Ageing and dementia 2

P2001

High-dose 13.3mg/24h rivastigmine transdermal patch demonstrates efficacy on instrumental activities of daily living: analysis of autonomy and higher-level function subscales

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Background: There is a need for improved therapeutic options for patients with Alzheimer’s disease (AD) to address decline in ability to perform instrumental activities of daily living (IADL). The objective of this analysis was to assess efficacy of a higher dose of rivastigmine transdermal patch (13.3mg/24h) on the IADL domain of the ADCS-ADL scale, focusing on autonomy and higher level function (HLF), in patients with mild-to-moderate AD.

Methods: Patients with AD meeting pre-specified decline criteria during initial open-label (IOL) treatment with 9.5mg/24h patch, entered a 48-week, randomised, double-blind (DB) phase (13.3 versus 9.5mg/24h). Change from DB-baseline to Week 48 on the ADCS-IADL (co-primary outcome) and autonomy and HLF subscales, was calculated and compared between treatment groups.

Results: Of 1584 patients enrolled into the IOL phase, 567 entered the DB phase (13.3mg/24h, n=280; 9.5mg/24h, n=287). Overall, the between-group difference in change from baseline on the ADCS-ADL was statistically superior with 13.3mg/24h patch from Week 16 onwards (p<0.05). The 13.3mg/24h patch showed statistical superiority over the 9.5mg/24h patch on the autonomy subscale at Weeks 24 (p=0.025), 32 (p=0.009) and 48 (p=0.041), and on the HLF subscale at Weeks 32 (p=0.006) and 48 (p<0.001).

Conclusions: The 13.3mg/24h rivastigmine patch significantly reduced deterioration on IADL compared with the 9.5mg/24h patch, with greater efficacy demonstrated on both autonomy and HLF. These results indicate that the higher-dose patch offers clinically meaningful benefits on IADL.

P2002

Abnormalities of functional connectivity in patients with frontotemporal dementia: a network analysis using resting state fMRI and graph theory

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Objective: To investigate the functional organization of large-scale brain networks in patients with the behavioural variant of frontotemporal dementia (bvFTD) using resting state functional MRI (RS-fMRI) and graph theory.

Methods: 18 bvFTD patients (mean age=61.9 years, SD=8.4, MMSE: 22+6), and 50 sex-matched healthy controls (mean age=61.9 years, SD=9.1) underwent RS fMRI examination. Whole-brain networks were assessed using graph theory. First, the correlation matrix between the 90 cortical regions of the automated anatomical labelling (AAL) atlas, representing functional connectivity inside the brain, was computed for each subject. This matrix was subsequently binarized at different thresholds. The overall topology of functional connectivity was examined at each threshold by computing the commonest graph theoretical metrics, comprising the degree, the clustering coefficient, the characteristic path length and the global efficiency. Between-group differences of network connectivity were investigated with a two-sample t-test.

Results: Most of graph theoretical metrics were significantly altered in bvFTD patients vs. healthy controls. In particular, the average degree and global network efficiency were significantly decreased in bvFTD patients vs. controls at all considered correlation thresholds (p ranging from 0.015 to 0.045). On the contrary, the average path length was significantly increased (p ranging from 0.015 to 0.03). The average clustering coefficient was significantly lower in bvFTD patients than in healthy controls at most of the examined correlation thresholds (p ranging from 0.02 to 0.09).

Conclusions: The large-scale functional network organization is significantly altered in bvFTD patients vs. control subjects, suggesting a loss of efficiency in information exchange between brain areas.
P2003

Combined nutrient enrichment induces changes in synaptic protein expression in-vitro

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Introduction: Alzheimer’s disease (AD) is a progressive neurodegenerative disease and although its etiology is not yet completely understood, it is clear that loss of dendritic spines and synaptic connections are one of the hallmarks of AD. Preclinical work indicates that nutrients such as DHA, EPA, UMP, choline, B-vitamins, folate, phospholipids, vitamin C and E, and selenium (combined in Fortasyn™ Connect, FC) are precursors or cofactors in the synthesis pathway of new neuronal membranes and act synergistically to support synapse formation. To explore the molecular mechanisms in which these nutrient combinations stimulate synaptogenesis, we tested their effects on synaptic protein expression in-vitro.

Methods: PC12 cells were differentiated with NGF to induce neuronal differentiation (characterized by neurite outgrowth and neuronal protein expression) and supplemented with or without combinations of DHA and EPA, UMP, choline, B-vitamins, folate, phospholipids, vitamin C and E, and selenium. Subsequently, the effects of multi-nutrient supplementation on gene expression of several proteins involved in synapse formation were determined using Real-Time PCR. In addition, changes in neurite length and in pre- and postsynaptic protein expression were investigated in control versus FC supplemented primary hippocampal mouse neurons, using high content analysis (Cellomics).

Results: Analysis of the data showed an increase in mRNA and protein expression of synaptic proteins related to neurite outgrowth and synapse formation upon nutrient supplementation.

Conclusion: In general, the specific nutrient combination in Fortasyn™ Connect increased synaptic gene expression more than the other nutrient combinations tested.

(Fortasyn™ Connect is a registered trademark of N.V. Nutricia)

P2004

Impaired nutritional status in patients with mild Alzheimer’s disease compared to healthy age-matched controls

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Introduction: Epidemiological studies suggest that low intake of n-3 fatty acids, B-vitamins, and antioxidants increase risk of Alzheimer’s disease (AD). Other studies suggest that patients with AD have lower plasma levels of these nutrients compared to age-matched controls, either due to reduced daily consumption, their increased use, different metabolism, or a combination of these factors. In this study, nutritional status in AD was further explored by comparing clinical nutritional characteristics and plasma micronutrient concentrations in mild AD patients with healthy age-matched controls.

Methods: Nutritional status was assessed in a subgroup of Dutch drug-naïve patients with mild AD (MMSE≥20) participating in the Souvenir II study and a group of Dutch healthy control subjects, matched for age and gender. Between-group differences in nutritional blood parameters and anthropometrics were analysed using ANCOVA, including age and nutritional supplement use as possible confounders.

Results: In total, 84 AD patients and 98 healthy controls were included in this investigation (overall age 72±9y, 47% male). Plasma selenium (p<0.001), vitamin D (p=0.084) and the proportion of DHA (p=0.006) and total long-chain n-3 PUFA (p=0.024) in erythrocyte membranes were lower in AD patients vs. controls. No statistically significant differences were observed for plasma fatty acids, choline and folate. Mini Nutritional Assessment screening score was significantly lower in AD patients (p=0.008), whereas BMI was comparable with healthy controls.

Conclusion: The nutritional status of patients with mild AD is impaired vs. healthy controls, suggesting that these patients could benefit from nutritional support, designed to meet specific nutritional requirements in AD.
P2005

Dendritic and synaptic pathology in mamillary bodies in Alzheimer’s disease

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Objective: Mamillary bodies are implicated in selective memory and learning, showing a significant volume reduction in Wernicke’s encephalopathy, Alzheimer’s disease and aging. We attempted to describe the morphological alterations of the neuronal networks of the nuclei of the mamillary bodies in Alzheimer’s disease, focusing our study on dendritic arborisation and synaptic morphology.

Methods: We applied Golgi technique, Golgi-Nissl method and electron microscopy in specimens of mamillary bodies derived from 12 early cases of Alzheimer’s disease, 6 men and 6 women.

Results: Decrease of the neuronal population was noticed mostly in the medial mamillary nucleus associated with marked loss of the tertiary dendritic branches. The dendritic spines were substantially decreased. Giant spines were frequently seen. No Alzheimer’s type pathology was noticed. Electron microscopy revealed poverty in synaptic vesicles in the prosynaptic terminals. Mitochondrial alterations were seen in the majority of neurons and in the synaptic profiles.

Conclusion: In early cases of Alzheimer’s disease mamillary bodies demonstrate neuronal loss, dendritic and synaptic pathology, but neither dendritic plaques nor tau pathology.

P2006

Developing our understanding of the pathogenesis of Alzheimer's disease using a systematically identified dataset of interventions tested in transgenic mouse models

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Introduction: Despite almost two decades of research testing interventions in transgenic mouse models of Alzheimer’s disease, success in clinical trials has remained elusive. A deeper understanding of characteristics of pathological outcomes reported in animal studies may help explain this translational failure.

