

Monday, October 28

Movement disorders 1

SC 201

Slower progression of Parkinson's disease in patients treated with ropinirole compared with L-dopa: REAL-PET – a randomised controlled 18F-dopa PET study

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Introduction A 2-year, double-blind, multicentre study was conducted to compare rates of loss of putamen dopamine terminal function in patients with early PD treated with ropinirole or L-dopa.

Methods The primary endpoint was change in putamen ¹⁸F-dopa uptake (Ki) measured using positron emission tomography. Data were transformed into standard stereotactic space and analysed with a standard region-of-interest template and statistical parametric mapping. Dyskinesias were defined as a score of at least 1 on item 32 of the Unified PD Rating Scale or their report as an adverse event.

Results 93 patients were randomised to each group; 73% of the ropinirole and 74% of the L-dopa group completed the study. Loss of putamen Ki was significantly less with ropinirole (–13%) than L-dopa (–20%; p=0.022). Nigral dopamine storage deteriorated with L-dopa but not ropinirole. The mean treatment difference at baseline was greater for the more affected side (9.4 [95%CI 2.4–16.4]) compared with the less affected side (4.3 [95%CI 1.9–10.5]). Fewer patients in the ropinirole group developed dyskinesias compared with the L-dopa group (3/92 and 23/91 of patients, respectively; p=0.0002). Within the L-dopa group there was no significant difference in median loss of putamen Ki for patients with dyskinesias (–23.3%, n=19) compared with those without (–18.5%, n=40; p=0.52).

Conclusion The loss of dopamine terminal storage capacity (a measure of disease progression) was 30% slower in patients with early PD taking ropinirole compared with those taking L-dopa. Additionally, use of L-dopa was associated with a 10-fold higher incidence of dyskinesias.

SC 202

Pramipexole versus Levodopa in the CALM-PD CIT study: Effects on Parkinson's disease progression assessed by dopamine transporter imaging

Parkinson Study Group

Presented by Kenneth Marek

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Introduction Dopamine transporter imaging with [¹²³I]b-CIT was used to compare the nigrostriatal dopaminergic degeneration after initial treatment with pramipexole or levodopa in early PD.

Methods Patients (N=82) in the CALM-PD study (JAMA 2000; 284:1931–1938), underwent 4 scans during a 46-month period. Participants were recruited at 17 centres in North America. The primary outcome variable was the percent change

from baseline in striatal [123I]b-CIT uptake after 46 months evaluation. Clinical severity of PD was assessed using the “defined off” UPDRS.

Results In the study cohort sequential SPECT imaging showed a decline in [123I]b-CIT striatal uptake from baseline of $10.3 \pm 9.8\%$ at 22 months ($n=78$), $15.3 \pm 12.8\%$ at 34 months ($n=71$) and $20.7 \pm 14.4\%$ at 46 months ($n=65$). Comparison of the treatment groups demonstrated that the percent loss in striatal [123I]b-CIT uptake from baseline was significantly reduced in the group initially treated with pramipexole compared to the group initially treated with levodopa: $7.1 \pm 9.0\%$ vs. $13.5 \pm 9.6\%$ at 22 months $p=0.004$; $10.9 \pm 11.8\%$ vs. $19.6 \pm 12.4\%$ at 34 months, $p=0.009$; and $16.0 \pm 13.3\%$ vs. $25.5 \pm 14.1\%$ at 46 months, $p=0.01$. The percent loss from baseline in striatal [123I]b-CIT uptake was correlated with the change from baseline in UPDRS at the 46 month evaluation, $r=-0.40$, $p=0.001$.

Conclusion Patients treated initially with pramipexole demonstrated a relative reduction in percent loss from baseline of striatal [123I]b-CIT uptake of approximately 40% compared to those treated initially with levodopa during a 46-month evaluation. These imaging data highlight the need to further compare imaging and clinical endpoints of PD progression in long-term studies.

SC 203

Cancelled

SC 204

Clinical impact of performing SPECT imaging with the dopamine transporter imaging agent 123 I-ioflupane (DaTSCAN™) in patients with a clinically uncertain diagnosis of Parkinsonian syndromes

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Introduction SPECT with DaTSCAN™ has been reported to be useful in the differential diagnosis of PS. This study was conducted to assess the impact of DaTSCAN™ both upon the neurologist’s diagnostic confidence of PS and clinical management of patients with clinically uncertain PS.

Methods A prospective, open clinical trial was conducted in 15 European hospitals. DaTSCAN™ SPECT was performed on 118 patients with clinically uncertain PS. Images were visually classified as normal (symmetric intense tracer uptake in striatum) or abnormal (asymmetric or bilaterally decreased putamen or whole striatal uptake). The level of confidence of the neurologist in the diagnosis of PS (not confident at all=0%, completely confident=100%), and the patients’ planned management were recorded before and after knowledge of the DaTSCAN™ image.

Results DaTSCAN™ imaging had an impact on diagnosis (either more confident with or a change in their initial diagnosis) in 109/118 patients. After imaging with DaTSCAN™ the neurologists became more confident with their initial diagnosis in 56 of these 109 and the initial diagnostic suspicion was changed from “PS” to “other than PS” or from “other than PS” to “PS” in the remaining 53. After imaging, planned clinical management was changed in 72% of patients. Changes involved therapy in 64.3% of cases, including either initiation or discontinuation.

Conclusion Visual assessment of SPECT with DaTSCAN™ increases the neurologist’s confidence in the diagnosis of patients who present with uncertain PS and can lead to changes in the initial diagnosis as well as in the clinical management of these patients.

SC 205

Service use and costs of Parkinson’s Plus syndromes

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Multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) are diseases that result in increasing disability and eventual death. MSA and PSP are likely to entail the use of a wide number of healthcare and social services and it is also probable that patients will require substantial support from family members. Therefore, the economic costs associated with PSP and MSA may be high, but no known health economic studies have previously been reported. This paper will present service use information and economic costs for around 800 patients with PSP or MSA in France, Germany and the UK from the NNIPPS (Neuroprotection and Natural History in Parkinson Plus Syndromes). Use of a wide range of formal services and informal care will be measured over a six-month period and costs will be calculated using an established method. Whilst the average costs of PSP and MSA will be of interest, it will be more informative to identify factors that are predictive of variations in cost. Therefore a multiple regression model will be presented with the dependent variable being service costs and patient and illness characteristics used as potential predictor variables. Such a model could be of use to those planning services for this patient group.

SC 206

Olfactory function distinguishes vascular parkinsonism from Parkinson’s disease

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Introduction Olfaction is markedly reduced in Parkinson’s disease (PD), irrespective of disease duration and treatment. We evaluated olfactory function in patients with a clinical diagnosis of vascular parkinsonism (VP).

Method The 40-odour University of Pennsylvania Smell Identification Test (UPSIT) was used. VP was diagnosed according to criteria proposed by Winikates&Jankovic 1. MRI inclusion criteria were modified based on findings by Zijlmans 2, requiring either bilateral white matter lesions or basal ganglia lesions. Significant cognitive impairment was an exclusion criterion. Each VP patient was matched for age, sex and smoking status with two normal controls and two PD patients.

Results Thirteen VP patients were tested (7 men, 6 women). Mean age was 73.5 years (range: 65–88). Mean UPSIT scores were: VP: 25.5 [SD 4.8]; PD: 16.1 [5.9]; normal controls: 27.5 [4.5]. The mean difference between VP and PD was 9.34 (95% CI 5.7, 13.0; $p < 0.0001$); mean difference between VP and normal controls: -2.0 (95% CI $-5.6, 1.4$; $p = 0.23$).

Conclusion Olfactory function was found to be significantly better in patients fulfilling clinical criteria for VP than in PD. Testing olfaction may help to differentiate between these two causes of parkinsonism.

Literature

- 1) Winikates J, Jankovic J (1999). Clinical correlates of vascular parkinsonism. *Arch Neurol*; 56:98–102.
- 2) Zijlmans JCM, Thijssen HOM, Vogels OJM, Kremer HPH, Poels PJE, Schoonderwaldt HC, et al (1995). MRI in patients with suspected vascular parkinsonism. *Neurology*; 45:2183–2188.

Multiple sclerosis

SC 207

Consensus guidelines for standardized MRI assessment of multiple sclerosis (MS)

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Introduction The objective of this study was to develop consensus guidelines for MRI standardized diagnostic protocols, and indications for follow up, in multiple sclerosis (MS). MRI is usually done as part of the diagnostic workup for MS. There are no guidelines for the use of MRI in practice. Standardized MRI protocols would help maximize the value of individual scans, as well as allow systematic data collection for clinical and comparison studies.

