Sunday, 9 September

Tournament for Young Neurologists (clinical)

T101

MRI based predictors of transient and prolonged dysphagia in acute supratentorial ischemic stroke

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Introduction: A review of the literature yielded 11 supratentorial regions of interest (ROI) related to swallowing in healthy individuals. To assess the relevance of these structures for transient or prolonged dysphagia we performed a lesion study in ischemic stroke patients.

Methods: Atlas-based localization analysis was performed using Talairach alignment of brain scans in consecutive patients with MRI-proven first-time acute supratentorial stroke. Standardized swallowing assessment was carried out within 48 hours and 8 to 10 days after hospitalization.

Results: Prospective analysis of 86 patients demonstrated significant odds ratios (OR) of acute dysphagia (n=31) for: insular cortex (ICo, OR=6.4, p<0.001), internal capsule (ICa, OR=5.5, p=0.001), frontal operculum (FO, OR=3.9, p=0.004), caudal sensorimotor and premotor cortex (CSMPC, OR=3.7, p=0.005), superior temporal cortex (STC, OR=3.1, p=0.01), sensorimotor integration area (SMIA, BA 5/7, OR=2.8, p=0.04), periventricular white matter (PVWM, OR=2.7, p=0.03) and basal ganglia (BG, OR=2.6, p=0.04). Significant odds of prolonged dysphagia (>7 days, n=16) were demonstrated for: FO (OR=55.0, p<0.001), ICo (OR=27.0, p<0.001), CSMPC (OR=7.0, p=0.001), STC (OR=6.1, p=0.002), PVWM (OR=5.1, p=0.01) and SMIA (OR=4.0, p=0.01).

Conclusions: Stroke involving the insular cortex and the internal capsule shows the highest odds of acute dysphagia. Lesions of the frontal operculum and the insular cortex substantially increases the odds of prolonged dysphagia, whereas stroke of the internal capsule and the basal ganglia appears to cause only transient dysphagia. These areas may represent critical nodes in the neuronal network underlying swallowing and, thus, determine the dynamics of recovery after ischemic stroke.

T102

Alcohol and intra-cerebral hemorrhage: impact on prognosis

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Introduction: We aimed to identify associated factors and influence on long-term outcome of heavy alcohol intake in a large prospective cohort of consecutive spontaneous ICH patients.

Methods: Between 11/04 and 03/09, we prospectively recruited 562 consecutive adults with a spontaneous ICH (PITCH cohort). We excluded patients without information on drinking habit (22). Heavy alcohol intake was defined as a regular consumption over 300 grams of alcohol per week. We performed bivariate and multivariate analysis (logistic regression) based on demographic and radiological models. Survival analyses were performed using Kaplan-Meier statistics.

Results: Among 540 ICH patients, 137 (25%) were heavy alcohol drinkers [median age: 60 years versus 74 years in non-abusers (p<0.0001)]. In multivariate analysis, associated factors with heavy alcohol intake were: in the demographic model, younger age (OR=0.97 per 1 year increase; 95CI 0.95-0.98), smoking habit (OR=3.96; 95CI 2.43-6.46), ischemic heart disease (OR 0.34; 95CI 0.15-0.77); in the radiological model, non-lobar location ICH (OR=1.71; 95CI 1.05-2.77) and leukoaraiosis (OR=0.76; per 1 step increase, 95CI 0.62-0.73). Platelet counts and prothrombin ratio were significantly lower among heavy alcohol drinkers (respectively p=0.01, p=0.017). Heavy alcohol intake was predictive of 2 years mortality only among patients younger than 60 years with non-lobar ICH (OR=1.96; 95CI 1.06-3.63).