Aims: To describe histological outcomes reported when testing interventions in transgenic models of Alzheimer’s disease, and to investigate potential relationships between neuronal loss, plaque burden and tau neurofibrillary tangles.

Methods: Electronic searching to identify publications reporting the efficacy of interventions in transgenic models of Alzheimer’s disease. We extracted data for plaque burden, tau neurofibrillary tangles (which included both the abundance and phosphorylation state of tau), neuronal damage, neuronal loss and regeneration. For each experiment we calculated standardised effect sizes and we used meta-regression to describe relationships between variables.

Results: We identified 427 publications, 355 interventions and 55 transgenic models. Plaque burden, tau and neuronal loss were reported in 54%, 9% and 10% of publications respectively. Indirect markers of neuronal injury (synaptophysin staining, caspase activity) were significantly more sensitive to treatments than direct measures of neuronal loss. Changes in plaque burden explained 61% of the variation in tau (33 experiments, p<0.01) and 85% of the observed variation in neuronal loss (31 experiments, p<0.01).

Conclusions: Few studies reported changes in tau or neuronal loss. Stratified analysis suggested that indirect measures of neuronal injury may over-estimate the effect of drugs on neuronal survival. Changes in plaque burden were closely related to changes in tau and to neuronal loss.
**P2007**

**Comparison of quantitative EEG between patients with Alzheimer’s disease and those with Parkinson’s disease with dementia**

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**Introduction:** Dementia frequently occurs in Parkinson’s disease (PD) but its pathophysiological basis is little known. Comparative EEG studies of AD and Parkinson’s disease with dementia (PD-D) are still rare, but could provide knowledge on the different pathophysiological mechanisms involved. The objective of the present study was to comparatively evaluate the absolute power and coherence on the EEG for patients with AD and PD-D.

**Methods:** 39 patients with AD, 12 with PD-D and a control group (CG) with 54 individuals were assessed using a neurological evaluation, CERAD neuropsychological battery (consortium to establish a registry for Alzheimer’s disease), Mini-mental Status Examination, executive functions examination and EEG. For the EEG the global absolute powers were calculated for the delta, theta, alpha and beta bands corresponding to the means of the absolute powers at the various electrodes, as also the inter-hemispheric and intra-hemispheric coherences.

**Results:** Significant differences were found between PD-D, AD and CG (ANOVA, p<0.001) for the log transformed absolute theta power (47.0±8.3, 38.7±9.85, 32.6±7.5, respectively) and F3-F4 beta coherence (0.54±0.14, 0.44±0.06, 0.49±0.07). The post-hoc tests verified differences between all pairs of groups. The mean frontal-occipital coherence was greater for PD-D than for AD or CG (0.50±0.13, 0.40±0.05 and 0.40±0.05).

**Conclusions:** The increase in theta power was greater in PD-D than in AD. For coherence, the alterations occurred in inverse directions: an increase in PD-D and decrease in AD. Such findings on the EEG are neurophysiological expressions of the different pathophysiological processes in AD and PD-D.

**P2008**

**The profile of dysexecutive disorders in Alzheimer’s disease and MCI. Implications for diagnosis**

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**Introduction:** Dysexecutive deficits have been reported with variable methodology in AD. Following validation of criteria of dysexecutive syndrome¹, we examined their frequencies in both behavioural and cognitive domains.

**Objective:** To determine the profile and frequency of dysexecutive disorders and syndrome in mild to moderate Alzheimer’s disease (AD).

**Methods:** Patients with probable or possible AD (n=72; age: 76.7±7.8; MMSE: 22.7±2.8) and amnestic MCI (n=18; age: 74.3±5.6; MMSE: 25.7±2.9) were matched to 90 controls. Executive disorders were assessed using a standardized battery including heteroquestionnaire (Behavioural Dysexecutive Syndrome Inventory) and 7 tests (Trail Making, Stroop, Modified Card Sorting, verbal fluency, Six Elements task, Brixton and Dual task).

**Results:** Behavioural dysexecutive syndrome was frequent (65%) and characterized by a high frequency of apathy (62%) and anosognosia (64%). Cognitive dysexecutive syndrome was frequent (73%) and characterized by a high frequency of deficit of generation (61%), planning (53%) and flexibility speed (53%). The profile was similar in MCI. The most frequent and discriminant impairments were apathy, generation and flexibility speed (p=0.0001). The presence of one of these deficits predicted dysexecutive syndrome of AD with high sensitivity (0.92; specificity: 0.4; PPV: 0.8; NPV:0.67).

**Conclusions:** Executive functions are impaired in AD even at the mild severity stage with a specific profile. This allows using a shortened diagnosis battery providing good sensitivity.

P2009

Specific memory complaints may influence the search for clinical care

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Introduction: The diagnosis of mild cognitive impairment relies on the presence of memory complaints. In proposed revised criteria for prodromal Alzheimer’s disease, the report by patients or informants of memory decline remains part of the core diagnostic features. However, memory complaints are very frequent in healthy people. The objective of this study was to determine the severity and type of memory difficulties presented by elderly patients who search for clinical help, as compared to the memory difficulties reported by subjects in the community.

Methods: Assessment of subjective memory complaints with the Subjective Memory Complaints scale (SMC) was performed. The Mini-Mental State Examination was used for general cognitive evaluation and the Geriatric Depression Scale for the assessment of depressive symptoms. Differences in the total SMC scores and individual SMC items were tested.

Results: 871 non-demented subjects older than 50 years were included. Participants in the clinical setting had a higher total SMC score (10.3±4.2) than those in the community (5.1±3.0). Item 3 of the SMC, “Do you ever forget names of family members or friends?”, contributed significantly more to the variance of the total SMC score in the clinical sample (18%) as compared to the community sample (11%).

Conclusion: Patients who seek for medical help report more pronounced memory complaints. Forgetting names of family members or friends seems to play an important role in subjective memory complaints in the clinical setting. This symptom is possibly perceived as particularly worrisome and likely drives people to search for clinical help.

P2010

Does Alzheimer’s disease with early-onset progress faster than with late-onset?
A case-control study of clinical progression and cerebrospinal fluid biomarkers

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Background: Early-onset Alzheimer’s disease (EOAD) is generally thought to have a more rapid course compared to late-onset AD (LOAD). The faster progression of EOAD observed in some studies, has also been thought to correlate with cerebrospinal fluid (CSF) biomarkers. Our clinical experience has not been suggestive of any difference in disease progression, thus we decided to investigate whether differences in clinical progression and CSF biomarkers between EOAD and LOAD could be demonstrated.

Methods: Case-control study with 42 patients, 21 EOAD and 21 matched LOAD patients. Rates of progression were calculated and these, as well as CSF biomarker levels, were statistically compared.

Results: There were no statistically significant differences in clinical progression between the EOAD-group and the LOAD-group. There was no significant difference in the absolute values of CSF biomarkers, but a tendency towards lower levels of beta amyloid in patients with EOAD was observed.

Conclusions: Our findings did not converge with results from the majority of previous studies, which have been suggestive of a faster clinical progression in EOAD. Possibly, the very strict algorithm by which our patients were matched explains our findings. However, the findings should be repeated in a larger study population.
P2011
Rapid progression from mild cognitive impairment to Alzheimer’s disease related with CSF biomarker abnormalities

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Introduction: Some studies have shown that CSF amyloid-beta 1-42 (Ab 1-42), total tau (T-tau) and tau phosphorylated at threonine 181 (P-tau 181p) proteins are useful diagnostic markers for distinguishing between clinically stable mild cognitive impairment (MCI) patients and those who will develop Alzheimer’s disease (AD).

Our objective was to test the ability of this technique to discriminate in our cohort of MCI patients, according to the clinical evolution, one year after lumbar puncture.

Method: 64 amnestic MCI patients were included from the local hospital memory clinic. Using INNO-BIA Alzbio-3 reagents from Innogenetics, we quantified CSF Ab 1-42, T-tau and P-tau 181p proteins and calculated the ratios T-tau/Ab 1-42 y P-tau 181p / Ab 1-42. This project was approved by the local Ethical Committee.

Results: One year after lumbar puncture, 29 MCI patients (45%) developed AD. These patients showed lower Ab 1-42 protein levels (308.3 vs. 435.8ng/ml, p<0.003) and higher of T-tau (113.5 vs. 71.6ng/ml, p<0.003) and P-tau 181p (62.2 vs. 48.6ng/ml, p<0.01) as well as T-tau / Ab 1-42 y P-tau 181p / Ab 1-42. This project was approved by the local Ethical Committee.

