9th PhD Symposium
Doctoral School of Neuroscience

University of Debrecen
2019

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9th PhD Symposium of Doctoral School of Neuroscience
6th September, 2019
Venue: UD Life Science Centre, Lecture room F008-F009

08:30-9:00 **Arrival**

9:00-9:05 **Welcome Address**
Miklós Antal Head of Doctoral School of Neuroscience

9:05-9:50 Presentations of research groups supported by the Hungarian National Brain Initiative 2 (2017-2021)

9:05-9:20 **Péter Szücs**
EXPLORATION OF NEURAL NETWORKS IN THE SPINAL CORD AND CEREBRAL CORTEX UNDERLYING PAIN AND VISUAL PROCESSING

9:20-9:35 **László Oláh**
INVESTIGATION OF CEREBRAL HEMODYNAMICS IN DIFFERENT DISEASES WITH POTENTIAL EFFECTS ON THE CEREBROVASCULAR SYSTEM

9:35-9:50 **Álmos Klekner**
SYNTHESIS OF CLINICAL DATA AND RESEARCH RESULTS OF BRAIN TUMORS FOR EPIDEMIOLOGICAL PURPOSES

Part I. Chairman: István Fekete
Reviewers: István Fekete and Álmos Klekner

10:00-10:10 **Dóra Sulina** (2nd year PhD student)
Supervisor: László Oláh
INVESTIGATION OF THE CEREBRAL HEMODYNAMICS IN DIFFERENT DISEASES WITH POTENTIAL EFFECTS ON THE VASCULAR SYSTEM, INCLUDING HYPERVISCOSITY SYNDROME AS WELL AS GRAND MAL SEIZURE

10:10-10:20 **Eszter Balogh** (2nd year PhD student)
Supervisor: László Oláh
EFFECTS OF ACUTE ALCOHOL CONSUMPTION ON NEURONAL ACTIVITY AND CEREBRAL VASOMOTOR RESPONSE

10:20-10:30 **Johanna Dömötör** (3rd year PhD student)
Supervisor: Béla Clemens
ELECTROPHYSIOLOGY OF NATURAL REMISSION OF EPILEPSY

10:30-10:40 **Krisztina Szonja Bábel** (2nd year PhD student)
Supervisor: László Oláh

INVESTIGATION OF THE CEREBRAL HEMODYNAMICS IN DIFFERENT DISEASES WITH POTENTIAL EFFECTS ON THE VASCULAR SYSTEM, INCLUDING HYPERTENSION OR SLEEP DEPRIVATION

10:40-10:50 **Katalin Szamos** (2nd year PhD student)
Supervisor: Végh Tamás

EFFECT OF LUNG PROTECTIVE ONE-LUNG VENTILATION WITH FIX AND VARIABLE TIDAL VOLUMES ON OXYGENATION AND POSTOPERATIVE OUTCOME: RANDOMIZED, CONTROLLED TRIAL

10:50-11:00 **István Szegedi** (3rd year PhD student)
Supervisors: László Csiba and Zsuzsa Bagoly

PAI-1 5G/5G GENOTYPE IS AN INDEPENDENT RISK OF INTRACRANIAL HEMORRHAGE IN POST-LYSIS STROKE PATIENTS

11:00-11:15 Coffee break

Part II. Chairman: László Oláh
Reviewers: László Oláh and Miklós Antal

11:15-11:25 **Richárd Csabalik** (2nd year PhD student)
Supervisor: Tünde Csépány

PHENOTYPES AND BIOMARKERS AFFECTING THERAPEUTIC DECISIONS IN MULTIPLE SCLEROSIS

11:25-11:35 **Márk Molnár** (1st year PhD student)
Supervisor: Klára Fekete

CLINICAL OUTCOME AND EEG PATTERNS IN SUPERREFRACTORY-NONCONVULSIVE STATUS EPILEPTICUS- SINGLE CENTRE EXPERIENCE

11:35-11:45 **Róbert Rostás** (3rd year PhD student)
Supervisor: István Fekete

BLINK REFLEX, APPROACH TO EXAMINE THE BRAINSTEM, FOCUSED ON PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS (ALS)

11:45-11:55 **Lilla Rácz** (predoctor)
Supervisor: Tünde Csépány

ASSESSMENT OF PROGNOSTIC VALUE OF BIOMARKERS IN MULTIPLE SCLEROSIS

11:55-12:05 **László Szivós** (1st year PhD student)
Supervisor: Álmos Klekner

INVESTIGATION OF GLIOMA PROGNOSTIC FACTORS

12:05-12:15 **Miklós Sivadó** (3rd year PhD student)
Supervisor: Péter Szücs

PUTATIVE POSTSYNAPTIC TARGETS AND FUNCTION OF LOCAL AXON COLLATERALS OF SPINAL DORSAL HORN PROJECTION NEURONS

12:15-12:30 Coffee break

Part III. Chairman: Péter Szücs
Reviewers: Péter Szücs and András Birinyi

12:30-12:40 **Eszter Vitális** (3rd year PhD student)
Supervisor: Béla Fülesdi

CANDIDAEMIÁK A DEOEC-EN 2006-2013 KÖZÖTT - KEZELÉS ÉS KIMENETEL (RETROSPEKTÍV ADATGYŰJTÉS)

12:40-12:50 **János Bencze** (3rd year PhD student)
Supervisors: Tibor Hortobágyi and Dag Aarsland

CORRELATION BETWEEN LEMUR TYROSINE KINASE 2 EXPRESSION AND THE SEVERITY OF TAU PATHOLOGY

12:50-13:00 **Camila de Oliveira Miranda** (1st year PhD student)
Supervisor: Miklós Antal

GLYCINERGIC NEURONS IN NEURONAL CIRCUITS PROCESSING PAIN IN THE SPINAL DORSAL HORN

13:00-13:10 **Zsuzsanna Ferenczi** (1st year PhD student)
Supervisor: Tamás Papp

THE EFFECT OF DIAGNOSTIC ULTRASOUND ON DEVELOPING NEURONS.