Method An expert consensus meeting on “MRI Protocols for the Diagnosis and Follow Up of MS”, sponsored by the Consortium of MS Centres (CMSC) was convened November 3–4, 2001 in Vancouver. Participants included MS neurologists and radiologists from North America, Europe, and New Zealand, with representation from the American Academy of Neurology, American Society of Neuroradiology, and Radiological Society of North America.

Results Preliminary results propose ten MRI guidelines. The guidelines suggest a standardized MRI protocol to image brain and spinal cord, with specified required and optional features. Images would be obtained on a 1 Tesla or higher machine, using a slice thickness of ≤ 3 mm (≤ 1.5 mm for 3D sequences), without gaps. Scan orientation would be on the subcallosal line using 3 planes, and a localizer if available. Routine follow up MRI's in practice are not recommended, until standardization has been validated. A prototype radiology report is suggested using standardized and consistent common language, describing such features as lesion number, location, size, shape, and character. A copy of the MRI should be retained permanently for future comparison.

Conclusions Consensus guidelines are available for review on the CMSC website for discussion and comment.

SC 208

Nitric oxide metabolites correlate with Gd-enhanced MRI activity in patients with multiple sclerosis

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Introduction Increased levels of the nitric oxide metabolites, nitrate and nitrite (NOx), were found in MS patients. This study aimed to investigate the relation of CSF and serum NOx to the disease progression and MRI markers of the disease activity.

Methods 33 MS patients [16 relapsing-remitting (RR) and 17 secondary progressive (SP) MS] and 15 control subjects were enrolled in the study. Total CSF and serum NOx was measured using a vanadium-based assay. MRI assessment included the number and volume of Gd-enhancing lesions, T1-hypointense and T2-hyperintense lesions. The clinical status of patients was assessed using the EDSS.

Results NOx was significantly raised in CSF ($10.0 \pm 5.1 \mu\text{M}$ vs. $6.3 \pm 2.2 \text{mM}$, $p = 0.001$) but not in serum ($42.4 \pm 11.1 \mu\text{M}$ vs. $36.8 \pm 15.7 \mu\text{M}$, $p = 0.1$) of MS patients compared to controls. We found significantly higher CSF NOx level in MS patients with $\text{EDSS} \leq 4.0$ compared to patients with more advanced disability ($\text{EDSS} > 4.0$) ($11.7 \pm 5.7 \mu\text{M}$ vs. $7.8 \pm 3.0 \mu\text{M}$, $p = 0.018$). The CSF/serum NOx index correlated with the volume of cerebral Gd-enhancing lesions ($R = 0.41$; $p = 0.014$). In the subset of patients with Gd-enhancing MRI lesions ($n = 11$), representing acute inflammatory activity, a stronger correlation between the volume of Gd-enhancement and both CSF NOx ($R = 0.74$; $p = 0.01$) and the CSF/serum NOx index ($R = 0.78$; $p = 0.007$) was found. There was no correlation between the CSF and serum levels of NOx.

Conclusion CSF NOx levels, an indicator of intrathecal NO production, were increased in mildly disabled MS patients and correlated with acute inflammatory disease activity as measured by Gd-enhanced MRI.

SC 209

Functional cortical changes in patients with multiple sclerosis (MS) and non-specific conventional MRI scans of the brain

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Method Using functional magnetic resonance imaging (fMRI), we assessed the patterns of brain activations associated with simple motor tasks in 12 right-handed patients with clinically definite multiple sclerosis (MS) and non-specific T2-weighted abnormalities on conventional MRI scans of the brain and compared them with those from 12 sex- and age-matched right-handed healthy controls. Also investigated were the extent to which the fMRI changes correlated with normal-appearing white matter and grey matter (GM) pathology, measured using diffusion tensor MRI.

Results When performing the simple motor task with the dominant hand, MS patients had more significant activations of the ipsilateral supplementary motor area (SMA), the ipsilateral

superior frontal sulcus, the contralateral superior temporal gyrus, and the thalamus than controls. On the contrary, healthy subjects showed more significant activations of the medial part of the contralateral parieto-occipital fissure and the ipsilateral primary sensori-motor cortex (SMC) than patients with MS. In patients with MS, the relative activation of the ipsilateral SMA was correlated with the peak height ($r=-0.88$, $p<0.001$) and position ($r=0.87$, $p<0.001$) of the GM mean diffusivity histogram.

Conclusion This study shows that cortical reorganization occurs over a rather distributed sensorimotor network even in patients with MS and non-specific abnormalities on conventional brain MRI scans. This suggests that, in patients with MS, an increased recruitment of movement-associated cortical network can be elicited by the presence of normal appearing brain tissue pathology, which is independent of macroscopic T2-weighted abnormalities.

SC 210

Evidence of more extensive tissue damage in MS patients with APOE-ε4: two-year MRI follow-up shows higher proportion of lesions evolving to “black holes”

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Introduction The APOEε4-allele (ε4) has been associated with clinical worsening in multiple sclerosis (MS) and more pronounced tissue damage on MRI and ¹H-MRS. We attempted to consolidate this assumption by using serial MRI of the brain to follow the evolution of “black holes”, a putative marker of matrix destruction and axonal loss.

Methods 99 individuals with clinically definite relapsing-remitting MS (age 35.3+/-9.5yrs, disease duration 6.6+/-7.2yrs, Expanded Disability Status Scale 1.5+/-1.2) underwent genotyping and clinical examination. T₂- and T₁-weighted axial MRI of the brain (1.5 T, TR/TE=2500/30 and 90; 600/15) for semi-automated lesion segmentation was performed at baseline and after 2.7+/-1.1 yrs. “Black holes” were defined as T₁-lesions with signal intensity between cortical grey matter and cerebrospinal fluid.

Results At baseline, T₂- and T₁-lesion loads (LL) were non-significantly higher in patients with ε4 (n=23; T₂-LL: 11.8±11.4; T₁-LL: 1.2±2.3ccm) than in those without ε4 (n=76; T₂-LL: 8.9±9.5; T₁-LL: 0.7±1.8ccm), despite a shorter disease duration (4.2±5.2 vs. non-ε4: 7.4±7.6 yrs, $p=0.06$) and the absence of significant differences in clinical variables between groups. During follow-up, T₂-LL significantly enlarged in patients without ε4 (10.6±11.0ccm; $p=0.001$), whereas it remained unchanged in ε4-carriers (11.3±11.7ccm). In contrast, T₁-LL significantly increased in the ε4-subgroup (1.7±2.7 vs. non-ε4: 0.8±1.5ccm, $p=0.039$). Moreover, the proportion of “black-holes” [(T₁LL/T₂LL)×100] increased significantly from 5.5±7.7% to 12.4±13.9% ($p=0.005$) in ε4-patients whereas it did not change significantly in non-ε4 patients (baseline: 5.0±7.9%, follow-up: 5.7±7.3%, $p=0.37$).

Conclusion The observed higher proportion of MRI brain lesions that develops into black holes in MS patients with ε4 provides further support for a more aggressive disease course in ε4 carriers.

SC 211

A combined fMRI-TMS study on the effects of 3,4-diaminopyridine on brain motor function in multiple sclerosis

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Introduction 3,4-diaminopyridine (3,4-DAP), a potassium channel blocker, improves motor function in Multiple Sclerosis (MS). Both axonal and synaptic mechanisms have been postulated. We evaluated the effect of a single dose of 3,4 DAP on motor function in MS by combining fMRI, transcranial magnetic stimulation (TMS), and quantitative EMG.

Method We conducted a double-blind, crossover, placebo-controlled study in 7 women (mean ±SD age 38.9±9.9 years; median, range EDSS 2.0, 1.0–2.5) with relapsing-remitting MS. Each patient underwent fMRI in two separate occasions (under 3,4-DAP and under placebo) while performing a sequential thumb to index finger opposition task with the right hand. fMRI data were analysed using SPM99. After each fMRI study, paired transcranial magnetic pulses were delivered in a conditioning-test design with stimuli given at 3 and 10 ms inter-stimulus intervals (Kujirai et al, 1993) to test cortical excitability. EMG at maximum voluntary contraction for 120 s was also performed.

Results At fMRI the extent of activation in motor related areas was greater under 3,4-DAP than under placebo. In particular, a significantly higher activation was observed in the contralateral premotor area and in the contralateral primary motor area ($p<0.05$, paired t-test).

At neurophysiological evaluation 3,4-DAP produced a significant increase in cortical excitability both by reducing intracortical inhibition and by enhancing intracortical facilitation. Left central conduction time did not change.

