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## VALIDATION OF THE CRASH PREDICTION MODEL IN PREDICTING 18 MONTHS MORTALITY AND UNFAVORABLE OUTCOME IN SEVERE TRAUMATIC BRAIN INJURY REQUIRING DECOMPRESSIVE CRANIECTOMY

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To assess the validity of the CRASH (corticosteroid randomization after significant head injury) collaborators prediction model in predicting mortality and unfavorable outcome at 18 months in patients with severe traumatic brain injury (TBI) requiring decompressive craniectomy. This prospective observational cohort study included all patients who underwent a decompressive craniectomy following severe TBI at the two major trauma hospitals in Western Australia from 2004 to 2012 and on whom eighteen month follow-up data was available. Clinical and radiological data on initial presentation was entered into the web-based model and the predicted outcome compared with the observed outcome. In validating the CRASH model, we used area under the receiver operating characteristic (ROC) curve to assess the ability of the CRASH model to differentiate between favorable and unfavorable outcomes. The ability of the CRASH 6-month unfavorable prediction model to differentiate between unfavorable and favorable outcomes at 18 months after decompressive craniectomy was good (area under the ROC=0.85, 95% confidence interval 0.80–0.90). The model's calibration was not perfect. The slope and the intercept of the calibration curve were 1.66 (standard error [SE] 0.21) and –1.11 (SE 0.14), respectively, suggesting that the predicted risks of unfavorable outcomes were not sufficiently extreme or different across different risk strata and were systemically too high (or over-pessimistic), respectively. The CRASH collaborators prediction model appears to be a valuable tool which can be used as a surrogate index of injury severity to stratify patients according to injury severity. We would however, caution clinicians not to make clinical decisions based solely on the predicted risks derived from the model.

**WITHDRAWN**

## SPREADING DEPOLARIZATION IN ACUTE NEURONAL INJURY

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In the evolution of the cerebral cortex, the sophisticated organization in a steady state far away from thermodynamic equilibrium has produced the side effect of two fundamental pathological types of neuronal mass discharge: ictal epileptic activity and spreading depolarization. Ictal epileptic activity describes the partial disruption and spreading depolarization the near-complete disruption of the physiological double Gibbs-Donnan steady state. Ictal epileptic activity and spreading depolarization are thus passive processes driven by the electrochemical gradients between intraneuronal and extracellular space, ictal epileptic activity being associated with partial and spreading depolarization with near-complete break-down of the transneuronal ion gradients. The toxic intracellular calcium surge during spreading depolarization in fact reaches a concentration of up to 25  $\mu$ M. The restoration of ion homeostasis is energy dependent because it requires the activation of ion pumps, in particular the activation of Na, K-ATPases. Therefore, even under otherwise physiological conditions, spreading depolarization causes an immediate decline in tissue ATP to about 50%. Spreading depolarization is moreover characterized by neuron swelling with dendritic spine distortion (cytotoxic edema) and marked glutamate release (excitotoxicity). The occurrence of ictal epileptic activity in patients has been known for decades. Recently, unequivocal electrophysiological evidence has been found in patients that spreading depolarizations occur abundantly in brain trauma and stroke. Specifically in brain trauma, it has been shown that spreading depolarizations are associated with unfavorable outcome.

## IMAGING COVERT COGNITION AND CONSCIOUSNESS

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Neuroimaging active, passive and resting state paradigms are being employed to investigate residual brain function of patients in a

vegetative state/unresponsive wakefulness syndrome (VS/UWS) and minimally conscious states (MCS). Using fMRI, a patient behaviorally diagnosed as unresponsive could follow two mental imagery commands, i.e., imagine playing tennis and visit the rooms of her house. These commands were further used as communication system for a patient also diagnosed unresponsive to provide “yes”/“no” responses to simple questions. However, absence of command following does not necessarily entail absence of awareness. Aphasia problems may hinder patients from comprehending and/or responding. Alternatively, passive paradigms using external somatosensory and auditory stimulations have shown that only sensory cortices are activated in patients in VS/UWS; in contrast, patients in MCS show more widespread cortical activation including hierarchically higher-order association areas. When such experimental setups are complicated, resting state studies show that unresponsive patients exhibit reduced global metabolism but recovery from VS/UWS does not necessarily coincide with resumption of global metabolic activity. Hence, some areas are more important than others to sustain conscious function. Indeed, patients in VS/UWS show impaired metabolism in midline and lateral frontoparietal cortices. Similarly using fMRI, posterior cingulate cortex, medial prefrontal cortex and posterior parietal cortices (areas broadly known as the default mode network) also show decreases in functional connectivity as a function of the level of consciousness. Such advances are expected to lead to medico-ethical and legal discussions, where patients’ competency will potentially need to be re-established in a context of contemporary technology usage.

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#### **FUTURE DIRECTIONS OF HYPOTHERMIA THERAPY FOR TRAUMATIC BRAIN INJURY FROM CLINICAL STUDIES IN JAPAN**

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Traumatic brain injury (TBI) has heterogeneous pathophysiology which can be classified into contusion, acute subdural hematoma, acute epidural hematoma, diffuse axonal injury and their combinations. Since their pathophysiologies differ, therapeutic strategies should also differ. A multicenter randomized controlled trial of patients with severe TBI who received either therapeutic hypothermia or induced normothermia was performed from 2002 to 2008 in Japan (BHYP0). Favorable outcomes in young patients (<50 years of age) with evacuated mass lesions significantly increased from 33.3% under normothermia to 77.8% under hypothermia ( $p=0.015$ ). Patients with diffuse injury III who were treated with hypothermia (53.8%) had significantly high mortality than patients in normothermia (11.1%) ( $p=0.041$ ). From July 2009 through June 2011, an observational study which was admitted severe TBI patients, called the Japan Neurotrauma Data Bank (JNTDB) Project 2009, was performed in Japan. In this study, multivariate analysis in patients with evacuated mass lesion showed that hypothermia (odds ratio, 5.547; 95% CI, 1.157–26.58;  $P<0.05$ ) were independent factors related to favorable outcome but not in diffuse injury. Further, the implementation rate of intracranial pressure (ICP) monitoring in hypothermia was significantly higher than the other groups. Patients with evacuated mass lesions are expected to be good candidates for hypothermia therapy. The temperature management under ICP monitoring is important for hypothermia therapy. In the future, a prospective multicenter randomized study which shows protective effects of hypothermia for patients with evacuated mass lesion has to be planned.

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#### **VERY HIGH RESOLUTION ULTRASOUND IMAGING TO ASSESS THE INJURED SPINAL CORD AND EXTENT OF BLOOD SPINAL CORD BARRIER DISRUPTION**

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To determine if very high resolution ultrasound (VHRUS) is able to depict and quantify blood spinal cord barrier disruption (BSCBD) secondary to experimental spinal cord injury (SCI) in rats at the acute and sub-acute phases (90 min and 24 h post-SCI). Eighty Wistar rats were used. Sham-operated animal underwent a Th10-Th12 laminectomy while injured animals underwent Th11 clip SCI. VHRUS images were compared with histology and fluorescent microscopy of extravasated Evans blue (injected intravenously). A protocol was developed for three-dimensional quantification of the VHRUS images and compared (Pearson coefficient) to the amount of haemoglobin and Evans blue extravasated in the parenchyma measured with spectrophotometry assays. Time-lapse videos were generated to understand how the parenchymal haemorrhage (PH) grows. VHRUS can depict the structural and vascular anatomy of the rat spinal cord and can be repeated in the same animal at successive time points. Following SCI, a hyperechoic lesion progressively extended. In the acute and sub-acute phase, this lesion depicts evolution of the PH and BSCBD. Significant correlations were found between VHRUS quantification and extravasated haemoglobin in the acute ( $r=0.88$ ,  $P<0.0001$ ) and sub-acute ( $r=0.85$ ,  $P<0.0001$ ) phases and extravasated Evans blue in the sub-acute phase ( $r=0.94$ ,  $P<0.0001$ ). Time lapse videos demonstrated that the expansion of the PH reflects the appearance of new foci of haemorrhage. VHRUS allows for imaging and quantification of PH and BSCBD following SCI in rats. This work has the potential for straight forward translation into the clinical setting.

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**WITHDRAWN**

### **CASE STUDY OF BRACHIAL PLEXUS TRANSFER IN RETURN OF UPPER LIMB FUNCTION FOLLOWING MULTITRAUMA AND BRACHIAL PLEXUS AVULSION**

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We report a 27-year-old woman who suffered multitrauma due to an agricultural accident. Notable injuries included: complete avulsion of her left brachial plexus and amputation of her right arm. Her right brachial plexus, however, remained functional and was transferred to her intact left arm to provide a basis for function and mitigation of phantom limb pain (PLP).

Outcome measures included neurological examination of the left upper limb (LUL) as well as the patient's perceived PLP. fMRI investigations using left elbow flexion and finger-tapping tasks were undertaken to derive possible correlations between instinctiveness of movement and BOLD changes at primary sensorimotor cortices.

LUL power and fMRI were examined some three years and eight months post-surgery. Flexor compartments displayed greatest return: biceps, wrist and finger flexion all showed 4/5 power. fMRI depicted cortical activation of the left hemisphere, reflecting incorporation of the right brachial plexus into the circuitry innervating the LUL. Significant cortical activation of the contralateral hemisphere was also present. This was more pronounced during elbow flexion than finger-tap, correlating with the patient's subjective feeling that elbow flexion had become second-nature. Major improvements in PLP were also reported.

This case illustrates that brachial plexus transfer can achieve some degree of functional recovery in patients following brachial plexus avulsion. At the cortex, fMRI showed the degree to which cortical rearrangement occurred correlated with subjective ease of movement, suggesting that functional improvements in limb mobility and reduced PLP are associated with increased activation in the sensorimotor cortex.

### **TREATMENT OF SPORTS RELATED CONCUSSION: SUMMARY OF THE CURRENT RECOMMENDATIONS OF THREE PROMINENT SPORTS MEDICINE ORGANIZATIONS**

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Currently there is considerable debate within the sports medicine community about the role of concussion and the risk of chronic neurological sequelae such as chronic traumatic encephalopathy (CTE). This concern has led to confusion among primary care providers and

athletic trainers about how best to identify those athletes at risk, and how to treat concussion. It also has led to reluctance among many parents to allow their children to participate in organized contact sports such as football or soccer. During the first quarter of 2013 three new or updated clinical practice guidelines were published on the diagnosis, treatment and management of concussion in sports. The goal of each group was to clearly define current best practices for the definition, diagnosis, and acute and post-acute management of sports-related concussion, including specific recommendations for return to play. Key recommendations of all three groups are that any athlete suspected of having a concussion should not be allowed to return to play on the day of the injury, and they also should not return to play until they have been evaluated by a licensed healthcare provider. Those who have sustained a concussion are more at risk for sustaining subsequent concussions. However, the association between one or multiple concussions, the severity of those concussions or the time interval between concussions and the development of CTE remains unclear. The goal for this presentation will be to compare the recommendations of each of the three guidelines groups and highlight those topics for which there is consensus.

### **APPROACHES AND DECISIONS FOR ACUTE PEDIATRIC TBI – AN INTERNATIONAL EFFORT**

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Traumatic brain injury (TBI) is the leading killer of children with over 7000 deaths reported in the United States in 2005. In addition to loss of life, the yearly cost of TBI in children is over \$2 billion with more than a million life-years at risk. Advances in care for children with severe TBI have been disappointingly slow. Randomized controlled trials (RCTs) of therapeutic agents have universally failed when applied across centers. Evidenced-based guidelines are insufficiently robust to generate meaningful recommendations because the literature has failed to demonstrate best practices. Variations in such practices are substantial, leading to wide variations in patient outcomes which may ultimately overwhelm treatment effects that could be found in a well-designed RCT. We have embarked on an observational cohort study of 1000 children with severe TBI to compare the effectiveness of pediatric TBI therapies within an international consortium from the US, UK and EU. We will test 3 specific aims that encompass a total of 6 TBI therapies - (i) intracranial hypertension strategies – cerebrospinal fluid diversion and hyperosmolar therapies; (ii) secondary insult detection – prophylactic hyperventilation and brain tissue oxygen monitoring (PbO<sub>2</sub>); (iii) metabolic support – nutritional support and glucose management. Statistical approaches to control for confounders will be employed including propensity score adjustments, regression analyses and novel statistical modeling. Successful completion of this proposal would provide compelling evidence to change clinical practices, provide evidence for several new recommendations for future guidelines and lead to improved research protocols that would be limit variability in TBI treatments.

### **EARLY INDUCTION OF HYPOTHERMIA FOR EVACUATED INTRACRANIAL HEMATOMAS**

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Hypothermia protects the brain after cardiac arrest and neonatal hypoxia/ischemia, probably by protecting from reperfusion injury, but has not proven protective after diffuse brain injury. Reperfusion does not occur in diffuse injury, but it does occur experimentally after evacuation of intracranial hematomas. The authors hypothesized, therefore, that cooling applied before evacuation of traumatic intracranial hematomas might be protective by a similar mechanism as cardiac arrest. We analyzed the results of hypothermia applied before craniotomy for hematomas in two clinical trials. NABIS:H I was a randomized multicenter clinical trial of 392 patients with severe brain injury treated using normothermia or hypothermia for 48 hours with patients reaching 33°C at 8.4±3 hours after injury. NABIS:H II was a randomized, multicenter clinical trial of 97 patients with severe brain injury treated with normothermia or hypothermia for 48 hours with patients reaching 35°C within 2.6±1.2 hours and 33°C within 4.4±1.5 hours of injury. Entry and exclusion criteria, management, and outcome measures in the 2 trials were similar. A meta-analysis of 46 patients with evacuated hematomas in both trials who reached 35°C within 1.5 hours of surgery start showed a significantly reduced rate of poor outcomes (41%) compared with 94 patients treated with hypothermia who did not reach 35°C within that time and patients treated at normothermia (62%,  $p=0.009$ ). We conclude that induction of hypothermia to 35°C before or soon after craniotomy with maintenance at 33°C for 48 hours thereafter may improve outcome of patients with hematomas and severe traumatic brain injury.

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### CEREBRAL EXTRACELLULAR CHEMISTRY AND OUTCOME OF PATIENTS WITH ACUTE SUBDURAL HEMATOMA

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It is recognized that extracellular metabolic markers are more accurate for predicting outcomes in patients with traumatic brain injury (TBI) because of reflecting their pathophysiological processes. Previous studies analyzed data in patients of all types of TBI for a long period, however, there is still less information about focusing on acute subdural hematoma for the first 24 hours. Nineteen patients with acute subdural hematoma underwent cerebral monitoring of extracellular chemistry with microdialysis catheter. Samples were collected with vial change of 1 hour. Cerebral extracellular biomarkers (glucose, lactate, pyruvate, glycerol, and glutamate) were measured and averaged for the first 24 hours of monitoring. Of 19 patients, 11 of patients were male and 8 were female. The mean age of patients was 61.3 years. Eight patients had a favorable outcome (Glasgow Outcome Scale (GOS) GR or MD) and 11 had an unfavorable outcome (GOS SD, PVS or D). The mean extracellular lactate concentration was 39.3 mmol/l in pa-

tients with a favorable outcome and 87.2 mmol/l in patients with unfavorable outcome ( $P=0.026$ ). The mean extracellular glycerol concentration was 142  $\mu\text{mol/l}$  in patients with a favorable outcome and 1288  $\mu\text{mol/l}$  in patients with an unfavorable outcome ( $P<0.001$ ). The mean lactate/pyruvate (L/P) ratio was 31.9 in patients with a favorable outcome and 80.8 in patients with an unfavorable outcome ( $P=0.002$ ). L/P ratio was the most consistent predictor in patient with acute subdural hematoma and can discriminate between favorable and unfavorable outcome for the first 24 hours at threshold of approximately 40.

