematics of premorbid personality. Consequently, the applied therapy is rather complex and often problematic. The psychiatric evaluation of the hospitalized patients is frequently required due to agitation and can often generate conflict among the staff as well as it rises the following questions: which ward should the patient be treated at, what is "more important" the symptom or the somatic disease, should we treat an agitated patient at a somatic ward or should we treat a potentially vitally endangered but agitated patient at a psychiatric ward? The applied therapy needs to be planned according to the clinical pharmacological characteristics of the given patient population such as the change that occurs in drug absorption as a result of ageing, the modifications in plasma protein binding, the

significant change of metabolism and elimination of several specific molecules and the change in the pharmacodynamic interaction of drugs with their receptors. Another major goal should be to avoid drug interactions which is a difficult task taking into consideration the high number of the concomitantly used compounds (the use of 6–8 different drugs being quite common). Our aim is to make an outline of the of different subtypes of agitation based on the Cohen–Mansfield Agitation Inventory, to point out the most frequent reasons of its occurrence, to make an overview of the possible pharmacological and non-pharmacological therapies, to speak about our experiences and applied strategy in the treatment of old-age agitation.

Different nature of late onset insomnia and non-sedative drugs in its treatment?

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Background/literature review: There are many papers on the frequent occurrence of sleep disturbances in different neuropsychiatric diseases of elderly but data on their significance treatment are practically missing. Poor sleep can influence even the cognitive performance of the geriatric patients. Successful treatment of old age insomnia has not been solved yet.

Working hypotheses: Late onset insomnia (LOI) might include a larger scale of syndromes from the classical (e.g. psychophysiological) forms to states (like sundown syndrome in dementias) much closer to delirium. One can suppose that in the majority of late onset insomnia also brain metabolic disturbances may have some etiological role.

Results: Authors constructed a bipolar axis containing all the typical symptoms of late onset insomnia. The position of a given symptom on the axis (i.e. its distance from the end points – psychophysiological and delirious insomnia) can give information on the probability of its organic nature. Furthermore the settlements on this axis might be in connection with the therapeutic responsibility of different drugs (including not only sedato-hypnotics but brain metabolic enhancers and nootropics as well).

Discussion: While sleep is an active process (at least theoretically) any causes leading to the disorder of the brain metabolism are able to produce or make worse late onset insomnia. We hope that using the above mentioned axis a detailed evaluation of the symptomatology of late onset insomnia it will lead to important therapeutic consequences.

Namely symptoms on the “metabolic side” can be improved by a single evening application of any drugs improving the function of the brain (brain metabolism

enhancers, nootropics, antioxidants or neuroprotective agents) might show an own “paradoxical hypnotic” effect or in combination with sleeping pills they can bring an additive effect in late onset insomnia patients. The efficacy of this treatment can also have a diagnostic value: it helps to differentiate between the primary (organic) and psychophysiological (situative or psychic) forms of late onset insomnia.

Our experiences with examinations of demented patients, using neuropsychological test battery – Results of the examinations during half a year

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Purpose of this examination was to value the results of neuropsychological tests and similar them to the clinical features.

During given period (half a year) we examined 63 patients, who had memory and/or orientation disturbances. Most of them were inpatients, some outpatients. The protocol of examination what we used was determined for The Centres of Dementia.

In every case we studied laboratory tests, CT or MRI, neurological and psychiatric examinations with anamnesis from relatives, and we used a neuropsychological test battery. Our test battery was: Beck depression scale, Subjective Memory Questionnaire (SMQ), Addenbrooke’s cognitive scale (ACS), Mini Mental State (MMS) and Clock-test. We valued the results as dementia: ACS: equal or less than 88, MMS: equal or less than 26, clock-test: equal or less than eight. We accounted a quotient, to sign the type of dementias (Alzheimer or frontotemporal).

The results: 62 ACS were made, and 49 showed adequate value of dementia. MMS was made in 63 cases, but only 31 showed such value as it was adequate to dementia. The clock test relate to dementia in 35 from 62 cases. It seems that in our study the most sensitive test was ACS.