Conclusion Our data suggest that 3,4-DAP modulates brain motor activity in MS by increasing the extent of cortical activated areas. This effect is probably due to an increased activity of excitatory synapses.

SC 212

Intense immunosuppression followed by autologous stem cell transplantation in severe multiple sclerosis

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Introduction Autologous haematopoietic Stem Cell Transplantation (ASCT) could be a new alternative therapeutic approach for severe cases of MS unresponsive to conventional therapies. Phase I studies have already been carried out, suggesting a possible clinical benefit but also showing a high mortality risk.

Method In Italy a phase II study has been organized, aiming to obtain information on the effect of ASCT on Magnetic Resonance Imaging (MRI) and other laboratory tests. 16 cases of secondary progressive multiple sclerosis (MS) patients, with EDSS between 5 and 6.5, unresponsive to traditional therapies, with MRI enhancing activity were treated with Cyclophosphamide 4grxm² followed by BEAM (BCNU, Cytosine-Arabinoside, Etoposide, Melphalan) conditioning regimen and rabbit ATG for T depletion in vivo. Patients were then submitted to monthly MRI, neurophysiological tests, quality of life evaluation, CSF examination (in 3 cases only).

Results In all patients we observed a complete abrogation of MRI enhancing activity which is sustained with time. The median follow up is now 24 months (range 5–42 months). Oligoclonal bands at immunoblotting were still found in the CSF after therapy. Quality of life improved. Clinically 14 cases remained stable or slightly improved while 2 cases resumed worsening after 9 and 36 months, respectively.

Conclusion These studies demonstrate that ASCT has a profound and sustained effect on MRI gadolinium enhancing activity. The clinical efficacy has to be demonstrated in a phase III study, comparing ASCT to standard immunosuppressive therapy.

Neuro-oncology

SC 213

Identification of DNA and amino acid metabolism in human gliomas by PET

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Introduction The objective of our study was to non-invasively compare DNA metabolism and amino-acid uptake in patients with gliomas by positron emission tomography (PET).

Method 7 patients (57.3±12.6 years) with astrocytoma WHO grade II (n=2), astrocytoma WHO grade III (n=1) and glioblastoma (n=4) were studied by multi-tracer PET on consecutive days. The DNA-, protein- and glucose-metabolism was determined by means of 3'-deoxy-3'-[18F]fluoro-L-thymidine (FLT), L-[methyl-11C]methionine (MET) and 2-[18F]fluoro-2-deoxy-D-glucose (FDG) PET after intravenous administration of [18F]FLT (251.6±114.7 MBq; range: 111–370 MBq), [11C]MET (720 MBq) and [18F]FDG (370 MBq), respectively. Moreover, high-resolution magnetic resonance imaging (MRI) was performed to allow co-registration of anatomical and metabolic data.

Results In all patients, [18F]FLT- and [11C]MET-PET images demonstrated a similar extent of tumour activity. Relative thymidine uptake (defined by [18F]FLT accumulation within the tumour in relation to a contralateral control region) was greater than relative methionine uptake. Maximal relative [18F]FLT uptake ratios ranged from 4.6±1.9 (astrocytoma grade II) to 12.7±1.9 (glioblastoma) and maximal relative [11C]MET uptake ratios ranged from 2.7±1.4 to 4.2±1.1, respectively. Moreover, one patient with glioblastoma demonstrated focal [18F]FLT uptake at the border of the tumour where relatively low methionine uptake was observed as possible indication for actively proliferating tumour tissue visualized by [18F]FLT-PET.

Conclusion [18F]FLT is a promising tracer to study tumour proliferation especially in areas with high [18F]FDG background, such as the brain. Relative [18F]FLT uptake within gliomas is greater than relative [11C]MET uptake indicating the possible role of [18F]FLT in improved diagnosis of critical tumour areas such as the glioma border and of low grade gliomas.

SC 214

In vitro model to assess neurotoxicity induced by anticancer chemotherapeutic agents

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Introduction Most chemotherapeutic agents have some deleterious side effects on normal host tissues. Also 5-Fluorouracil (5-FU) carries a risk of central nervous system toxicity such as leukoencephalopathy. We examined the ability of 5-FU exposure to kill cultured mouse cortical neurons and glia.

Method Mixed neuron/glia, astrocytic, and mixed oligodendrocyte/astrocyte cultures were exposed to 5-FU for 24 hours. Neuron and astrocyte damage was assessed by LDH assay and oligodendrocyte death was assessed by counting the number of viable galactocerebroside-positive (Gal-C(+)) cells per 100× field.

Results Neurons and astrocytes exposed to 10, 30, 100 and 300 μM 5-FU produced no changes in morphology and level of LDH. But mixed oligodendrocyte/astrocyte cultures exposed to 10, 30, and 100 μM 5-FU developed concentration-dependent oligodendrocyte death. Most oligodendrocytes were damaged by 100 μM 5-FU, but there was little damage on astrocytes.

Conclusion These findings suggest that oligodendrocytes are selectively vulnerable to 5-FU, and neurons and astrocytes were relatively resistant to 5-FU. Present observations raise the possibility that leukoencephalopathy associated with 5-FU may be caused by the drug-induced death of oligodendrocyte.

SC 215

Molecular imaging in the development of efficient gene therapy of human glioma

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Introduction The objective of our study was to non-invasively evaluate the safety and efficiency of vector delivery and gene transduction after gene therapy of patients with recurrent glioblastoma by positron emission tomography (PET) and magnetic resonance imaging (MRI).

Method 8 patients (age: 49–67) received a stereotactically guided Gd-DTPA infusion with subsequent MRI and intratumoral convection-enhanced-delivery (CED; max. flow: 0.6 ml/h, volume 30–60 ml) of a liposome-gene-complex (LGC; DAC-Chol/DOPE [w:w; 30:70]) transducing herpes simplex virus type 1 thymidine kinase (HSV-1-TK). Thereafter, PET was performed after injection of [124I]-2'-fluoro-2'-deoxy-1-β-D-arabinofuranosyl-5-iodo-uracil ([124I]FIAU), a specific marker substrate for HSV-1-TK. Ganciclovir (GCV) treatment (2 x 5 mg/kg; 14 days) was started four days after LGC-infusion. Treatment response was recorded by MRI, [18F]-2'-fluoro-2'-deoxy-D-glucose (FDG) and L-[methyl-11C]-methionine (MET) PET.

Results Infusion of LGC was tolerated well. In 1/8 patient specific [124I]FIAU-accumulation was observed as indication for HSV-1-TK expression in co-registration to signs of necrosis after GCV treatment (FDG-/MET-PET). In 4/8 patients [18F]FDG- and [11C]MET-uptake was focally decreased in

areas co-registering to the distribution volume of Gd-DTPA. One patient showed transient reduction of the methionine positive tumour-volume by 50%. All patients developed tumour relapses outside areas with reduced tracer activity.

Conclusion Intratumoral CED of LGC is safe and leads to focal alterations of tumour activity. However, overall therapeutic efficacy is low indicating that more efficient vectors have to be engineered. Non-invasive imaging of vector distribution and vector-mediated gene expression by PET and MRI shall contribute to the development of standardized gene therapy protocols and improve efficiency and safety of vector applications in humans.

SC 216

ACNU + VM 26 as an alternative to PCV in chemotherapy of oligodendroglioma.

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Objective This study looks for a possibly better and less toxic regimen than PCV chemotherapy for recurrent oligodendroglioma.

Methods 12 patients (8 oligodendrogl., 3 oligoastroz., 1 radiological/clinical diagnosis only) with progressive contrast enhancing tumors in MRI/CCT received 2–7 cycles ACNU/VM 26 chemotherapy. ACNU dose: 90–100 mg/qm, VM 26 dose: 60–72 mg/qm. 2 of the oligodendrogliomas were newly diagnosed, the 10 others were recurrences. 9 of these were chemo-naive, 1 patient had received radiotherapy+PCV, 2 others had had adjuvant radiotherapy. Response was evaluated by McDonald's criteria based on CCT or MRI.

Results All patients clinically responded to ACNU/VM 26 with improvement in seizure frequency, focal signs and symptoms of intracranial hypertension, often already after application of one single cycle of chemotherapy. According to imaging criteria there were 3 (25%) complete and 3 (25%) partial responses, 6 (50%) had stable disease, no primary progression. The average time to tumor progression was 15.6 months (oligodendroglioma 16,8 months, oligoastrozytoma 12 months). The median time was 15 months. 5 patients (41.7%) had no tumor relapse up to now. 2 patients died after 12 and 41 months because of tumor progression. The follow-up was 5 to 48 months, in average 23 months. Side effects were minor with nearly exclusively hematological toxicity of moderate degree not requiring supportive therapy.