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### SEIZURE SUSCEPTIBILITY AFTER TRAUMATIC INJURY TO THE PEDIATRIC MOUSE BRAIN

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The occurrence of post-traumatic epilepsy (PTE) is particularly high after injury at a young age, and has been associated with poorer functional outcomes, suggesting that the developing brain may show particular vulnerability to post-traumatic epileptogenesis. However, most existing models of PTE examine injury to the adult brain. Here, we have investigated seizure susceptibility in mice after injury at post-natal day 21, using a well-characterized model approximating a toddler-aged child. The convulsant pentylenetetrazol (PTZ) was administered at either adolescence or adulthood after injury or sham-operation, and behavioral responses were scored blinded. As early as 2 weeks post-injury, brain-injured mice showed a pronounced seizure response to PTZ (higher Racine scores) compared to sham-operated controls, as well as reductions in the latency to immobility, the first myoclonic jerk, and generalized seizure. At 3 months post-injury, a positive association was found between latency to PTZ-induced generalized seizure and the degree of volumetric loss in the ipsilateral hippocampus calculated from coronal Nissl-stained sections. Brains were also examined for mossy fiber sprouting by ZnT3 immunofluorescence, another pathological hallmark of PTE. Of note, abnormal mossy fiber sprouting was absent at 2 weeks but detected in all brain-injured samples at 3 months post-injury, particularly in regions of hippocampal deformation. This finding suggests that functional alterations in neuronal circuitry which contribute to increased seizure susceptibility occur prior to detectable mossy fiber sprouting. This model of increased seizure susceptibility lays the foundation for investigating the mechanisms of epileptogenesis after traumatic injury in the developing brain.

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### CYTOSKELETAL MECHANISMS OF AXONAL GROWTH AND REGENERATION

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After central nervous system (CNS) injury, axon regeneration is prevented by growth inhibitory factors in the lesion scar as well as by poor intrinsic axon growth potential. Microtubule stabilization controls scar formation and axon growth. However, the action of microtubule stabilization on these processes has remained unclear. Here, systemic and post-injury administration of a blood-brain barrier

permeable microtubule stabilizing drug, epothilone B, decreased scarring in spinal cord injured rodents by disrupting cell polarity of meningeal fibroblasts, which abrogated directed cell migration. Further, epothilone B propelled axon growth through an inhibitory environment by enabling microtubule protrusion into the axon tip. Finally, epothilone B treatment improved walking disabilities after spinal cord injury. As epothilones received recently clinical approval, they hold promise for clinical translation in enabling axon regeneration and functional recovery after CNS injury.

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#### **OXIDATIVE STRESS PROTECTION BY APOCYNIN AND ALLOPURINOL IN FOREBRAIN ISCHEMIA/REPERFUSION RATS**

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Free radical plays a central role in ischemia/reperfusion injury as an initiator of endothelial activation and early inflammation. To suppress the cascade of free radical might decrease the inflammatory response after ischemia/reperfusion. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and xanthine oxidase (XO) are the main sources of free radicals caused by ischemia/reperfusion injury. This study examined the effects of either apocynin or allopurinol alone, and their combinational therapy on the oxidative stress, endothelial injury, and early inflammation. Adult male Wistar rats were randomly assigned to four experimental groups: a control group, an apocynin group (30 mg/kg), an allopurinol group (100 mg/kg), an apocynin (30 mg/kg) and allopurinol (100 mg/kg) group. The rats in each group (n=7) received designated agents or its vehicle delivered intraperitoneally one hour before forebrain ischemia. Under mechanical ventilation, forebrain ischemia was induced for 10 minutes, followed by reperfusion. At 120 minutes after reperfusion, the blood and brain were sampled and malondialdehyde (MDA), high mobility group box 1 (HMGB1) and intercellular adhesion molecule-1 (ICAM-1) were analyzed. In results, MDA levels in plasma and brain were significantly lower in the rats administered apocynin and/or allopurinol than those in the control group. The synergy effect of apocynin and allopurinol on MDA suppression was not shown. The similar results were observed in HMGB1 and ICAM-1 levels in plasma and brain. From these results, the use of either apocynin or allopurinol attenuated oxidative stress in ischemia/reperfusion injury, whereas the combinational therapy did not show the synergy effects.

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#### **MORTALITY IN ELDERLY PATIENTS WITH MULTIPLE TRAUMA**

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Reduction of elderly people physiological reserve limits organism response to traumatic stress and aggravates prognosis. Study the relationship of lethality terms in polytrauma of various severity and comorbid conditions in age-related aspect. We retrospectively reviewed 107 lethal outcomes cases of polytrauma. Two groups of patients: I - 65 patients under 60 years; II - 42 patients who were older than 60. Besides, cases were chosen according to lethality terms: up to 2 days, from 3 to 13 days and over 13 days; according to ISS values:

> 16; 16 – 24; >24. Logistic regression method used for determining the death risk dependence after 13 days on comorbid conditions. For a period of 48 hours 22 (33.8%) patients of I group and 9 (21.4%) patients of II group with ISS>24 died (p>0.05). One patient (1.5%) of I group and 14 (33.3%) of II group with ISS < 16 died after 13th day (p=0.01). Nineteen patients of I group (29.2%) and 38 patients of II group (90.5%) had certain comorbid conditions (p=0.0001). Thereby risk of death after second week from the moment of trauma increases in the presence of premorbid background which is intrinsic to elderly patients (OR=2.8; p=0.04). Mortality in early stage of multiple trauma has direct relationship with the severity of injury and traumatic shock and does not depend on comorbid conditions and age of patients. Elderly patients with mild and moderate trauma have heightened risk of late death due to the development of medical complications.

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#### **COAGULOPATHY AS A PREDICTOR OF EXACERBATION IN MILD-TO-MODERATE TRAUMATIC BRAIN INJURY PATIENTS**

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We have reported before that the acute operation induced by exacerbation was required of 9.5%, and outcome was poor at 13.1% of mild-to-moderate traumatic brain injury (TBI) patients. Therefore prudent observation is required in even mild-to-moderate TBI patients after admission. In this study, we have examined the factors of aggravation in mild-to-moderate TBI patients. 96 mild-to-moderate single TBI patients (Glasgow Coma Scale score at admission 9–15) were admitted to our hospital in the period from September 2008 to October 2010. Of these, the patients with antiplatelet therapy or anticoagulation therapy were excluded. The 84 patients with mild-to-moderate single TBI were included in this study. Patients were divided into two groups (surgery, conservative) based on the performance of acute surgery induced by exacerbation. Further we divided patients into favorable outcome (GOS score 4–5) and poor outcome (GOS score 1–3) based on GOS at discharge. We performed comparison between each two groups about patients age and blood test results at admission. Patients of surgery group were 8 (9.5%), and conservative group were 76 patients (90.5%). PT-INR (1.22 vs 1.02), APTT (37.9 vs 28.6 sec), FDP (112.9 vs 38.2  $\mu\text{g/ml}$ ), and D-dimer (69.6 vs 20.4  $\mu\text{g/ml}$ ) in surgery group were statistically significant increased than in conservative group. Further, favorable outcome group were 73 patients (86.9%), and poor outcome group were 11 patients (13.1%). Age (53.2 vs 73.5 y/o), PT-INR (1.02 vs 1.15), APTT (28.6 vs 36.3 sec), FDP (33.5 vs 112.5  $\mu\text{g/ml}$ ), and D-dimer (18.8 vs 67.4  $\mu\text{g/ml}$ ) in poor outcome group were statistically significantly increased, and blood platelets (25.8 vs 18.8  $10^4 \mu\text{g/ml}$ ) in poor outcome group were statistically significantly reduced than in favorable outcome group.

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#### **BLOCKING P75NTR SIGNAL REDUCES WHITE MATTER DAMAGE AND AIDS RECOVERY AFTER CONTROLLED CORTICAL IMPACT BRAIN INJURY**

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Traumatic brain injury can lead to progressive damage in white matter including oligodendrocyte cell death and subsequent demyelination, resulting long-term sensori-motor and cognitive deficits. Previously, we reported that oligodendrocytes are vulnerable to apoptotic cell death and subsequent demyelination through proNGF-p75NTR signaling after a spinal cord injury (Beattie et al, 2002). Here, we examine if blocking proNGF-p75NTR signaling prevents oligodendrocyte cell death *in vitro* and after TBI *in vivo*. We found that proNGF treatment of oligodendrocyte precursor cell and mature OL cell cultures results in apoptotic cell death. Treatment with SarA (1, 10, 30, 100, 300 nM), a selective p75NTR antagonist, reduced OPC/OL cell death by 80–90% compared to untreated cells. In addition, proNGF treatment increased p75NTR expression on OPC/OL cells, and this was blocked by SarA. SarA was then tested *in vivo* by intravenous administration (1, 3, 10 mg/kg) in rats with unilateral controlled cortical impacts (5 mm diameter probe, 4 m/s, 2 mm depth, 150 msec dwell time). Rats were dosed at 4 hrs after injury and then daily for 7 days and euthanized on day 8. Volumetric analyses were performed using the Stereoinvestigator. TBI significantly reduced total cortical volume (sham,  $3.44 \times 10^{10}$   $\mu\text{m}^3$  vs injury+vehicle,  $2.46 \times 10^{10}$   $\mu\text{m}^3$ ), and, white matter volume (sham,  $7.45 \times 10^9$   $\mu\text{m}^3$  vs injury+vehicle,  $5.56 \times 10^9$   $\mu\text{m}^3$ ). SarA prevented white matter tissue loss (vehicle,  $5.56 \times 10^9$   $\mu\text{m}^3$  vs Sar127963,  $7.36 \times 10^9$   $\mu\text{m}^3$ ). In addition, SarA treatment enhanced tissue sparing and recovery of paw-plate in the cylinder test in a dose-dependent manner. Our findings suggest p75NTR is a possible therapeutic intervention for TBI.

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### EEG NEUROFEEDBACK THERAPY: CAN IT ATTENUATE BRAIN CHANGES IN TBI?

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EEG Neurofeedback (NFB) therapy has several potential beneficial effects in terms of improving cognition and electrophysiological regulation among patients with brain injury. However, *in vivo* structural and functional changes remain less studied or less explored. The aim of the present study is to explore EEG NFB induced *in vivo* changes in TBI patients.

Two TBI patients with mean age of 15 years and with mean GCS score of 10 indicating moderate head injury with more than seven post concussion symptoms and poor cognitive performances (<5 percentile) were subjected to 20 sessions of EEG NFB training. The neuropsychological test scores, post concussion symptoms and MRI scan of the brain were recorded pre-post EEG NFB.

During EEG-NFT the cognitive scores and concussion symptoms improved significantly ( $p < 0.05$ ). The EEG NFB has shown significant increase in cortical grey matter (GM) volumes ( $p < 0.0001$ ) and fractional anisotropy (FA) of cortical white matter (WM) tracts ( $p < 0.0001$ , voxel max 60 and above). There was a significant decrease in global, local efficiency, cost and Clustering coefficient of functional connectivity (Wilcoxon Sign Rank Test  $p < 0.05$ ). Interestingly there was a significant increase in thalamo-cortical connection (increase FA value) after EEG NFB therapy.

The EEG NFB therapy has shown significant changes in structural and functional connectivity among moderately injured TBI patients.

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### LESSONS IN CRITICAL CARE RESEARCH FROM A GLOBAL PHASE 3 TRIAL OF PROGESTERONE IN PATIENTS WITH SEVERE TRAUMATIC BRAIN INJURY (sTBI)

Neta R Nelson  
VP Project Management & Operations Besins Healthcare/BHR Pharma, LLC affiliate

BHR-100 progesterone i.v. infusion is being studied as a potential neuroprotectant for severe TBI. The SyNAPSe Phase 3 placebo-controlled randomized clinical trial was conducted in 21 countries on patients with severe TBI (Glasgow Coma Scale 3–8). Enrollment was completed, overcoming numerous challenges in clinical trial research in the critical care environment. Sites were selected based on patient potential and standardized care according to Brain Trauma Foundation or equivalent treatment guidelines. Centralized review of CT scans, Glasgow Outcome Scores (GOS), and protocol compliance was conducted. Subjects required proxy consent to enter the study and were randomized in a 1:1 ratio to BHR-100 or placebo. The study drug infusion must have been initiated within 8 hours of brain injury, and administered for 120 continuous hours. Patient follow-up continues to 6-months post-injury, or death if earlier. Nearly 1200 subjects were randomized in 36 months. Most sites were able to overcome challenges of the 8-hr treatment window and enroll at least one patient. Successful sites had organized study teams and adequate resources, with at least one study 'champion'. Training or experience in emergency consent was essential, as well as thorough knowledge of all study assessments to ensure protocol compliance and data quality. Rigorous follow-up and site and patient support was needed to collect the primary endpoint (GOS). The sponsor oversaw three CROs, three central services, and over 150 centers to conduct the trial. Completion of the SyNAPSe trial provides lessons for planning of future TBI or other critical care trials.

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### PATIENT CHARACTERISTICS IN SyNAPSe, A GLOBAL PHASE 3 TRIAL OF PROGESTERONE IN PATIENTS WITH SEVERE TRAUMATIC BRAIN INJURY (STBI)

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BHR-100 i.v. progesterone is a promising potential neuroprotectant for severe TBI, based on preclinical and clinical evidence. SyNAPSe is a Phase 3 placebo-controlled randomized clinical trial conducted in 21 countries on patients with severe TBI. This presentation summarizes key characteristics of the patient population enrolled into the trial. Subjects entered the study following proxy consent, and were centrally randomized in a 1:1 ratio of BHR-100 or placebo. Subjects were treated with study drug as continuous i.v. infusion for 120 hours, initiated within 8 hours of injury. The primary endpoint is the Glasgow Outcome Scale (GOS) assessed at 6-months post-injury, or death prior to 6 months. Secondary endpoints include the GOS-Extended, mortality, and the SF-36. Enrollment of 1180 patients was completed at nearly 150 participating centers. Three quarters of patients were male. Ages ranged from 16 to 70, with most being less than 50 years of age; 42% were 30 or less. Patients with Glasgow Coma Scale (GCS) 3–8 were included. Most patients were enrolled in the latter half of the 8-hour treatment window. Causes of TBI included motor vehicle accidents, falls, and assaults. Data are presented on GCS scores, timing of study enrollment, and hours from injury to randomization. Gender differences are also examined. Based on the

patient demographics and baseline criteria, the study population was similar to that used as a baseline model for the study design (IMPACT database). If successful, BHR-100 may become the first approved drug in the acute treatment of sTBI patients.

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## **ANIMAL MODELS OF PEDIATRIC TRAUMATIC BRAIN INJURY**

Susan S Margulies

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Animal models are used as surrogates for understanding mechanisms of traumatic brain injuries (TBIs) in humans, including understanding the biomechanics factors associated with tissue injuries and the cascade physiological, functional and pathological responses at prescribed time-points after injury. Although they are our best substitute for humans, there are four challenges in using animal models to understand TBIs in children. First, fidelity in the metrics and methods used to assess responses in animals may not be analogous to those used in humans. Second, animal models should mimic the injuries observed in children, yet most brain injury models create focal hemorrhagic cortical lesions caused by direct impact to the skull or exposed brain, while the human TBI is more commonly associated with distributed white matter alterations, with or without focal lesions. Third, most TBI models use adult animals and, given the alterations in the metabolism, cerebral blood flow, synaptic density, myelination and functional organization during development, applications of adult animal models to the child should be made with caution. Finally, the rodent and murine animal models are the most commonly used models for TBI, but recent reports indicate that these species may have limited fidelity to human responses, injury time-courses, and anatomy, underscoring the importance of utilizing immature large animal models to complement rodent studies. In summary, animal models provide a valuable platform for determining how head movements and impacts may produce a spectrum of brain injuries, for developing novel injury intervention strategies, and for testing new therapies.