The quotient what we calculated every patients showed only in 18 cases similar result than clinical features.

We picked out those patients, who were clinically diagnosed Alzheimer’s diseases, but the quotient did not show the same. Studying these patients, we found, that they had other illnesses too, as cerebral ischemic lesions, hydrocephalus internus and externus, progressive supranuclear palsyndrome.

Summing, this test battery is adequate to use for examination of dementia and we hope, if we have more experience, we will have more possibility to diagnose the different dementias in early state.

Consequences of the carotid Duplex ultrasonography in cognitive impairment

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Background: Researchers reveal that vascular factors have a great importance in Alzheimer's disease as well. The clinicopathological overlap is important in different types of dementia. Our clinical experience that the role of the vascular factors are important in BPSD, independently from aetiology of dementia. In spite there are only a few experiences with the carotid duplex ultrasound examination (CDUE) according to cognitive impairment (CI). According to these our preliminary study aimed at the usefulness of the CDUE in this field.

Method: Retrospective evaluation of data of 60 consecutive CI inpatients according to CDUE from 1st January, 2004.

Results: 39 female and 21 male were involved, average age was 75.2 (30–95 years). The aetiology of CI was different: Eight patients with probable Alzheimer's disease according to the NINCDS-ADRA, 23 patients with vascular disease, 16 patients with vascular and Alzheimer's disease, four patients with Lewy-body disease, three patients with pseudodementia, one patients with Huntington-disease, five patients with unknown disease. We found that, acute BPSD occurred most frequently related to the vascular factors. There was made 32 CDUE: negative: four, intima-media thickness: three, atherosclerosis: 21, non-significant stenosis: four. Among the primer neurodegenerative group (12 patients) there were nine CDUE, and only two of them were negative, we found arteriosclerosis in seven patients.

Conclusions: According to our preliminary hypothesis, data suggest that atherosclerosis may play role in accordance of reversible psychosyndrome, such as BPSD and CDUE could take part in the management of BPSD. However it needs a prospective study.

An improved synthesis of β -amyloid peptides and preparation of oligomers and fibrills for in vitro and in vivo studies

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Alzheimer's disease is a neuro-degenerative disease that is clinically characterised by the gradual onset and progressive decline in memory and other cognitive functions. While the histopathological hallmarks of the disease include the extracellular deposition of amyloid- β peptides ($A\beta$). $A\beta$ is excised from the amyloid precursor protein (APP) by the sequential action of β - and γ -secretase enzymes. Knowledge of the structure of $A\beta$ is essential for understanding the abnormal assembly of them. The peptides undergo a conformational change as a consequence of their propensity to aggregate and to form very stable water-insoluble fibrills. $A\beta$ 1-42 forms a β -sheet structure and amyloid fibrills much more readily than does $A\beta$ 1-40.

In our study, we introduce an improved method for $A\beta$ synthesis using anisole during solid-phase synthesis with Fmoc- α -amino protection. The effect of varying the solvents and choice of cleavage conditions were exam-

ined. The use of anisole improved the swelling of the resin. For the final cleavage of $A\beta$ peptides from the resin, a mixture has been introduced which contained 95% of trifluoroacetic acid, 2.5% of dithiothreitol and 2.5% of water and proved to be optimal. In order to prevent aggregation, peptides were immediately purified on a preparative HPLC, C-4 column without lyophilization after the final cleavage. A wide range of HPLC conditions for the purification of the peptides were examined and an acetonitril-based solvent system with trifluoroacetic acid provided efficient purification. 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was found to be the best solvent for solubilizing the $A\beta$ 1-42 for analytical HPLC test. The purified and lyophilized peptides were redissolved in distilled water and the pH of the solution was adjusted to 7.0 with diluted ammonia solution, in order to increase the solubility of the peptides. After the lyophilization from the solution, the $A\beta$ peptides show good aggregation properties according to electron microscopic studies.