Conclusion ACNU/VM 26 chemotherapy in oligodendroglioma and oligoastrozytoma is a highly effective alternative with considerably less toxicity than what is reported for the PCV-regimen.

SC 217

Survival and prognostic factors of patients with brain glioma in Estonia

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Introduction 667 patients were diagnosed with brain glioma in Estonia between 1986 and 1996. The aim of the study was to find out survival and prognostic factors comparing our results with other surveys.

Method To maximize case ascertainment we obtained material from hospital records, the Estonian Cancer Registry and the Estonian State Statistical Office. All cases were histologically

confirmed. Survival analyses was carried out on 590 patients, cases discovered at autopsy, lost to follow-up and diagnosed with another were excluded. Survival rates at 1 and 5 years and median survival were estimated.

Results Median survival was the best in low-grade (G1 and G2) astrocytomas (54.2 months), very poor in anaplastic astrocytomas and glioblastomas (8.3 and 6.2 months, respectively). Patients with glioblastoma and anaplastic astrocytoma had the worst long-term outcome (5-year survival 8.6 and 15.8%, respectively). Approximately half of the low-grade astrocytomas patients (49.8%) survived beyond 5 years. 54% of patients were only operated on, 34% received additional radiation, 7% of patients additional radiation and chemotherapy. In multivariate analysis the best prognosis had low-grade astrocytoma ($p < 0.0001$) and oligodendroglioma ($p < 0.05$) patients of younger age, better clinical condition (Karnofsky score more than 60). There were no significant differences in patients who underwent surgery or received additional chemotherapy or radiation.

Conclusion The outcome of malignant gliomas is somewhat worse compared to other studies. We suggest the cause of such tendency is the shortcomings of neuro-oncology system in Estonia.

SC 218

A home care programme (HCP) for patients with advanced primitive brain tumours (APBT): the model of the Udine health district (HD)

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Introduction This paper reviews the model and 1 year activity data regarding a HCP for APBT patients in a HD with a territorial medical oncology service (MOS) integrated in a palliative care network.

Method The MOS providing specialist advice (Oncologist-Palliativist, OP), support for the general practitioner (GP) and oncological nurses providing pain and infusional therapy, feed tube, clinical follow-up during home-chemotherapy (e.g. with temozolomide) and laboratory examination. 24 hour-continuous-care by nursing and physicians in order to maintain at home e.g. patients with endocranial hypertension and dying ones. Emergency consultation through a 24 hours telephone service is available. The home care service is completely free for the patient. The OP provides this service upon request from the GP for outpatient or from the hospital doctor for inpatients, which are seen at the hospital.

Results From Jan 01 to Dec 01, 11 APBT patients (accounted for 4.6% of advanced cancer subjects supported at home); median age 62 yrs (range 40–74) 9 with glioblastoma multiform, 2 anaplastic astrocytoma. Average care duration 89 days. Prevalent symptoms: confusional state, asthenia, incontinence, oral candidiasis and anorexia. 6 patients (55%) had pain; 1 (9%) was tube fed. Admission to hospital during the 2 weeks before death 2 (18%); dead at home 5 (63%); 4 alive. The patients required 17 medical visits; 1512 nurse interventions, 88 physiotherapeutic interventions.

Conclusion The HCP can allow continuous care in APBT patients improving their Quality of Life (monitored with Therapy Impact Questionnaire), decreasing days of hospitalisation and resulting in cost saving for the Health Service.

Cerebrovascular diseases 2

SC 219

Risk of stroke in Type 1 diabetic subjects in Finland

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Introduction Type 1 Diabetes Mellitus (T1DM) is associated with increased mortality from stroke. The impact of the late complications of T1DM on the risk of subarachnoid haemorrhage (SAH), intracerebral haemorrhage (ICH) and ischaemic stroke (IS) is insufficiently known.

Method We prospectively analysed the incidence of stroke by several variables, including attained age (up to 50 years old) at the end of follow-up (lasting up to 28 years), and duration of diabetes in all 5166 subjects participating in the Finnish T1DM register (diagnosed T1DM before the age of 18 years). We also studied whether the presence of diabetic nephropathy (DN) increased the risk of SAH, ICH and IS.

Results There were 118 patients with diagnose of stroke during the follow-up. The relative risk for T1DM patients with DN compared with patients without DN was 4.7 and 9.1 for SAH and ICH, respectively. In addition, we observed a 6-fold increase in the risk of IS, similar in men and women. The cumulative incidence of IS by the age of 50 was 14% in T1DM subject with DN, and only 2% in subjects without DN, irrespective of gender.

Conclusion Childhood-onset of T1DM increases the risk of all stroke subtypes already at young age, in both men and women. The increased risk strongly depends on the presence of DN.

SC 220

Stroke incidence and 30-day case-fatality in Tbilisi: an interim data analysis of the first population-based study in Georgia

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Introduction Until recently no population-based study of stroke incidence has been conducted in Georgia. We aimed to determine incidence and short-term case-fatality rates of a first-ever stroke using data of the ongoing prospective Swiss-Georgian population-based project on stroke epidemiology.

Method We identified all first-ever strokes from November 2000 to March 2002 in a defined population of 54 320 residents in the Nadzaladevi district of Tbilisi using immediate notification system and standard diagnostic criteria. Crude average annual incidence rates for each stroke subtype and 30-day case-fatality were calculated.

Results The average annual incidence rate for all strokes was estimated as 157 per 100 000 residents. Regarding stroke subtypes, the incidence rate was 86 per 100 000 residents for ischaemic stroke (IS), 60 per 100 000 for hemorrhagic stroke (HS) and 15 per 100 000 for subarachnoidal haemorrhage (SAH). Fifty-three percent of stroke victims were women. One-month case-fatality rates were 16%, 47% and 40% for IS, HS and SAH, respectively.

Conclusion Stroke incidence rate in Georgia is comparable to that reported in developed countries, but significantly lower than in most countries in transition of Eastern Europe and former Soviet Union. Furthermore, IS incidence is among the lowest ever reported. On the other hand, there is rather high frequency of HS among all stroke types. Mortality at 30 days is also much higher for HS than for IS. Geographical and lifestyle variations may serve as a cause of such difference between Georgia and other countries with similar to Georgia's socio-economic and public health status.

SC 221

Predictors of post stroke epilepsy, the Copenhagen stroke study

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Introduction Post stroke epilepsy (PSE) is a frequent finding reported in 3-5%. In this study we sought to find predictors of PSE.

Method In this community-based study, we prospectively and consecutively investigated 1197 patients with acute stroke. Patients were followed for 7 years. We defined PSE as epileptic seizures with onset after stroke and requiring prophylactic anti-epileptic treatment. PSE was related to clinical factors (age, gender, onset stroke severity, lesion size on CT scans, stroke subtype, and risk factor profile) in univariate analyses. Independent predictors of PSE were identified through multiple logistic regression analyses.

Results Overall 38 patients (3.2%) developed PSE. PSE was significantly related to younger age at stroke onset (66 years vs. 75 years, $p < 0.001$), ICH (21% vs. 7%, $p = 0.007$), larger lesions (50 mm vs. 39 mm, $p = 0.03$), and AF at stroke onset (3% vs. 19%, $p = 0.009$). In a multiple regression model for the dependent variable PSE, independent predictors were younger age (OR 1.7 per 10 years; 95% CI 1.3 to 2.1), onset stroke severity (1.3 per 10 points decrease; 95% CI 1.0 to 1.6), lesion size (OR 1.2 per 10 mm enlargement; 95% CI 1.0 to 1.3), and ICH (OR 3.3; 95% CI 1.3 to 8.6).

Conclusion Post stroke epilepsy occurs in approximately 3% of all stroke patients within seven years after stroke. Factors such as age, ICH, lesion size, and onset stroke severity are predictors of PSE. The risk of PSE appears to be highest among younger stroke patients who have severe haemorrhagic strokes.

SC 222

Time from symptom onset to arrival in the stroke unit: analysis of 1.090 consecutive patients

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Introduction The timing of arrival of patients to a Stroke Unit (SU) and the factors that may delay their admission are relevant issues in order to obtain an optimal management of acute stroke. The objectives of our study were to record timing from clinical onset to admission to our SU and to identify the reasons for delay.

Method We prospectively examined acute stroke patients consecutively admitted to SU of Perugia (Italy) in the period between January 1st 2000 and March 31st 2002. Demographic and stroke characteristics, aetiology and time from symptom onset to the arrival in SU were recorded.