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## **REPETITIVE MILD TRAUMATIC BRAIN INJURIES**

Mayumi L Prins

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Among the 2.3 million annual new head injury cases is a growing sub-population of children and young adults who experience repeat traumatic brain injury (RTBI) with consequent long-term behavioral and cognitive dysfunction. Repeat TBI is a growing problem for children, teens and young military personnel and occurs during a time of ongoing cerebral development. Much of the epidemiological data has been obtained from sports activities where repeat concussions frequently occur. Several of these small-scale studies estimate the incidence of RTBI to range between 5.6–34.9% of the annual TBI cases. The national incidence of RTBI per age group and gender has not been acquired. While the exact rates of RTBI may remain unclear, it is known that the risk for subsequent TBI increases with the number of previous concussions and with age (Annegers, 1980). The increased national awareness of concussions and repeat concussions necessitates more research to address the many unanswered questions. In addition to parameters such as age, gender, injury severity and recovery profiles, RTBI studies must incorporate injury number, locations, intervals and duration of vulnerability. With these considerations in mind,

this review will discuss the current experimental models of RTBI, specifically addressing findings in anatomical pathologies, behavioral deficits, metabolic alterations, pituitary dysfunction and the evidence for long-term consequences.

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## **LIFETIME PERSPECTIVE ON HEAD INJURY**

Thomas A Gennarelli

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This clinician researcher has witnessed a revolution of information and innovation regarding head trauma. Insights into the mechanisms by which mechanical energy affects the nervous system has now run the geometric scale from genetic to whole brain populations.

When my journey in neurotrauma began in the 1970's, we had only indirect measures of anatomical or physiological changes (cerebral angiography, ICP, JVO<sub>2</sub>) and classification systems were just beginning to be used (GCS, focal vs. diffuse injuries, AIS, ICD).

Later, injuries were detected more directly with CT, CBF, Tc99, SPECT and PET and later still with better clinical resolution (MRI). Now we have evolved to utilize sophisticated high resolution tools (SWI, DTI, fMRI, FA, connectivity). These diagnostic improvements allowed more precise diagnoses and more rational treatment.

Collaboration with trauma surgeons improved pre-hospital care, classification of multiple injuries and comparison of outcomes between centers. Coupled with neurosurgical intensive care units staffed by neuro-intensivists and neuro-nurses, the mortality of the severely brain injured markedly decreased.

Pre-clinical research increased logarithmically as neuroscientists became involved alongside of what was traditionally principally a neurosurgical research venue. Largely unsuccessful clinical trials of neuroprotective agents taught us much about how to conduct these trials for the future.

Currently, there is a trend to emphasize less severe injury with struggles to define this end of the TBI spectrum and to define its homogeneous groups.

Most importantly, TBI has been transformed from an entity that only a few cared about to a visibility that every citizen confronts daily.

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## **SPREADING DEPOLARIZATIONS: MONITORING A NEURONAL PATHOPHYSIOLOGIC PROCESS IN TRAUMATIC BRAIN INJURY**

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Decades of electrophysiologic studies in ischemic stroke have established a framework for understanding the development of cortical lesions based on the phenomenon of spreading mass neuronal depolarizations. These slow (1–5 mm/min) waves in cerebral cortex expand damage through energy depletion, microvascular constriction, and excitotoxicity. Although spreading depolarizations scarcely occur in rodent models of traumatic brain injury (TBI), there is now firm evidence that they occur abundantly in severe clinical TBI and may serve as a basis for real-time monitoring and therapeutic targeting. Surgical patients monitored with subdural electrodes have a ~55% incidence of depolarizations, and patterns very widely from occasional events to continuous, repetitive events causing prolonged (hours to days) silencing of cortical activity – a state analogous to ischemic penumbra. The first series of 103 patients showed that such

isoelectric spreading depolarizations carry an independent 7-fold higher risk of poor outcomes, and larger cohorts hold promise to identify further criteria for more refined risk stratification. It is unknown to what degree spreading depolarizations may occur in non-surgical patients, including moderate and mild TBI. However, the use of depth electrodes for minimally invasive monitoring through a burr hole is currently being evaluated. Furthermore, a high percentage of spreading depolarizations have correlates in continuous scalp EEG recordings, raising hope that non-invasive monitoring may be possible, particularly with the aid of quantitative techniques. Thus, with further study, spreading depolarizations may provide a basis for application of precision medicine principles by allowing therapeutic targeting of a monitored neuronal pathomechanism.

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### FUNCTIONAL MRI IN TBI

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Advances in magnetic resonance imaging (MRI) have improved the diagnostic process in patients with traumatic brain injury (TBI). Structural images have been traditionally used to assess brain damage although recently functional MRI (fMRI) has been gaining ground in the assessment of TBI. At the acute stage, resting state fMRI provides valuable information on the patients' degree of consciousness. Indices of functional connectivity, especially of the default mode network, have been shown to correlate with levels of consciousness. At the chronic stage of TBI, task fMRI has advanced our understanding of disorders of consciousness by demonstrating that some patients are able to process stimuli in a more complex manner than previously thought possible. Patients who recover are likely to suffer from neuropsychological sequelae such as loss of memory and personality changes. The neural bases of these changes have traditionally been investigated using neuropsychological testing and structural MRI. However, it is not atypical for patients who perform poorly on neuropsychological assessments to have normal structural MRI scans. fMRI is helping to disambiguate this phenomenon by revealing the exact neural mechanisms underlying neurocognitive deficits following TBI. Furthermore, task fMRI is being used to evaluate the efficacy of drug treatments in chronic patients. My talk will explore traditional experimental paradigms and analysis of fMRI data as well as analysis methods and paradigms that are changing the way we understand TBI. By elucidating the precise nature of the injury we may help more focused rehabilitation interventions.

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### NON-INVASIVE ICP MONITORING

Marek Czosnyka

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Continuous non-invasive ICP is considered as the Holy Grail in multimodal brain monitoring. Many innovative techniques were proposed for snap-shot measurement rather than monitoring, like Ragauskas' double depth insonation of ophthalmic artery, the ocular nerve sheath diameter assessment, tympanic membrane displacement, MRI cerebral volume accounting. Monitoring transcranial Doppler (TCD) techniques are available, but long-term good quality middle cerebral artery insonation is non-feasible. Recording is limited to few-hours periods on each day or twice a day (intermittent monitoring). Few methods based on physiological models or 'black box' structures are described in a literature, with overall accuracy of ICP estimation around  $\pm 12$  mmHg. Better results can be achieved for non-invasive detection of increased ICP dynamics

like frequency and duration of ICP plateau waves. Distinction between normal ICP (below 15 mm Hg) and increased ICP (above 30 mmHg) can be done with a good predictive power (usually above 80%). In contrast, the TCD derived Pulsatility Index is not a good estimator of ICP, with 95% confidence limit for prediction in TBI being as large as 25–30 mm Hg. Pulse waveform of ICP is easier detectable than mean ICP. Methods based on rheoencephalography, ultrasound based time-of-flight, or skull deformation can be considered. This way, secondary indices describing cerebrospinal compensation (like the RAP index- correlation coefficient between pulse amplitude and mean ICP) and pressure-reactivity index (PRx) may be assessed non-invasively. Particularly for non-invasive evaluation of PRx, the use of Near Infrared Spectroscopy indices based on the calculated total hemoglobine value is promising.

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### QUANTIFYING PAROXYSMAL SYMPATHETIC HYPERACTIVITY IN TRAUMATIC BRAIN INJURY

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Paroxysmal sympathetic hyperactivity (PSH) is characterized by episodic, hyperadrenergic alteration in vital signs after traumatic brain injury (TBI). A reproducible PSH severity scale could provide clinicians with a method of quantifying PSH. A prospective cohort of consecutive TBI patients (GCS  $\leq 12$ ) were enrolled and monitored for evidence of PSH. PSH was defined as a paroxysm of 3 or more of the following characteristics: (1) tachycardia, (2) tachypnea, (3) hypertension, (4) fever, and (5) dystonia (rigidity or posturing) (6) diaphoresis, with no other obvious causation. The "Clinical Feature Severity Scale" (CFSS), was applied to each participant once daily for 5 days, calculated from the most deranged set of vitals recorded in that 24-hour period. Pre-defined ranges of each of the vitals were assigned point values on an ordinal scale. 105 patients were enrolled, 12 of whom met criteria for PSH. Maximum CFSS scores were higher in the PSH group (10 [7–11] v. 7 [6–9],  $P < 0.01$ ). Mean ICU length of stay ( $20 \pm 12$  days v.  $8 \pm 7$  days,  $P = < 0.01$ ) and hospital length of stay ( $39 \pm 23$  days v.  $16 \pm 15$  days,  $P = 0.03$ ) were longer in the PSH group. When controlling for age, GCS, and APACHE II score, maximum CFSS scores were predictive of ICU length of stay ( $t = 2.9$ , 95% CI: 0.4–2.1,  $P < 0.01$ ) and hospital stay ( $t = 3.2$ , 95% CI: 1.0–4.6,  $P < 0.01$ ), despite PSH status. This study provides the first, preliminary evidence that CFSS score may be predictive of increasing length of stay and might be used to guide future therapies.

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**WITHDRAWN**

### ELEVATED INTRACRANIAL PRESSURE AND IMPAIRED BRAIN METABOLISM CORRELATE WITH FATAL OUTCOME AFTER SEVERE BRAIN INJURY

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New brain tissue monitoring techniques (tissue oxymetry, microdialysis) provide direct information about the state of brain oxygenation and brain metabolism in patients with severe traumatic brain injury (TBI). Despite this information being limited to a small region of brain surrounding the probes, it could be associated with such global parameters as the clinical outcome. To study the predictive value of monitoring brain oxygenation and metabolism on clinical outcome in patients in the acute phase of severe TBI. A prospective observational study of 20 patients with severe TBI was undertaken, utilizing intracranial pressure (ICP), brain tissue oxymetry and brain metabolism monitoring. We correlated the clinical outcome of the patients with the following parameters: ICP, brain tissue oxymetry (PbtO<sub>2</sub>), glucose and glycerol levels, and the lactate/pyruvate (LP) ratio. Further, we analyzed the relationship between ICP, PbtO<sub>2</sub> and the metabolism parameters. We found a correlation of the mean ICP, the LP ratio and glycerol with the clinical outcome. High ICP correlated with both a high LP ratio and also an elevated glycerol, while low PbtO<sub>2</sub> correlated with a high LP ratio. High ICP, an elevated mean LP ratio and high glycerol concentrations in the acute phase predict fatal outcome 6 months after TBI.

### ENVIRONMENTAL ENRICHMENT RESTORES ATTENTIONAL SET-SHIFTING AND BEHAVIORAL FLEXIBILITY AFTER CONTROLLED CORTICAL IMPACT INJURY IN MALE RATS

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Cognitive impairment associated with prefrontal cortical dysfunction is a major component of disability in traumatic brain injury (TBI) survivors. Specifically, deficits in executive function and behavioral

flexibility are present across all injury severities. While impairments in spatial learning have been extensively reported, experimental models of TBI investigating more complex cognitive disabilities are relatively scarce. To expand on this important issue, we have begun to employ the attentional set-shifting test (AST), which is novel to experimental TBI. The AST involves a series of increasingly difficult discriminative tasks to obtain food reward, including simple and compound discriminations, stimulus reversals, and intra- and extra-dimensional (ED) shifts. In a previous study, we demonstrated that a controlled cortical impact (CCI) injury (2.8 mm cortical deformation depth at 4 m/s) produced significant impairments in executive function and cognitive flexibility in the AST, tested at 4 weeks post-surgery. The current study evaluated whether environmental enrichment (EE), a preclinical model of neurorehabilitation, would restore cognitive performance post-injury. Our EE paradigm consisted of increased living space, complex stimuli and social interaction and has consistently been shown to facilitate spatial learning and memory retention, as well as provide histological protection after CCI. Thirty-one isoflurane-anesthetized male rats received a CCI or sham injury and then were randomly assigned to two TBI and two sham groups that were further divided into EE and standard (STD) housing (n=6–10/group). Cognitive performance in the AST was assessed at 4 weeks post-surgery. The data showed that TBI impaired ED set-shifting and stimulus reversal learning and increased total response errors and set loss errors (i.e., after 50% or more of the contingency rule has been achieved), which replicated previous findings from our laboratory. Moreover, the data revealed that EE significantly attenuated the detrimental effects of TBI on cognitive performance in the AST, suggesting that EE may be a viable preclinical model of cognitive rehabilitation. These novel findings demonstrate that executive function and behavioral flexibility deficits in our CCI model are sensitive to the beneficial effects of EE. Ongoing studies are evaluating pharmacological and cognitive rehabilitation therapies as a clinically relevant combinational paradigm, as well as elucidating mechanisms underlying the neuropsychological deficits.

### MANIPULATING INITIATION TIME AND DURATION OF ENVIRONMENTAL ENRICHMENT EXPOSURE AFTER TRAUMATIC BRAIN INJURY TO MORE ACCURATELY MIMIC CLINICAL REHABILITATION

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Environmental enrichment (EE) consists of increased living space, complex stimuli, and social interaction that promotes exploration and confers improvements in behavioral outcome and histopathology after experimental traumatic brain injury (TBI) vs. standard housing. However, as a model of rehabilitation, continuous EE is not clinically relevant due to the timing parameters of the typical EE and thus translatability could be limited. Specifically, TBI patients typically receive rehabilitation only after critical care has been provided and then only for 3–6 hours per day. Thus, to mimic the clinic, the goal of this study was to determine whether delaying EE by three days and providing only six hours per day would provide benefits similar to continuous EE. To address this rehabilitation relevant issue, isoflurane-anesthetized male rats were subjected to a controlled cortical impact or sham injury and randomly assigned to TBI+EE (con-

tinuous), TBI+EE (3 day delayed, 6 hr day), and respective sham controls. Motor function (beam-balance/beam-walk) was assessed on post-operative days 1–5. Spatial learning/memory (Morris water maze) was evaluated on days 14–19. The data showed that EE, regardless of timing, improved motor and cognitive function compared to STD housing ( $p < 0.0001$ ). Moreover, there were no differences between the TBI+EE (continuous) and TBI+EE (3 day delayed, 6 hr day),  $p > 0.05$ . These data demonstrate that delayed and abbreviated EE produces motor and cognitive benefits similar to continuous EE after TBI and thus further supports EE as a preclinical model of neurorehabilitation. Ongoing studies are evaluating the effects of longer delays in implementing EE after TBI.

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### **APOLIPOPROTEIN E PROPERTIES AS THE BASE OF DEVELOPMENTS IN THERAPEUTICS FOR TRAUMATIC BRAIN INJURY**

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Apolipoprotein E (APOE, gene; apoE, protein) is widely synthesized in the brain in response to injury being involved in the redistribution of cholesterol from cells during membrane synthesis, as well as neuritic growth and branching. According to current literature, apoE exerts its neuroprotective effects through normalization of lipid component of neural cells, regulation of glial reactions and CNS inflammatory response to injury, antioxidant protection, regulation of cell death mechanisms, expression of other genes and genomic response in the neural tissue to its diseases and injuries. In our experiment, rat hippocampus exhibited prominent delayed secondary damage after weight drop TBI including neuronal loss with presence of apoptotic-like neurons, reactive astrogliosis, microglial activation, mitochondrial damage, brain edema, diffuse axonal injury and damage to myelin fibers. Injured rats displayed significant deficits in spatial acquisition and working memory accompanied by increased anxiety-like behavior. Cationic liposome-mediated APOE3 gene transfer by means of intraventricular infusion significantly prevented the evolution of secondary hippocampal injury, as well as improved spatial memory, learning, searching behavior and emotionality. Other authors have shown that small peptide molecules derived from the apoE receptor binding region can traverse blood-brain barrier after intravenous administration and improve functional and morphological outcomes in mice with TBI (Hoane et al., 2007; Laskowitz et al., 2007). The similar data were obtained in a rat model of focal brain ischemia (Tukhovskaya et al., 2009). Taken together, these data suggest that the new approaches to the treatment of TBI may be based on the unique set of apoE molecular and biological properties.