We prepared $A\beta$ 1-42, 1-40, 4-42, 5-42 peptides. All of these peptides were neurotoxic in MTT test. The above method is advantageous for the preparation of $A\beta$ peptides for physiological and biophysical studies. The strategy used to elucidate appropriate conditions for the synthesis and purification of these peptides is generally applicable to other peptides that are difficult to synthesize and purify.

Word fluency test in the diagnosis of dementia

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The diagnosis of dementia similar to a puzzle. The word fluency test may be one part of the diagnosis. It is a very simple method for the measuring of the verbal abilities. There are a variety of verbal fluency test in use. The investigator is given a letter of the alphabet and asked to say as many words as possible that begin with that letter in three minutes. At least two letters are given and registered the answers. The author studied answers of 30 Alzheimer's (AD), and 10 vascular demented (VD) patients. Fifteen persons with similar age and education were the control. In Alzheimer's diseases was the account of the words less, the least in the second minute and characteristic the perseveration and slowly in tempo. In vascular demented there are few answer and absent the perseveratio. The decrease of the account of answers is parallel with the progression of dementia.

The role of the social support system and social workers in the care of elderly people with dementia

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While the social support system plays very important role in the care of elderly people with dementia, according to the statistics only 10-15% of the clients are treat-

ed by the care system, and most of the clients are cared by their families without social support.

The main reason of this situation is the inefficient capacity of the home care system, and the lack of specialized programmes for the clients with dementia within the Day Care Centers.

Another problem is that we have not have any counseling and support services for the relatives of elderly people with dementia.

Our residential homes basically are custodial institutions without special programmes in care of dementia. Usually the staff have not appropriate knowledge and skills for the treatment and care of these clients.

In this presentation the author gives a view of the complex care programme including the support services for families, and special programmes in cognitive rehabilitation in the day care and institutional setting.

The key person in this kind of complex psychosocial programme is the social worker, who works in a wider context within the multidisciplinary team. His/her role is more complex than the traditional case manager-coordinator role. The social workers participate in the assessment and monitoring of cognitive functions, and social skills. They also work as counsellors for families. Organising skill developing and cognitive rehabilitation programmes is a very important part of their work too. Building up this complex psychosocial care programme for elderly people with dementia will be the task of the near future in Hungary.

Neuroimagines in the diagnosis of dementia

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Neuroimagine studies have an important role in the diagnosis of dementia, by itself they cannot diagnose dementia.

The author compared neuroimagines (CT, MRI, SPECT, PET scans) of 42 demented patients with their clinical state. There were performed 33 CT, seven MRI, 18 SPECT and two PET scans. The clinical diagnosis was made after BNO-X, MMSE, the clock test, the Hachinski score, and the Lund–Manchester criteria. There were 13 vascular, 16 Alzheimer's, six fronto-temporal, three mixed, two alcoholic dementia and two age associated memory impairment. It is important that a normal CT or MRI does not rule out dementia at an early stage. The volumen measurement of the hippocampus was impossible. MRI is more sensitive to lesions in the brain than CT, but this is not necessarily an advantage in the diagnosis of vascular dementia. MRI can show also demyelinations in the alcoholic dementia. The SPECT were most incongruent with the clinical diagnosis. The results of the different assessments in few cases were inconsistent. In these cases the diagnosis was based on clinical symptoms. One clinical demented patient using of CT, SPECT and PET scans weren't correlate with the memory scores.

Protective oligopeptides against A β 1-42 excitatory effect on CA1 hippocampal neurons in vivo

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Alzheimer's disease is characterized by amyloid plaques (formed by A β 1-42 peptide) and neurofibrillary tangles (abnormally twisted forms of the τ protein). The toxicity of the plaque is in correlation with its aggregation properties. Protective oligopeptides (FRHDS, RIIGL and LPYFD) were tested, whether they prevent neuronal toxicity of A β through their amyloid surface binding (ASBIM), functional-antagonist/inverse antagonist (FAIA) effect, or both.