13:10-13:20 **Zsolt Kocsis** (2nd year PhD student)
Supervisor: Zoltán Kisvárday

HIGH-RESOLUTION RETINOTOPIC MAPPING IN CAT PRIMARY VISUAL CORTEX WITH INTRINSIC SIGNAL OPTICAL IMAGING

13:20-13:30 **Renáta Nóra Szabó** (2nd year PhD student)
Supervisor: Tibor Hortobágyi

GENE EXPRESSION ANALYSIS OF BRAIN METASTATIC MELANOMAS

Conclusion

End of Symposium

ABSTRACTS
of PhD students

(in alphabetical order)

INVESTIGATION OF THE CEREBRAL HEMODYNAMICS IN DIFFERENT DISEASES WITH POTENTIAL EFFECTS ON THE VASCULAR SYSTEM, INCLUDING HYPERTENSION OR SLEEP DEPRIVATION

Krisztina Szonja Bábel MD (2nd year PhD student)

Supervisor: László Oláh MD

Department of Neurology, University of Debrecen, 4032 Debrecen, Hungary

Investigation of cerebral hemodynamics includes the examination of neurovascular coupling, cerebrovascular reactivity and cerebral autoregulation. 1. The ***neurovascular unit (NVU)*** is composed by neurones, astrocytes, endothelial cells of blood–brain barrier (BBB), myocytes, pericytes and extracellular matrix components. These cells, through their intimate anatomical and chemical relationship, detect the needs of neuronal supply and trigger necessary responses (vasodilation or vasoconstriction) for such demands. Visual stimulation evoked neuronal activation in the occipital cortex can be assessed by measurement of flow velocity in the posterior cerebral artery. 2. ***Cerebrovascular reactivity*** means the temporal change in cerebral blood flow in response to a vasodilatory or vasoconstrictive chemical stimulus. Cerebrovascular reactivity can be evaluated by breath holding test (BHI), which results increase of partial pressure of CO_2 in blood, and consequently vasodilatation in the brain arterioles. Vasodilation of cerebral resistance vessels leads to increase in flow velocity in the middle cerebral artery, which can be detected by transcranial Doppler ultrasound. 3. **Cerebral autoregulation** is defined as the maintenance of relatively constant cerebral blood flow despite changes in cerebral perfusion pressure. Autoregulation can be assessed by using head up tilt table test (HUTT). HUTT results in decrease of the perfusion pressure at the level of the middle cerebral artery. The decrease in perfusion pressure is compensated by dilatation of cerebral arterioles in healthy people, leading to lack of significant change in flow velocity.
Hypertension has been known to influence the cerebral hemodynamics, while the effect of sleep deprivation on cerebral circulation has not been investigated. Our aim is to examine the cerebral hemodynamics before and after blood pressure reduction in patients with hypertension. In addition to evaluation of chronic effect of antihypertensive treatment, we also aimed to investigate the effect of acute decrease in blood pressure on cerebral hemodynamics. We seek the answer how the actual blood pressure values influence the vascular responses. Sleep deprivation is known to increase the vascular risk, therefore, we aimed to test the effect of sleep deprivation on cerebral hemodynamics. For testing the acute effect of blood pressure (BP) reduction on cerebral hemodynamics, we plan to compare cerebral vasoreactivity measured at systolic blood pressure above 170 mmHg and after blood pressure reduction with captopril below 140 mmHg (N=20). In patients with high blood pressure perindopril with or without indapamid is administered for long term BP adjustment (N=15). Before the therapy we perform the breath holding test, examine the neurovascular coupling in the posterior cerebral arteries and perform the visual evoked potential (VEP) test. Six and twelve months later we repeat the examinations to follow the effect of chronic BP adjustment on cerebrovasular hemodynamics. In the sleep deprivation study, breath holding test, VEP test and examination of neurovascular copling are performed before and after 24 hours of sleep deprivation. Till now we could include 4 patients in the hypertension study and 5 patients in the sleep deprivation study, therefore statistical analysis has not been performed yet.

EFFECTS OF ACUTE ALCOHOL CONSUMPTION ON NEURONAL ACTIVITY AND CEREBRAL VASOMOTOR RESPONSE

Eszter Balogh (2nd year PhD student), Tamás Árokszállási, Katalin Körtefái, Veronika Nagy, László Csiba

Supervisor: László Oláh

Department of Neurology, University of Debrecen, 4032 Debrecen, Hungary.

Introduction: Alcoholism is a global problem nowadays. Our aim was to study the effects of acute alcohol consumption on the neuronal activity, the neurovascular coupling and the cerebral vasoreactivity.

Patients & Methods: Thirty young healthy adults (15 women, 15 men) was included in our study. Neuronal activity of the visual pathway was evaluated by pattern-reversal visual evoked potential (VEP) examination. By using a visual cortex stimulation paradigm, visually evoked flow velocity response during reading was measured by transcranial Doppler in both posterior cerebral arteries (PCA). Cerebral vasoreactivity was investigated by analysing the effect of breath holding on the flow velocity increase (breath holding index, BHI) in both middle cerebral arteries. Every examination was evaluated before and after drinking alcohol. Cardiovascular effects were measured by blood pressure and heart rate detection. The aim blood alcohol content (BAC) was 1 ‰. Data were analysed by paired sample T-test.