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### **THE AUSTRIAN PROJECT. IMPROVEMENT OF PRE-HOSPITAL AND EARLY HOSPITAL CARE OF TBI PATIENTS: GOAL AND METHODS OF THE STUDY**

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Earlier evidence in management of traumatic brain injury (TBI) patients shows that early care is most important. The objectives of this study were

- (1) to analyze current state of early TBI care in Austria
- (2) to define areas for improving outcomes using comparative effectiveness research
- (3) to implement the proposed changes
- (4) and to analyze the effect of the implemented changes.

16 Austrian centers participated in the study. Between 2009 and 2012 all patients with Glasgow Coma Scale score  $< 12$  and/or AIS head  $> 2$  were enrolled. Demographic data, data on treatment and outcomes (hospital mortality, 6-month extended Glasgow Outcome Scale score) was collected in 2 phases. In the first phase data on 448 patients was collected and analyzed. The IMPACT extended prognostic model was used to estimate expected outcomes. The ratio between observed and expected outcomes (O/E ratio) was calculated for all treatment options. Treatment options that were associated with O/E ratios  $< 1$  were selected for a set of recommendations. Main recommendations included direct transport to appropriate center, prehospital monitoring of pulse oximetry, blood pressure and capnography (in ventilated patients), maintaining normoventilation, avoidance of Ringer’s lactate solution in prehospital fluid resuscitation, start of first CT scan within 60 minutes, and start of neurosurgery (when indicated) within 120 minutes after hospital arrival. After the implementation of the recommendations data on 330 patients was collected and analyzed in the second data collection phase. Finally, the impact of the recommendations on patient outcomes was assessed.

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### **SURVIVAL WITH SEVERE DISABILITY: THE ISSUE OF RETROSPECTIVE CONSENT**

Stephen Honeybul, Kate Kruger, Courtney Janzen, Kwok Ho  
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To assess the long-term outcome and quality of life of patients who have survived with severe disability following a decompressive craniectomy for severe traumatic brain injury (TBI). This study assessed outcome beyond three years amongst a cohort of thirty nine patients who had previously been adjudged either severely disabled or in vegetative state, 18 months after decompressive craniectomy for TBI. The issue of retrospective consent for surgery was also assessed. Of the thirty nine patients, seven had died and twenty patients or their next of kin consented to participate. Of those twenty patients, the five patients who were in vegetative state at 18 months remained so beyond three years and the remaining 15 patients remained severely disabled after a median follow-up period of 5 years. The patients’ average daily activity (Pearson correlation coefficient  $[r] = -0.661$ ,  $p = 0.01$ ) and SF-36 physical score ( $r = -0.543$ ,  $p = 0.037$ ) were inversely correlated with the severity of TBI. The mental SF-36 scores of the patients were, however, reasonably high (median 46, interquartile range 37–52). The majority of patients and their next of kin felt that they would have provided retrospective consent for surgical decompression even if they had known their eventual outcome. Substantial physical recovery beyond 18-month after decompressive craniectomy for severe TBI was not observed however, many patients appeared to have recalibrated their expectations regarding what they felt to be an acceptable quality of life.

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### **DECOMPRESSIVE CRANIECTOMY FOR SEVERE TRAUMATIC BRAIN INJURY: ETHICAL CONSIDERATIONS**

Stephen Honeybul, Grant Gillet, Kwok Ho  
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In all fields of clinical medicine there is an increasing awareness that outcome must be assessed in terms of quality of life and cost effective-

tiveness rather than merely length of survival. This is especially the case when considering decompressive craniectomy for severe traumatic brain injury. The procedure itself is technically straightforward and involves temporarily removing a large section of the skull vault in order to provide extra space into which the injured brain can expand. A number of studies have demonstrated many patients go on to make a good long-term functional recovery, however, this is not always the case and a significant number survive but are left with severe neurocognitive impairment. Unfortunately many of these patients are young adults who were previously fit, and well and are therefore likely to spend many years in a condition that they may feel to be unacceptable and this raises a number of ethical issues regarding consent and resource allocation. In an attempt to address these issues we have used the analytical framework proposed by Jonsen that requires systematic consideration of medical indications, patient preferences, quality of life and contextual features.

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### **THE AUSTRIAN PROJECT IMPROVEMENT OF PRE-HOSPITAL AND EARLY HOSPITAL CARE OF TBI PATIENTS RESULTS OF THE STUDY**

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The goal of the project was to improve outcomes of patients with TBI by improving prehospital and early hospital care. Patients in the first (n=448) and the second (n=330) data collection phases were comparable; demographic data and injury severity were not different. Recommended treatment changes were implemented successfully. Compared to phase 1, prehospital intubation was associated with better outcomes (mortality 27 vs. 36%), there was a lower rate of hyperventilation (17 vs. 46%) and a higher rate of hypoventilation (36 vs. 10%), pulse oximetry was used more frequently (87 vs. 82% of all patients), and capnography was used more frequently (91 vs. 60% of all ventilated patients). CT scans were done faster, and more patients had thrombelastometry (TEM). These changes lead to significant improvement of patient outcomes. In phase 1, mortality was 31.8% (11% higher than expected), 79% of the survivors had favorable outcome, and 11 patients with expected unfavorable outcomes had good outcomes. In phase 2, mortality was 26.5% (20% lower than expected), 77% of the survivors had favorable outcome, and 50 patients with expected unfavorable outcomes had good outcomes.

The new guidelines were successfully implemented leading to better prehospital management, especially by ambulance teams, increased use of capnography, better prehospital ventilation, and increased use of TEM. Compliance with the new guidelines was associated with lower mortality and a comparable rate of good outcome in survivors.

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### **DOPAMINE TRANSPORTER EXPRESSION IN THE BRAIN FOLLOWING TRAUMATIC BRAIN INJURY AND RESTRAINT STRESS IN A MOUSE MODEL**

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An association between trauma and neurological degenerative diseases, including post-traumatic Parkinson's syndrome, has been suggested. Disruption of dopamine homeostasis in the dopaminergic neurons in the midbrain is the primary mechanism of Parkinson's syndrome. Because patients with brain injury are frequently under substantial stress due to multiple injuries or complications, we hypothesized that dopamine transporter (DAT) expression will change in the midbrain following traumatic brain injury (TBI) and restraint stress. We examined time-dependent changes in the DAT in the midbrain after TBI and restraint stress by using a mouse controlled cortical impact (CCI) model. Mice were subjected to restraint stress for 14 hours at 1, 4, 7 and 14 day after CCI. A monoclonal antibody for DAT was used for immunohistochemistry. The numbers of DAT immunoreactive neurons in the retrorubral field (RRF) of the midbrain were counted and compared among the sham and the mice with CCI or restraint stress or both. In the mice with CCI, the numbers of immunoreactive neurons in the RRF significantly decreased at 14 days after trauma. In the mice with CCI and restraint stress, the numbers of immunoreactive neurons in the RRF significantly decreased at 7 and 14 days after trauma. These findings indicate that TBI and restraint stress inhibit DAT expression at 7 days following trauma. Because DAT pumps dopamine out of the synapse back into the cytosol and maintains dopamine homeostasis, the decreased expression of DAT after TBI and restraint stress may result in decreased dopamine neurotransmission in the brain.

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### **EPIDEMIOLOGIC ANALYSIS OF PATIENTS WITH SEVERE TRAUMATIC BRAIN INJURY IN SHIRAZ, IRAN; 2011–2013**

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Traumatic brain injury (TBI) remains the leading cause of mortality and morbidity worldwide. With changes in demographic status, improvements in technology and introducing novel medical and surgical guidelines for management of TBI patients, regular evaluation of epidemiological profiles, injury severity classification, and outcomes are required. A form was designed to record demographic data, trauma event history and TBI-related variables such as GCS, pupils, brain CT findings, vital signs, arterial blood gas results, and final GOSE after 6 months follow-up. From March 2010 till June 2012 all Patients with severe TBI admitted in Shahid Rajaei hospital affiliated to Shiraz University of Medical Sciences, Shiraz, Iran was reviewed. Available data were filled within the mentioned forms and then transferred to SPSS 16 software for analysis. Of 681 patients with TBI who had GCS  $\leq 10$ , 98 (14.4%) were female and 583 (85.6%) were male. The most frequent mechanism of trauma was motor-vehicle accident (MVA) (65%) followed by pedestrian (17.3%), fall (12.3), and assault injuries (5%). Mean age ( $\pm$ SD) of our patients was 36.1( $\pm$ 18) years with 68% were young ( $\leq 40$  y), 17.6% Middle-aged (40–59), and 14.1% Old ( $\geq 60$ ). Six-months GOSE score of these patients, which shows 80% of our patients, had favorable outcome (GOSE  $> 4$ ) with 41% full recovery (GOSE = 7&8). Shahid Rajaei trauma center which was one of the largest referral trauma centers in southern Iran has achieved similar favorable outcomes as other trauma centers worldwide which had presented their epidemiologic data.

## FOLLOWING NEUROTRAUMA, ACUTE PHASE S100B DOES NOT PREDICT FUNCTIONAL OUTCOME BUT A LONG-TERM S100B RELEASE SUGGESTS A PARTICIPATION IN NEUROREGENERATION

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The neuromarker S100B is reported to correlate positively with brain injury and negatively with outcome. Experimental evidence on the other hand suggests S100B to participate in repair mechanisms. The aim of the present study was to correlate S100B levels in the acute and chronic period with functional recovery following brain injury.

We measured S100B in the cerebrospinal fluid and serum in patients treated with a ventricular drainage following subarachnoid hemorrhage (SAH, Hunt&Hess I:n=2, II:n=5, III:n=2, IV:n=7, V:n=1) daily during the acute phase (n=17) and after 5–8 months (n=6). Functional recovery was assessed neuro- and neuropsychologically. A cranial MRI documented morphological sequelae. A long-term follow-up was performed utilizing the QoLiBrI assessment after 3 years (n=8). The value of S100B to predict survival and functional outcome was analyzed.

S100B<sub>serum</sub> and S100B<sub>CSF</sub> peaked at up to 300-fold values on day 1 with a subsequent decline that was more pronounced in survivors (n=11) than in non-survivors (n=6). Group comparison revealed a statistical significant difference of S100B<sub>CSF</sub> on day 6 (p=0.019) and S100B<sub>serum</sub> on day 12 (p=0.006). S100B did not correlate with the functional outcome at 6 months or 3 years. The QoLiBrI assessment revealed an overall quality of life of 79.70 (scale 0–100) and a satisfaction with personal mental skills of 4.30 (scale 0–5). Interestingly, in 2 out of 5 patients S100B<sub>CSF</sub> was increased at 6 months (1.82/3.55 ug/l) despite a satisfying neuropsychological performance.

Following neurotrauma, S100B<sub>serum/CSF</sub> neither allows a reliable detection of survivors nor predicts long-term functional outcome. 6 months after the initial injury, S100B<sub>CSF</sub> is increased in one third of patients suggesting a participation of S100B in ongoing neuroregenerative processes.

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### PROTECTING GLIA FROM OXIDATIVE STRESS DURING SECONDARY DEGENERATION FOLLOWING NEUROTRAUMA

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Following neurotrauma, tissue adjacent to the primary injury undergoes a cascade of cellular and molecular events termed secondary degeneration, leading to further loss of neurons, glia and function. Mediators of secondary degeneration, including Ca<sup>2+</sup> and reactive species, diffuse and may spread *via* connections between astrocytes, oligodendrocyte precursor cells (OPCs) and axons.

Using immunohistochemical and labelling techniques we have demonstrated *in vivo* increases in reactive species, oxidised products and anti-oxidant enzymes in CNS glia vulnerable to secondary degeneration, following partial transection of adult rat optic nerve. Oxidative stress in oligodendrocytes is associated with alterations in structure of node of Ranvier/paranode complexes. We observe significant lengthening of the paranodal gap and paranode as well as paranode disorganisation. A high proportion of OPCs vulnerable to secondary degeneration proliferate in the first week following optic nerve injury, and the appearance of shortened myelin internodes at 3 months suggests remyelination. However, OPCs die and total numbers remain chronically lower, accompanied by persistent myelin decompaction, axon swelling and functional loss. We have used multiple combinations of Ca<sup>2+</sup> channel inhibitors to treat secondary degeneration *in vivo* and demonstrated that combinations that include the L-type voltage gated calcium channel inhibitor lomerizine, improve myelin compaction. Treatment with a combination of three inhibitors (lomerizine, YM872 and oxATP) reduces indicators of oxidative stress, prevents lengthening of the paranodal gap and preserves visual function. Strategies to reduce the spread of excess Ca<sup>2+</sup> and resultant reactive species may protect oligodendroglia from oxidative stress and thereby preserve function following neurotrauma.

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### ASSESSMENT OF THE CEROX CEREBRAL OXYGENATION MONITOR IN SEVERE TRAUMATIC BRAIN INJURY PATIENTS

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Development of a non-invasive monitor to assess cerebral oxygenation has long been a goal in neurocritical care. We evaluated the feasibility and utility of the CerOx 3110 non-invasive monitor, which uses near infrared spectroscopy and ultrasound, to measure regional cerebral tissue oxygenation in severe TBI patients and compared these measurements with those obtained from invasive cerebral monitoring. Patients with severe TBI admitted to the intensive care unit at Hadassah-Hebrew University Hospital requiring intracranial pressure (ICP) monitoring and advanced neuromonitoring were included in this study. We studied 18 patients with severe TBI with the CerOx monitor and invasive advanced cerebral monitors. The mean age was 45.3±23.7 years and the median GCS on admission was 5 with an interquartile range of 3 – 7. Eight patients underwent unilateral decompressive hemicraniectomy and one patient underwent craniotomy. Sixteen patients underwent insertion of a jugular bulb venous catheter, and 18 patients underwent insertion of a Licox brain tissue oxygen monitor. We found a strong correlation (r=0.60, p<0.001) between the jugular bulb venous saturation from the venous blood gas and the CerOx measure of regional cerebral tissue saturation on the side ipsilateral to the catheter. A multivariate analysis revealed that among the physiological parameters of mean arterial pressure, ICP, brain tissue oxygen tension, and CerOx measurements on the ipsilateral and contralateral sides, only ipsilateral CerOx measurements were significantly correlated to jugular bulb venous saturation (p<0.001). Measuring regional cerebral tissue oxygenation with the CerOx monitor in a non-invasive manner is feasible in severe TBI patients in

the neurointensive care unit. The correlation between the CerOx measurements and the jugular bulb venous measurements of oxygen saturation indicate that the CerOx may be able to provide an estimation of cerebral oxygenation status in a non-invasive manner.