Conclusion: Our MCI patients with lower Ab 1-42 protein levels and increased tau proteins progressed rapidly to EA. These results may help to identify those MCI patients with a worse prognosis.

P2012
Mortality risk factors in a population older than 65: follow-up after 11 years

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Introduction: Studies analyzing the relationship between dementia, sleep disturbances and mortality are lacking in the literature; in particular, we are not aware of studies which considered these three variables altogether. The aim of our study was to evaluate, in a population of older adults, whether the risk of mortality increases when sleep disturbances and dementia are associated.

Methods: Death records from 752 patients enrolled in a previous study (Merlino et al. Sleep Medicine 2010; 11: 372-377) were consulted after 11 years of follow-up. Mortality curves were obtained and a possible relationship between mortality and sleep disturbances (restless leg syndrome, excessive daytime sleepiness, insomnia, sleepwalking, snoring or sleep apnoea, nightmares) was considered.

Results: After 11 years, 9 patients were lost; among the other 743 patients, 308 (41%) were dead and 435 (57.8%) were still alive. In particular, 83.7% of patients with cognitive decline died, whereas only 35.5% of patients not affected by dementia died (p=0.001). Mean age of death did not differ significantly between the two populations. The independent risk factors of mortality in that population were age (OR:1.12), smoke (OR:1.62) and dementia (OR:2.76). Patients with dementia and excessive daytime sleeping had a higher mortality than patients with dementia and no sleep disorder (p=0.07).

Conclusions: Our study shows that not only excessive daytime sleepiness is associated with a higher prevalence of cognitive decline, but that dementia is associated with a higher mortality, especially if associated with excessive daytime sleepiness.
**P2013**

**Ile143Thr presenilin 1 mutation in sporadic atypical early-onset Alzheimer’s disease**

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**Introduction:** Early-onset Alzheimer’s disease (EOAD) accounts for about 5% of all AD cases. As with senile AD, it presents with gradual memory impairment, followed by progressive global cognitive decline, but typically affects subjects <65 years old. Most commonly, EOAD concerns genetically predisposed families carrying mutations in the Amyloid-Precursor-Protein, Presenilin(PSEN)1 and PSEN2 genes. Sporadic, non-familial cases of EOAD positive for one of the predisposing genotypes, have rarely been described.

**Methods:** We present a case of sporadic EOAD with an atypical clinical presentation, positive for the ile143thr mutation in the PESN1 gene.

**Results:** A 34-year-old previously healthy male with no family history of dementia, presented with a 12-month history of an evolving neuropsychiatric condition. His symptoms consisted of apathy, withdrawal, mood and concentration disturbance, followed by confabulation for which he had been treated with antidepressants and antipsychotics. Ten months later, memory and visuospatial impairment appeared. Neurological examination was normal, except for generalized myoclonic jerks. Neuropsychological assessment revealed significant deficits in memory (MMSE=19), visuospatial ability, and executive functions. Common laboratory tests and neuroimaging were normal. Further investigation for Creutzfeldt-Jacob's disease, Wilson's disease and autoimmune encephalitides was negative. CSF analysis was indicative of a neurodegenerative condition (increased p-tau, decreased Aβ42-amyloid), later confirmed by identification of the ile143thr PSEN1 mutation, which set the diagnosis of EOAD.

**Conclusion:** This atypical case of EOAD underlines the importance of genetic testing even in patients with sporadic, non-familial EOAD, and suggests that the disease may initially present with refractory neuropsychiatric symptoms and non-amnestic cognitive decline.

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**P2014**

**Role of neuroimaging in the diagnosis of Alzheimer’s disease, with emphasis on brain MRI and SPECT**

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Alzheimer’s disease (AD) is difficult to diagnose in its early stages. Imaging modalities such as MRI, SPECT, and PET are promising tools as early markers of brain pathology in AD. PET is best, but not widely available. The aim of this study was to examine the usefulness of MRI and SPECT to diagnose AD.

**Methods and patients:** 168 AD patients were divided into two groups by their age at the initial examination: 36 Alz-E group (aged 54-69 years), and 132 Alz-L (70-95). The AD patients fulfilled the DSM-IV criteria for dementia and the NINCDS-ADRDA criteria for probable AD. Each patient underwent the Mini-Mental State Examination (MMSE), WMS-R, and a questionnaire containing 31 items. A voxel based specific regional analysis system for AD (VSRAD) was used for the analysis of MRI images by using the Sigan HDx, 3T Z-score imaging system and the Voxel Based Stereotactic Extraction Estimation (vbSEE) was used for the quantitative assessment of brain SPECT images.

**Results:** The vbSEE analysis of SPECT images in AD showed significant hypoperfusion in the inferior parietal lobules, angular gyrus, supramarginal gyrus, middle temporal gyrus, inferior temporal gyrus, precuneus and posterior cingulate gyrus. At least two of the hypoperfusion regions suggested AD. The sensitivity, specificity and efficiency of VSRAD were 55.6, 81.8, 71.4% in Alz-E, and 55.3, 89.4, 64.2% in Alz-L, respectively, while those of SPECT-vbSEE were 75.0, 96.4, 87.9% in Alz-E, and 69.7, 93.6, 76.0% in Alz-L, respectively.

**Conclusions:** The SPECT-vbSEE analysis was more useful than VSRAD for the diagnosis of AD.
**P2015**

**Apathy, as a prodrome of future conversion to dementia in patients with amnestic mild cognitive impairment**

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**Aims:** Dementia patients often show depressive mood or apathy. Although depression and apathy were suspected to be the risk of future cognitive decline, there were only a few studies in Asian people. The present study was designed to elucidate the relationship between affective symptoms and cognitive status in Japanese mild cognitive impairment (MCI) patients.

**Methods:** The present study was based on 131 amnestic MCI patients who visited our memory clinic from 2005 to 2011. All subjects underwent mini-mental state examination (MMSE), Zung’s self-rating depression scale (SDS) and Starkstein’s apathy scale (SAS) at baseline and follow-up evaluation which was performed in one year interval. Student’s t-tests were performed about the correlation between MMSE and SDS/AES at the baseline and follow-up evaluation. The subjects were classified into three groups according to the tertiles of SDS and AES.

**Results:** 40 of our 131 MCI patients were diagnosed as converted to AD in one year. The SAS correlated negatively with MMSE score (p<0.05), whereas no relationship was found between SDS and MMSE. The highest SAS tertile group showed a significantly greater decline in MMSE score in one year than the lowest SAS tertile group (-1.953 vs. -0.617, p=0.0247). No such relationship was found between SDS and MMSE score.

**Conclusion:** Apathy was considered to be one of the prodromes of future conversion to dementia in amnestic MCI patients.

**P2016**

**Angiotensinase activities are modified in early stage Alzheimer’s disease**

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Hypertension has been identified as a strong risk factor for Alzheimer type dementia (ATD), and both angiotensin converting enzyme (ACE) inhibitors and angiotensin II (AngII) receptor blockers (ARBs) have been found helped to preserve cognitive function through a mechanisms independent of their antihypertensive effects. Also, the neurotoxicity of Aβ has been shown associated with small changes in the Aβ42/Aβ40 ratio, and AngII induces shifts in this ratio. Several enzyme activities called angiotensinases (aspartyl aminopeptidase (ASAP), aminopeptidase A (APA), aminopeptidase N (APN) and aminopeptidase B (APB)) are involved in the catabolism of circulating angiotensins. In the present work, we have analysed in plasma of male and female ATD patients (n=46) and their age-matched controls (n=46) specific ASAP, APA, APN and APB activities. We found a significant decrease of APA in ATD patients, whereas APN and APB activities increase significantly. Neither significant change in ASAP specific activity nor gender differences were found. These results suggest an accumulation and/or increased bioavailability of AngII in ATD patients. The formation of AngII has been generally found to interfere with memory acquisition, probably interfering with acetylcholine release, which in turn could interfere with cognitive processing. Also, AngII potentiates amyloidogenesis in vivo through the modulation of various components of the APP processing pathway. Our results also support the hypothesis that ACE inhibitors and ARBs facilitate cognitive functioning by reducing the synthesis/availability of AngII. The present results support an important role of the renin-angiotensin system in ATD. (Supported by Junta de Andalucía, Spain.)
P2017
Superoxide dismutase (SOD1) functioning as a predictor of memory decline in Down syndrome (DS)

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Background: By the age of 40, virtually all patients with DS have neuropathological changes characteristic of Alzheimer’s Disease (AD). The aim of our study was to investigate whether the levels of superoxide dismutase (SOD1), glutathione peroxidase (GPx), or their ratio could predict cognitive decline in people with DS over a 4-year period.