Extracellular, single-unit recordings were taken from the hippocampus. Carbon fiber containing multibarrel electrode assemblies were used to record cellular responses as well as to deliver NMDA, oligopeptides, β -amyloid 1-42, and pontamine-sky blue by means of microiontophoresis. Neurons were excited by repetitive iontophoresis of NMDA every minutes for five seconds. The spiking frequency of the neuron was recorded. After establishing a stable control, an oligopeptide was co-iontophoresed for three minutes, then immediately amyloid for one minute, or a mixture of A β 1-42 and an oligopeptide was ejected for one minute. The location of the electrode was verified by means of histology.

All of the three oligopeptide tested were effective in reducing the excitatory effect of A β . The integrin analogue, FRHDS was more effective, when its ejection preceded the A β application. In contrast, RIIGL decreased toxicity in a greater manner in the mixture form. The best effect was achieved with the LPYFD pentapeptide, which proved to be the most potent inhibitor, independently of the application method. The potent inhibitors might have potential therapeutical relevance. Amyloid 1-42 neurotoxicity could be prevented by short oligopeptides in vivo.

Prefrontal lobe

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Alteration of the prefrontal lobe functions develops most frequently in elderly, in cases with subcortical ischemic insults, Parkinson's disease, and several forms of frontotemporal degeneration. In the last decade experimental data and human observations defined five functional units within the prefrontal lobe. The dorsolateral cortex (coordinator) controls the gaze, the voluntary movement and working memory. Regions (Br46, 9, 8A/B, Br10) are target of dorsolateral circuit via caudatum – globus pallidus internus – substantia nigra and thalamus dorsomedialis nucleus and has a rich connection with the hip-

pocampus. The DA system has a particular function in the evaluation of visual patterns. Lesion of the dorsolateral cortex causes severe deficit in working memory regarding temporary storage of information, complex cognition and problem solving. In cases with minimal cognitive deficit anisotropy in the anterior white matter was found by diffusion tensor MRI in elderly. Loss of the prefrontal connections was considered to be a structural bases for selective loss of executive functions. Periventricular prefrontal white matter proved to be a hazard zone for microcirculation, which develops frequently in hypertensive encephalopathies, amyloidosis and CADASIL. The ventro-medial-orbital prefrontal region (motivator), regulates motivation, imotions, behavior, self-elaboration of internal strategies (Br10, 11, 12, 14, 47). The neuronal circuit is relayed by ventro medial caudatum, medial-dorsomedial globus pallidus internus, anterior ventral thalamus and dorsomedialis nucleus. Giant cells project to limbic structures, small cells are targeting the cognitive areas. Systems serving motivation and drive exert a strong influence on cognitive systems. Anterior cingular area (attender) is a part of the limbic system. It organizes attentional functions (Br24, 25, 32, part of Br11, 12). The circuit regulates the initiation of actions and integrates emotions. The Br32 region was attributed to be an affective zone Br24 is a movement related area, the middle cingular territory serves cognition. Structures, directly connected are: ventromedial striatum, nucleus accumbens, rostro-medial globus pallidus, ventral pallidum, rostro-caudal substantia nigra. Indirect connections: ventral striatum, rostral pole of globus pallidus internus, medial part of substantia nigra, and ventral pallidum. The ventro-lateral prefrontal cortex (perceiver) on both sides, organizes self-awareness and conscious recognition of the environment (Br47, 45, 46, 11, 13). Area 46 is involved in spatial working memory. The “verbalize” area (Br45, 47 – left ventral lateral cortex) coordinates motor speech. Local damage in key structures of prefrontal circuits induce characteristic clinical symptoms. Strategic infarcs in the thalamus cause transcortical aphasia, memory disturbances, lack of awareness and concern impairment of movement execution. Isolated left sided lesion of dorsomedialis causes apathia, disturbed memory and pure word fluency. Lesion of the dominant caudatum causes memory, language and attention deficit. Localized ventral infarcts result in euphoric disinhibition and decline in social interpersonal conduct. Globus pallidus internus infarcts lead to memory deficits and mental plasticity. Upper central borderzone infarcts cause complex cognitive and executive disturbances, such as slowness, hypokinesia, decreased speech initiation, and impaired memory. Most of the executive syndroms are the consequences of subcortical ischemic microangiopathy. Frontal dysexecutive amnesia in elderly can be explained by the impaired retrieval in contrast with relative maintained memory. In patients with Parkinson’s disease executive dysability appear during trials to solve new, non-routine problems. Disturbance of internally guided behavior was also

observed. Constructional apraxia can be explained with visuo-perceptive deficit. Delayed responses in motor tasks reflect functional impairment of the prefrontal lobe.