Conclusion: Alcohol abuse is associated with the occurrence of ICH at a young age. However, the underlying vasculopathy remains unexplored in these patients. Indirect markers suggest small-vessel disease at an early stage that might be enhanced by moderate hemostatic disorders.
T103
4-aminopyridine and its influence on cerebellar gait disorders - a retrospective study

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The fall risk of patients with cerebellar disorders is markedly increased. Falls cause immobility due to injuries or a fear of falling. Therefore, the major goal in a symptomatic treatment of cerebellar gait disorders is to reduce the fall risk. We retrospectively examined the effect of 4-aminopyridine (4-AP) on the gait performance of patients with different cerebellar syndromes. In animal experiments, 4-AP has shown to improve Purkinje cell function. 31 patients with different cerebellar gait disorders (16 downbeat nystagmus, 8 sporadic adult-onset ataxia, 3 CACNA 1A mutation, 2 cerebellar stroke, 2 multisystem atrophy) received 4-AP as an individual treatment attempt. Gait performance was measured using a sensor carpet system (GaitRITE®). Subjective ambulatory functions were also acquired using a Falls Efficacy Scale (FES-I) and the Activities-specific Balance Confidence Score (ABC-Score). The coefficient of variation of stride time decreased during therapy with 4-AP from 7.8±5.4% to 3.4±2.0% (p<0.001). Subjective ambulatory function and fall risk also improved significantly. A high coefficient of variation of stride time before treatment correlated with the improvement of objective gait parameters and with reduction of subjective gait performance (p<0.001). This retrospective study indicates that the gait of patients with different cerebellar disorders improves during therapy with 4-AP. The treatment also reduces the subjective risk of falls and balance confidence. Gait variability at baseline has a predictive value for the improvement of gait and fall risk during treatment. 4-AP may be a promising approach for the symptomatic treatment of cerebellar syndromes.

T104
Impaired primary motor cortex LTP/LTD-like plasticity in multiple system atrophy

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Introduction: In humans intermittent and continuous theta-burst stimulation (iTBS and cTBS) are currently used for inducing long-term changes in motor evoked potential (MEP) amplitudes reflecting long-term potentiation (LTP)- and depression (LTD)-like plasticity in primary motor cortex (M1). Recent studies have reported that LTP/LTD-like plasticity as tested by TBS is reduced in Parkinson's disease (PD) and increased in patients with Progressive Supranuclear Palsy (PSP). In this study we investigated possible abnormalities of LTP/LTD-like plasticity in M1 in patients with Multiple System Atrophy (MSA).

Methods: We studied 10 patients with MSA and 10 healthy subjects. We clinically evaluated patients using the Unified Multiple System Atrophy Rating Scale (UMSARS). The left M1 was conditioned in separate sessions with iTBS and cTBS. Twenty motor evoked potentials (MEPs) were recorded from right first interosseous muscle before, 5, 15 and 30 minutes after iTBS and cTBS at the intensity able to evoke at baseline MEPs of about 1mV amplitude.

Results: ANOVA showed that in healthy subjects after iTBS, MEPs increased whereas after cTBS, they decreased in amplitude significantly at 5, 15 and 30 minutes (P<0.05 for all comparisons). Conversely, in patients with MSA, both iTBS and cTBS left MEP amplitudes were unchanged.

Conclusion: M1 LTP/LTD-like plasticity is impaired in patients with MSA. Mechanisms underlying abnormal M1 plasticity in MSA are similar to those present in PD rather than in PSP.
T105

Ictal EEG-fMRI in localization of epileptogenic area in refractory neocortical focal epilepsy

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Purpose: To evaluate the usefulness of EEG-combined functional magnetic resonance imaging (EEG-fMRI) in localizing the epileptogenic zone in refractory neocortical focal epilepsy.

Methods: From the EEG-fMRI database of our institution including 62 adult patients, 14 (age 18-46 years) experienced some clinical or electrographic ictal event during the test. Data were segmented into ten-second blocks, analyzing the results by contrasting each block to the contiguous 10-s block from the onset of seizure onwards, or else by contrasting each block to a baseline condition in the framework of the general linear model (GLM) of analysis. Regions of activations were compared to results from the different techniques performed during presurgical evaluation, such as SISCOM, PET and invasive subdural EEG monitoring.