Methods: 32 adults with DS participated in a longitudinal study with SOD1 and GPx assays at baseline. Informants rated their functional ability and memory function at baseline and at 4 years follow-up. The more able adults with DS also completed assessments of language skills and memory, at two different time points 4 years apart.

Results: 26 individuals with DS completed assessments of memory (Modified Memory Object Task, MOMT), Adaptive behaviour (ABAS) and receptive vocabulary (British Picture vocabulary, BPVS) at both time-points. Superoxide Dismutase inhibition positively correlated with change on the MOMT score (r=0.578, p=0.015). There were no significant correlations between GPx level or SOD1/GPx ratio and temporal changes in ABAS, BPVS or MOMT scores.

Conclusion: Our results suggest that SOD1 functioning predicts memory decline over time and that this anti-oxidant enzyme could be a potential target for prevention of memory deterioration in adults with DS. Further research is required to test whether supplements which improve SOD1 function can also prevent cognitive decline. These findings may also have implications for prevention of cognitive decline in other groups which are at high risk of developing dementia, such as adults with familial AD or mild cognitive impairment.

P2018
Real-time QUIC (RT-QUIC) assay for the clinical diagnosis of genetic human prion disease

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Background: Prion diseases are fatal neurodegenerative disorders characterized by the accumulation of abnormal prion protein (PrPSc) in CNS. Genetic form of human PrD (gPrD) is caused by mutations in prion protein gene, and is classified into genetic CJD (gCJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), and fatal familial insomnia (FFI). The patients with GSS and FFI have symptoms such as dementia, dyskinesia and sleep disorders, and showed no typical signal in diffusion-weighed MRI. Therefore, it is clinically important to discriminate GSS and FFI from non-prion diseases such as chronic refractory sleep disorders and spinocerebellar ataxia. We recently developed a new in vitro amplification technology, “RT-QUIC”, for the detection of PrPSc in CSF of sporadic CJD. We evaluated this assay in gPrD, and high positivity was observed in all tests.

Method: We retrospectively analyzed 46 CSF samples obtained from gPrD patients, including 22 cases of gCJD E200K, 20 cases of GSS P102L, 2 cases of FFI and 2 cases of gCJD V203I.

Results: We analyzed 24 CSF samples from E200K. The detection sensitivities of RT-QUIC, total tau (T-tau) and 14-3-3 protein assays were 81.8%. The positivity of RT-QUIC was 90% in GSS and 100% FFI. 80% of GSS cases, however, showed negative in T-tau and 14-3-3 proteins, and also were negative in all FFI. Although we were able to analyze only 2 cases of V203I, both cases showed positive for QUIC and only one was positive for biomarkers.

Conclusion: Our study demonstrates that RT-QUIC assay of CSF have clinical utility for laboratory diagnosis for gPrD.
**P2019**

**Safety and tolerability of 9.5mg/24h(10cm2) and 13.3mg/24h (15cm2) rivastigmine patches: results from the OPTimising Transdermal Exelon In Mild-to-moderate Alzheimer’s disease (OPTIMA) study**

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**Introduction:** The OPTIMA study design provided the opportunity to compare safety and tolerability of the 13.3mg/24h rivastigmine patch with the currently approved dose (9.5mg/24h) during a 48-week double-blind (DB) phase, and follow-up safety of the 9.5mg/24h patch during a 48-week extended open-label (EOL) treatment phase.

**Methods:** Patients meeting pre-specified decline criteria (decliners) during a 24-48-week initial open-label (IOL) phase (9.5mg/24h patch), entered a 48-week, randomized, DB phase (9.5mg/24h versus 13.3mg/24h patch). Non-decliners could continue treatment with 9.5mg/24h patch in a 48-week EOL phase. Adverse events (AEs) and serious AEs (SAEs) were recorded.

**Results:** In total, 1584 patients were enrolled: 1085 completed the IOL phase, 567 were classified as decliners and randomized (13.3mg/24h patch, n=280; 9.5mg/24h patch, n=287); 457 were classified as non-decliners and treated in the EOL phase. During DB phase, AEs were reported more frequently with 13.3mg/24h (75.0%) than 9.5mg/24h patch (68.2%); however, discontinuations due to AE were fewer with 13.3mg/24h (9.6% versus 12.7%). The 9.5mg/24h patch was well-tolerated during extended treatment (up to 96 weeks), with incidences of AEs decreasing over time (IOL, 68.4%; EOL, 57.5%). In all study phases, most common AEs included: general disorders and administration site conditions, psychiatric, nervous system, and gastrointestinal disorders.

**Conclusion:** In this study, no unexpected safety findings were observed following 48 weeks of treatment with the new high-dose 13.3mg/24h rivastigmine patch. The 9.5mg/24h patch remained well-tolerated for up to 2 years.

**P2020**

**A trajectory analysis of cognitive function, functional dependency, and self-reported health service use: the memory loss transition**

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The objective of this analysis was to examine whether significant changes in functional dependence and health service use occurred in the years prior to a physician-identified memory problem in a nationally-representative sample of older adults. Longitudinal data from the RAND Health and Retirement Survey was utilized. Those who reported a physician-identified memory problem were compared to a matched race, gender, and age group who did not indicate a memory problem (N=774). Multi-level linear models were used to construct trajectories for various measures of cognitive status, functional dependency, health service use, and out-of-pocket medical expenses in the years prior to and following memory problem identification. Trajectories for several variables demonstrated significant rates of change (p<0.05 to 0.001) in the years leading up to a physician-identified memory problem, including total cognitive score (B=-0.20), standardized fine motor skills (B=0.05), instrumental activities of daily living (B=0.15), out-of-pocket medical expenses (B=0.18), and night stays in hospitals (B=0.18). These trajectories suggest that for higher-order functional tasks (e.g., shopping, arranging finances, taking and managing medications, etc.) and for overall cognitive function, significant decreases are apparent for those who experience a later memory concern. The results here build on earlier findings by also suggesting that hospital use and out-of-pocket medical expenditures increase in the years prior to a potential dementia. It remains to be determined whether earlier diagnosis may lead to reductions in costs.
P2021

Relationship between self-assessed and proxy-assessed quality of life (QoL) and dependence in Alzheimer’s disease (AD): results from dependence in AD in England (DADE) study

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Introduction: The DADE study determined how patient self-assessed and proxy-assessed QoL changes with increasing dependence.

Methods: 249 patients with possible/probable AD according to NINCDS/ADRDA criteria participated in a multi-centre, cross-sectional, observational study. Patient dependence (Dependence Scale, DS), self-assessed QoL and utility (DEMQOL; Bath Assessment of Quality of Life in Dementia, BASQID; EQ-5D) were completed by patients with MMSE of ≥10 only and caregiver proxy assessed scales (DEMQOL proxy, EQ-5D proxy) were completed for all patients. EQ-5D responses were converted into utility scores using a UK algorithm. Bivariate (Pearson correlation) and multivariate analyses (GLM) were used to assess relationships between dependence and QoL and utility.

Results: The mean (SD) score for MMSE was 14.6 (6.8). Pearson correlations revealed significant associations between DS and EQ-5D utility (r=-0.19, p<0.05), proxy-assessed EQ-5D utility (r=-0.42, p=0.0001) and BASQID total scores (r=-0.38, p=0.0001) and no significant associations with the DEMQOL (r=0.14, NS) and DEMQOL-proxy(r=-0.12, NS). When patient age and gender were controlled, multivariate analyses confirmed significant associations between dependence and the two EQ-5D utility assessments (p<0.01) and BASQID total score (p<0.0001). Using a similar model, significant associations between dependence and both the DEMQOL and DEMQOL-proxy were observed (p<0.05). It is expected that a one point increase in dependence is associated with the following point decreases: 0.017 (EQ-5D utility), 0.039 (EQ-5D proxy utility), 1.03(DEMQOL), 0.66 (DEMQOL proxy) and 1.395 in the BASQID total score.