Results 38% of 1,090 patients admitted to SU arrived within 3 hours and 64% within 6 hours. In the remaining patients (36%) the underestimation of symptoms was the cause of delay in 56.5% of the cases. More hemorrhagic stroke patients than ischemic stroke patients arrived within 3 hours ($p < 0.02$). 80.1% of the patients who arrived within 6 hours presented a Rankin score ≥ 3 in comparison with 60.7% of the patients who arrived after 6 hours ($p < 0.001$). Considering TOAST and OCPS criteria, there are significant differences between stroke subtypes; TACI subtypes arrived earlier ($p < 0.001$) probably because of the severe clinical presentation.

Conclusion 64% of 1,090 consecutive stroke patients admitted to SU arrived within 6 hours; the main reason for delay was underestimation of symptoms. Patients with hemorrhagic strokes arrived earlier. The severity of deficit seems to be the main reason for earlier arrival to the SU.

SC 223

Systemic thrombolysis in acute stroke patients: survival, residual disability and complications. The Austrian Stroke Registry for Acute Stroke Units

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Introduction The aim of this study was to assess the outcome of thrombolysed stroke patients on Austrian stroke units for the years 1999 and 2000.

Method The Austrian Stroke Registry for Acute Stroke Units was designed to prospectively monitor the quality of performance. Among others, data on systemic thrombolysis were analysed.

Results 94 of 2313 patients (4.1%) received thrombolysis. Mean age was 66.7 years (med 70, STD 13.6). On admission, 11 patients had a mild stroke (NIHSS 0–7; 11.7%), 38 patients had a moderate stroke (NIHSS 8–14; 40.4%), and 45 patients had a severe stroke (NIHSS >14; 47.9%). Mean NIHSS was 14.7. Complications on the stroke unit were recurrent stroke in 6.4%, brain oedema in 10.6%, extracerebral bleeding in 3.2%, clinically relevant intracerebral bleeding in 7.4% (17 missing), and 9 patients (11.8%) died on the stroke unit. At 3 months follow-up modified Rankin Scale (mRS) was assessed in 59 patients (62.8%). Disability was none (mRS 0–1) in 20 patients (33.9%), mild to moderate (mRS 2–3) in 10 patients (17%), severe (mRS 4–5) in 15 patients (25.4%), 14 of 73 patients with available data had died (23.7%).

Conclusion Systemic thrombolysis was performed on 4.1% of patients treated in Austrian stroke units in the period 1999–2000. The results compare with other national surveys.

SC 224

Percutaneous left atrial appendage transcatheter occlusion (PLAATO) to prevent stroke in patients with atrial fibrillation - first human experience

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Introduction Anticoagulant therapy is effective in reducing stroke in patients with atrial fibrillation. However, it has a narrow therapeutic range and is contraindicated in many. The left atrial appendage is the source of thrombi in >90%. Obliteration of the appendage may prevent cardioembolic complications. We report the 1st human experience with percutaneous left atrial appendage transcatheter occlusion (PLAATO).

Method PLAATO was attempted in 31 patients (66–74 years) with atrial fibrillation, additional stroke risk factors, and contraindication to coumadin. The PLAATO™ device consists of a self-expanding cage covered with ePTFE delivered through a 12Fr transseptal sheath specially designed to access the left atrial appendage. Animal studies have shown efficacy at sealing the appendage with complete encapsulation and endothelialization by 1–3 months. Angiography and transoesophageal echo is used to determine the device diameter.

Results Implantation of the device was successful in all patients, in one of them during a second attempt. Hemopericardium during the procedure occurred in 2 patients, pericardiocentesis was performed without sequelae. No other complications occurred. Devices with diameters between 18 and 32 mm were implanted. Transesophageal echocardiography showed the device well seated. Follow up x-rays and echocardiograms revealed stable implants.

Conclusions Transcatheter closure of the left atrial appendage is feasible. This novel technology may offer an option for patients with atrial fibrillation who are not candidates for anticoagulation. Further clinical trials are needed to show the long-term safety and efficacy in reducing stroke.

Ageing and dementia 1

SC 225

Platelet amyloid precursor protein forms for the early identification of Alzheimer's disease among mild cognitive impairment (MCI) patients

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Introduction Patients affected by sporadic Alzheimer's disease (AD) show a significant alteration of amyloid precursor protein (APP) forms in platelets when compared both with non-Alzheimer's disease demented patients and age-matched controls. The objective of our study was to evaluate platelet APP forms' ratio (APPr) in early-stage AD and in MCI and its potential as a biomarker for the early identification of AD.

Method A community population-based sample of patients was admitted to 4 AD centres for investigation of cognitive disturbances. 60 patients with mild AD (mAD), 40 subjects with mild cognitive impairment (MCI), and 25 age-matched controls (CON) were included. APPr was evaluated by Western Blot analysis in platelet homogenate. All patients performed a neuropsychological evaluation and neuroimaging study (CT). In a subset of AD and MCI patients, SPECT was also administered.

Results Compared to CON (mean \pm SD = 0.93 ± 0.3), mean APPr was decreased in mAD (mean \pm SD = 0.45 ± 0.26 , $p < .0001$). With regard to the MCI group, a significant decrease in APPr was found compared with CON (mean \pm SD = 0.60 ± 0.33 , $p < .0001$). Fixing a cut-off score of 0.6, sensitivity was 88.6% (31 of 35) for mAD while specificity was 88% (22 of 25) for CON. Among MCI, 23 of 40 individuals displayed APPr values below the cut-off.

Conclusion Alteration of APP metabolism is an early event in AD and the measurement of platelets' APPr may be useful for the identification of pre-clinical AD in MCI subjects.

SC 226

Glucocorticoids regulate pro-inflammatory cytokines phenotype in patients with Alzheimer's disease

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Introduction Pro-inflammatory phenotype can play a role in pathogenesis of Alzheimer's disease (AD). We used whole blood assay to determine the release of tumour necrosis factor (TNF alpha), interleukin-10 (IL-10) and interleukin-12 (IL-12) in AD patients and to establish how dexamethasone (DEX) regulates these cytokines synthesis.

Method 16 patients with probable AD and 11 control subjects were included. Cytokine level was measured using ELISA method, after 24 h of whole blood stimulation with LPS (10 ng/ml) or LPS and DEX (1 micromol/L) in 37 degrees Centigrade, 5% CO₂.

Results Cytokine levels before whole blood stimulation, after stimulation with LPS and after treatment with LPS and DEX didn't differ significantly in AD patients as compared to control group. AD patients had higher TNF/IL-10 ratio before (159.3 ± 450.2 vs 20.3 ± 8.7 , $p = 0.01$) and after stimulation with LPS (513.4 ± 1694.7 pg/ml vs 47.5 ± 11.6 , $p = 0.03$) than control group. After incubation with LPS and DEX, TNF/IL-10 ratio was higher in AD patients than in control group, but that difference was not statistical significant (80.0 ± 267.1 vs 9.2 ± 3.7 , $p = 0.21$). In addition DEX inhibited significantly stronger TNF production in AD patients (5.9-times vs 4.4-times, $p = 0.01$). Since IL-12 release was similar in both groups, this cytokine is probable not responsible for increased interferon gamma synthesis described previously in AD patients.

Conclusion Pro-inflammatory phenotype defined as TNF alpha/IL-10 ratio can be counter-balanced in AD patients by glucocorticoids, which shift cytokines production towards anti-inflammatory molecules.

SC 227

Neurotoxicity of antipsychotic drugs in Alzheimer's disease

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Introduction Tissue transglutaminase (tTG), a protein-cross-linking enzyme, which is involved in apoptosis, could be a biochemical marker for cell damage or apoptosis in neurodegenerative diseases. Although a pronounced increase in tTG activity or protein was found in post-mortem Alzheimer's disease (AD) brains, tTG protein expression was not measured in vivo so far.

Method TTG was examined in the cerebrospinal fluid obtained from 51 patients with dementing disorders (33 patients with AD and 18 patients with vascular dementia (VaD)), and compared to those from 33 patients without neuropsychological deficit. 21 controls and 10 Alzheimer patients were under neuroleptic medication in the last 24 hours before lumbar puncture.

Results We found a significant difference ($p < 0.01$) between the AD and the other two groups (7.58 pg/ml vs 2.95 pg/ml). VaD and controls did not differ (2.93pg/ml vs 2.99 pg/ml). A highly significant influence of neuroleptics in the AD group (12.62pg/ml vs 5.39pg/ml) and the non-AD group (5.72pg/ml vs 1.04pg/ml) was revealed.