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#### **INJURY SEVERITY AND SEIZURE DEVELOPMENT AFTER TRAUMATIC BRAIN INJURY**

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Traumatic brain injury (TBI) is a major risk factor for the development of seizures and a diagnosis of posttraumatic epilepsy. The influence of injury severity on seizure development chronically has not been well characterized. Mild (1.5–1.7 atm; n=8), moderate (1.8–2.1 atm; n=8) or severe (2.2–2.5 atm; n=6) fluid percussion brain injury was performed in the rat. Animals were assessed 1 year post-TBI or in age-matched naive rats (N=5) via electrocorticographic (ECoG) recordings and video. Rats were implanted with 2 epidural electrodes near the injury site 24 hr prior to video/ECoG recording using Powerlab. Fast Fourier Spectral Analysis was conducted offline using EEGLab on the MatLab software platform. Two hours of recordings were performed prior and post administration of a sub-threshold dose of pentylenetetrazol. Seizure activity was quantified by measuring the power for six frequency bands (Delta, Theta, Alpha, Beta1, Beta2, and Gamma) in 2 sec intervals and was considered to be an epileptic event if the power in all spectral bands was 4 standard deviations greater than that recorded in non-seizing control animals. All injury severities showed evidence for subclinical seizures during baseline. These epileptic events were also observed in the mild TBI animals. After PTZ injection, behavioral seizures were seen in all injury severities with video monitoring correlated with seizure event detection. The importance of using age-matched controls when assessing for seizures should be emphasized as seizure events were detected in some cases. These data demonstrate that not only are non-convulsive and convulsive seizures observed after moderate or severe TBI but mild TBI appears to induce chronic seizures as well. Abnormal seizure activity may influence outcome in a large population of brain injured patients.

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#### **EXTRACELLULAR MATRIX BIOMARKERS FOR ACUTE NEUROLOGICAL INJURY**

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The extracellular matrix (ECM) links neuronal, glial and vascular compartments together through specific ligand-receptor interactions. The ECM is composed of integrins, cell adhesion molecules, and glycoproteins, which are constantly remodeled to promote CNS

functions. The ECM is susceptible to alterations and modifications from the mechanical forces or enzymatic pathways of traumatic brain injury (TBI), providing a source for biomarkers of injury. This presentation tests the hypothesis that the extracellular matrix serves as a biomarker source specific to brain injury mode (focal vs. diffuse) and severity. Experimental TBI was induced in adult, male rats by controlled cortical impact (CCI) or midline fluid percussion injury (FPI) at mild and moderate severity. Blood and tissue from cortex, hippocampus and thalamus at 1d, 3d, 7d, and 14d post-injury were quantified by western blot for fibronectin, laminin, and reelin. Laminin showed acute degradation in hippocampal CA1 (1-3d) and later degeneration in CA3 (7-14d) after focal injury. Laminin degradation may not result from diffuse brain injury. Fibronectin showed injury severity dependent increases in cortex, hippocampus and thalamus in both focal and diffuse TBI. Moreover, fibronectin was increased acutely (1-3d) in plasma in both focal and diffuse injury. Reelin quantification is ongoing. These studies continue to show the potential diagnostic value of ECM biomarkers in the context of TBI with respect to injury mode and severity.

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#### **TBI-PRECLINICAL NEUROPROTECTION**

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Despite strong preclinical data, over 30 TBI neuroprotection clinical trials have failed to date. These translational failures reflect numerous methodological differences including use of limited therapeutic targeting, failure to address either multiple cell death mechanisms or effects of chronic inflammation, and inadequate sample sizes, among others. Improved translation requires better understanding of targeted mechanism(s); demonstration that such mechanisms occur clinically; robustness of therapeutic effect (not just statistical significance); demonstration of effectiveness across models, species and labs; use of drug sensitive end points; knowledge of drug pharmacokinetics and brain penetration; and adequate power. Newer experimental approaches have focused on use of multi-factorial treatments that target concurrently multiple secondary injury processes and/or multiple cell types, or combined modulation of secondary injury and neurorestorative factors. There has also been increased recognition that TBI is a chronic neurodegenerative disorder, in part related to chronic inflammation, which suggests use of both different and potentially strategies with a much longer therapeutic window. Recent experimental examples are detailed that demonstrate the potential benefits of targeting multiple cell types and cell death mechanisms, use of highly delayed modulation of neuroinflammatory mechanisms, and implementation of pluripotential treatment strategies.

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#### **AMELIORATION OF TRAUMATIC BRAIN INJURY-INDUCED INCREASED CEREBROVASCULAR PERMEABILITY BY ENDOTHELIAL PROGENITOR CELLS IN MICE**

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Traumatic brain injury (TBI), the most common cause of death and disability, is accompanied with an increased cerebrovascular

permeability to blood proteins. It is thought that impairment in endothelial cell properties can be a main cause of enhanced vascular permeability. We tested the hypothesis that TBI-induced increase in cerebrovascular permeability can be ameliorated by elevation of number of endothelial progenitor cells (EPCs), which can repair damaged endothelium. Permeability of pial venules in pericontusional area of mild injury was studied in C57BL/6J mice. Mouse bone marrow-derived cells were grown on fibronectin-coated tissue culture plates to confluence and Flk-1+ /Sca-1+ (markers of endothelial and stem cell phenotype, respectively) EPCs were isolated by flow cytometry sorting. After induction of mild TBI, mice were infused with EPCs suspended in 100  $\mu$ l of phosphate buffered saline (PBS) or with PBS alone (control group) through an external jugular vein. After 14 days, pial venular permeability was assessed in these mice by measuring the extravascular accumulation of fluorescein isothiocyanate-labeled bovine serum albumin using an intravital fluorescence microscopy. Cerebrovascular leakage was decreased in mice infused with EPCs compared to that in mice infused with PBS alone. These results suggest that TBI-induced increased cerebrovascular permeability can be reversed by enhancing the number of EPCs, which can restore impaired property of vascular endothelium in pericontusional area. Our data indicate a novel functional role of EPCs in post-TBI treatment of cerebrovascular pathology.

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#### **DEFINING PLATELET FUNCTION IN POLYTRAUMA PATIENTS WITH TRAUMATIC BRAIN INJURY UPON ADMISSION TO THE EMERGENCY DEPARTMENT**

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Hemostatic function is impaired by multisystem injury and impacts survival. The aim of this study was to define the relationships between platelet (PLT) function and injury severity in traumatic brain injury (TBI) patients upon admission to the emergency department (ED). A prospective observational study was conducted on polytrauma patients presenting to Virginia Commonwealth University Medical Center. Blood collected on ED arrival was analyzed for hemostatic parameters, viscoelastic clot strength by thrombelastography (TEG) with PLT mapping to identify PLT-specific deficits in clot formation; PLT-induced clot contraction and effect on clot structure; PLT aggregation by aggregometry in response to collagen and ADP; PLT-associated thrombin generation using calibrated automated thrombography (CAT); flow cytometry for PLT activation and expression by CD62p. The data were analyzed using Kruskal-Wallis nonparametric test. Of the 110 polytrauma study patients, 27 had TBI and were grouped by admit injury severity score (ISS) (minor/moderate[M/M]: ISS < 16 (n=4); severe[S]: ISS 16–24 (n=8); and profound[P]: ISS 25–75 (n=15)). Increasing ISS in TBI patients was associated with increased PT/INR (P vs M/M and S,  $p < 0.02$ ) and PTT (P vs S,  $p < 0.03$ ); lower Fib (P vs S,  $p < 0.01$ ); weaker clots in P vs S as noted by PCF and CEM ( $p < 0.03$ ); slower clot initiation in P vs S, ( $p = 0.045$ ), and more thrombin generation in P vs M/M ( $p = 0.03$ ). D-dimer was greater in P and S vs M/M ( $p < 0.01$ ). TBI polytrauma patients with increasing ISS scores demonstrated impaired hemostasis and PLT-specific clot formation using multiple hemostatic measures. This data can help to improve diagnosis and therapeutic strategies in TBI patients.

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#### **THE EFFECTIVENESS EVALUATION OF HELICOPTER AMBULANCE TRANSPORT AMONG NEUROTRAUMA PATIENTS IN KOREA - NEUROSURGICAL HELICOPTER AMBULANCE TRANSPORT IN SMALL COUNTRY**

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Helicopter ambulance transport (HAT) is a highly resource-intensive facility that is a well-established part of the trauma transport system in many developed countries. Its efficacy for neurotrauma patients has not been analyzed in the reports. Here, we review the benefit of HAT for neurosurgical patients in Korea.

This retrospective study followed neurotrauma patients who were transferred by HAT to a single emergency trauma center over a period of 2 years. The clinical benefits of HAT were measured according to the necessity of emergency surgical intervention and the differences in the time taken to transport patients by ground ambulance transport (GAT) and HAT.

Ninety-nine patients were transferred to a single university hospital using HAT, of whom 32 were taken to the neurosurgery department. Of these 32 patients, 10 (31.3%) needed neurosurgical intervention, 14 (43.8%) needed non-neurosurgical intervention, 3 (9.4%) required both, and 11 (34.4%) did not require any intervention. The transfer time was faster using HAT than the estimated time needed for GAT, although for a relatively close distance (<50 km) without ground obstacles (mountain or sea) HAT did not improve transfer time. The cost comparison showed that HAT was more expensive than GAT (3,292,000 vs. 84,000 KRW,  $P < 0.001$ ).

In this Korean-based study, we found that although HAT has a clinical benefit for neurotrauma cases involving a transfer from a distant site or an isolated area. A more precise triage for using HAT should be considered to prevent overuse of this expensive transport method.

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**WITHDRAWN**

### INFILTRATING MYELOID-DERIVED SUPPRESSOR CELLS (MDSCs) SECRET MATRIX METALLOPROTEINASES-9 AFTER TRAUMATIC BRAIN INJURY IN MICE

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Matrix metalloproteinases (MMPs) play a major role in maintaining the integrity of the Blood Brain Barrier. In the recent clinical studies, MMP-9 in blood is associated with hemorrhagic transformation of lesion and death after ischemic injury. The reason why MMP-9 concentration in blood reflects the fragility in brain after injury has not been revealed. Hypothesis: Myeloid-derived suppressor cells (MDSCs), a heterogeneous population of immature myeloid cells, accumulate and secrete MMP-9 in the injured brain. Controlled cortical impact was induced in the cerebral hemisphere of adult male mice. Cells from the injured side of the cerebral cortex were isolated and analyzed using flow cytometry. The time course of the accumulation of immune cells in the injured brain, separated by differential CD45, CD11b, Ly6C, and Ly6G expression was analyzed which cells secrete MMP-9. Adoptive transfer experiments and bone marrow chimeras were used to distinguish between the resident cells and the infiltrating blood-derived cells in the injured brain. MDSCs in sham brain were approximately 1%. These cells increased to approximately 25% in injured brain 1 day post-injury. MDSCs dominantly secrete MMP-9 in blood and brain. Neither macrophage (CD45<sup>high</sup>/CD11b<sup>+</sup>) nor microglia (CD45<sup>low</sup>/CD11b<sup>+</sup>) secrete MMP-9 in brain. In bone marrow chimeras [CD45.1 → CD45.2], MDSCs in the injured brain expressed CD45.1, but not CD45.2. MDSCs infiltrate brain parenchyma after TBI and secrete MMP-9 in both blood and brain. Our new method using flow cytometry suggests that MMP-9 concentration in blood well reflects the severity of brain edema or bleeding after injury.

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#### ACTIVITY-REGULATED CYTOSKELETAL (ARC) GENE EXPRESSION AS A MOLECULAR BIOMARKER OF CIRCUIT INTEGRITY AFTER DIFFUSE TRAUMATIC BRAIN INJURY

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Activity-regulated cytoskeleton-associated protein (Arc), an immediate early gene considered to be the master regulator of synaptic plasticity and expression, is tightly coupled to behavioral paradigms *in vivo*. Here we demonstrate the time course of Arc gene expression after manual whisker stimulation at chronic time points in uninjured and diffuse traumatic brain-injured (dTBI) rats. In rodents, dTBI leads to late-onset, gain-of-function behavioral sensory sensitivity to manual whisker stimulation 28 days post-injury (Thomas et al., 2010), which arises from progressive circuit reorganization in response to injury-induced circuit dismantling.

For this study, adult male Sprague Dawley rats (~300 g) were subjected to a single moderate severity midline fluid percussion injury and 28 days post-injury exposed to manual whisker stimulation. At several time points following whisker stimulation, animals were euthanized and tissue was removed from the whisker circuit relays in primary somatosensory barrel field (S1BF) cortex and ventral posterior medial nucleus (VPM) of the thalamus for quantitative real-time PCR analysis. At 30 minutes after manual whisker stimulation, Arc mRNA expression increased significantly in the S1BF of dTBI animals compared to sham. At 15, 60 and 90 min after whisker stimulation, Arc mRNA expression was significantly decreased in the VPM of dTBI animals compared to sham. These results implicate Arc gene expression as a molecular biomarker of circuit activation that can distinguish reorganization of the whisker sensory circuit after dTBI compared to control. Arc expression at 30 minutes can be implemented to evaluate efficacy of therapeutic intervention to mitigate circuit reorganization after TBI.

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#### ANALYSIS OF DATA FROM THE U.S. CLINICAL TRIALS DATABASE REVEALS POOR CLINICAL TRIAL EFFORT FOR TRAUMATIC BRAIN INJURY, COMPARED WITH STROKE

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Traumatic brain injury (TBI) is an important public health problem, comparable to stroke in incidence and prevalence. Few interventions, however, have proven efficacy in TBI. This may be due to comparatively lower clinical trial activity in TBI. We aimed to quantitatively analyse and compare the clinical trial landscape in stroke and TBI.

This is an observational, cross-sectional study of all clinical studies in TBI and Stroke registered on the Clinical Trials Database between January 2000 and January 2013. This database is the most comprehensive clinical trial database and has been used for similar studies in other conditions. The analysis was conducted and reported according to the internationally agreed STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) criteria.

The clinical trial research effort in stroke is substantially greater than TBI, as measured by enrolment number (stroke n=1953349 vs TBI n=456517), number of studies (stroke n=1503 vs TBI n=402) and number of interventional studies (stroke n=1168 vs TBI n=268). Interventional studies make up 77% (n=1168) and 66% (n=268) of registered stroke and TBI studies respectively. Sixty percent (n=1168311) [95% CI: 62-58%] of participants in stroke studies and 79% (n=359482) [95% CI: 75-82%] in TBI studies are enrolled in interventional studies. The discrepancy of the clinical trial research effort between stroke and TBI is in direct contrast to the comparative public health impact of these two diseases. Our study is limited by the use of a single trial database.

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#### ALBUMIN RESUSCITATION FOR TRAUMATIC BRAIN INJURY: IS INTRACRANIAL HYPERTENSION THE CAUSE OF INCREASED MORTALITY?

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To identify the mechanisms which were potentially responsible for the marked difference in mortality confirmed between albumin and saline resuscitation in patients with moderate and severe TBI. In patients from the Saline vs. Albumin Fluid Evaluation (SAFE) study with TBI who underwent intracranial pressure (ICP) monitoring, interventional data were collected from randomization to day 14 to determine changes in ICP and in therapies used to treat increased ICP. Pattern mixture modelling, designed to address informative dropouts, was used to compare temporal changes between the albumin and saline groups. 321 patients were identified, 164 (51.1%) received albumin and 157 (48.9%) received saline. There was a significant linear increase in mean ICP and significantly more deaths in the albumin group compared with saline when ICP monitoring was discontinued during the first week ( $1.30 \pm 0.33$  vs.  $-0.37 \pm 0.36$ ,  $p=0.0006$ ; and 34.4% vs. 17.4%;  $p=0.006$  respectively). There were statistically significant differences in the mean total daily doses of morphine ( $-0.42 \pm 0.07$  vs.  $-0.66 \pm 0.0$ ,  $p=0.0009$ ), propofol ( $-0.45 \pm 0.11$  vs.  $-0.76 \pm 0.11$ ;  $p=0.034$ ) and norepinephrine ( $-0.50 \pm 0.07$  vs.  $-0.74 \pm 0.07$ ) and in temperature ( $0.03 \pm 0.03$  vs.  $0.16 \pm 0.03$ ;  $p=0.0014$ ) between the albumin and saline groups when ICP monitoring ceased during the first week. The use of albumin for resuscitation in patients with severe TBI is associated with increased ICP during the first week. This is the most likely mechanism of increased mortality in these patients.