Conclusions: Patient QoL and utility decreases as AD illness progresses and dependence on others increases.

P2022

Caregiver burden as illness progresses in Alzheimer’s disease (AD): association with patient dependence and other factors: results from dependence in AD in England (DADE) study

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Introduction: Understanding drivers of caregiver burden is important if patient management in AD is to be optimized. The DADE examined how perceived caregiver burden and caring time changes with increasing patient dependence.

Methods: 249 patients with possible/probable AD according to NINCDS/ADRDA criteria participated in a multi-centre, cross-sectional, observational study. Assessments included patient dependence (Dependence Scale; DS), caregiver burden (Zarit burden interview; ZBI), and for co-resident caregivers only, the proportion of time patients could be left alone.

Multivariate analyses (GLM) were used to assess the relationship between the ZBI and the DS.

Results: The mean (SD) MMSE was 14.6 (6.8). GLM confirmed a significant association between dependence and ZBI score (p<0.0001), when controlling for patient age, and gender, caregiver age and gender, caregiver relationship to patient and patient accommodation status. Other predictors of ZBI score were patient accommodation (p<0.0001) and whether the caregiver was the patient’s child (p<0.05). The model suggests a 1 point increase in dependence is associated with 2.15 point increase in ZBI. In addition, if the patient is not in a nursing home/residential care facility, the ZBI score is expected to increase by 19 points. If the caregiver is the patient’s child, an increase of 9.2 points in ZBI is expected. For co-resident caregivers, the proportion of the time that patients could be left alone decreases as DS score increases.

Conclusions: The results suggest that perceived caregiver burden increases with patient dependence and is higher when caregivers are the son/daughter of patient compared with spouse/partner caregivers.
P2023

Plasma nutrient status of Alzheimer’s disease patients compared to cognitive intact elderly controls: a systematic review and meta-analysis

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Alzheimer’s disease (AD) patients are at risk of nutritional insufficiencies due to physiological and psychological factors. Since several nutrients are known to influence molecular mechanisms that maintain mental functions, alterations in their levels may have an important impact on AD outcome. To our knowledge, we here provide the first systematic meta-analysis that compares plasma levels of vitamins, minerals, trace elements, and fatty acids in AD patients to those in cognitive intact elderly controls. The literature published after 1990 in Cochrane Central Register of Controlled Trials, Medline, and Embase electronic databases was systematically analyzed using the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (Moher et al. 2009). We retrieved 3080 publications of which 78 met all inclusion criteria. Significant lower plasma levels of vitamin A (p=0.0106), C (p=0.0250), E (p=0.0003), folate (p=0.0000), vitamin B12 (p=0.0191), calcium (p=0.0168), and zinc (p=0.0328) were found in AD patients compared to controls using the random effects mixed model (Sheu et al. 2001). Also, significant lower contents of docosahexaenoic acid (DHA) (p=0.0347) and eicosapentaenoic acid (EPA) (p=0.0353) were found in plasma phospholipids, and of EPA in cholesterylesters (p=0.0467) of AD patients versus controls. No significant differences were observed for plasma levels of vitamin D, copper, iron, magnesium, and selenium; and insufficient publications were retrieved for manganese, vitamin B1, and B6 to perform the meta-analysis. These overall lower plasma nutrient levels indicate that AD is accompanied by specific nutritional requirements.

P2024

Cognitive and neuropsychiatric implications of deep nuclei neuronal degeneration in autopsy series

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Objective: To compare degeneration of deep nuclei of brain and to define their correlations with cognition and behavioural/neuropsychiatric symptoms in subcortical vascular disease (SIVD) to normal control, Alzheimer’s disease, and mixed pathology.

Method: Nucleolated neuronal counts of nucleus basalis of Meynert (NB) and pigmented cell counts of locus coeruleus (LC) in each group were measured. Their correlation with the Mini-Mental State Exam (MMSE) scores, global cognitive function scores (GLOBSC), and the presence of behavioural/psychotic symptoms i.e. psychosis, depression, apathy, anxiety, and aggression were also analyzed.

Results: The neuron counts of NB of LC were not decreased in SIVD compared to age-matched control, in contrast to AD where significant neuronal degeneration. The cell count of mixed group of LC was between those of control and AD, which indicating trend for degeneration, while mixed group of NB showed significant neuronal loss. The cell counts of NB in AD were correlated with cognition (GLOBSC, ρ=0.138, p=0.009) and the Clinical Dementia Rating (CDR) scores (ρ=-0.847 p<0.0001), while cell counts of NB and LC in SIVD and LC in AD were not associated with cognition and CDR scores. Whereas MMSE, GLOBSC showed significant difference among the all study groups (p<0.0001 for each), behavioural/psychotic symptoms were not different.

Conclusion: We confirmed that neurons of deep nuclei of NB and LC preserved in SIVD in contrast to AD where significant neuronal degeneration. We confirmed lack of association between the loss of LC neurons and behavioural/psychotic symptoms.
P2025

Effects of memantine in patients with moderate Alzheimer’s disease receiving stable doses of donepezil

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Introduction: This post hoc meta-analysis compared the efficacy and safety of memantine (20mg/day) and placebo in patients with moderate Alzheimer’s disease (AD) receiving stable doses of donepezil (10mg/day).

Methods: Data for 367 patients with moderate AD (MMSE 10-19) were derived from two placebo-controlled trials (MEM-MD-02 and MEM-MD-12). Efficacy assessments included cognition (SIB or ADAS-Cog), function (ADCS-ADL19/23), and global status (CIBIC-Plus). Changes from baseline at week 24 (LOCF) were compared between groups using standardised mean difference (SMD). In addition, pooled data on marked clinical worsening (decline of ≥4 points on ADAS-Cog or ≥5 points on SIB, plus any decline on ADCS-ADL19/23 and CIBIC-Plus) were examined. Adverse events (AEs) were also pooled.

Results: At week 24, patients receiving memantine + donepezil significantly outperformed those receiving placebo + donepezil on overall measures of cognition (SIB/ADAS-Cog: SMD=0.28; p=0.008), function (ADCS-ADL19/23: SMD=0.21; p=0.04), and global status (CIBIC-Plus: SMD=0.28; p=0.008). Marked clinical worsening occurred in significantly fewer patients receiving memantine + donepezil, versus placebo + donepezil (4.3% vs. 13.3%; p<0.01). The incidence of AEs was similar in the memantine + donepezil (75.8%) and placebo + donepezil groups (73.5%). The most common AEs in memantine-treated patients were: dizziness (8.9% vs. 8.6%), diarrhoea (6.3% vs. 7.6%), falls (5.3% vs. 5.9%), and urinary tract infection (5.3% vs. 4.3%).

Conclusion: In moderate AD, combination treatment with memantine and donepezil was well tolerated, produced significant benefits in the key domains of cognition, function and global status, and reduced marked clinical worsening, compared with donepezil monotherapy.

P2026

Cognitive ability and cerebral perfusion (HMPAO-SPECT) in individuals with subjective cognitive complaints with and without cognitive deficits and with mild cognitive impairment

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Purpose: Comparative evaluation of regional brain perfusion measured by HMPAO-SPECT of persons with mild cognitive impairment (MCI) and such with subjective cognitive complaints (SCC) with and without minimal cognitive dysfunction, but not MCI.

Methods: SPECT-data of 54 MCI patients and 70 SCC persons with cognitive abilities superior to MCI criteria (34 persons with minimal cognitive impairment (SCC+) and 36 persons with subjective cognitive complaints without any detected cognitive impairment (SCC-)) were analysed.

Results: No perfusion difference was found between SCC- and SCC+ subjects for any of the assessed regional, hemispheric or global ROIs. MCI patients significantly differed from the SCC group concerning perfusion in left hemispheric medial temporal as well as right hemispheric thalamus ROIs. SCC- subjects showed higher perfusion than MCI subjects in left hemispheric parietotemporal ROI.