Results: Regarding the structural MRI findings, 5 of them were considered normal, 5 revealed malformations of cortical development, 3 presented a porencephalic cyst, and 1 patient presented a cavernous angioma. From the total of 9 lesional patients, 8 presented the BOLD area of activation in the same area as the lesion. SISCOM studies were performed in 11 patients; 9 were partially or totally concordant with the increase in BOLD signal. Eleven patients underwent PET studies, being partially or totally concordant in 8 of them. Finally, 3 patients performed invasive EEG-evaluation and all of them presented seizure onset in the initial area of BOLD activation.

Conclusion: This study constitutes the largest case-series on ictal EEG-fMRI, supporting the integration of EEG-fMRI in the multidisciplinary presurgical workup in patients with refractory epilepsy.

T106

Body core temperature regulation in spinal cord injury patients

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Introduction: Individuals with spinal cord injury (SCI) have an abnormal cardiovascular regulation and sudomotor dysfunction below the level of the lesion and may present thermal dysfunctions [1-5]. So far only a single ambulatory study examined body core temperature (BcT) in SCI [6].

Objective: Aims of the study were to assess the circadian modulation of BcT in SCI individuals and able-bodied controls, relating the findings to the lesion level and sleep function.

Patients and methods: 5 cervical SCI with tetraplegia (TETRA), 6 thoracic SCI with paraplegia (PARA) and 7 control subjects (CNT) underwent a 24h polysomnography associated with rectal temperature monitoring under controlled environmental conditions. The following parameters of BcT were assessed: daytime and night-time mean; day-night variations; time- and state-dependent modulation; rhythmicity (cosinor method).

Results: TETRA compared to CNT presented a reversed pattern of 24-h BcT. TETRA daytime and night-time BcT values were significantly higher and the nocturnal decline significantly reduced compared to PARA and CNT. TETRA exhibited a significantly higher mesor compared to PARA and CNT, while amplitude and acrophase were comparable. BcT was significantly higher in TETRA during wake, NREM and REM sleep stages compared to PARA and CNT. Furthermore, both TETRA and PARA did not display the physiological modulation of BcT during sleep.

Conclusions: TETRA presented a pronounced disturbance of the circadian variation of BcT. Both TETRA and PARA did not display the physiological modulation of BcT during sleep. The pathogenetic mechanism and the possible consequence of such alterations are yet to be determined.
Monday, 10 September

Tournament for Young Neurologists (basic)

T201
Zinc induces long-term upregulation of T-type calcium current in hippocampal neurons in vivo

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In both humans and animals, brain insults such as status epilepticus, ischemia and trauma may induce a chronic epileptic condition. However, very little is known about the pathogenic mechanisms underlying the development of this condition, a process termed epileptogenesis. Extracellular zinc can induce numerous acute and persistent physiological and toxic effects in neurons by acting at their plasma membrane or intracellularly following permeation or uptake into them. Zinc acutely blocks T-type voltage-gated calcium current (ICaT), but the long-term effect of zinc on this current has not been studied. Since chemically induced status epilepticus (SE) results in the release of zinc into the extracellular space, as well as in a long-lasting increase in ICaT in CA1 pyramidal cells, we hypothesized that zinc may play a causative role in ICaT upregulation. We tested this hypothesis by monitoring the effects of zinc injected into the lateral ventricle, on ICaT in rat CA1 pyramidal cells. Zinc caused upregulation of a nickel-sensitive ICaT in a subset of contralateral CA1 pyramidal cells, appearing 2 days after injection and lasting for about 2 weeks thereafter. These data indicate that extracellular zinc causes a long-term upregulation of ICaT. By understanding this mechanism better it might be possible to chelate (bind) the excessive released zinc immediately after a trauma or status epilepticus and preventing its devastating effect on the later development of spontaneous seizures and thus preventing the development of epilepsy before the occurrence of seizure.