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#### QUANTITATIVE MEASUREMENT OF BRAIN INJURY USING MRI AFTER DECOMPRESSION CRANIECTOMY: A PILOT STUDY

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Bilateral frontotemporal craniectomy (BFC) does not improve outcome of TBI patients with refractory intracranial hypertension. To explore why BFC patients had worse long-term outcome we used T2-weighted and diffusion tensor imaging (DTI) MRI to assess brain injuries after unilateral and bilateral decompression craniectomy. Nine patients (M=6, F=3; aged 19 to 61 years) with severe TBI were studied. Three patients did not have craniectomy (NC), 3 had unilateral temporal craniectomy (UTC) and 3 had BFC. A 1.5Tesla MR was used to acquire T2-Flair and DTI sequences. Volumes are presented as mm<sup>3</sup>/ICA. Values are expressed in mean +/- SD. Mean GCS on admission was 5 +/- 1.6. Normalized injury volumes (T2-Flair) were not different between BFC and UTC patients but were higher compared to NC patients. A trend for lower mean fractional anisotropy (FA) values after BFC in the corpus callosum (CC) ( $0.497 \pm 0.07$ ) and the frontal ( $0.422 \pm 0.02$ ) areas was observed compared to UTC (CC: $0.542 \pm 0.004$ ; Frontal: $0.434 \pm 0.02$ ), and to NC (CC: $0.552 \pm 0.02$ ; Frontal: $0.464 \pm 0.007$ ). In this pilot study we report for the first time that after BFC patients had greater injuries in the CC and frontal areas assessed by DTI. This difference was not seen in the temporal region after UTC. Our data suggest that frontal brain swelling after

BFC may lead to secondary injury due to the white matter stretch. These findings are preliminary due to sample size and don't allow us to rule out diffuse injury due to the severity of the initial brain insult.

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#### MEASUREMENT AND OPTIMISATION OF SPINAL CORD PERFUSION PRESSURE IN ACUTE SPINAL CORD INJURY

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We describe a novel technique to measure intraspinal pressure (ISP) at the injury site in patients with severe acute traumatic spinal cord injury (TSCI), analogous to measuring intracranial pressure after traumatic brain injury. We recruited 18 - 70 year old patients with severe acute TSCI. A Codman ICP probe was placed subdurally during spinal stabilisation. ISP was monitored within 72 hours from injury, for up to one week. Spinal cord blood flow was assessed using indocyanine green fluorescence, autoregulation using sPRx and sRAP, and cord function with motor evoked potentials. We determined the effect of different treatments on spinal cord perfusion pressure (SCPP) and cord function. 30 subjects were recruited (14 with TSCI, 16 without). No complications arose related to ISP monitoring. The injury site had higher ISP than below indicating focal cord swelling. ISP was initially high (>20 mmHg) and normalised (21%), normal and then high (29%), high throughout (29%) or normal throughout (21%). ISP remained high in 78% patients after bony decompression, suggesting dural compression. Laminectomy was potentially detrimental by exposing the swollen cord to external compression forces. p<sub>a</sub>CO<sub>2</sub>, sevoflurane and mannitol had no significant effect on ISP or SCPP. Inotropes increased SCPP ( $p<0.05$ ) and blood flow at the injury site. Optimal SCPP varied between patients. Optimising SCPP improved autoregulation and motor evoked potential amplitudes ( $p<0.01$ ). After severe TSCI, ISP at the injury site is elevated and SCPP is reduced. Our data indicate high ISP and low SCPP are harmful. By intervening to increase SCPP, we could improve spinal cord function in some patients.

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#### RECOMBINANT HUMAN INTERLEUKIN-1 ANTAGONIST MODIFIES THE NEURO-INFLAMMATORY RESPONSE TO SEVERE TRAUMATIC BRAIN INJURY

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Interleukin-1 receptor antagonist (IL1ra) is an endogenous competitive antagonist at the Interleukin-1 Type-1 Receptor (IL-1R). Antagonism at the IL-1R confers neuroprotection in several rodent models of neuronal injury (i.e., trauma, stroke, excitotoxicity). Previous studies of putative neuroprotective agents have failed for several reasons including poor blood brain barrier penetration of the drug, inappropriate timing of drug delivery, a conceptual misunderstanding of the complexity of mechanisms of action, and an inability to determine whether the drug concentration achieved in humans is sufficient to exert a biological effect. We describe a single centre, phase II, open label, randomised-control

study of recombinant human IL1ra (rhIL1ra, anakinra) in severe traumatic brain injury (TBI), at a dose of 100 mg subcutaneously once a day for 5 days in 20 patients randomised 1:1. As well as providing safety data in this patient population we have utilised cerebral microdialysis to directly determine brain extracellular concentrations of IL1ra and to measure the biological impact on 41 cytokines and chemokines. IL1ra penetrated into plasma and the brain extracellular fluid. PCA demonstrated a separation in cytokine profiles following IL1ra administration. A candidate cytokine from this analysis, Macrophage Derived Chemoattractant, was significantly lower in the rhIL1ra treated group. By using Partial Least Squares Discriminant Analysis (PLS) we have demonstrated that IL1ra administration increases chemokines which we speculate to be related to macrophage recruitment. This combination of randomised trial methodology and a thorough assessment of the downstream biological consequences has the capacity to increase our understanding of the complexity of neuro-inflammation following TBI.

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#### **COX-2 REGULATION DIFFERS BETWEEN SEXES IN THE SECONDARY INFLAMMATORY RESPONSE FOLLOWING EXPERIMENTAL PENETRATING FOCAL BRAIN INJURY IN RATS**

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Traumatic brain injury (TBI) is followed by secondary neuronal degeneration, largely dependent on an inflammatory response. This response is probably gender specific, since females are generally better protected than males in animal models and human epidemiological studies of TBI. The reasons are not fully known. We examined aspects of the inflammatory response following experimental TBI in male and female rats to explore possible gender differences. A penetrating brain injury model was used to produce focal TBI in male (n=10) and female (n=10) rats. After 24 h and 72 h the brains were removed and subjected to immunohistochemical analyses and in situ hybridization. Cox-2 mRNA was elevated in the perilesional area compared to the un-injured contralateral side, and significantly higher in males compared to females at 24 h and 72 h ( $p < 0.05$ ). iNOS mRNA and protein expression, GFAP, osteopontin, 3-nitrotyrosine and Fluoro Jade positive cells were upregulated in the perilesional area at 24 h with no difference between sexes. Our findings showed a gender difference in posttraumatic Cox-2 levels in Sprague-Dawley rats. It is possible that the sex specific trait of the secondary inflammatory response may be connected to prostaglandin regulation rather than oxidative stress also in clinical contexts. The difference did, however, not correlate with altered neuronal death at 24 h. Astrogliosis and microgliosis did not differ between sexes. This heterogeneity comprises a sex dependent quality. The identification of gender specific post-traumatic processes demonstrates a gender-specific metabolic quality, which may partially explain variances in outcome after TBI.

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#### **IMPACT OF WINTER SPORTS HELMETS IN SKIERS AND SNOWBOARDERS ON HEAD TRAUMA INCIDENCE AND SEVERITY**

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Head injuries are major cause of death and morbidity in skiing and snowboarding accidents. Despite the increased use of helmets it is perceived that the incidence and severity of snow sports related head injuries has not changed. Our aim was to examine the rate of helmet use, their efficiency as well as other possible predictors of outcomes in skiers/snowboarders treated for head injuries.

Retrospective review of all head trauma admissions due to Snowboarding/Skiing accidents to a Level 1 Trauma centre 2000/01–2010/11. Patients were called to enquire whether they wore a helmet at the time of the accident and for assessment of the outcome using the Glasgow Outcome Scale.

Of the 363 snowboarders (117) and skiers (246) helmet data and Glasgow Outcome Score could be obtained from 222 (72 snowboarders/150 skiers). 54% of snowboarders and 52% of skiers wore helmets. 33 patients received neurosurgical interventions: 18 invasive ICP monitoring, 12 craniotomy and 3 burr holes. 38% (8/21) of respondents who received various neurosurgical interventions wore helmets. We found no statistically significant correlation between wearing a helmet and outcome. Helmet use increased greatly from 2000–2011. The incidence of severe head injury did not decrease. A significant correlation with the severity of head trauma was found for skiing/snowboarding off the marked slope.

Patients that required any neurosurgical intervention were less often wearing a helmet compared to the entire cohort. We recommend that skiers and snowboarders wear helmets and place more emphasis on risk taking behaviours in snow sports in the prevention of head injuries.

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#### **PART 1–TIME COURSES OF NEUROINFLAMMATION, CORPUS CALLOSUM DEMYELINATION, SENSORIMOTOR DEFICITS, EDEMA AND LESION AFTER TRAUMATIC BRAIN INJURY BY CONTROLLED CORTICAL IMPACT IN MICE**

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Traumatic brain injury (TBI) results in neuroinflammation that may participate to white matter injury (WMI). The latter, evidenced by demyelination, is associated with neurological disorders. As only few data are available, the objective was to study their time-courses after TBI induced by controlled cortical impact (CCI) on adult male Swiss mice between 6 h and 12 w post-TBI.

Microglia activation was present from 24 h ( $558 \pm 51$ CD11b+ cells,  $P < 0.001$ ) up to 7d post-TBI ( $390 \pm 42$ CD11b+ cells,  $P < 0.001$ ), showing neuroinflammation. TBI induced a decrease of MBP protein expression in the ipsi- and contralateral corpus callosum at 7d (ipsi:  $1437 \pm 289$  AU,  $P < 0.01$ ; contra:  $1160 \pm 276$  AU,  $P < 0.01$ ) that persisted at 12 w (ipsi:  $885 \pm 459$  AU,  $P < 0.01$ ; contra:  $1141 \pm 476$  AU,  $P < 0.01$ ), demonstrating bilateral demyelination. Moreover, it promoted a bilateral increase of CNPase expression at 48 h (ipsi:  $273 \pm 41$  AU,  $P < 0.01$ ; contra:  $238 \pm 42$  AU,  $P < 0.01$ ) suggesting TBI-induced maturation of non-myelinating oligodendrocyte to myelinating oligodendrocyte with a decrease at 12 w. TBI increased brain water content at 6 h ( $81.6 \pm 0.2\%$ ,  $P < 0.001$ ) that persisted until 5d ( $81.4 \pm 0.4\%$ ,  $P < 0.01$ ), demonstrating edema. A cerebral lesion was visible at 24 h ( $9.4 \pm 2.5$  mm,<sup>3</sup>  $P < 0.001$ ) persisting up to 72 h ( $5.6 \pm 1.8$  mm,<sup>3</sup>  $P < 0.01$ ) that evolved toward a scar. Sensorimotor deficits were observed at 6 h (string test:  $0.97 \pm 0.43$ ,  $P < 0.05$ ; grip test:  $17.6 \pm 3.2$  s,  $P < 0.05$ ; adhesive removal time for contralateral front paw:  $46.7 \pm 13.0$  s,  $P < 0.01$ ) until 72 h (string test:

0.97±0.43, P<0.05) and at 12 w (string test: 0.33±0.13, P<0.05; grip test: 12.3±1.8 s, P<0.05).

Our data afford an overall view of neuroinflammation, demyelination and sensorimotor deficits in CCI model of TBI that could help to validate pharmacological strategy for preventing post-traumatic WMI.

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## **PART 2-LATE NEUROBEHAVIORAL DISORDERS AFTER TRAUMATIC BRAIN INJURY BY CONTROLLED CORTICAL IMPACT IN MICE**

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Traumatic brain injury (TBI) results in white matter injury, evidenced by demyelination, that is associated with late neurological disorders in traumatized patients. Our data, submitted in another INTS2014 abstract, showed *corpus callosum* demyelination after experimental TBI. So the objective was to study the time-courses of behavioral disorders after TBI by controlled cortical impact on Swiss mice at 2 and 4 weeks post-injury.

Sensorimotor performances were determined with the pole test and actimetry. The spatial learning and memory, strategy and adaptability behavior were assessed with Barnes maze, a dry-land one less anxiogenic than Morris Water Maze. Anxiety-like behavior was measured by marble-burying test. TBI did not modified locomotor activity nor the time to turn and descend from the pole, showing unmodified sensorimotor performances. The time for burying marbles were not modified after TBI, suggesting no anxiety-like disorders. At 2 weeks, spatial learning performances were not disturbed. In the retention test, all mice discriminated the target area. However injured mice persisted to explore the target hole without escape box, suggesting a stubbornness. At 4 weeks, the unadapted behavior of injured mice was also present when moving the escape box location. Moreover, injured mice did not discriminate the target area, suggesting a spatial retention memory disorder. TBI-induced unadapted behavior suggests a decision-making disorder that is associated with demyelination, as in traumatized patients. Behavioral evaluations will be continued at 2, 3 and 6 months that will afford an overall view of neurobehavioral disorders in TBI that could help to validate pharmacological strategy.

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## **NEW STRATEGIES FOR CHILDHOOD REHABILITATION FOLLOWING TRAUMATIC BRAIN INJURY**

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Acquired brain injuries (ABI) in childhood represent a major cause of morbidity and mortality during development. Pediatric traumatic brain injuries (TBI) constitute a major patient group. The goal of rehabilitation is to ameliorate the long-term outcome. In the Stockholm region neurorehabilitation following childhood ABI takes place at Astrid Lindgren Children's Hospital at the Karolinska University Hospital. In 2007 the neurorehabilitation program was reconstructed to include three integrated multi-disciplinary teams: the *hospital neurorehabilitation team*, the *school rehabilitation team* and the *outreach rehabilitation team*. The teams were established to offer individualized rehabilitation based on injury severity and/or neurological or cogni-

tive dysfunctions. As a consequence, we are able to offer long-term rehabilitation in a school environment over the course of 20 weeks following the rehabilitation in the hospital setting.

We hypothesize that the reconstructed neurorehabilitation care chain will improve long-term outcome following TBI in childhood.

Pediatric TBI patients enrolled in the rehabilitation program from 1998 to 2013, with at least 6 months interval since trauma, will receive a validated questionnaire (Mayo-Portland Adaptability Inventory-4) for long-term follow-up after TBI. Patients will be grouped according to injury related medical parameters and stratified with regard to when the patient was enrolled in the rehabilitation program: before or after the reconstruction.

It is of great importance to assess the impact of rehabilitation efforts on long-term outcome after childhood TBI.

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## **NOVEL MICRODIALYSIS METHOD TO STUDY THE ACUTE CYTOKINE RESPONSE TO DIFFUSE TRAUMATIC BRAIN INJURY IN THE RAT**

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In traumatic brain injury (TBI) experimental and clinical studies have demonstrated a highly complex neuroinflammatory response including production of inflammatory mediators and immune cell recruitment. In neurointensive care (NIC) patients with diffuse TBI microdialysis (MD) data has shown concentrations of many cytokines and chemokines to be higher than in plasma suggesting intracerebral production. However, there is a delay of several hours before patient arrival to the NIC unit when MD sampling can be started.