Screening of dementia and co-morbid psychiatric disorders in old population

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Background, hypotheses: Insomnia in healthy elderly is frequent. The high prevalence of insomnia may be in connection with a diffuse cerebral dysfunction or a sub-clinical affective disorder. Aim of our study was to investigate this possible relationship.

Subjects: 35 healthy (or in stable health condition) elderly (age of 78,57±7,74 year) were recruited from a nursing home.

Methods: Mini Mental State Examination (MMSE), Hamilton Depression Rating Scale (HD), sleep questionnaire (SQ) were done. Satisfaction of all subjects was also evaluated.

Results: MMSE 25,15±3,78 (11 demented), HD 12,68±7,46 (mild or severe depressive symptoms in 10 subjects). Data based on the SQ subscale showed that 10 of subjects suffer from insomnia. The satisfaction was average. There was a statistically significant relationship (p=0,04) between MMSE and insomnia symptoms.

Conclusion: Based on our results we can conclude that insomnia in elderly occurs frequently (30%) and is in connection with impaired cognitive performance demonstrated by MMSE. Insomnia has less influence on affective state.

Connection between Alzheimer’s disease and vascular dementia

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The main causes of dementia in later life are Alzheimer’s disease and vascular dementia. In the last century a more or less sharp distinction was supposed between the two diseases. We have now accumulating data about their close connection. Epidemiological (sharing risk factors), genetic (role of apolipoprotein E ε4) data, certain neuroradiological signs (hypoperfusion) and neuropathological features (amyloid angiopathy) are suggesting common etiopathogenetic mechanism. The connection is further complicated by the fact that in about one third of pure form of Alzheimer’s diseases cerebrovascular infarcts can be detected in the brain, but the opposite is true as well: cerebrovascular disease not infrequently can mask the primary degenerative process. Despite these and other arguments about the wide overlap, certain clinical symptoms are different and the neuropathological assessment especially reveals a basic dif-

ference between the two ailments. The similarity of the basic neurotransmitter deficits and of cerebral hypoperfusion makes it possible to use sharing symptomatic treatment possibilities – older (nootropics) and new ones (cholinergic, glutamergic) in both conditions. Further clinical observations supplemented with epidemiological, neuroradiological and neuropathological investigations seem to be basically important for further elucidation of both the distinction and the overlap of the two diseases.

Clinical presentation and importance of aprosodia

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Prosody consists of different variations in sound pitch, stress and rhythm underlying speech melody and inflection. The prosodic components of speech assist in inferring the attitude and emotion of the speaker and are vital in everyday communication. A review of the literature suggests that the left hemisphere is responsible for modulating the linguistic components of prosody (e.g., timing), whereas the right hemisphere is predominantly responsible for modulating the affective components of prosody (e.g., spectral information or pitch).

Aprosodia, the inability to either produce or comprehend the affective components of speech or gesture, is a common occurrence after brain injury. The two basic forms are: executive and receptive ones. Both forms are extremely important in the communication abilities of the patient. Receptive dysprosodia separates the patients from the emotions of others; motoric dysprosodia impairs the ability to adequately communicate. Disorders of affective aprosodia have been classified along the same dimensions as the aphasias. Bedside evaluation and neuroimaging have been used to identify and classify types of aprosodia. The treatment goals for aphasia may be adapted and applied to aprosodia. Additionally, pharmacotherapy and biofeedback have been found useful in the treatment of aprosodia and associated features. Neuroanatomical basis of dysprosodias are widespread: several brain regions are involved (executive forms: frontal, hemisphere lesions, basal ganglia dysfunction, cerebellar lesion etc; receptive forms: right temporoparietal regions). Especially right temporoparietal lesion can cause both forms of dysprosodias. Recent study highlighted the frequency of aprosody in patients suffering from Alzheimer's disease opposed to patients with vascular dementia.