Results: The latency of the VEP P100 wave increased after alcohol consumption (108,0±2,4 ms vs. 110,8±3,4 ms; p=0,001). Compared to the control phase, both the maximum blood flow velocity in the PCA after alcohol consumption (127,3±7,6% vs. 125,6±7,1%; p=0,024), and the rise of the curve decreased (4,73±1,4 cm/s^2 vs. 3,24±1,0 cm/s^2, p<0,001). The BHI (44,8±11,2% vs. 36,1±13,2%, p=0,001) was also smaller after than before alcohol consumption. The absolute flow velocity values increased, whereas the pulsatility indices in the PCA decreased after alcohol consumption. The blood pressure didn't change, but the heart rate increased from the fifth minute of the measurement.

Conclusion: Our measurements proved that acute alcohol consumption inhibits the neuronal activity of the visual pathway. In addition, acute consumption of alcohol results in dilation of cerebral arterioles, thus decreases cerebral vasoreactivity. These effects may be in the background of the decreased neurovascular coupling after acute alcohol consumption.

CORRELATION BETWEEN LEMUR TYROSINE KINASE 2 EXPRESSION AND THE SEVERITY OF TAU PATHOLOGY

János Bencze[1] (3rd year PhD student), Viktor Bencs[1], Máté Szarka[2]

Supervisors: Tibor Hortobágyi[3,4,5] and Dag Aarsland[5]

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Lemur tyrosine kinase 2 (LMTK2) has important role in physiological axonal transport, regulation of apoptosis and phosphorylation of microtubule-associated tau protein. Since, disruption of these mechanisms identified in the early stages of Alzheimer's disease (AD), LMTK2 may contribute to the AD pathogenesis.

Our aim was to characterize the connection between tau pathology and LMTK2 expression in different neuropathological (Braak) stages of AD.

We selected formalin-fixed paraffin-embedded samples of 5-5 patients with stage I. and stage VI. AD pathology. The regions of interest were determined by neuropathologist (TH): middle frontal gyrus – spared in early stages of AD, and anterior hippocampus – affected in both stages. Immunohistochemical reaction was performed according to the manufacturer's protocol. After scanning the slides, we took 5 photos/cases at 400x magnification and performed the digital analysis with ImageJ software. We measured the mean grey value of the neurons and determined the mean and median intensity profiles for each case. Results were compared between Braak stage I. and Braak stage VI. groups. For statistical analysis we used SPSS 24 software.

In the three regions which are affected by tau pathology - ant. hippocampus in stage I. and ant. hippocampus and middle frontal gyrus in stage VI. - we detected statistically significant alteration ($p<0,001$) in the mean and median LMTK2 greyscale intensities compared to the relatively spared middle frontal gyrus in Braak stage I. Among the LMTK2 intensitites of the three tau-affected regions there were no statistically significant difference.

According to our results the expression of LMTK2 decreases with the progression of tau pathology. These findings suggest that the modification of LMTK2 protein level may be a future therapeutic target in Alzheimer's disease.

Acknowledgement: Supported by the ÚNKP-19-3 New National Excellence Program of the Ministry of Human Capacities (JB); EFOP-3.6.3-VEKOP-16-2017-00009 (JB and MSz); GINOP-2.3.2-15-2016-00043 and Hungarian Brain Research Program (2017-1.2.1-NKP-2017-00002) (TH).

GLYCINERGIC NEURONS IN NEURONAL CIRCUITS PROCESSING PAIN IN THE SPINAL DORSAL HORN

Camila de Oliveira Miranda (1st year PhD student)

Supervisor: Miklós Antal

Department of Anatomy, Histology and Embryology, Faculty of Medicine, University of Debrecen, 4032 Debrecen, Hungary

A growing body of evidence indicates that glycinergic neurotransmission in the spinal dorsal horn play a critical role in the development of hyperalgesia and allodynia. It is, however, poorly understood how glycinergic neurons contribute to the formation of neural circuits underlying spinal pain processing. The lack of this essential knowledge makes the interpretation of the role of glycinergic neurons in spinal pain processing vague. Thus, our present experiments are focused on the morphological and functional properties of glycinergic neurons in laminae I-IV of the spinal dorsal horn. We label glycinergic neurons with the aid of a transgenic technology, crossing GlyT2::Cre mice (kind gift of H.U. Zeilhofer, Zurich, Switzerland) with tdTomato reporter mice. In order to be sure that we can really visualize glycinergic neurons with this transgenic technology, first we performed some control experiments. Tissue sections obtained from the spinal cord of GlyT2::Cre-tdTomato mice were immunostained for PAX2, a nuclear transcription factor characteristic for inhibitory (both GABAergic and glycinergic) neurons, and we found that 95.6 ± 3.4 % of tdTomato expressing neurons in the spinal dorsal horn were PAX2 positive. To explore whether the tdTomato labeled axon terminals are axon terminals of local spinal glycinergic neurons, we performed hemisections at the level of Th12 segment of the spinal cord. The hemisection decreased the numbers of both tdTomato labelled profiles and GlyT2-IR axon terminals, indicating that approximately one-third and a bit more than 10 % of the GlyT2-IR axon terminals in laminae I-II and lamina III, respectively, are terminals of axons descending form higher brain centers; but the rest can be regarded as axon terminals of local spinal neurons. The results show that the tdTomato labeled cells in the GlyT2::Cre-tdTomato mice are indeed glycinergic, and they may have a wide axonal arbor in the superficial spinal dorsal horn.