Conclusion Our results show that tTG is leaked out of the brain into the CSF. We could demonstrate acute neuronal cell death in vivo in AD patients. We furthermore could document acute neurotoxicity of neuroleptics, especially in AD patients. We conclude that tTG may serve as a biochemical marker for acute cell death to assess the efficacy of possible new anti-apoptotic drugs. We furthermore suggest that neuroleptics should be strictly limited in AD patients.

SC 228

Donepezil treatment benefits caregivers of patients with moderate to severe Alzheimer's disease (AD)

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Introduction This analysis investigated whether treatment benefits with donepezil in patients with moderate to severe AD are associated with measurable benefits to caregivers.

Method 290 patients with moderate to severe AD (standardized MMSE score 5–17) were randomised to receive either donepezil or placebo for 24 weeks. Caregivers were evaluated for their levels of stress with a modified, 20-item Caregiver Stress Scale (CSS). Time spent helping patients with both basic and instrumental ADLs was recorded using modifications of the Physical Self-Maintenance Scale (PSMS+) and Instrumental Activities of Daily Living Scale (IADL+).

Results Caregivers of donepezil-treated patients (n=141) did not differ significantly from caregivers of placebo-treated patients (n=146) with respect to age, gender, education, relationship to patient, or duration as caregiver. Similarly, at baseline, the mean total scores on the CSS did not differ significantly between the caregiver groups of donepezil- and placebo-treated patients. 87% of donepezil- and 88% of placebo-treated patients were community-dwelling at baseline. At week 24 (LOCF),

CSS total scores remained close to baseline for caregivers of the donepezil group (mean change=0.08±0.83), in contrast to a decline from baseline of 1.98±0.79 for caregivers of the placebo group. Caregivers of donepezil-treated patients reported spending less time assisting with both instrumental and basic ADLs during the study than did caregivers of patients receiving placebo (total treatment difference at week 24 LOCF=63.8 minutes/day).

Conclusion In this study, treatment benefits with donepezil in patients with moderate to severe AD were associated with measurable benefits in levels of caregiver stress and time spent care-giving.

SC 229

Donepezil slows functional deterioration in patients with vascular dementia

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Introduction Cholinesterase inhibitor therapy may have functional benefits in patients with vascular dementia (VaD). The objective of our study was the Evaluation of the functional and cognitive efficacy of donepezil in patients with probable or possible VaD.

Method This paper reports a combined analysis of two large-scale, randomised, double-blind, placebo-controlled, 24-week, parallel-group studies with identical protocols (Studies 307 and 308). A diagnosis of probable or possible VaD according to NINDS-AIREN criteria was required for inclusion; patients with a prior diagnosis of Alzheimer's disease were excluded. Patients were randomised to receive placebo, donepezil 5 mg/day or donepezil 10 mg/day (5 mg/day for first 28 days). Functional efficacy was assessed by the ADFACS. Results are reported for intent-to-treat observed cases.

Results Overall, 1219 patients were enrolled (392 placebo, 406 donepezil 5 mg/day, 421 donepezil 10 mg/day); 73% had probable VaD and 27% had possible VaD. At Week 24, both donepezil-treated groups showed significant improvements in cognitive function compared with placebo (ADAS-cog LS mean change from baseline score effect size: donepezil 5 mg/day, -1.79, $P<0.001$, $n=317$; donepezil 10 mg/day, -2.28, $P<0.001$, $n=298$). Donepezil-treated patients showed significant benefits over placebo-treated patients in their ability to perform activities of daily living (ADFACS mean change from baseline score treatment difference at Week 24: donepezil 5 mg/day, -1.014, $P=0.02$, $n=306$; donepezil 10 mg/day, -1.010, $P=0.02$, $n=297$).

Conclusion Significant benefits of donepezil compared with placebo treatment were observed on measures of cognition and function, indicating that donepezil may have an important role in the management of these symptoms in patients with probable or possible VaD.

SC 230

NNT data of galantamine for patients with "advanced moderate" Alzheimer's disease

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Introduction Galantamine (Reminyl®) is beneficial in patients with mild-to-moderate Alzheimer's disease (AD), also in those who are in the more advanced stage of the disease. In order to emphasise the efficacy in this last group, a number needed to

treat (NNT) analysis was performed on the pooled data of patients with "advanced moderate" AD from three large-scale Phase III studies of 5–6 months duration.

Method Of the 705 patients that received galantamine 24 mg, 178 patients with baseline AD Assessment Scale-cognitive subscale (ADAS-cog) scores of >30 and 86 patients with baseline Mini-Mental State Evaluation (MMSE) scores of ≤14 were used in the NNT analysis. Patients were assessed for treatment responses compared with matched placebo groups ($n=183$ and 101 , respectively). The NNT analysis was performed on responder data for improvements of ≥0, ≥4 and ≥7 points on ADAS-cog and "improved or unchanged" Clinician's Interview-Based Impression of Change plus caregiver input (CIBIC-plus).

Results In patients with baseline ADAS-cog scores of >30 the NNT is 3 for ADAS-cog improvement of ≥0 points, 4 for ADAS-cog improvements of ≥4 and ≥7 points and 5 for CIBIC-plus "improved or unchanged". In patients with baseline MMSE scores of ≤14 the NNT is 3 for ADAS-cog improvements of ≥0 and ≥4 points, 5 for ADAS-cog improvement of ≥7 points and 4 for CIBIC-plus "improved or unchanged".

Conclusion These consistently small NNT data for cognitive and global outcome in both subgroups strengthen the conclusion that galantamine treatment is very efficient in "advanced moderate" AD patients.

Autonomic nervous system Clinical neurophysiology Critical care

SC 231

Sildenafil has no negative effects on the autonomic cardiovascular modulation during exercise

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Introduction There is controversy whether Sildenafil (Viagra) enhances sympathetic activity during stress and increases cardiovascular risk (Phillips et al.: *Circulation* 2000;102:3068-73). In this study, we determined effects of Sildenafil on autonomic cardiovascular modulation at rest and during exercise.

Method In 40 healthy volunteers (16 women; 27.9±5.4 years), we monitored heart rate (HR), radial artery blood pressure (BP), respiratory frequency (RF) [RespiTrace™], end-tidal carbon dioxide (CO₂) and transcutaneous oxygen saturation (SatO₂) [Colin Pilot™], during 10 min rest and ergometric exercise at 50, 100, 150 and 200 W (3 min each) (test 1). After 24 hours, the participants repeated the test 45 minutes after intake of 100mg Sildenafil or placebo (test 2). At rest and during exercise, we determined mean values and spectral powers of the signals in the low (LF: 0.04–0.15 Hz) and high frequency (HF: 0.15–0.5 Hz) ranges reflecting sympathetic and vagal influences on HR and BP oscillation.

Results HR, BP, RF and LF powers of HR and BP increased while HR-HF powers decreased with increasing exercise ($p<0.05$). SatO₂ remained unchanged, CO₂ increased slightly. Results of tests 1 and 2 and of the Sildenafil and placebo group did not differ, apart from lower BP values in the Sildenafil group at rest and at 150 and 200-Watt challenge.

Conclusion Sildenafil has no negative effects on autonomic cardiovascular modulation at rest or during physical challenge. The lower BP after Sildenafil suggests some protective cardiovascular effects.

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SC 232

A systematic analysis of dose related local anhidrotic effects of botulinum toxin type B injections as measured by sudometry

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Introduction Until now, no systematic data are available on the effect of botulinum toxin type B (BoNT/B, Neurobloc®; Elan) on sweating. The objective of our study was to analyse dose dependency of BoNT/B-derived suppression of sweat gland activity.

Method Employing a standardised scheme (four injections in a 2 cm² area), different doses of BoNT/B (2-1000 U in a 1 mL saline solution) were injected subcutaneously in 15 healthy volunteers. Sweat tests were performed before, 3 weeks and 3 months after BoNT/B injections. Sweating was visualised by staining with iodine starch, and quantified by capacitance hygrometry after carbachol iontophoresis, the quantitative sudomotor axon reflex test (QSART).

Results Iodine starch staining indicated a threshold dose of 15 U leading to visible anhidrotic skin spots (>5 cm²) after 3 weeks in all subjects. This was maintained for 3 months with doses of 62.5 U or higher, although the size of the anhidrotic skin area decreased over time (p=0.001) indicating partial recovery at the edges. After 3 weeks, QSART was significantly reduced (>90%) and completely suppressed by doses of 32.25 U or more. Both methods indicated that the suppression of sweating by BoNT/B is dose dependent.