Short case history of eight patients of the Memory Clinic are briefly presented having dysprosody of non-aphasic origine. Their observation underly the heterogenic origine of the symptome that can be present in the frame of dementia disease, mild cognitive impairment of unknown origine, deiseases of basal ganglia and furthermore mixed or pure psychogenic origine as well.

Dual role of serum amyloid P component in the mechanism of the neurodegeneration

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Serum amyloid P component (SAP), a member of the pentraxin serum protein family, is synthesized in the liver with elevated rate in different chronic diseases, including Alzheimer's disease (AD). However its physiological role is not known exactly, it is presumed, that it has role in the protection against different bacterial infections and autoimmune reactions. This protein is present in all types of amyloid deposits including the amyloid plaques of Alzheimer's disease. SAP binds to the A β peptide, promotes its aggregation and increases its proteolytic stability. In the CNS it can be originated either from the circulation by penetrating the blood-brain barrier by an unknown mechanism, or by in situ expression by the pyramidal neurons.

Here we show that SAP has neurotoxic effect on primary cerebro-cortical culture. Following treatment, SAP enters to the neurons and induces apoptosis and β -amyloid (A β) production. In in vivo experiments both intrahippocampal and intracerebroventricular administration of SAP into the rat brain caused the significant elevation of the number of apoptotic nuclei in the cortex and also in the hippocampus after four-week exposure.

We also demonstrate that the inhibition of the SAP-A β interaction promotes the proteolysis of A β , which may result in the clearance of amyloid.

We suggest that the inhibition of the neurotoxic effect of SAP or the reduction of the stability of the deposits by the inhibition of SAP-A β interaction may be promising pharmacological targets in the therapy of Alzheimer's disease.

GSK-3 β is involved in the fast neuronal degeneration evoked with soluble amyloid- β 25-35 peptide in in vitro primary cultures

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In Alzheimer's disease brain samples, large amounts of amyloid- β (A β) accumulate intra- and extracellularly in the various brain areas. According to the amyloid cascade hypothesis, A β contributes directly to neurodegeneration and the development of neurofibrillary degeneration in the Alzheimer's disease brain. It has also been shown that, in primary neuronal cultures, A β induces the degeneration of nerve cells. Our earlier studies revealed that such degeneration begins at the neurites and the process takes several days. Previous findings suggested that the

morphological alteration in the neurons is caused by the fibrillar form of A β . More recently, however, an increasing amount of experimental evidence has accumulated indicating that not only is the fibrillar form of A β toxic to the nerve cells, but the soluble form of the peptide also plays a significant role in the degeneration processes. Glycogen synthase kinase-3 β (GSK-3 β) has been implicated in many fundamental cellular functions; among others, it has the ability to phosphorylate τ proteins.

The aim of the present investigation was to discover the neurotoxic effect of soluble A β 25-35 in neuronal cultures and to reveal whether the degeneration of the nerve cells is a fast or a slow process. We also wished to demonstrate the effects of A β exposure on GSK-3 β and the phosphorylation of τ proteins.

For immunohistochemical demonstration of the effects of A β , the basal forebrain of embryonic day E18 rat was used in these experiments. The neurons were treated with freshly dissolved 10 μ M A β 25 between day in vitro (DIV) 3 and DIV 9 for 5, 10, 15, 30, 60 or 120 minutes. After treatment, the cells were fixed and incubated with various antibodies [GSK-3 β , GSK-3 β (Ser9), GSK-3 β (pY216), anti- β III tubulin, F-actin, τ -5 and τ -pS202]. The neuronal growth cone structures were revealed with specific stains.

The quantitative alterations in the active and inactive forms of GSK-3 β , GSK-3 β (Ser9), GSK-3 β (pY216), τ -pS202 and τ -pS396 were demonstrated with a Western blot technique.