To fill this knowledge gap we have used a midline fluid percussion injury (mFPI) to induce a diffuse TBI<sup>1</sup> in rats (n=6) and immediately afterwards implanted dual 100kDa cut off CMA-12 MD-probes, surface modified with Pluronic® F-127 and perfused with artificial CSF with Dextran 500 to improve sampling performance.<sup>2</sup> Duplicate samples were analyzed using a multiplex MagPix kit for 27 different cytokines and chemokines. Sham-operated animals not subjected to mFPI served as controls (n=4).

Fifteen out of 27 biomarkers increased within the six hours of collection, with MIP-1 $\alpha$ , leptin, IL-1 $\alpha$  and IL-1 $\beta$  showing the greatest increase. Out of the 12 biomarkers that did not differ between injured and sham animals, 8 have previously been found to peak at later time points after TBI in patients and 4 showed no change.

This approach gives insight into the early cytokine and chemokine response to diffuse TBI and may be useful to fill the knowledge gap in NIC patient studies.

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## **ENERGY METABOLISM IN HUMAN TRAUMATIC BRAIN INJURY: 13C-LABELLED CEREBRAL MICRODIALYSIS AND HIGH-RESOLUTION NUCLEAR MAGNETIC RESONANCE STUDIES**

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Human brain chemistry is incompletely understood and better methodologies are needed. TBI causes metabolic derangement, with increased lactate production. Attention has largely focused on glycolysis, whereby glucose is converted to pyruvate, generating ATP and lactate, which is exported from cells and is proposed to act as an energy source by feeding into neurons' tricarboxylic acid (TCA) cycle. Also reportedly upregulated by TBI is the pentose phosphate pathway (PPP) that does not generate energy but produces molecules that are neuroprotective, antioxidant and reparative, in addition to lactate. We used a combination of microdialysis to deliver  $^{13}\text{C}$ -labelled substrates into brains of TBI patients and recover the  $^{13}\text{C}$ -labelled metabolites, and high-resolution  $^{13}\text{C}$  NMR analysis. Perfusion with 2- $^{13}\text{C}$  acetate or 3- $^{13}\text{C}$  lactate produced  $^{13}\text{C}$  signals for glutamine C4, C3 and C2, indicating TCA cycle operation. Perfusion with 1,2- $^{13}\text{C}_2$  glucose resulted in  $^{13}\text{C}$  signals as doublets for the C3 and C2 of lactate, indicating glycolysis as a major pathway. Small enrichment above natural abundance  $^{13}\text{C}$  was seen as a lactate C3 singlet representing PPP production of lactate. This was also apparent in normal brain but not in muscle. The injured brain can utilise lactate via the TCA cycle. Lactate production is mainly via glycolysis while PPP production of lactate is minor. This is the first direct comparison of glycolysis and PPP in human brain by  $^{13}\text{C}$ -labelled cerebral microdialysis. The technique will be extended to other substrates to further elucidate brain chemistry.

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#### MILD TRAUMATIC BRAIN INJURY: CHANGES IN THE SEROTONERGIC, NORADRENERGIC AND GALANIN SYSTEMS, REFERENCE TO PTSD

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A new array of diseases is being associated with mild blast traumatic brain injury (mbTBI). There is no acute symptomatology or structural damage to the brain but months to years post injury there can be emotional and cognitive disturbances. Extreme stress without physical injury frequently results in post-traumatic stress disorder (PTSD). PTSD is characterised by anxiety and depression, an inability to regulate emotion and similar symptoms are also observed in mbTBI. The serotonergic and noradrenergic system found in the dorsal raphe (DRN) and locus coeruleus (LC) respectively, are involved in mood regulation and the neuropeptide galanin is co-expressed in these neurones. In order to identify the mechanism of mood disturbances in mbTBI, in this study, we analysed the temporal pattern of injury-induced changes in the above neurotransmitter systems in the select brain regions using an established model of mbTBI. We found that immediately post exposure (2hrs) the levels of both tyrosine hydroxylase (the biosynthetic enzyme for noradrenaline) and galanin are upregulated in the LC. In the DRN, tryptophan hydroxylase (the biosynthetic enzyme of serotonin) is slightly elevated immediately post exposure but returned to sham levels by 1 day. While galanin levels gradually increased and remained upregulated at 7 days post trauma. The observed temporal pattern of changes in the various neurotransmitter levels reveal the brain region's differential sensitivity to injury and provides new insight into the mechanism of mood disturbances in mbTBI.

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#### THE ATTENUATED RENAL S100B ELIMINATION FOLLOWING NEUROTRAUMA SUGGESTS A PHYSIOLOGICAL CONSERVATION SYSTEM FOR NEUROTROPHIC PROTEINS

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The neurotrophic glial protein S100B has been promoted as a marker of brain injury for more than a decade. However, no data exist about the renal elimination of S100B. Furthermore, evidence suggests that extracranial sources may contribute to S100B levels. In the present study we aim investigate the S100B elimination from serum to urine in a larger cohort. In 154 subsequent patients treated on the operative intensive care unit, we measured S100B and creatinine in serum and urine. Blood samples were taken daily, immediately centrifuged for 10 min at 1.300xG and 4°C and stored at a temperature of -80°C until the assays were performed. Analysis was performed with commercially available kits on automated immunoanalyzers (LIAISON® Sangtec®100 by chemiluminescence immunoassay, Diasorin). The sensitivity of the assay was 0.02 ng/ml. Statistical analysis was performed with SPSS, and  $p < 0.05$  was accepted as significant. The mean age of the patients was 66.1 (17 to 95) years, 74 were male and 80 female. Patients were included following procedures involving the central nervous system (CNS,  $n=49$ ), surgical procedures without intracranial injury (Surgery,  $n=99$ ), and for exclusively conservative treatment (ICU,  $n=9$ ). Group comparison by a rank sum test revealed that S100B was significantly increased following surgical procedures (CNS: serum  $0.46 \pm 0.12$  ng/ml, urine  $0.04 \pm 0.01$  ng/ml; Surgery:  $0.41 \pm 0.06$  ng/ml, urine  $0.07 \pm 0.03$  ng/ml) as compared to conservative treatment (ICU: serum  $0.26 \pm 0.06$  ng/ml, urine  $0.01 \pm 0.00$  ng/ml). The renal function as estimated by the creatinine clearance did not affect the S100B elimination into urine. Interestingly, the renal S100B elimination ( $\text{S100B}_{\text{urine}}/\text{S100B}_{\text{serum}}$ ) normalized for the creatinine clearance was significantly attenuated following neurosurgical procedures. The 10.5 KD monomeric protein S100B is not completely reabsorbed in the kidneys following an increased release into serum and urine measurements may thus offer an alternative source to screen for elevated S100B levels. Major surgery even without concomitant brain injury does affect S100B serum levels significantly. The attenuated renal S100B elimination following CNS injury suggests a physiological conservation system for neurotrophic proteins.

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#### TREATMENT WITH COMBINED EPO AND BDNF SUPPORTS HIPPOCAMPAL NEUROGENESIS AND IMPROVES FUNCTIONAL OUTCOME FOLLOWING FOCAL TBI

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Neurogenesis in the hippocampal dentate gyrus (DG) and subventricular zone (SVZ) is stimulated by traumatic brain injury

(TBI), and provides a compelling target for novel therapies to improve recovery following trauma. In this study, we attempted to augment specific stages of neurogenesis in a closed head injury (CHI) model of unilateral focal TBI, by treatment with erythropoietin (EPO), brain-derived neurotrophic factor (BDNF), or EPO+BDNF. Adult male C57BL/6 mice were subjected to CHI or sham-operation. All mice received BrdU (150 mg/kg x2 daily, days 1–4 post-CHI) to label proliferating cells, and were treated with EPO (days 0–11 post-CHI) and/or BDNF (days 7–11 post-CHI), or vehicle. Following twice-weekly functional assessment, brains were collected at 1, 2 and 6 weeks post-CHI (n=6–8). Treatment with EPO+BDNF improved behavioral (P<0.001) and motor (P=0.002) outcomes of CHI mice compared to individual factors and vehicle controls. Numbers of BrdU+ cells, DCX+ neuroblasts, and new mature BrdU/NeuN+ neurons were not affected by any treatment post-CHI in the SVZ or pericontusional cortex. However, in the DG, while no treatment affected proliferation at 1 week, EPO+BDNF increased the number of DCX+ neuroblasts at 2 weeks post-CHI by 50% (P<0.05 vs. vehicle), and BrdU/NeuN+ neurons at 6 weeks by 60% (P<0.05). These data demonstrate that a combination of EPO and BDNF, rather than either factor alone, is necessary to support post-traumatic neurogenesis.

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#### CHARACTERISATION OF A NOVEL MODEL OF CHRONIC TRAUMATIC ENCEPHALOPATHY

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Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease associated with exposure to repetitive mild traumatic brain injury (rmTBI). It is characterised by accumulation of phosphorylated tau and long-term cognitive deficits. Currently a number of *in vivo* models of rmTBI are in development, however there are concerns with their ability to replicate the human condition. This study aimed to characterise a model of rmTBI that accurately portrays the short and long-term clinical and histopathological features of clinical CTE. Forty-one male Sprague-Dawley rats were randomly subjected to 0, 1 or 3 mTBIs, spaced 5 days apart, induced by dropping a 450 g weight from a height of 1 m onto a steel disc attached to the skull. Motor and cognitive outcomes were assessed in the 12 weeks post-injury, with histopathology conducted in a subgroup of animals 24 hrs post-injury. 3 mTBI animals showed mild learning deficits as reflected by increased escape latency on the Barnes Maze (p<0.001) and progressive decline in Y Maze performance, with associated decreased exploratory behaviour on the Open Field (p<0.05) reflecting anxiety-like behaviours. Notably, no motor deficits were recorded on the rotarod at any timepoint following injury. 3 mTBI animals also showed increased tau phosphorylation (p<0.01), astrocyte reactivity (p<0.05) and microglial activation (p<0.001) within the cortex, without overt tissue loss. The presence of persistent cognitive deficits associated with tau phosphorylation, in the absence of tissue loss or motor deficits, is consistent with descriptions of clinical CTE; therefore this may represent a clinically relevant model to further explore the pathophysiology of CTE.

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#### MEASUREMENT OF BIOMARKERS OF BRAIN DAMAGE IN TBI PATIENTS RECRUITED IN THE EPO-TBI RANDOMISED CLINICAL TRIAL

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A key problem in the management of traumatic brain injury (TBI) is the lack of diagnostic measures to elucidate severity of injury, detect occurrence of secondary insults, and predict long-term outcome. Serum biomarkers could provide valuable information in both an acute and a subacute setting, and may assist in the timing of interventions. By measuring biomarker levels over a time-course, it is possible to have a direct measure of the ongoing injury state of the brain, and uniquely, the efficacy of drug treatment in clinical trial. Erythropoietin (EPO) has been posited as a neuroprotective agent capable of attenuating secondary pathology after TBI, and showing promising efficacy in other CNS pathologies such as stroke. EPO-TBI is a prospective, multicentre, double-blind, randomised controlled clinical trial to assess the efficacy of EPO in patients with moderate to severe TBI. In this study, a 6 day time-course of serum samples from 56 patients enrolled in the EPO-TBI trial will be examined for specific biomarkers of neuronal, axonal and astrocytic damage (S100 $\beta$  [neuronal], UCHL-1 [neuronal], neurofilament 200 kDa heavy chain [NF-200; axonal], and glial acidic fibrillary protein [GFAP; astrocytic]). Biomarker levels will be correlated with the Extended Glasgow Outcome Scale (GOSE) 6 months post-injury. We hypothesise that the production of biomarkers will be inversely correlated with the patients' GOSE scores, and a neuroprotective effect of EPO will be associated with a decrease in serum biomarker concentrations. Such a finding could allow biomarkers to be easily translated into clinical practice for the management and monitoring of TBI patients.

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#### EVALUATING APP96-110, A PEPTIDE DERIVED FROM THE AMYLOID PRECURSOR PROTEIN, AS A NOVEL THERAPEUTIC AGENT AGAINST TRAUMATIC BRAIN INJURY

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Traumatic Brain Injury (TBI) often results in considerable neurological damage which occurs through a cascade of deleterious physiological events over subsequent days. To date, no effective drugs exist to prevent this. The amyloid precursor protein (APP) and APP96-110 (a peptide corresponding to APP residues 96-110) have been identified as offering neuroprotective activity following TBI. This study examined the efficacy of intravenous administration of a single dose of 2.5  $\mu$ M, 25  $\mu$ M and

250  $\mu$ M APP96-110 at 30 minutes following moderate-severe diffuse impact acceleration injury, to identify an optimal dose. Rats were assessed for motor deficits using the rotarod and cognitive deficits using the Y maze. Brains were perfused fixed at either 24 hours or 7 days post TBI, and examined histologically for axonal injury (AI), reactive astrogliosis (RA) and microglial activation (MA). Rats treated with 25  $\mu$ M APP96-110 showed an improvement in both motor and cognitive outcome, an effect not seen with either the 2.5  $\mu$ M or 250  $\mu$ M doses. This was accompanied by a reduction in AI in the corpus callosum and MA in both the cortex and corpus callosum at 7 days. Interestingly, the 25  $\mu$ M treatment elicited a peak in RA that exceeded vehicle levels at 24 hours post-injury in the cortex and corpus callosum, but was followed by a reduction to near-sham level by 7 days, suggesting that early RA may be a beneficial. This study identifies APP96-110 as a novel therapeutic option following moderate-severe TBI given its ability to attenuate neurological deficits, AI and neuroinflammation.

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#### **HYPOTHERMIA IN TBI FOR CONTROL OF INTRACRANIAL HYPERTENSION: STANDALONE THERAPEUTIC OPTION OR ADJUNCT? (DATA FROM THE EURO THERM3235 TRIAL IN INDIA)**

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Hypothermia reduces intracranial pressure, neuroprotectant and reverses key destructive mechanisms postTBI. Present study tests titrated hypothermia for ICP reduction after TBI. Hypothesis is that therapeutic hypothermia will reduce morbidity/mortality compared to those receiving standard care. This prospective RCT examines effects of hypothermia (32–35°C) on raised ICP after TBI. Adults with primary closed TBI with raised ICP > 20 mmHg for  $\geq$  5 minutes after first line treatments and with no obvious reversible cause are randomized to either hypothermia or normothermia group. Hypothermia initiated with refrigerated 0.9% saline/maintained using surface cooling blankets. Depth of hypothermia guided by ICP with higher pressure level warranting cooler target temperature. Therapeutic hypothermia is maintained for > 48 hours in treatment group but if there is inadequate response to hypothermia patients are taken up for decompressive craniectomy. 28 patients (13 in hypothermia group, 15 in control group), mean age was 35.3 yrs, mean IC was 22.6 and 24 mm Hg in hypothermia and control group respectively. CT Marshall grade observed in 18/28 cases. Three patients in each group required decompressive craniectomy and two patients in each developed pneumonia. There were no coagulation abnormalities in either group. Mean duration of ICU/hospital stay was 10.2 days/9.5 days and 19.5/18.6 days in normothermia/hypothermia group respectively. Admission was longer in control group (p:NS). Hypothermia is safe as adjunct to other modalities for controlling ICP in severe TBI. It is not associated with a longer duration of ICU/ hospital stay when compared with controls.