PHENOTYPES AND BIOMARKERS AFFECTING THERAPEUTIC DECISIONS IN MULTIPLE SCLEROSIS

Richárd Csabalik (2nd year PhD student)

Supervisor: Tünde Csépány

Department of Neurology, Faculty of Medicine, University of Debrecen, 4032 Debrecen, Móricz Zsigmond krt 22. Hungary;

Multiple sclerosis (MS) is a chronic, progressive, multifocal inflammatory disease of the central nervous system. New and promising therapeutic approaches have emerged in recent years, but we are still lacking biomarkers that could help us prospectively assess the course of the disease or the efficacy of a disease modifying drug. The aim of this study is to analyse the biomarker profile and paraclinical phenotypes of our MS patients.

In our study we continue the examination of cerebral haemodynamical changes in MS. In one of our earlier studies we have shown that mean arterial pressure changes differently in MS patients and healthy individuals during a tilt-table test. By retesting our patients after a 10 year period we can provide long term data regarding the changes in cerebrovascular autoregulation in MS.

Vegetative dysfunction and cognitive impairment are common symptoms of MS. We assess the vegetative functions of our patients using the COMPASS31 (Composite Autonomic Symptom Score) questionnaire, which has never been used in Hungarian language before, so validation is part of our job here. Cognitive functions are measured by the widely used BICAMS (Brief International Cognitive Assessment for MS) test. Besides these we try to exclude pseudodementia with the Beck Depression Inventory (BDI) and assess quality of life with the SF-54 questionnaire.

Vitamin D is thought to be an etiologic factor in MS. We edit and continuously update a complex database containing the serum vitamin D values of our patients and all the relevant clinical data. We try to find correlations between low levels of vitamin D and vegetative and cognitive functions, and measurable parameters of clinical and radiological activity (like EDSS score, relapse rate, T2 lesion load).

Our results may provide evidence that some of our examined parameters and tests deserve a role in the routine neurological follow-up to detect subclinical changes and predict the course of the disease.

Acknowledgement: The authors thank Jánosné Virág for her valuable contribution.

ELECTROPHYSIOLOGY OF NATURAL REMISSION OF EPILEPSY

Johanna Dömötör[1] (3rd year PhD student)
Béla Clemens M.D., Ph.D.[1], Szilvia Puskás M.D., Ph.D.[1], András Fogarasi M.D, PhD.[2] , Miklós Emri PhD.[3,] István Fekete M.D., Ph.D.[4]

Supervisor: Béla Clemens, MD, PhD[1].

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Background: Epilepsy that starts in the first two decades is self-limited in many patients. However, neuronal mechanisms of spontaneous recovery remain hidden. Aim of the study was to develop an EEG-based state descriptor that characterizes brain activity at onset of the disease and in the presumed resolved condition. Correlation between long-term EEG changes and clinical outcome was analyzed.
Patients and methods: Twenty-three patients with benign epilepsy of childhood with rolandic spikes (BERS) and cryptogenic focal epilepsy (FE) were investigated, treated and followed.
21-channel EEG was recorded at onset of the illness in the unmedicated state. The second EEG was carried out several years later, in the presumed resolved condition, after drug discontinuation. Three minutes of waking-relaxed EEG background activity was analyzed. The LORETA (Low Resolution Electromagnetic Tomography) software computed current source density for 2394 cortical voxels in the 1-7 Hz ("slow") frequency band. Raw LORETA values underwent age-correction and Z-transformation. The state descriptor was the average of the voxel-vise CSD values in the slow band. This variable was computed for each patient and setting. Algebraic difference between the two settings was calculated and correlated to clinical outcome.
Results: Increased CSD (as compared to the population mean) characterized the active phase of the illness. 20/23 patients resolved and 3/23 relapsed in the follow-up period. Statistically significant relationship was demonstrated between direction of CSD changes and clinical outcome ($p<0.0008$). Decrease and increase of CSD was associated with resolved epilepsy and recurrent seizures, respectively.
Discussion / conclusion: Results are concordant with developmental hypothesis of epilepsy. Long-term changes of EEG background activity suggested self-correction of transiently delayed brain maturation.

THE EFFECT OF DIAGNOSTIC ULTRASOUND ON DEVELOPING NEURONS.

Zsuzsanna Ferenczi (1st year PhD student)

Supervisor: Tamás Papp

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Dendritic growth and branching is essential for circuit formation and correct function of neurons, dendritic arborization predominantly determines their synaptic input. Ultrasound (US) examination is one of most important and commercial examination during pregnancy worldwide. US stimuli can modify the morphology and number of the proliferation of neurons *in vivo* and *in vitro*, but we do not know exactly how this stimuli effects on dendritic differentiation.

Our goal is to investigate the effect of US stimuli on dendritic development in the frontal cortex and the hippocampus of prenatal mice.

Developing cortical and hippocampal pyramidal neurons were transfected by in utero electroporation at E14.5 with pCAG-GFP and BB plasmid. At the gestation age of E18.5 pregnant mice were treated with GE Logiq V2 US machine (parameters: time: 10 min, FR: 3 MHz, MI:0,9, TI:0,8). At PN3, pups were sacrificed, GFP signal was intensified with chicken polyclonal serum. Sections were incubated with the primary antibodies for 48h at 4 °C. Following washing steps, sections were incubated with the appropriate secondary antibodies conjugated with Alexa dyes for 2h at RT, and mouted with Hidromount. Fluorescent confocal images were taken with Olympus Fluoview FV3000 attached to an Olympus IX83 microscope. The processes of ultrasound stimulated and non-treated, GFP and BB labeled neurons were drawn and annotated with Neurolucida software. Total process number, average segment tort and lenght, terminal distance and dendrite length were counted and examined.

Our results indicate that the number of dendrites have been altered in US treated pyramidal cells compared to untreated neurons. The other investigated parameters did not show significant difference beetwen the groups. Our data suggests that ultrasound causes prolonged effects on the morphology of differentiating cortical neurons.