T202
Genetic study of demyelinating form of autosomal-recessive Charcot-Marie-Tooth disease in Russia


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Charcot-Marie-Tooth disease (CMT) is the most common inherited neuropathy. During the scale analysis of the demyelinating form of CMT in Russia, the necessity was presented of research of autosomal-recessive CMT (AR-CMT) was presented. The aim was focused on the molecular analysis of the selected genes associated with AR-CMT and construction of a molecular and genetic diagnostic algorithm in this group of disorders in the Russian population. We analyzed a group of 92 unrelated patients with probably autosomal recessive inheritance. The study covered analysis of coding regions of the GDAP1 gene using sequencing and molecular genetic analysis of 8 frequently occurring mutations using two Multiplex Ligation Probe Assay (MLPA) systems. The first MLPA-system contained 6 of frequently occurring mutations in four genes: FGD4 (Met298Thr, Met298Arg), FIG4 (Ile41Thr), GDAP1 (Leu239Phe), SH3TC2 (Arg954Stop, Arg658Cys). The second MLPA-system contained two frequency Gypsies mutation in two genes: NDRG1 (Arg148Stop) and SH3TC2 (Arg1109Stop). The cause of AR-CMT was determined in 26% of the cases (24 patients). Mutations in GDAP1 gene were most frequent (18.5% or 17 patients). The mutation Arg148Stop of NDRG1 gene was found in 3 patients (3.2%). Mutations Arg954Stop of SH3TC2 gene and Ile41Thr of FIG4 gene were found in 2 patients (2.2%). This is the first study that in focused in autosomal recessive Charcot-Marie-Tooth disease in the Russian population, which is essential for molecular diagnostics in CMT disease.
T203
Mitochondrial impairment in Parkinson’s disease patients with LRRK2 mutations
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Introduction: Mutations in leucine-rich repeat kinase 2 (LRRK2) are the most common known causes of late-onset autosomal dominant Parkinson’s disease (PD), but have also been identified in sporadic cases. The protein associates with the outer mitochondrial membrane. In keeping with this finding, G2019S-mutant LRRK2 has been shown to impact on mitochondrial function and morphology in PD patients’ fibroblasts. To further define the function of LRRK2, we investigated various mitochondrial parameters in fibroblasts from LRRK2-mutant patients.

Methods: Fibroblasts were obtained from 3 LRRK2-mutant cases (p.R1441C, p.G2019S and p.G2019S) and three age-matched, unrelated mutation-negative controls. ATP synthesis rates were determined luminometrically. Oxygen consumption rates were investigated with 'BOFA' experiments on a Seahorse extracellular flux analyzer. The mitochondrial membrane potential was detected using JC-1. MtDNA integrity and quantity were assessed by real-time PCR. Mitochondrial morphology was examined by calculation of the form factor after immunocytochemistry, confocal microscopy and image analysis with a self-designed macro in ImageJ.

Results: LRRK2 mutants showed bioenergetic abnormalities. In patients’ cells, a decrease in ATP synthesis rates was detected in combination with reduced mitochondrial membrane potential. The investigation of other features of mitochondrial function did not reveal any differences between mutant and control fibroblasts. Also, the assessment of mitochondrial interconnectivity was unremarkable.

Conclusion: Our findings suggest an involvement of LRRK2 in bioenergetic mechanisms. Further investigations will be necessary to clarify whether this effect is a primary or secondary result of LRRK2 mutations.

T204
IFN-γ deficiency exacerbates experimental autoimmune neuritis in mice via upregulating Th17-cells despite a mitigated systemic Th1 immune response
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Introduction: Previous studies have shown that interferon-gamma (IFN-γ) is a proinflammatory cytokine that contributes to the pathogenesis of human Guillain-Barré syndrome (GBS).

Methods: To clarify the role of IFN-γ in the pathogenesis of autoimmune demyelinating diseases, we used P0 protein peptide 180-199 to induce experimental autoimmune neuritis (EAN), an animal model of GBS, in IFN-γ knockout (KO) mice.