The immunohistochemical results demonstrated that freshly dissolved A β 25-35 exerts a very fast effect on the neuronal growth cone for filopodia and lamellipodia. After 5 and 10 minutes, the number of filopodia was greatly reduced and the growth cone collapsed. The total amount of GSK-3 β remained unchanged, but the inactive and the active forms of GSK-3 β were altered, similarly as for the phosphorylated and hyperphosphorylated τ .

The results reveal that soluble A β 25-35 regulates the function of microtubule-associated proteins, and the morphological changes in the primary neuronal cultures are closely associated with functional changes in GSK-3 β during neuronal development. The effects of A β 25-35 appear first in the neuronal growth cone, from where they spread towards the perikarya of the cell.

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Parkinson disease? Primer dementia? – Demented patient from the point of view of a neurologist and a psychiatrist

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Short case history of a 60-year-old patient: reflux oesophagitis, nephrolithiasis, cholelithiasis, benign prostata enlargement. No alcohol and nicotin. No genetic diseases in family case history. No skull injury.

On July 2002 he was admitted to neurological department, because of behavioural disturbances, general

weakness, vertigo, depression, and hyperkinesises on the right lower extremity. Skull CT: bilateral calcification of basal ganglions. Because of Parkinson-symptoms and cognitive disturbances skull MRI, carotis ultrasound, liquor examination, blood tests (B₁₂, folic acid, liver, kidney and thyroid gland serum levels) had been measured. MMSE 27 points, watch drawing test: 8 points. No severe alterations on the results. Therapy: selegiline (2 \times 5 mg) and piracetam (2 \times 2400 mg) and regular medical contoll. First psychiatric admittance in August 2003: Parkinson-symptoms with anxiety, hostility, depression, behavioural disturbances. Therapy: SSRI antidepressant and anxiolytics. At the same time, because of severe Parkinson-symptoms we started to substitute the L-dopa. After four weeks: confusion, acustic hallucinations, paranoid delusions. (MMSE 26 points – no changes in parkinsonian symptoms.) Therapy: Decrease of L-dopa, and administration of antipsychotics. After two days the patient became more confused. The disturbances of thinking, the rapid changes of other symptoms, and the decrease of MMSE (16–20 points) were also characteristic. Skull CT: frontal and temporal atrophy (minimal level).

During severe hypokinesia the patient infected by an antibiotics resistant pneumonitis – and died.

Although the family did not permitted the pathological examinations – the most possible diagnosis was the diffuse Lewy-body disease. The case history of our patient shows the good example of the necessity of the collaboration and “together thinking” among neurologists and psychiatrists.

Possible methods for the identification of neuronal cells in mixed neuroglial culture

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Previously we examined the effects of aggregated amyloid β (A β 1-42) on the morphology of the cells in differentiated SH-SY5Y neuroblastoma cell culture. These examinations provided us a good model for measuring in vitro neurite degeneration. The A β 1-42 induced morphological changes of cells in mixed neuroglial cell culture (isolated from the neurocortex of a two day old rat) were also examined. However, these cells could not be distinguished from each other with absolute certainty as glial or neuronal cells.

It is very important to distinguish neuronal cells from glial cells, because the ratio of neuronal cells to glial cells have to be determined for working with the cell culture. The examination of neurite degeneration also needs the identification of neuronal cells.

Immunocytochemical staining provides a possible method for the identification of cell types using specific markers following fixation. Primary antibody to micro-

tubule associated protein 2 (MAP 2) and fluorescein isothiocyanate (FITC) -conjugated secondary antibody were used for the identification of neuronal cells. Primary antibody to glial fibrillary acidic protein (GFAP) and tetramethylrhodamine-5-(and 6-) isothiocyanate (TRITC) -conjugated secondary antibody were used for the identification of glial cells. After the immunocytochemical identification, we examined the morphological features of these cells. The shape and size of cell bodies, the morphological features of the emergence, the length and the characteristic branching pattern of processes were observed.