Acknowledgement: I really appreciate the help and useful advices of Zoltán Mészár, Péter Szücs and Bernadette Szilágyi during the experiments.

HIGH-RESOLUTION RETINOTOPIC MAPPING IN CAT PRIMARY VISUAL CORTEX WITH INTRINSIC SIGNAL OPTICAL IMAGING

Zsolt Kocsis (2nd year PhD student), Mohit Srivastava, Zoltán Kisvárday

Supervisor: Zoltán Kisvárday

MTA-Debreceni Egyetem Neuroscience Research Group, Department of Anatomy, Histology and Embryology, University of Debrecen, 4032 Debrecen, Hungary

In the primary visual cortex, integration of contour elements is inherently related to visual field position. Retinotopy is the representation of the visual field, as it is projected through the optics of the eye onto the retina, then via the retino-geniculo-cortical projection system into the primary visual cortex. Our aim is to obtain high-resolution retinotopic maps in the visual cortex whereby neuronal connections can be substituted (modelled) with visual field polar coordinates and hence estimate their role in contour integration process.

Anesthetized, paralyzed cats were prepared for in vivo intrinsic signal optical imaging. Monocular visual stimuli were presented on a computer screen 57 cm in front of the animal's eye. The stimulus consisted of a sequence of elongated luminance bars shifted at 1.5 deg steps in vertical (for elevation) and in horizontal (for azimuth) directions. Data acquisition lasted for 4.5 sec for each stimulus condition and was repeated 15 times. First, the acquired images were subjected to noise reduction (normalization with the "cocktail blank", first frame analysis, low pass spatial filtering). Analysis consisted of the determination of the vertical meridian, calculation of iso-azimuth and iso-elevation lines. The high-resolution retinotopic map was generated using linear interpolation algorithm.

Next, we are going to employ high-resolution retinotopic maps on the distribution of long-range cortico-cortical connections which have been implicated visual contour integration already in V1.

Acknowledgement: *Supported by NAP2 (2017-1.2.1-NKP-2017-00002).*

CLINICAL OUTCOME AND EEG PATTERNS IN SUPERREFRACTORY-NONCONVULSIVE STATUS EPILEPTICUS- SINGLE CENTRE EXPERIENCE

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Supervisor: Klára Fekete

Background: Nonconvulsive status epilepticus (NCSE) is a life threatening condition with very high mortality rate. The diagnosis is mainly based on electroencephalograpy (EEG). The aim was to study the EEG findings and epidemiology of superrefractory NCSE (SR-NCSE) in our center.

Material and Methods: A retrospective database was compiled from patient files between 2013 and 2018. From 150 status epilepticus patients 13 were found to have SR-NCSE. EEG was evaluated according to the Salzburg Consensus Criteria. The following parameters were collected: status epilepticus severity score (STESS) and epidemiology-based mortality score in status epilepticus (EMSE), time until the diagnosis and clinical outcome.

Results: From the SE patients 8,6% had SR- NCSE, 77% of them female. The average age was 71,4 ±21years (<65 38%, > 90 30%.) The average time until the first EEG was 15,49 hours, at the time of the diagnosis already in superrefractory stage. The mortality rate was very high (77%). The survivors had good outcome, modified Rankin scale 0-1. STESS and EMSE scores gave a good prediction of outcome. The 4 patients with burst-suppression pattern on EEG all died. The others had continuous epileptiform discharges (EDs, spikes and sharp waves). All who survived were alert or somnolent, and had an acute treatable aetiology. Only one patient had epileptic seizures previously and recovered.

Conclusion: Most NCSE cases stay hidden, or are diagnosed already in a refractory stage. Using STESS and EMSE scores helps to predict the outcome. Surveillance and education may improve the outcome and diagnosis of NCSE.

ASSESSMENT OF PROGNOSTIC VALUE OF BIOMARKERS IN MULTIPLE SCLEROSIS

Lilla Rácz[1](Predoctor), Anita Szentpéteri[2], Richárd Csabalik[1], József Balla[2], Ildikó Seres[2], Tünde Csépány[1]

Supervisor: Tünde Csépány

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Introduction: Several lines of evidence support a possible role of oxidative stress in inflammatory processes and in the pathogenesis of neurodegenerative disorders, such as Multiple Sclerosis (MS). Paraoxonase1 (PON1), an enzyme associated with high density lipoprotein (HDL), plays an important role in the anti-oxidant and anti-inflammatory properties of HDL. Recently L- arginine metabolites have come in the focus of interest, because they could also be markers of neurodegeneration and endothelial dysfunction among progressive MS patients. The asymmetric dimethylarginine (ADMA) concentration is suspected to be the most reliable marker of the oxidative stress. It is produced by the methylation and degradation of proteins. According to our hypothesis the ADMA concentration changes depending on the inflammation.

Objectives: The aim of this study was to investigate the paraoxonase and arylesterase activities of PON1, asymmetric dimethylarginie (ADMA) values and lipid profiles in patients with different types of multiple sclerosis (MS) and with different treatment.

Methods: We have data from our previous study, which involved 197 MS patients. Paraoxonase and arylesterase activities of serum were measured spectrophotometrically. PON1 activities and lipid profiles were compared in subgroups of relapsing-remitting (135), benign (14), primary progressive (12), secondary progressive (19), relapsing progressive (4) and clinically isolated syndrome (13) at different stages of the disease. In this study we measured PON1 activities of 131 patients (4 secondary progressive, 5 primary progressive, 122 relapsing-remitting). From 73 patients we have previous activity values, but 38 of them have another therapy since then. We plan to measure ADMA concentrations of 80 patients from different treatment groups with competitive ELISA kit.