Conclusion: The potential of HMPAO-SPECT in differentiating persons with subjective cognitive complaints or MCI was limited. The difference in left hemispheric medial temporal perfusion between all persons with SCC and MCI patients may correspond with higher sensitivity for verbal than for nonverbal memory loss in our assessment. Additionally, persons might earlier seek medical advice on regarded verbal memory deficits than on problems concerning nonverbal or spatial memory in everyday life.
**P2027**

**Putative role of insulin-regulated aminopeptidase (IRAP) as biomarker of Alzheimer's disease**

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In the last few years it has been demonstrated that angiotensin IV (AngIV) has the ability to significantly improve memory in rats suffering from dementia. Thus, rats treated either surgically (bilateral perforant pathway knife cuts) or chemically (scopolamine hydrobromide) to induce amnesia are unable to perform simple memory related tasks such as remembering the location of a hidden platform in swim mazes or avoiding areas in a two compartment chamber that emits weak, electric shocks (passive avoidance paradigm). Infusion of AngIV into the brains of these rats enables them to successfully complete these simple behavioural tasks by reversing their memory loss. It was demonstrated subsequently that the high affinity AngIV binding site was the insulin-regulated aminopeptidase (IRAP). In the present work, we analyze specific IRAP activity in plasma of patients with Alzheimer’s disease (AD) and elderly healthy volunteers. Cognitive scores (Minimental, Blessed and FAST) allowed the classification of patients by their evolutive situation. Our results show a significant decrease in IRAP activity in AD patients suggesting a slower catabolism of AngIII, a decrease in the circulating levels of AngIV, and a decrease in the interactions of AngIV with its receptor. It could be a reflect of the impairment in cognition and memory characteristics of the disease. Furthermore, ROC curve analysis indicates an AUC of 0.815, with a sensitivity of 90.91 and a specificity of 61.54, with make IRAP suitable to be used as biomarker for the earliest stages of the disease. Supported by Junta de Andalucía, Spain.

**P2028**

**Rapidly progressive dementia as presenting feature in inflammatory bowel disease**

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**Introduction:** Inflammatory bowel disease (IBD) is a group of idiopathic intestinal disorders of complex pathogenesis. The most frequent neurologic complications of IBD include neuropathy, cerebrovascular and demyelinating disease that may be due to malabsorption and nutritional deficiencies, metabolic agents, infections, medication side effects, thromboembolism and immunological abnormalities. On the other hand, rapidly progressive dementias (RPD) represent a challenging differential diagnosis requiring a systemic approach. A variety of underlying causes including neurodegenerative, autoimmune, infectious, malignancies and toxic-metabolic, may present as RPD.

**Cases report:** We report two patients who presented with RPD. According to recommended initial screening tests for evaluation of RPD and after exclusion of all possible causes, full gastrointestinal endoscopy (GE) was performed due to past medical history of chronic constipation, hemorrhagic diarrhoeas and deterioration in cognition with per os nutrition intake. GE revealed Cohn’s disease (case 1) and intermediate type of colitis (case 2). Both patients were treated with prednisolone and on follow up assessment their cognitive function was significantly improved.

**Conclusion:** There are only few reports of affected cognition in IBD, including Wernicke’s encephalopathy, cognitive impairment due to vasculitis and acute confusional state. In addition, IBD patients have shown short term memory dysfunction, verbal deficits and low scores on object recognition tasks, compared with controls. Herein we report 2 cases of RPD due to IBD, which is not included in the differential diagnosis of RPD. Although further studies are needed, we propose that IBD must be taken into consideration as possible diagnosis in RPD.
Identification of metabolites as predictive biomarkers for dementia

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Dementia, the rapid decline of cognitive ability, is the most pronounced symptom caused by neurodegenerative disorders. For slowing down the rate of disease progress and eventually treat it, the disease needs to be diagnosed in preclinical stage. For this reason, we aimed to search for a group of metabolites which can be used as reliable and accurate biomarkers for early diagnosis, classification and progression of dementia. We will take advantage of the Bioinformatics and Chemometric techniques as mass spectrometry and analyze saliva and serum samples belonging to a longitudinal study of memory at Umeå University calling for the Betula project. In this project, 4500 project participants, 25-100 years old, have been interviewed and examined medically and psychologically on five occasions (T1, T2, T3, T4, T5). A preliminary result from mass-spectrometry followed by PLS analysis, showed a significantly different expression level of metabolites between the groups of 5 un-demented and 5 demented patients. Additional analyses of metabolites in samples from 18 demented and 72 controls showed a group separation and selection of 180 distinct metabolites which expressed significantly different between the two groups. Furthermore, we will select samples from the participants who were not diagnosed with dementia at T4 but got the diagnosis at T5 and also controls that were not diagnosed as demented at T4 stayed still non-demented at T5. This analysis will finally reveal certain metabolites already in the preclinical phase which can be used as dementia predictors.

Cerebrospinal fluid biomarkers in Alzheimer’s disease, Parkinson’s disease and atypical parkinsonism in a Serbian group of patients

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Introduction: Cerebrospinal fluid (CSF) biomarkers: the 42-amino-acid isoform of amyloid β (Aβ42), total tau (T-tau) and phosphorylated tau protein (P-tau) shown to reflect pathogenic mechanisms underlying Alzheimer’s disease (AD) can be a useful tool in differential diagnosis of AD to other neurodegenerative diseases, such as Parkinson’s disease (PD) and atypical parkinsonism. 

Aim: To compare the levels of CSF Aβ42, T-tau and P-tau in patients with AD, PD, atypical parkinsonism and healthy control group.

Methods: In this report, the CSF biomarkers analysis from the patients attending the Center for memory disorders, Neurology Clinic, Belgrade, Serbia from June 2008 to June 2011 will be presented. This work includes 50 patients with atypical parkinsonism, 60 patients with PD and 60 patients with AD. The Innotest, ELISA sandwich test (Innogenetics - Belgium) was used for measuring the CSF levels of T-tau, P-tau and Aβ42.

Results: Mean levels of CSF T-tau and P-tau were significantly higher in the patients with AD (p<0.001) compared to the PD patients, patients with atypical parkinsonism and control group in contrast to significantly lower CSF Aβ42 in AD group (p<0.001). Also we showed that specific profile of CSF T-tau and P-tau levels in combination with Aβ42 level can be used in differentiating the PD and atypical parkinsonism.

Conclusion: Our experience showed that the analysis of CSF biomarkers in patients with AD, PD and atypical parkinsonism are reliable, sensitive and reproducible.
**P2031**

**Oxidative stress in patients with mild cognitive impairment and depression: a possible factor for increasing the risk of developing dementia?**

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**Objective:** Mild cognitive impairment (MCI) has been defined as a transitional state between regular aging and dementia. Still, not all patients with mild cognitive impairment develop dementia. It has been proved that patients with depression and mild cognitive impairment present a doubled risk of developing dementia of Alzheimer type as those with MCI only. Our current objective was to determine the level of oxidative stress in MCI patients with depression, compared with non-depressed MCI patients.

**Methods:** The patients were selected using Petersen criteria for MCI and NINCDS ADRDA criteria for AD. The cognitive performance was assessed using MMSE (Mini Mental State Examination), Clock Drawing Test and Verbal Fluency Test. Psychiatric examination for depression was based on structured interview and Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition criteria.

We assessed the levels of some enzymatic antioxidant defences like superoxid dismutase (SOD) and glutathione peroxidase (GPX), as well as lipid oxidation makers like MDA (malondialdehyde).

**Results:** A decrease in the specific activity of SOD and GPX was found in MCI patients with depression compared with non-depressed MCI patients. Also, the concentration of serum MDA was increase in MCI patients with depression. We also observed a correlation between the cognitive alteration and the levels of oxidative stress in depressed patients with MCI.

**Conclusions:** We conclude that patients with MCI and depression have an increased level of oxidative stress, compared with non-depressed MCI patients. This could explain the increased risk of patients with depression and mild cognitive impairment of developing dementia-Alzheimer type.

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**P2032**

**INROADS: an international registry of Alzheimer’s disease patients - ongoing clinical trial**

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**Introduction:** To summarize the need and rationale for a longitudinal, multicenter registry of patients with mild to moderate Alzheimer’s disease (AD).

**Methods:** Registries of AD patients, including Consortium to Establish a Registry for AD (CERAD), AD Neuroimaging Initiative (ADNI, ADNI-2), and Australian Imaging Biomarkers and Lifestyle study (AIBL), are aimed to standardize instruments used in diagnosis, elucidate disease pathogenesis, and develop diagnostic and prognostic biomarkers. However, these existing registries are limited in terms of: restrictive inclusion/exclusion criteria similar to clinical trials; small samples; short duration; and/or were completed over a decade ago (i.e., CERAD 1988-1997). An unmet need remains to fully understand prognostic factors, disease course, disease burden, and patterns of care in ‘real world’ current day practice. The goal of the International Registry Of Alzheimer’s Disease patientS (INROADS) is to address knowledge gaps in AD, including natural history of disease, rates and characteristics of co-morbidities, time to therapy initiation, factors influencing choice of treatments, and impact of therapy.