These examinations provided us the possibility of distinguishing neuronal from glial cells simply by their characteristic morphological features with light microscopical observations.

In vitro UVB-irradiation-induced apoptosis in lymphocytes of Alzheimer's disease patients

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Introduction: The age is the one of the important risk factors for the development of dementia (Alzheimer's disease, vascular dementia, Lewy-dementia). In elderly the cells become more susceptible to death and this phenomenon is even more pronounced in neurodegenerative diseases. However, the pathological processes are not limited only to central nervous system but they appear in non-neuronal, peripheral tissues as well.

Methods: Peripheral blood mononuclear cells were prepared from venous blood of 17 Alzheimer's disease patients and 12 age-matched controls and irradiated by UVB laser in an increasing dose (100, 200, 300 mJ/cm²). Paraformaldehyde was used to fix and saponin to permeabilise the cultured (20 h) cells. Finally, they were stained with anti-human CD3-FITC mAb and Apo2.7-PE mAb. The ratios of apoptotic T-lymphocytes were determined by flow cytometry.

Results: Lymphocytes, derived from control and Alzheimer's disease persons, cultured without irradiation underwent minimal apoptosis that is considered as a baseline (3.14±1.70%; 3.81±1.82%) (mean±SD). Deaths of lymphocytes from control patients increased according to the doses of the radiation (55.52±9.42%, 69.40±6.87% and 69.51±9.23%) respectively. However, the Alzheimer's disease lymphocytes showed significantly (p<0.001) lower apoptotic levels (35.04±8.68%; 51.76±9.48%; 55.81±9.76%).

Conclusion: Our major finding indicate that the lymphocytes are more resistant to UVB-irradiation in

Alzheimer's disease than in control patients. The small basal apoptosis-values suggest similar states of lymphocytes in both groups. Therefore, the cause of the divergent degrees of the cell deaths could be in the different susceptibility of lymphocytes. One explanation of these observations may be that the ongoing chronic inflammatory events render the lymphocytes of Alzheimer's disease less sensitive to the UVB-induced stress.

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Immunohistochemical localization of active and inactive GSK- β in the hippocampus of human brain samples

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Alzheimer's disease is characterized neuropathologically by the presence of neurofibrillary tangles and the deposition of amyloid- β in the cerebral cortex, especially the hippocampus. In the neurofibrillary tangles in the Alzheimer's disease brain, the normal cytoskeleton is disrupted and replaced by neurofibrillary tangles. Thus, it is likely that the abnormal hyperphosphorylation of τ in Alzheimer's disease may lead to the depolymerization of microtubules, impaired axonal transport and neuronal degeneration. The glycogen synthase kinase (GSK-3 β) involved in the phosphorylation of τ is responsible for this neuronal malfunction. Phosphorylation at the various sites is reported to cause the decreased microtubule binding of τ and the dysfunction of the affected neuron. GSK-3 β has been suggested to play a role in neurofibrillary tangles formation.

In the present study, we investigated the distribution of active and inactive GSK-3 β in the hippocampus of control and Alzheimer's disease brain samples.

Autopsy brains were investigated. The ages varied between 51 and 92 years. The neuropathological changes were revealed by means of Gallyas silver impregnation and various immunohistochemical techniques. For the demonstration of the inactive and active GSK-3 β , GSK-3 β (Ser9) and GSK-3 β (pY216) antibodies were used, respectively. The presence of extracellular A β was demonstrated by using C-terminal A β antibody.

In most of the control brain samples, only a few A β -positive senile plaques could be detected, but a large number of plaques were revealed in the hippocampus of the Alzheimer's disease samples. The use of specific antibody against active GSK-3 β (GSK-3 β pY216) pointed to the colocalization with neurofibrillary tangles.

The immunohistochemical results provide evidence that A β may induce the activation of GSK-3 β in some neurons in the hippocampus of the Alzheimer's disease brain, and thereby induce τ hyperphosphorylation and neurofibrillary tangles formation. The activated GSK-3 β therefore plays a significant role in the aetiology and pathogenesis of Alzheimer's disease.

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