Results: After the acute phase of EAN, the clinical signs of IFN-γ KO mice were significantly more severe than those of wild type (WT) controls. After antigenic stimulation, the proliferation of splenic mononuclear cell was significantly higher in IFN-γ KO than WT mice with EAN. At the peak of EAN, the proportion of interleukin (IL)-17A expressing cells in cauda equina (CE) infiltrating cells, and the levels of IL-17A in sera were elevated in IFN-γ KO mice when compared with their WT counterparts. The proportions of MHC II, ED1, and IL-12/IL-23p40 expressing cells, relative to total CE infiltrating cells were correspondingly higher in IFN-γ KO than WT mice with EAN. However, IFN-γ deficiency reduced the production of NO by cultured macrophages in response to proinflammatory stimuli and induced a systemic Th2-oriented immune response.

Conclusion: IFN-γ deficiency exacerbates EAN via up-regulating Th17-cells despite a mitigated systemic Th1 immune response.
**T205**

**Dissociation of sarcolemmal nNOS: a novel fatigue mechanism in MG**

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Myasthenia gravis (MG) patients suffer from chronic fatigue of skeletal muscles, even after initiation of proper immunosuppressive medication. Since the localization of neural nitric oxide synthase (nNOS) at the muscle membrane is important for sustained muscle contraction, we here study the role of nNOS in mice with experimental autoimmune MG (EAMG). EAMG was induced in 8-week-old male wild-type mice by immunization with AChRs purified from torpedo californica. Wild-type mice and mdx mice, a model for Duchenne muscular dystrophy, were used for comparison. At EAMG disease grade 3 (severe weakness), the triceps, sternomastoid and masseter muscles were collected and nNOS levels were analyzed in whole muscles and in the cytosolic versus the membrane muscle fractions. Immunostaining of muscle cross-sections localized nNOS and its binding partner syntrophin a-1. As a consequence of blocked neuromuscular transmission, nNOS dissociated from the sarcolemma to the cytosol in muscle fibers from EAMG mice. Unlike mdx mice, the protein and expression levels of nNOS, as well as the presence of the binding partner syntrophin a-1, were not altered in EAMG. Transcript levels of the atrogenes atrogin-1 and MuRF-1 were up-regulated in all muscles, indicative of muscle atrophy. We propose that dissociation of sarcolemmal nNOS provides a novel mechanism for the chronic muscle fatigue in EAMG. Considering that many MG patients develop muscle atrophy from chronic fatigue, future treatment strategies aimed at improving exercise-induced signalling via the nNOS pathway may hold future promise as symptomatic medication in MG.

**T206**

**Changes in glutamatergic neurotransmission within the migraine cycle**

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**Background:** Although some neurophysiological studies have shown cortical excitability changes during different phases of the migraine cycle, the pathophysiological mechanisms underlying attack recurrence remain unknown. Here we evaluated the response of the migraine motor-cortex to brief trains of 5Hz repetitive transcranial magnetic stimulation (rTMS) in order to study, indirectly, presynaptic mechanisms of glutamatergic neurotransmission across the different phases of the migraine cycle.

**Methods:** 40 migraine with aura (MwA) and 40 migraine without aura (MwoA) patients underwent suprathreshold (130% of the resting motor threshold) brief trains of 5-Hz-rTMS to the motor-cortex, recording Motor Evoked Potentials (MEPs) at each train stimulus. Patients were studied whatever the phase of the migraine cycle was: interictal (n=51), preictal (n=9), ictal (n=10) or postictal (n=10).

**Results:** As previously shown, in the interictal phase MEPs decreased significantly in size during 5Hz trains. A significant greater inhibitory response was recorded during the ictal and post-ictal phase. Conversely, in the pre-ictal phase, we observed a facilitatory response to the trains similar to that of normal subjects. No significant differences were recorded between MwA and MwoA patients.

**Conclusions:** Our results support the hypothesis that in migraine a transient increase in intracortical glutamatergic activity could trigger the migraine attack. Inhibitory homeostatic mechanisms of glutamate release could be involved in the resolution of the migraine attack and in preventing further attacks.