**Results:** INROADS will enrol up to 4,000 patients with clinically diagnosed mild to moderate AD across approximately 400 sites initially in the US, Canada, and Europe. Patients will be followed every 6 months for at least four years. Patient population, inclusion/exclusion criteria, data collection, and adverse event capture will be presented.

**Conclusion:** INROADS will be the largest, most comprehensive, real world AD registry to-date, capturing data on AD patient progression, cognition, mood, behaviour, dependence, functional impairment, resource utilization, and caregiver burden. Patient recruitment is planned to begin in 2012.
P2033

Memantin enhances autonomy in moderate to severe Alzheimer’s disease patients already receiving donepezil

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Introduction: Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by progressive loss of cognitive and functional abilities. A previous study has shown that memantine can prolong autonomous living in patients with moderate to severe AD, as shown on Activities of Daily Living (ADL) Scale (Rive et al. 2004).

Methods: The patient population consisted of 403 patients with baseline MMSE scores of 5 to 14 from a multicenter, randomized, placebo-controlled clinical trial (24-week duration) comparing the efficacy and safety of memantine versus placebo in patients with moderate to severe AD already receiving stable treatment with donepezil (Tariot et al. 2004). The current study is a post-hoc evaluation of the ADL assessments. At baseline, all patients were dichotomized according ADL capabilities into either being autonomous or dependent regarding ADL facilities using an automatic classification process. The same criterion is later used to obtain the autonomy status of the patient at study end. Factors influencing patient autonomy status at study end were investigated by a logistic regression model.

Results: 290 of the 403 patients were classified autonomous, 105 dependent at study baseline. Patients with dependency have lower basic and lower instrumental ADL scores at baseline. These patients had declined cognitive abilities and more pronounced behavioural disturbances.

Memantine treatment has a beneficial effect on patients autonomy status at study end, reaching significance in the LOCF analysis (p=0.03) by logistic regression model. (OC analysis favours memantine, p=0.06).

Conclusions: Memantine is beneficially influencing autonomy status in patients with moderate to severe AD already receiving donepezil.

P2034

Abstract cancelled

P2035

Epigenetic mechanisms in a rare case of monozygotic twins discordant for Alzheimer’s disease

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Case report: Target genes in Alzheimer’s disease (AD) have been identified. The study of rare monozygotic (MZ) twins discordant for AD provides a unique opportunity to evaluate the role of environmental factors in the etiology of the disease. Since epigenetic differences could contribute to phenotypic differences, we investigated either global changes in selected chromatin modifications as well as DNA methylation in peripheral blood mononuclear cells of a couple of these MZ twins. Moreover, we analysed the gene expression of DNA methyltransferases (DNMTs) and histone deacetylases (HDACs) directly recruited by DNMTs. We observed, in the AD twin, markers of transcriptional activation namely a strong reduction in DNA methylation, revealed by higher levels of [3H]methyl group incorporated into DNA (AD twin=2.86±0.23 fold over healthy twin =1±0.16), as well as a clear reduction in histone 3 acetylation at lysine 9 (AD twin=34% versus healthy twin=100%). Consistently, we observed increases in the gene expression of few HDACs isoforms in the AD twin (HDAC2 (3,39), HDAC6 (2,08) HDAC9 (4,16) versus healthy twin =1) and no changes in all the others. Finally, slightly changes were observed in the other histone modifications investigated (Histone 3 Lysine 4 trimethylation, Histone 3 Lysine27 trimethylation) and in all the DNMTs isoforms mRNA levels. Our results unravel epigenetic differences potentially helpful in the understanding of environmental factors and phenotypic differences in MZ twins. We also confirm the use of peripheral blood cells as useful model for the study of gene regulation that mirrors the alterations within the brain.
P2036

The effect of Mozart’s music on hippocampal content of BDNF in postnatal rats

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Introduction: It has shown that listening to Mozart's music can potentiate spatial tasks in humans and reduce seizure attacks in epileptic patients. A few studies have reported the effects of prenatal plus post-partum exposure of mice to Mozart music on brain-derived neurotrophic factor (BDNF) in the hippocampus. Here we investigated the effect of post-partum exposure to Mozart's music on BDNF concentration in the hippocampus of rat.

Methods: 30 male one-day old Wistar rats were divided randomly in two equal experimental and control groups. Experimental group was exposed to slow rhythm of Mozart's music (Mozart Sonata for two pianos KV 448, 6 hours per day; sound pressure levels, between 80 and 100dB) for 60 successive days. The control group was kept in a separate room with housing conditions like the experimental group except music exposure. After 60 days the rats were euthanized and hippocampi extracted; then the content of BDNF protein was measured using ELISA sandwich method.

Results: Data analysis revealed that rats exposed to Mozart's Sonata music had significantly increased BDNF content in the hippocampus as compared to control rats (p<0.01). The concentrations of BDNF were 86.30±2.26 and 94.60±6.22 ng/g wet weight in control and music exposure groups, respectively.

Discussion: Exposure to Mozart's music early in life can increase the BDNF concentration in the hippocampus in rats.

P2037

Memantine and the acetylcholinesterase inhibitors - the 3-neurone model of their complementary mechanisms of action in the treatment of Alzheimer's disease

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Introduction: In Alzheimer’s disease (AD), the N-methyl-D-aspartate (NMDA) receptor antagonist, memantine, addresses dysfunction in glutamatergic transmission, while the acetylcholinesterase inhibitors (AChEIs) increase pathologically lowered levels of acetylcholine (ACh). Clinical experience indicates that their dual mechanisms could offer superior benefit as combination therapy.

Results: The basis of the 3-neurone model is that the glutamatergic system ('neurone 1') innervates the cholinergic regions of the basal forebrain ('neurone 2'), with input coming from many nuclei, including the cortex. Cholinergic neurones in the basal forebrain then project to the neocortex, releasing ACh and facilitating cognitive processes (via 'neurone 3'). In AD, hippocampal/cortical glutamatergic over-activity renders physiological signals difficult to detect against an increased background 'noise'. Cholinergic neurones degenerate, reducing ACh levels and signalling in both the cortex and hippocampus. The resulting decreased neurotransmission and impaired synaptic plasticity/long-term potentiation (LTP) leads to cognitive decline. Pre-clinical studies have shown that memantine prevents LTP impairment by amyloid-beta in the hippocampus (relevant to spatial memory). Furthermore, its action in the basal forebrain improves cholinergic function and the attention-related aspects of cognition. Memantine also protects these neurones from chronic excitotoxicity. In the 3-neurone model, memantine normalises glutamatergic transmission via the NMDA receptor, so that incoming signals can be distinguished. Supplementing this, AChEIs prolong the activity of ACh at the synapse, and preserve/strengthen neurotransmission, facilitating LTP and memory.

Conclusion: Combination therapy with memantine/AChEIs has shown significant advantages in the clinical setting, and represents the most up-to-date and efficacious treatment regimen for patients with AD.
P2038

Effectiveness of memantine in autonomy of Alzheimer's patients with or without co-existing vascular risk factors


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Objective: To investigate in daily clinical use the effectiveness of memantine treatment on the autonomy of Alzheimer's Disease (AD) patients with and without co-existing vascular risk factors.

Methods: In this 6-month, observational, open-label study conducted in 118 investigational sites in Greece, the Dependence Scale (DS) was used for the assessment of patients’ autonomy. Four vascular risk factors were considered, according to patients’ reports: Hypertension, diabetes mellitus, hyperlipidemia, and obesity. Patients were evaluated at 3 and 6 months (Intent-To-Treat: ITT and Per-Protocol-Set: PP).