Conclusion Our findings suggest that the effectiveness of BoNT/B can be quantified by testing sudomotor function. For the first time threshold doses for the suppression of sweating have been defined for BoNT/B. Compared with the equivalent motor endplate blocking dose previously reported by our group for BoNT/A1, BoNT/B seems to be more effective in inhibiting sweat production.

SC 233

Postural blood pressure and catecholamine responses in uremic type 1 diabetic patients prior to and after kidney and pancreas transplantation

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Introduction Orthostatic hypotension caused by autonomic neuropathy (DAN) is frequent in uremic diabetic patients. The study aim was the assessment of postural blood pressure (BP) and catecholamine (CA) responses in Type 1 diabetic (DM1) patients before and after kidney/pancreas transplantation (KPT).

Method 12 DM1 patients (mean age 44±12 years, 6 patients dialysed, creatinine 380±151mmol/l in 6) were examined before and 10±4 months after KPT with long-term normoglycemia. 10 healthy subjects were used as controls (C). DAN was tested by heart rate (HR) variability during deep breathing

(inspiration-expiration (I-E) HR, abnormal <10/min). Systolic(s), diastolic (d) BP, plasma norepinephrine (NE) and epinephrine (E) levels were measured in supine position and at min 5 after standing up. BP was determined by cuff sphygmomanometry, CA levels by HPLC with fluorimetric detection. Two-sample Mann-Whitney and Wilcoxon paired tests were used for inter- and intra-group comparisons.

Results DAN was present in all DM1 patients (I-E: 3.4±2.5/min). After standing up, sBP (min5 vs.0: 131±22 vs.155±16 mmHg, p=0.002) and dBP (86±14 vs.92±12 mmHg, p=0.03) decreased in DM1 group, but not in C. However, similar CA responses occurred in both groups with NE increases (min5 vs.0: 2.5±0.8 vs.1.7±0.5, p=0.02 and 2.3±0.9 vs.1.4±0.4 nmol/l, p=0.006, for DM1 and C) and no E changes. BP and CA responses did not change in the DM1 group after KPT.

Conclusion Despite the presence of DAN and decreases in BP, no difference in postural CA responses in comparison with C was found in uremic DM1 patients. After a successful KPT, no significant change in postural BP and CA responses occurred. Supported by Czech MH IGA NB/6394-3 grant

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Effect of acetyl-L-carnitine on painful HIV-related neuropathy

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Introduction Acetyl-L-Carnitine (ALC) is a safe and well-tolerated drug in the treatment of peripheral neuropathy in HIV infected patients. ALC efficacy is mainly focused on the modulation of TNF-alpha expression. Moreover, HIV infected patients present with reduced blood levels of endogenous acetyl-carnitine. So ALC supplement may represent a valid therapeutic option. Peripheral nervous system is frequently involved during HIV infection and distal sensitive polyneuropathy appears in up to 30% of AIDS patients. Aetiology is still unknown. One of the pathogenetic hypotheses is the role of proinflammatory cytokines (TNF-alpha) in causing neuropathic pain.

Method 20 HIV- positive patients with neuropathic pain and EMG-evidence of axonal alterations were enrolled; we excluded patients with mini-mental test score less than 24, acute cytomegalovirus infection, chronic demyelinating neuropathies. All patients were treated with ALC at the dose of 1 gram 3 times daily for 4 weeks. A visual analogue scale (VAS) was used to evaluate characteristics of patient's pain before, during, and after treatment. Electromyographic and neurographic assessment was performed before and after treatment. To evaluate changes in VAS score we used non-parametric Friedman's test (F). Wilcoxon's test (W) was performed to timing the appearance of pain improvement and to evaluate neurophysiological data.

Results The changes in VAS score were statistically significant during ALC treatment (mean score: before 6.7±2.1 – after treatment 5.0±2.1) (F=P<0.001). Therapeutic effect appeared during the first (W=P<0.03) and the fourth (W=P<0.05) week of treatment.

Analysis of neurophysiological data showed a statistically significant improvement of peroneal nerve motor parameters: reduced motor distal latency (W=P<0.02), increased amplitude of compound motor action potential at distal (W=P<0.02) and proximal (W=P<0.05) site of stimulation.

Conclusion Our data show the efficacy of ALC in the treatment of neuropathic pain, confirming previous results (Scarpini E. et al., 1997). Moreover, the analgesic effects appear during the

first week of treatment according with pre-clinical data in different experimental models of pain (Ghilardini C. et al., 2002, submitted). Among mechanisms for ALC efficacy in those patients there is a neurotrophic effect as evidenced from patch-skin biopsy evaluation (Haart A. M. et al., 2002, submitted).

SC 235

Intraoperative recording of local field potentials for assisting localisation of the targets for deep brain stimulation

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Introduction Deep brain stimulation (DBS) is an effective treatment for many movement disorders. To improve accuracy of anatomically localising the target beyond using fused CT and MRI images, and to avoid the long operating times that are needed for single unit recording, we recorded focal field potentials (FPs) during electrode implantation.

Method In 32 consecutive cases of electrode implantation (12 advanced Parkinson's disease; 3 multiple sclerosis; 2 essential tremor; 1 post-traumatic tremor; 2 myoclonic dystonia; 4 generalised dystonia and 5 chronic central pain), FPs were recorded via the DBS electrodes from targets including the subthalamic nucleus, the ventral thalamus, the zona inserta, the medial pallidum and the periventricular grey, respectively.

Results Oscillatory activity of various frequencies could be detected as local FPs in movement disorders and in pathogenic pain. Functional localisation of a target could be achieved according to the graded changes in FPs recorded via different electrode contacts corresponding to their positions relative to the target. During tremor and rhythmic myoclonus, the oscillatory activity was coherent with the EMG bursts in the frequency range of the symptoms. The function-anatomy correlation of the selected target could be revealed by superimposing recordings on fused images of the post-op CT onto the pre-op MRI.

Conclusion FP recording was helpful for improving the accuracy of image-guided localisation of the targets for DBS. Our results suggest that FP recording offer a useful alternative to microelectrode recording.

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SC 236

Risk factors for critical illness polyneuromyopathy

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Introduction The aetiology and mechanisms of neuromuscular involvement in critically ill patients are not completely understood. Numerous clinical, laboratory, and pharmacological variables have been reported as significantly associated with the development of critical illness polyneuromyopathy (CIPM).

Method We performed a prospective one-month observational clinical and electrophysiological study aimed at the identification of the risk factors for CIPM. The detection of CIPM was based primarily on electrophysiological criteria. 79 critically ill patients (median age 59, 33 women, 46 men) were enrolled into the study and 48 completed the 28-day follow-up.

Results Electrophysiological signs of CIPM were detected in 27 critically ill patients. The development of CIPM was significantly associated with the presence and duration of systemic inflammatory response syndrome (SIRS) and the severity of multiple organ failure (MOF) expressed as the sequential organ failure assessment score (SOFA). The mean 28-day total SOFA score reflecting the cumulative severity of MOF during the first month shows the closest correlation with CIPM development. The respiratory and central nervous systems were the only two systems whose failure displayed independent significant association with CIPM. A multivariate logistic model utilising these variables was able to correctly predict the development of CIPM at the end of the first month in about 85% of our cases.

Conclusion The presence and duration of SIRS and the cumulative severity of multiple, respiratory and neurological failures are associated with increased risk for the development of CIPM. These variables could be used for prediction of CIPM development.

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Neurology and art History of neurology

SC 237

The original contribution of arts and theatre to the understanding of Alzheimer Disease

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Music, painting, sculpture, poetry and theatre are part of man's cultural DNA. In this expression of imagination and intellect he has found many cultural answers and explanations to some of the basic questions of life. Art is an essential component in any social and human context. The work of art (in this case theatre) is the expression of a visual event which aims to lead the user to a state of identification, that is empathy or involvement, purely through a mental process. The piece "A come non so" presented here is a monologue written and performed by Carlo Pontesilli. The piece shows the characteristic aspect of Alzheimer's disease from the first to the last stage: amnesia, aphasia, agnosia, and apraxia, as well as the different behaviour patterns and relations with the outside world of the patient, while the degenerative process gains ground. It tells the story of Carlo Pontecoli, gerontologist and specialist in cardiovascular and mental illnesses. He lives with his mother, who is affected by the disease and already reaching the very end of here life. Dr. Pontecoli is writing a report on "The elderly ad sexuality" for an important national congress on Alzheimer disease. While he is writing it, the doctor presents the initial signs of the disease that killed his mother not so long before. Pontecoli is also going to die because of the illness, and is going to go through all the phases of the disease, facing behaviour and language disorders, losing mental and intellectual faculties. The monologue aims to be a new contribution to the whole understanding of the problems concerning Alzheimer's disease through their observation and visual communication of the problems.