Results: In our previous results PON1 activity did not differ in the subgroups regarding of the course of MS but it had a tendency to be higher in patients with higher EDSS. PON1 activities were different (lower in INF and responders) in the groups according to the treatment type and the therapeutic response. Patients with stabile disease activity and therapy have similar PON values like earlier. The assessment of the ADMA concentrations is still in progress.

Conclusion: Our preliminary results did not demonstrate association between altered lipoprotein peroxidation and different clinical types of MS. Further investigation is required to prove the value of PON1 activity as a possible marker in monitoring the response to immunomodulatory treatment.

Acknowledgement: We would like to thank for our medical statistician Dr. László Kardos, for his work.

BLINK REFLEX, APPROACH TO EXAMINE THE BRAINSTEM, FOCUSED ON PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS (ALS)

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Background

ALS is an incurable disease, but with the treatment of the symptoms, better quality of life could be achieved. So early diagnosis is important, especially in the case of bulbar sympto Blink reflex examination is a reliable measure of the microstructural brainstem integrity. Our aim was to examine the correlation of the presence of bulbar symptoms in ALS and the findings of blink reflex, to have a new supportive testing which indicates loss of the motor neurons and at the same time find parameters in estimating prognosis.

Material and methods

Blink reflex findings were analysed between the 1st of June 2018 and 31st of December 2018. R1, ipsi- and contralateral R2 was evaluated. Seven patients fulfilled the International ALS Guideline's criteria. As a control group healthy adults were recruited.

Results

Average age was 69 years. The parameters of blink reflex were as follows: the latency of R1 was increased in 42% of the patients (12 ± 0.8 ms) and normal in 58%, the ipsilateral R2 wave's latency was increased in 71% and in 29% absent, the contralateral R2 wave was absent in 86% and 14% had increased latencies (35.5 ± 3.4 ms). All patients had pathological values of blink reflex showing the damage of brainstem interneurons, although with imaging techniques no abnormality was seen and on physical examination 37.5% of the patients had no bulbar symptoms.

Conclusion

Blink reflex could be a useful tool to support suspected ALS diagnosis, or bulbar involvement and to estimate the prognosis.

PUTATIVE POSTSYNAPTIC TARGETS AND FUNCTION OF LOCAL AXON COLLATERALS OF SPINAL DORSAL HORN PROJECTION NEURONS

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Approximately ten years ago our research group was the first to report that the main axon of projection neurons (PNs) in the superficial spinal dorsal horn (SDH) – involved among other tasks in pain transmission – give rise to distinct types of local axon collaterals before leaving the spinal grey matter. The course and distribution of the collaterals suggest that they establish local and propriospinal synaptic connections. However, the target neuronal elements and the function of these synaptic contacts remain to be elucidated.
To achieve the above goal we used retrograde tracing methods to identify and selectively manipulate PNs in the SDH. 1) DiI was injected in the parabrachial complex to allow identification of PN somata during in vitro recordings. 2) AAV-pgk-Cre was injected in the parabrachial complex of tdTomato reporter mice to allow visualization of PN collateral axons without prior biocytin staining. 3) The same retrograde vector was injected into ChR2 reporter mice to allow selective activation of PNs or their axon collateral terminals during in vitro recordings.
We found that axon terminals of PNs contact mostly local interneurons within the SDH. Contacts are present on somata and proximal dendrites of SDH neurons. The activation of PNs (or their axons) evoked different types of responses in the recorded non-PN neurons including slowly developing tonic depolarization and fast transient inhibitory events.
Our preliminary findings support our earlier hypothesis that PNs are not simple output elements of the SDH circuitry but active participants of local information processing.

INVESTIGATION OF THE CEREBRAL HEMODYNAMICS IN DIFFERENT DISEASES WITH POTENTIAL EFFECTS ON THE VASCULAR SYSTEM, INCLUDING HYPERVISCOSITY SYNDROME AS WELL AS GRAND MAL SEIZURE

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Cerebral autoregulation, neurovascular coupling and cerebral vasoreactivity are the main aspects of cerebral hemodynamics. Neural activity causes local vasodilation and increase incerebral blood flow (CBF), which mechanism is defined as neurovascular coupling. Neurovascular coupling can be examined by the so called visual stimulation paradigm. Visual stimulus evokes neuronal activation in the occipital cortex and causes increase in flow velocity in the posterior cerebral arteries, which can be detected by transcranial Doppler (TCD) ultrasound. Disturbance of the neurovascular coupling is a sensitive marker for damage of cerebral vessels. Besides measurement of the flow response, examination of the visual evoked potential (VEP) is also essential in order to assess the neural activity. Cerebrovascular reactivity is the change in cerebral blood flow in response to carbon-dioxide or other vasodilatory stimulus. Cerebrovascular reactivity can be evaluated by breath holding test, which results in increase of partial pressure of carbondioxide in blood, and causes vasodilation in the brain arterioles. Vasodilation of cerebral resistance vessels leads to increase in blood flow velocity in the middle cerebral artery, which can be detected by transcranial Doppler ultrasound.

It is well known that diseases associated with hyperviscosity (such as polycythemia vera or extreme hypertriglyceridaemia) elevate the risk of cerebrovascular diseases. Our aim is to examine whether hyperviscosity without any neurologycal symptomes influence the neurovascular coupling or cerebrovascular reactivity. In addition to studying the effect of hyperviscosity on neurovascular coupling, our study may help to understand better the effect of viscosity on cerebral microcirculation and hemodynamics. Patients with polycitaemia vera (n=15) and severe hypertiglyceridaemia (n=15) are planned to include in the study. Before and 2 days after phlebotomy and removal of 300 mL blood TCD monitoring of the visually evoked flow velocity changes in the posterior cerebral arteries, breath-holding test and VEP examinations are performed in the polycitaemia group. We use the same protocol in the hypertriglyceridaemia group before and 2 days after rheopheresis.