Results: 1,321 patients were included in the study (mean age 75.9±6.5, 52.9% women). Mean DS score (±SD) significantly improved from 6.8 (±3.2) at baseline to 6.1 (±3.1) at 3 months and to 5.8 (±3.4) at 6 months (ITT, Hotelling’s test, p<0.001). Patients at higher dependency (levels 4 and 5) were decreased, while the lower dependency population (levels 0,1,2) was increased at 6 months (Friedman test, p<0.001). 6.1% of patients discontinued memantine treatment; only 0.3% of total population retired due to AE and 0.1% due to lack of efficacy. Patients with one or more vascular risk factors (N=809) were improved more than patients not having vascular risks (N=512, ITT, Pearson-Coefficient=-0.088, p=0.003). No statistical differences were detected between these 2 groups in demographics and tolerability data.

Conclusion: Memantine improved autonomy of AD as evaluated by both their DS score and the level of dependency after a 6-month treatment and it was well tolerated. The co-existence of vascular risk factors predicted a greater improvement of patients’ dependency.

P2039

Identifying predictive factors of adherence and persistence to rivastigmine patch

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Introduction: Transdermal rivastigmine has benefits over oral rivastigmine in patients with Alzheimer’s disease (AD), including quicker access to clinically beneficial doses and fewer side effects. Many caregivers of AD patients prefer patch over oral rivastigmine. However, adherence and persistence with any cholinesterase inhibitor are generally poor.

Methods: We conducted a PubMed search to identify the most important patient and caregiver factors associated with adherence and persistence with rivastigmine patch, using combinations of the following terms: Alzheimer’s disease; cholinesterase inhibitors; adherence; compliance; persistence; caregiver, non-adherence. Results were assessed for relevance using titles/abstracts.

Results: Predictors of adherence and persistence to AD therapy included patient clinical factors (health; treatment issues) and psychosocial factors (beliefs; cognitive/emotional state; living conditions). Caregiver predictors included age, health and a range of psychosocial factors (treatment efficacy expectations; beliefs about medicines and AD; mood [e.g. depression/anxiety]). However, these predictors were not extensively tested or specific to transdermal delivery. Therefore, the non-interventional Screening Tool for Transdermal Therapy (STATT) study was designed to identify the strongest predictors of adherence and persistence to rivastigmine patch. This ongoing study will inform design of an evidence-based checklist, enabling physicians to better identify patients suitable for rivastigmine patch therapy. Approximately 150 patients with mild-to-moderate AD will be enrolled; primary endpoints include adherence and persistence, 3 and 6 months after treatment initiation.

Conclusion: Clarifying factors predictive of adherence and persistence will help physicians identify patients with AD likely to benefit from rivastigmine patch therapy and caregivers likely to experience alleviation of burden with transdermal administration.
P2040
The effects of a paraventricular nucleus lesion on cognitive functions and oxidative stress in rats
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Introduction: The stress response is mediated by the hypothalamo-pituitary-adrenal (HPA) system. Activity of the corticotropin-releasing hormone (CRH) neurons in the hypothalamic paraventricular nucleus (PVN) forms the basis of the activity of the HPA-axis. The current study was therefore designed to determine whether a unilateral 6-hydroxydopamine (6-OHDA) lesion of the PVN, which produce a marked decrease of brain noradrenaline and dopamine, leads to a deactivation of HPA-axis and affects the cognitive functions and oxidative stress levels.
Methods: Behavioural tests (Y-maze, radial-arm-maze and elevated-plus-maze) started 2 weeks after neurosurgery. We assessed the levels of some enzymatic antioxidant defences like superoxide dismutase (SOD) and glutathione peroxidase (GPX), as well as lipid oxidation makers like malondialdehyde (MDA).
Results: Lesion of the PVN resulted in a significant impairment of short-term memory, explored by means of Y-maze task. Also, 6-OHDA lesion of the PVN induced a significant increase in the number of working and reference memory errors in radial-arm-maze. In the elevated-plus-maze task sham-operated rats spent less time on the open arms, suggesting that 6-OHDA-lesions significantly diminished anxiety state. Alterations in the specific activity of the antioxidant enzymes (SOD and GPX) were found in lesioned rats and also MDA levels were significantly increased.
Conclusions: These data indicate that PVN may have important implications in memory processes and oxidative stress status of the brain, with relevance for some neurodegenerative diseases, considering that during aging, the activation of the HPA system and CRH neurons in the PVN is affected, as in Alzheimer’s disease and major depression.

P2041
Reduced cerebrovascular reactivity as a biomarker of impaired microvascular flow in Alzheimer’s disease
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Introduction: The cerebral blood flow in Alzheimer’s disease (AD) is diminished. Whether this is a sole consequence of brain atrophy or whether microvascular impairment plays an additive role is unknown. We hypothesized that microvascular flow impairment, if present in AD but not in control subjects, would be revealed by transcranial Doppler ultrasound and a breath-holding manoeuvre.
Methods: Mild to moderate AD patients and non-demented control subjects with no history of stroke underwent a neurosonological assessment of peak systolic, mean and end-diastolic flow velocities, and resistance and pulsatility indices in ACA, MCA, PCA, VA bilaterally, and BA. The average breath-holding index (BHI) was calculated from 3 measurements in MCA for each side. The results from AD and control subjects were compared and also correlated with cognitive impairment using MMSE and ADAS-Cog.
Results: We enrolled 8 AD patients (3 males, 74.5±8.7 years, MMSE 19±4) and 11 risk factors-matched controls (8 males, 71.5±6.1 years, MMSE 29±1). Mean BHI in AD vs. controls was 0.45 vs. 0.78 (p=0.126) for right MCA and 0.26 vs. 0.79 (p=0.016) for left MCA, respectively. The decrease in BHI correlated significantly with MMSE (r=0.479, p=0.038). Other differences were non-significant.
Conclusion: The results support our hypothesis and suggest that impaired brain microcirculation in AD patients is expressed as a decreased cerebrovascular reactivity in the dominant hemisphere. This pilot study warrants further investigation of BHI as a biomarker of microvascular impairment in AD patients.
P2042
The validation of abbreviate mental test score (AMTS) in Greek patients with Alzheimer's disease and related dementias suffering from communication deficits
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P2043
The validation of clock drawing test for dementia: a comparison between demented and non-demented patients with language deficits in Greece
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P2044
Altered frontal brain oxygenation in Alzheimer's disease as assessed by near-infrared spectroscopy (NIRS)
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P2045
FDG-PET study before the onset of dementia in the case of sporadic Creutzfeldt-Jakob disease
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P2046
Some cardiovascular risk factors as potential markers for mild cognitive impairment and Alzheimer's disease
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P2047
Analysis of inflammatory cytokines in CSF in relation to behavioural and psychiatric symptoms in dementia (BPSD) in demented patients
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P2048
Acute onset Creutzfeldt-Jacob disease: a stroke-like presentation
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P2049
The effects of medical food on the organisation of functional brain networks in patients with Alzheimer's disease (AD)
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P2050
Abstract cancelled

P2051
Sociopathy in dementia
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P2052
Pituitary incidentalomas in the elderly: what to do?
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P2053
Citicoline in treatment of mild cognitive impairment at the Mental Health Research Center of RAMS, Moscow, Russia
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P2054
The effects of a longitudinal language intervention program to the general cognitive function in mild Alzheimer’s disease
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P2055
Clinical distribution of dementia syndrome in Armenia: results of a 3-year study
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P2056
A possible advantageous role of paraoxonase 1 in dementia
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P2057
Alzheimer’s disease risk in elderly persons with rheumatoid arthritis
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P2059
The 1-hour assessment protocol (1-HAP) for diagnosing mental, communication and emotional status in a demented population
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P2060
Validation and reliability of instrumental activities of daily living (IADL) in Greek patients with Alzheimer’s disease and related dementias with language deficits
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P2061
Abstract cancelled

P2062
Do leisure activities explain the correlation between personality and cognitive capacity in later years?
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P2063
Care giving in ageing in the monastic community of Mount Athos: compassion, devotion and mercy
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P2064
Depression among Iranian elderly
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P2065
Poor memory as chief complaint - how important is it?
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P2066
A different face of Fahr’s syndrome or two diseases together?
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P2067
Abstract cancelled

P2068
Asymmetry in parkinsonian symptoms and orthostatic hypotension as predictors of psychotic disturbances in PDD and DLB patients
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P2069
CSF biomarkers analysis in Polish patients with MCI and Alzheimer’s disease
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P2070
Prospective assessment of cognitive functions in neurological patients
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P2071
Reminyl as the first-line drug in anti-dementia therapy: an observational study
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P2072
Genetic and biochemical determinants of dementia
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