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SC 238

Neurology in Thomas Mann's novels

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Thomas Mann (1875–1955) is one of the most interesting authors of the 20th century. Although his own health was excellent (he even survived a lung-cancer), most of his novels contain medical subjects. I will try to give an overview of the neurological topics presented his novels.

Firstly “Buddenbrooks” (1901)–the novel that provided him with the Nobel prize in 1929; he is telling the story of degeneration of a family by disease over four generations: by a lot of neurological cases, from “too short nerves”, migraine, tremors and a terrible death by cerebral typhus. The main topic in “Der Zauberberg” (1924) is the inside life of tuberculosis as lived in a sanatorium–with many psychoneurological complications. In the gigantic four-volume novel: “Joseph und seine Brüder” (1933–43) we meet a lot of neurological conditions, as they were experienced in biblical times. Shorter novels such as “Der Tod in Venedig” (1912) tell us about cholera, neurological complications and death.

Thomas Mann tries to give a sort of “philosophy of disease”–most convincing in the short novel: “Goethe und Tolstoy” (1921)–and above all in: “Doktor Faustus” (1947). This book is a must for every neurologist/every human for its deep wisdom of our human condition and for its description of various neurological conditions from hereditary migraine to epilepsy. And above all it is a sort of “bible of syphilitic”. What was the Devil in old German tradition (from 1587) and transformed by Goethe in “Faust I and II”–is transformed by Thomas Mann to be a syphilitic tragedy.

My aim is to show most of the neurological implications in Thomas Mann's work, their importance – and to express my admiration: where did he get his medical knowledge from?

SC 239a

Neuro-expressionism, Egon Schiele and Arthur Schüller

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The term “expressionism” is used to describe any art that raises subjective feelings above objective observations. Affected by the anxieties of accelerated social change, expressionist artists employed violent exaggerations and distortions of form and colour.

Austrian expressionist artist Egon Leo Adolf Schiele, born June 12, 1890, died October 31, 1918, was at odds with art critics and society for most of his brief life. Even more than Gustav Klimt, Schiele made eroticism, in a dystonic way with stronger linear effects and harsher outlines, one of his major themes. Schiele's narcissism, exhibitionism and persecution-mania can all be found united in the poster “St. Sebastian”, such as spasms of facial muscles in “Selbstbildnis mit Hand und der Wange”.

Arthur Schüller, the father of neuroradiology, was born in the north of Vienna and began his medical career in the field of neuropsychiatry.

In 1905 his first book “The skull base on the radiogram” was published and expressionism developed almost simultaneously in different countries. It was a comprehensive description of normal and pathologic anatomy as well as of many special radioprojections, like Schiele's linear effects, of the skull base. Later on Francis Bacon's work maintains a sense of strict control, even precision. His use of Schüller's views from the book “Positioning in Radiography” give a further quasi-documentary atmosphere. Bacon is in accord with expressionism in his painful abrasions and distortions of faces evoking an agonized picture.

Among these artists who have tried to represent the inwardness of the body, Schüller holds a high place, along with Schiele and Bacon. Does neurology express art?

SC 239b

Neuro-expressionism, Otto Klemperer and Martha Graham

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Otto Klemperer (1885–1973) was born in Poland. First as revolutionary groundbreaker, later as champion of the classics from Bach to Mahler, amassed a recording legacy of masterworks perhaps unmatched by any other conductor, unequalled in their vision, depth, and power. After 1918 he emerged as one of the leading German conductors of his generation. His sympathy for and authoritative performances of an unusually wide range of contemporary music, as well as a less overtly emotional interpretation of the classics made him appear an expression of the “new age”. At the age of 48, Klemperer immigrated to the United States and conducted the Los Angeles Philharmonic. In 1939 he underwent an operation for a brain tumour and his health and stability were gravely undermined. Later on, he was named principal conductor of the Philharmonic Orchestra of London. His performances were distinguished by a power and intensity in spite of having suffered further accidents and illnesses.

Martha Graham (1894–1991) was a major figure in the American modern dance. By 1930 she was beginning to identify a new system of movement and new principles of choreography, a method of breathing and impulse control she called “contraction and release”. Her work was focused on emotional themes such as her famous solo “Lamentation”. The narrative of the dance uses only a pure, abstract movement vocabulary to bring its story to life. At the age of 94 she suffered a stroke with aphasia. Her good recovery was clearly illustrated in her piece “Night Chant”. Does neurology express art?

SC 240

Tremor in painters: the movement disorder of

Max Svabinsky

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Max Svabinsky (1873–1962), one of the most illustrious Czech graphic artists of the 20th century, suffered from hand tremor that substantially marked his handwriting. The aim of the present study was to ascertain the kind of his tremor and to deter-

mine how it influenced Svabinsky's production. We studied Svabinsky's personal correspondence, graphic artefacts, and newsreel films preserved in the archives.

Chronological analysis of Svabinsky's handwriting and signature shows a progressive deterioration since the 1930s, with angular and uneven script. After 1950, the writing is considerably altered, with scattered characters and coarse lines. The listing of Svabinsky's art works demonstrates a definite change in graphic techniques, since 1944 moving to chalk lithography that is less sensitive than other techniques to uneven hand movements and shaking. Newsreel shots show significant action tremor of hands, however it scarcely interferes with Svabinsky's drawing. Svabinsky never sought medical care for tremor. He was cognitively intact and artistically active until his last days.

Based on typical symptoms including action tremor of hands, preserved cognitive and creative faculties and longevity, we believe that Max Svabinsky suffered from essential tremor. Despite its high prevalence, few cases of essential tremor were reported in artists (1). Curiously enough, different brain mechanisms might be involved in handwriting and drawing. We hypothesise that tremor may more interfere with automatic action of handwriting than with volitionally controlled drawing.

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SC 241

Jan Evangelista Purkinje (1787–1896), Founder of modern neurophysiology and mediator between two countries

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Purkinje, born in Libochowitz (Bohemia), aroused interest with his thesis submitted to the University of Prague, entitled “Knowledge of Visual Impressions from a Subjective Point of View” – based on Goethe's “Theory of Chromatics”. In 1823 he was called to Breslau but returned to Prague in 1849. He founded Institutes of Physiology at both universities.

Purkinje established basic scientific knowledge – but not only in the fields of physiology and microscopic anatomy. He improved the techniques applied in microscopy and also made contributions to cell research in general; the term protoplasm was coined by him. Most important were his achievements in neurology and neurophysiology. He described cells and various structures of nerves, but mainly he was the first to discover cells in the CNS which were later named Purkinje cells located in the cerebellum. He published several studies about vertigo and about experimentally induced lesions in the brain to facilitate neurological diagnosis. He also performed self-experiments to test substances acting on the nervous system and revealed previously unknown interactions between brain function and localisation, explaining waking state, sleep and dream. Purkinje (in Czech: Jan E. Purkyně) presented his lectures in Prague both in German and Czech yet he was not only concerned with the Czech language as an instrument of scientific communication but has also made important contributions to improving mutual understanding between the Czech- and German-speaking population in Bohemia and Moravia. His tireless and fruitful efforts resulted in the founding of the Czech Karls-Universität in Prague.

SC 242

Neurology – myth and reality

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Since the age of enlightenment the sovereignty of reason had always claimed to be scientifically pure, but the objectivity claimed by this science is not entirely free from subjectivity. These subjective aspects may be traced not only to empirical art and literature, called realism and naturalism, and not only to socio-economic theories that claim to be scientific, but also to fields which by nature must be scientific and devoid of subjectivity. This brief summary sets out to trace the string of illusions in describing maladies. The descriptions of those illnesses have been proven to be developed by myth and fancy-like spermatorrhea to maladies. Their subjective origin is highly suspicious, but yet many neurologists use them like TOS. It must be noted however that emergence of these diagnoses as mixture of objectivity and subjectivity at any given time has had its particular economy and often served as needed.

The spectrum of these neurological diagnoses are from spermatorrhea – a strange diagnosis very popular at the beginning of 20th century today not well known – to a diagnosis like TO – a very weakened concept but yet living to RSD – a very loose concept of symptoms and signs – to other diagnoses such as pronator teres syndrome with an apparently strong basis but doubtful in the view of some well-known electrodiagnostic specialists.

In this paper I will review the evolution of these concepts in literature and the current situation of them with objective viewpoints.