In the second part of our study, we seek the answer whether disturbance of cerebral vasoreactivity or neurovascular coupling can be detected several hours after grand mal epileptic seizure. During epileptic seizures an enormously increased neuronal activity is associated with increased metabolism and cerebral blood flow. However, after the seizure, brain activity, metabolism and cerebral blood flow are reduced. Patients are usually unconscious for minutes or hours followed by tenebrosity. Finally, the patients regain their conciousness and become alert. We aim to investigate patients in the first 12 hours after grand mal seizures (n=20). Only those patients are included who do not get any sedatives or antiepileptic drugs during the seizure and become alert and oriented within 12 hours after the seizure. TCD monitoring of the visually evoked flow velocity changes in the posterior cerebral arteries, breath holding test, VEP examination and EEG are performed within12 hours after the seizure. We repeat the examinations one week later. Comparison of VEP and the visually evoked flow tests shortly after the sizure and one week later may reveal whether the neurovascular coupling and cerebrovascular reactivity are impaired some hours after extreme increase of brain activity in already fully alert patients.

Till now we could include 4 patients in the hyperviscosity and 3 patients in the epilepsy studies. Due to the small sample size, statistical analysis could not be performed yet. We try to speed up the inclusion of the patients in the future.

GENE EXPRESSION ANALYSIS OF BRAIN METASTATIC MELANOMAS

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Introduction: Malignant melanoma (MM) is one of the most aggressive tumours. It is present in 40-70 percent of advanced cases. Despite efforts to treat patients, mortality and morbidity rates are still high, mainly due to resistance to conventional therapies.

Although the molecular background of brain metastasis in MM is extensively studied, it is far from sufficiently understood. There are many genetic abnormalities affecting essential pathways and regulatory mechanisms in the cell.

Aims: We aimed at investigating the expression pattern of metastases-related genes in cerebral MM metastases for future correlation with pathological and clinical features (including survival and response to treatment).

Materials and Methods: In a retrospective study of formalin-fixed paraffin-embedded tissue samples of surgically resected melanoma brain metastases (n=27) and relevant control tissues were used. We specified the viable and representative tissue fragments by examining the H&E-stained histopathological specimens. Next, we isolated RNA from subsequent tissue sections of the preselected part of the tumour. After cDNA synthesis Tumour Metastasis RT^2 Profiler PCR Array (Qiagen) has been applied. It contains 84 metastasis-related and five housekeeping genes. We quantified results by the Livak method.

Results: Genes have been grouped according to their key function and relevance to pathway. The following categories have been established: genes of adhesion molecules, extracellular matrix, cell cycle, growth, proliferation and apoptosis.

Discussion: The gene expression patterns and pathways are in the focus of our analysis. We plan to continue our work with epigenetic studies. Deviation from normal DNA methylation pattern cause pathologic alterations in gene expression. Our findings may contribute to achieve longer survival time and development of more effective treatment strategies.

EFFECT OF LUNG PROTECTIVE ONE-LUNG VENTILATION WITH FIX AND VARIABLE TIDAL VOLUMES ON OXYGENATION AND POSTOPERATIVE OUTCOME: RANDOMIZED, CONTROLLED TRIAL

Katalin Szamos (2nd year PhD student)

Supervisor: Tamás Végh

Physiological breathing patterns are usually highly variable and, to some extent, unpredictable. The variability of a pattern is usually quantified by the coefficient of variation (CV), which is approximately 33 ± 14.9 % of the tidal volume in healthy spontaneous breathing at rest. Breath-by-breath variation in tidal volume and respiratory rate contribute to sustaining fast state transition while minimizing the ratio between tissue stress and strain. In experimental models, in ARDS the mechanical ventilation with variable parameters improved the breathing mechanisms and the oxygenation compared to mechanical ventilation with fix parameters. The results of using double lung ventilation (DLV) with variable parameters during abdominal surgery are contradictory. There are no data if variable parameters have already been used during one-lung ventilation (OLV).

Aim of our study was to compare the effect of one-lung ventilation with fix and variable tidal volumes on oxygenation and postoperative outcome during thoracic surgeries.

After approval from the Ethics Committees written informed consent was obtained from 140 ASA I-III patients scheduled for lung resection surgery and finally data of 128 persons were analyzed.

During standard anaesthesia, patients were randomized into two groups. In FIX Group patients were ventilated with 6 ml/kg tidal volume, while in the Variable Group tidal volume was 6 ml/kg±33 % during one-lung ventilation. Tidal volumes were determined with randomization software and changed in every 5 minutes. Arterial blood gas results (ABG), hemodynamic and ventilatory parameters were recorded during DLV and OLV in every fifth minute. During hospital stay lung function tests, ABG, x-ray examinations were done. These tests were repeated on the 30th and the 90th postoperative day.

There were no significant differences in the oxygenation, ventilatory and hemodynamic parameters, nor in the postoperative lung function, neither in postoperative complications and mortality.

In patients at increased risk for postoperative pulmonary complications undergoing thoracic surgery, intraoperative variable ventilation did not improve intraoperative oxygenation and outcome. The clinical value of intraoperative variable ventilation remains unproven.

PAI-1 5G/5G GENOTYPE IS AN INDEPENDENT RISK OF INTRACRANIAL HEMORRHAGE IN POST-LYSIS STROKE PATIENTS

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Objective: Thrombolysis by recombinant tissue plasminogen activator (rt-PA) is the main pharmacological therapy in acute ischemic stroke (IS), however, it is only effective in a subset of patients. Here we aimed to investigate the role of plasminogen activator inhibitor-1 (PAI- 1), an effective inhibitor of t-PA, and its major polymorphism (PAI-1 4G/5G) in therapy outcome.

Methods: Study population included 131 consecutive IS patients who all underwent thrombolysis. Blood samples were taken on admission, 1 and 24 h after rt-PA infusion. PAI-1 activity and antigen levels were measured from all blood samples and the PAI-1 4G/5G polymorphism was determined. Clinical data including NIHSS was registered on admission and day 1. ASPECTS was assessed using CT images taken before and 24 h after thrombolysis. Intracranial hemorrhage (ICH) was classified according to ECASS II. Long- term outcome was defined 90 days post-event by the modified Rankin Scale (mRS).

Results: PAI-1 activity levels dropped transiently after thrombolysis, while PAI-1 antigen levels remained unchanged. PAI-1 4G/5G polymorphism had no effect on PAI-1 levels and did not influence stroke severity. PAI-1 activity/antigen levels as measured on admission were significantly elevated in patients with worse 24 h ASPECTS (<7). Logistic regression analysis including age, sex, NIHSS on admission, BMI, history of arterial hypertension and hyperlipidaemia conferred a significant, independent risk for developing ICH in presence of 5G/5G genotype (OR:5.03, 95%CI:1.22-20.74). PAI-1 levels and PAI-1 4G/5G polymorphism had no influence on long-term outcomes.

Interpretation: PAI-1 5G/5G genotype is associated with a significant risk for developing ICH in post-lysis stroke patients.

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INVESTIGATION OF GLIOMA PROGNOSTIC FACTORS

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We conducted investigations about glioma prognostic factors in various aspects during my first year of PhD studies. This year consisted of a throughout study of literature, addressing research hypotheses, clinical data processing and compilation of research projects according to the following steps: 1, Optimalization of the invasion panel that our gene expression and proteomic studies based on. The roles of approximately 100 molecules were put under the scope according to the results of scientific community and our own ones in the topic of invasion-related extracellular matrix (ECM) components to determine the final set of molecules. 2, Determination of the subgroups of a study conducted on fresh-frozen tumor samples of diffusely infiltrating gliomas along with clinico-pathological data processing of the corresponding patients. Study being started: Analysis of the gene expression of 80 samples by TLDA. 3, Compilation of a Hungarian scientific review about the possible role of molecular biological markers in low-grade gliomas to establish relevant risk groups. 4, Clinical data processing of the low-grade glioma patients diagnosed at the Depart. of Neurosurgery, University of Debrecen (UD) during the last 15 years. 5, Publication of a review about the role and significance of liquid biopsy, extracellular vesicles and circulating cell-free nucleic acids in glioblastoma. 6, Study being started: Proteomic analysis of ECM molecules in 332 serum samples of primary and secondary brain malignancies. 7, Study being started: Comparison of serum samples of tumor-free and glioblastoma patients to detect invasion-related miRNAs. Number of samples: 26 samples in each group. 8, Clinical data processing secondary brain malignancies diagnosed at the Dept. of Neurosurgery and Dept. of Oncology, UD, during the last 10 years.

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CANDIDAEMIÁK A DEOEC-EN 2006-2013 KÖZÖTT - KEZELÉS ÉS KIMENETEL (RETROSPEKTÍV ADATGYŰJTÉS)

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Supervisor: Béla Fülesdi

Irodalmi adatok szerint a Candida fajok a véráramfertőzések 4. leggyakoribb kórokozói, ráadásul a candidaemiáknak a jelenleg érvényben lévő ajánlások betartása mellett is 35-49%-os attributív mortalitást tulajdonítanak. Mint ismeretes, Magyarországon az egészségügy anyagi helyzete miatt a candidaemiák kezelésében még mindig első helyen áll a fluconazol.

Munkámban a Debreceni Egyetem klinikáin 2006 és 2013 között candidaemiával diagnosztizált betegek adatait dolgoztam fel retrospektív módon a számítógépes adatbázis segítségével.

A 8 év alatt összesen 216 beteg volt, közülük 128-an haltak meg (60%). A rizikófaktorokat vizsgálva a bélperforáció/ bélműtét és pancreatitis fordult elő a leggyakrabban, ennek megfelelően a legtöbb beteget a sebészeten kezelték. Ha összehasonlítjuk a mortalitást a csak fluconazolt kapó betegcsoport (70exit/108 beteg) az antifungalis terápiában nem részesített csoporttal (33 exit/52 beteg), a betegek halálozásában szignifikáns különbség nincsen (P=0,86). Ha azonban a fluconazolt kapó betegeket a bármilyen más antifungalis szerrel (AmB, echinocandinok, voriconazol) kezelt betegekkel hasonlítjuk össze (23 exit/65 beteg), az utóbbi csoportban a túlélés szignifikánsan jobb (P<0,001).

Mivel az alkalmazott dózisokról és egyéb befolyásoló tényezőkről nem áll rendelkezésemre elég adat, a kapott eredményekből nagyon messze menő következtetéseket nem lehet levonni, de a nagy betegszám mellett talált mortalitási mutatók miatt ennek ellenére kijelenthetjük, hogy candidaemia esetén a fluconazol kezelés semmivel sem hozott jobb eredményt, mint a kezelés elmaradása, ami teljesen egybe vág az érvényben lévő ajánlással.

Időközben az adatfeldolgozást folytattam, jelenleg a 2014-18 közötti időszak candidaemiás betegeinek adatait gyűjtöm. Ha ezek is feldolgozásra kerülnek, az sok újat fog tudni hozzátenni az eddigiekhez, ugyanis éppen ezekben az években kezdtek szélesebb körben is elterjedni az echinocandinok a hazai gyakorlatban is, így ezt a gyógyszercsoportot illetően is lesz értékelhető adat.

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