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#### **BRAIN EDEMA AND SWELLING PATHOGENESIS AND OPTIMAL PHARMACOTHERAPY SUBSTANTIATION IN CASE OF SEVERE CRANIOCEREBRAL TRAUMA**

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The research is devoted to clarification of pathogenesis of brain edema and swelling in dynamics of initial period of traumatic disease among the patients with severe craniocerebral trauma. The diagnostics of brain edema and swelling is improved and prognosis of trauma outcome and cerebral death is elaborated according to clinical, morphological, instrumental, pathophysiological and biochemical research methods in the dynamics of brain traumatic disease. Discovered morphological changes in the brain under the severe craniocerebral trauma in clinical ways determine the development of post-traumatic brain edema and swelling. Its manifestation depends on the grade of brain tissue damage, hemato-encephalitic barrier permeability, activation of lipid peroxidation, blood and liquid circulation damage. The method of hydration estimation of components of inner cerebral content is elaborated by us by means of computed tomography, that allows us to estimate selectively the degree of brain white and grey substance manifestation edema and swelling under the severe craniocerebral trauma. White substance and grey substance edema-swelling is developed in equal proportions in case of intracranial hematomas and brain contusion development. Within the period of 5 days in the development of brain edema and swelling there's a high pathogenesis significance of lipid peroxidation products (LPP), hypernatremia, osmotic pressure changes. These indices may be a kind of prognostic criteria of craniocerebral trauma outcome. The decrease in lethality is 19% in case of citicoline (Ceraxon) and acetogevin administration.

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#### **NEW MICRODIALYSIS METHOD FOR PROTEIN BIOMARKER SAMPLING IN THE NEUROINTENSIVE CARE SETTING**

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Cerebral microdialysis (MD) is currently well established for sampling of low molecular weight (MW) biomarkers of energy metabolic perturbation and cellular distress in the neurointensive care (NIC) setting. There is now a growing interest in MD for sampling of protein biomarkers of secondary injury mechanisms in traumatic brain injury (TBI). Published data point to inherent problems with this methodology including protein adhesion, protein-protein interaction and biofouling, potentially leading to unstable MD catheter performance, i.e., fluid recovery (FR) and extraction efficiency (EE). Our recent results suggest that a surface modified MD catheter in combination with high MW colloid addition to the perfusate leads to a more robust *in vitro* performance with less protein adsorption, optimized FR and improved EE.

In the present work we tested the new MD method in a porcine brain death model. Two adjacent MD catheters (71 High Cut-Off Brain Microdialysis Catheter, M Dialysis AB, Stockholm, Sweden), one naïve and one surface modified by Pluronic F-127, inserted in the frontal cortex, were perfused with mock CSF with 3% Dextran 500 addition. Naïve catheters showed an unstable FR sensitive to ICP changes which was stabilized by surface modification. Routine low MW biomarkers analyzed with the ISCUflex showed a similar and expected response to the step-wise ICP elevation for both catheters. MD samples were analyzed by iTRAQ + nanoflow LC-MS/MS identifying 17 proteins in all 7 pigs with  $\geq$ 95% confidence. These proteins showed a more homogenous response to the ICP intervention in surface modified MD catheters with an improved EE for most of the proteins. The new MD method appears to be a promising tool for more accurate protein biomarker sampling in the NIC setting.

### EFFECTS OF HYDROSTATIC CEREBROSPINAL FLUID PRESSURE IN DIFFERENT BODY POSITIONS ON CEREBROSPINAL FLUID MOVEMENT

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According to classical hypothesis of cerebrospinal fluid (CSF) physiology, it is clear that the pressure gradient which enables the unidirectional CSF circulation should include the following: the highest pressure value has to be at the site of the CSF secretion inside the ventricles, it should be somewhat lower in the cisterna magna and around the subarachnoid space, and the lowest at the site where CSF is passively absorbed. However, unknown factors determine CSF pressure inside craniospinal space during body position changes. In this paper a new CSF pressure regulation hypothesis is proposed. According to this hypothesis, the CSF pressure depends on the laws of fluid mechanics and on the anatomical characteristics inside the cranial and spinal space, and not, as is today generally believed, on CSF secretion, circulation and absorption. The volume and pressure changes in the newly developed CSF model, which by its anatomical dimensions and basic biophysical features imitates the craniospinal system in cats, are compared to those obtained on cats with and without the blockade of craniospinal communication in different body positions. During verticalization, a permanent appearance of negative CSF pressure inside the cranium without changes in the blood and CSF volume was observed. CSF pressure gradients change depending on the body position, but those gradients do not enable unidirectional CSF circulation from the hypothetical site of secretion to the site of absorption in any of them. Thus, our results indicate the existence of new physiological/pathophysiological correlations between CSF and blood inside the craniospinal space.

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### EFFECTS OF OSMOTIC AND HYDROSTATIC PRESSURE CHANGES ON CEREBROSPINAL FLUID VOLUME REGULATION

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It is not known how hydrostatic and osmotic changes in cerebral blood and CSF affect the CSF volume and pressure. In order to examine this, we used three different models on cats (ventriculo-cisternal perfusion, free drainage model, and ventriculo-aqueductal perfusion). Using the model of ventriculo-aqueductal perfusion, which has been developed in our laboratory, it has been noticed that there is no net formation of CSF volume inside the isolated ventricles, even during the period of

several hours. Namely, during the perfusion of ventricular system by isoosmolar mock CSF, the same volume that has been infused was also collected. However, an increase of the perfusate osmolarity instantly leads to an increase of the output volume, and even greater output volume is collected if the same hyperosmolar mock CSF is used to perform a ventriculo-cisternal perfusion (perfusion across the greater/wider CSF system surface). It was noticed on the models of spontaneous CSF leakage that an increase of the blood osmolarity decreases the output CSF volume, and that a decrease of blood osmolarity increases the output CSF volume, together with a decrease in cerebral metabolites concentration, such as 5-HIAA and HVA. These results clearly indicate that CSF volume inside the isolated ventricles, as well as inside the entire CSF system, is under the influence of/controlled by osmotic forces that exist inside the CSF system and CNS microvessels.

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### TBI IN AN AGING POPULATION WITH CO-MORBIDITIES AND THEIR THERAPIES

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The Trauma Audit and Research Network (TARN) is the largest European trauma and TBI registry. It has been collecting data and auditing trauma care since 1989 in English, Welsh and European trauma receiving hospitals. It now contains detailed records of 80,000 TBI victims. In 2000 only 20% of all TBI victims were over 65 years but the proportion is now >30% in 2013. During my presentation I will highlight the findings of TARN data to demonstrate that older TBI victims differ from younger adults in terms of

- (i) A higher prevalence of low energy falls and pre-existing diseases.
- (ii) A higher presenting Glasgow Coma Score but worse outcome for any given TBI in low energy falls, particularly in patients with co-morbidity.
- (iii) Types of co-morbidity that increase exponentially in prevalence with ageing, and those that reduce with age.
- (iv) Some of the management challenges that this increasingly important group present to clinicians with particular reference to anti-coagulation, and likely benefit (or/not) from specialist care

The presentation will utilise published and unpublished TARN analyses and refer to other published work where relevant, together with the latest iteration of NICE Head Injury Guidance (2014).

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### MULTI-TARGET, DUAL-ELECTRODE DEEP BRAIN STIMULATION OF THE THALAMUS AND SUBTHALAMIC AREA FOR TREATMENT OF HOLMES' TREMOR AFTER BRAIN INJURY

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Post-traumatic tremor is the most common movement disorder that results from severe brain injury. It can occur within a month or years after the actual trauma and can include resting, postural, kinetic, and intention tremor. The combination of resting, postural, and intention tremor is often referred to as Holmes' tremor (HT). The tremor is defined by the following criteria proposed by the Movement Disorder Society: (1) the presence of both resting and intentional tremor, (2) a slow frequency, usually below 4.5 Hz, and (3) a variable delay between lesion occurrence and first appearance of the tremor. Deep brain stimulation (DBS) therapy for essential tremor and Parkinsonian tremor has been quite successful. On the other hand, outcomes of surgical treatment for HT have been disappointing. The authors applied two DBS electrodes (one at Vo/Vim and the other at the subthalamic area) in four HT patients including a case of post-traumatic tremor. Tremor at rest and intention tremor in all patients were improved significantly. Stimulation with both electrodes provided greater effects on tremor than stimulation with one electrode. The presence of tremor at rest and intentional tremor suggests the combined destruction of the pallidothalamic and cerebellothalamic pathways. Therefore, a larger stimulation area may be required in cases of HT.

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#### **INDICATORS OF QUANTITATIVE EEG CAN BE USED TO PREDICT RECOVERY OF CONSCIOUSNESS IN ACUTE CEREBRAL INSUFFICIENCY OF VARIOUS ORIGINS**

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103 patients (aged from 28 to 67 years) with severe traumatic brain injury (STBI) - 55 patients, with acute stroke (AS) - 48 patients - we examined. The depth of coma was estimated using the Glasgow Coma Scale (GCS). EEG recordings using neurophysiological complex with an Medico electroencephalograph were performed.

Levels of 1st integral coefficient ( $(\delta + \theta + \beta_1) / (\alpha + \beta_2)$ ) in 32 patients with acute cerebral insufficiency was fixed within Me ( $\pm 95\%$ ) = 4.36 (3.55 - 5.04) (1 group) and were higher ( $p \leq 0,05$ ) parameters in 51 patients (Me ( $\pm 95\%$ ) = 3.23 (3,11-3,6)) (2 group). The complex of intensive therapy included drug Gliatilin a daily dose of 1000–2000 mg. By the 7th day of treatment in group 1 score GCS increased to Me ( $\pm 95\%$ ) = 12 (11–14), but was lower ( $p \leq 0,05$ ), than in group 2-Me ( $\pm 95\%$ ) = 14 (13–15).

The values of the 1st integral coefficient of less than 3,5 corresponded to higher levels of AFM in the range of 0–1 Hz, 4–5 Hz and 6–8 Hz, associated with functional viability neuroglial, adrenergic and cholinergic activity of CNS. Reduction in neurological deficit GCS in 1st group study took place more slowly than in 2nd group.

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#### **BIOMARKERS OF MILD TBI**

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Minor head injury represents 95% of all head injuries. Management involves in-hospital observation and/or computed tomography (CT). In-hospital observation is relatively expensive. Risk of deterioration in patients presented as GCS 15 and an early negative CT scan is low,

approximately 1/21.700, but CT is often impractical. Between 37–51% of the TBI patients are alcohol intoxicated, with a subsequent risk of aspiration and poor quality CT scans due to uncontrolled movements. CT involves potentially harmful ionizing radiation. Furthermore, only a limited number of patients with mild head injury have intracranial injuries and even fewer require neurosurgical intervention. The astrocytic protein S100B has been suggested to detect intracranial pathology, and the risk of a negative S100B sample despite positive findings on CT is regarded low. A total of 6 patients out of 2.466 (0.26%) included in a review study showed low S100B serum levels despite positive CT scans but only 1 of these patients (0.04%) had a clinically relevant CT finding. Approximately one third of performed CT scans on patients suffering from MHI have been regarded possible to omit in a defined patient group. The role of the biomarker S100B in the assessment of patients suffering from mild head injury is discussed.

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#### **THE NEUROPROTECTIVE THERAPEUTIC WINDOWS FOR INHIBITING POST-TBI SECONDARY INJURY ARE SIMILAR IN ANIMALS AND HUMANS**

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Over the last three decades there has been intense effort to discover pharmacological or hypothermic neuroprotective therapies to limit secondary injury after traumatic brain injury (TBI) in animal (mostly rodent) models and to translate those into improved survival and neurological outcome in large phase II and III clinical trials. However, despite often impressive results in the animal models none of the trials have revealed clinical efficacy in terms of improving the primary outcome measure. Many plausible reasons have been identified for the failure to achieve successful translation from mouse and rat TBI models to man (Narayan et al., *J. Neurotrauma* 19:503-557, 2002). One of the contributors has been a lack of comparison of the time course of the targeted secondary injury mechanism in animals and man. It has long been assumed that since mice and rats have higher metabolic rates than humans, the evolution of post-TBI secondary injury is likely to be faster in the animal models compared to humans. Accordingly, TBI clinical trials to date have been designed with a time to treatment in excess of what was predicted for the therapeutic efficacy window predicted from animal data. In contrast, recent biomarker results will be presented comparing the time courses of oxidative, mitochondrial and proteolytic damage in animals versus man suggesting that the progression of secondary injury mechanisms, and accordingly the neuroprotective efficacy window, may not be significantly different between rodent and the human. If true, then future clinical trials need to be designed such that the demonstrated preclinical therapeutic efficacy window is taken more literally.

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#### **PRE-CLINICAL DISCOVERY SESSION PRO AND CON**

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In spite of numerous pre-clinical studies, which taught us about the pathophysiology of TBI, and novel promising therapeutic agents which were tested in clinical trials, careful perusal of the results of the human studies shows that, to date, the attempts to translate from the bench to the clinic failed. Several barriers may account for this failure to crossing the

translational gap. These include either using inappropriate animal models, mainly the lack of pre-clinical studies with large animals, or lack of long-term monitoring of the clinically relevant physiological parameters and the functional and cognitive outcomes in the small animal models. However, the failure to successfully translate therapeutic modalities into human TBI may not result only from limitations of the animal models or the lack of adequate monitoring. Of no less importance is the lack of proper translation of the timing or the dosing for treatment. As an example of the failure to achieve a successful translation probably due to a poor clinical study design, this presentation will review how the NMDA antagonists, that were shown to be beneficial in many experimental models of TBI, failed in the clinical application.

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### ALCOHOL AND LONG-TERM MORTALITY FOLLOWING SEVERE TRAUMATIC BRAIN INJURY

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Positive blood alcohol concentrations (BAC) have been associated with a lower risk of short-term mortality in TBI patients. However, little is known about the relationship between BAC and long-term mortality, or the influence of chronic alcohol abuse (CAA). A retrospective analysis of all TBI patients admitted to a neurosurgical ICU during a four-year period (2009–2012), who had BAC measured on admission, was conducted. Patients were categorized as: no (0.0‰), low (<2.3‰) and high ( $\geq 2.3$ ‰) BAC with or without CAA. Multivariate logistic regression analysis was used to assess the independent relationship between BAC, CAA and 6-month mortality, adjusting for markers of injury severity using the IMPACT (International Mission for Prognosis and Analysis of Clinical Trials in TBI) prognostic model, independent of GCS variables as BAC is known to impede with these. Of 400 patients included; 25% were classified as no, 34% as low and 41% as high BAC; 47% had a history of CAA. In univariate analysis, patients with CAA had a significantly lower mortality compared to those with no CAA (30%, 17%,  $p=0.003$ ) and trend towards a lower mortality in patients with low BAC compared to high and no BAC was noted (18%, 30%, 24%,  $p=0.080$ ). After adjusting for markers of injury severity, CAA (OR 2.07, 95% CI 1.16-3.70) and low BAC (OR 0.44, 95% CI 0.21-0.96) showed a significant association with 6-month mortality. Our results show that low BAC significantly decreases while a history of CAA significantly increases the risk of six-month mortality following TBI.

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### A NOVEL MOUSE MODEL OF PENETRATING TBI

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A penetrating traumatic brain injury (pTBI) occurs when an object hits the head with sufficient force to penetrate the skin, skull, and meninges, and inflict injury directly to the brain parenchyma. This type of injury has been notoriously difficult to model in small laboratory animals. We recently developed a rat model for pTBI (Plantman et. al. *J Neurotrauma* 2012 29:1219-32). The present study describes the adaptation of this model for use with mice. Our novel pTBI model is based on a modified air rifle that accelerates a pellet,

which in turn hits a small probe that then causes the injury to the animal's brain. The speed and depth of penetration is controlled by adjusting the loading pressure in the air-rifle. The present study includes a technical characterization of issues such as the relationship between loading pressure and depth of penetration. Further, we have characterized the tissue destruction, including increasing cavity formation, neuronal degeneration, blood-brain barrier defects, and gliosis. We also evaluated basic outcome measures (survival, weight gain and performance on rotarod). We expect this model will prove useful in our efforts to unravel the biological events underlying injury and regeneration after pTBI.

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### THE STOCKHOLM EXPERIENCE OF INTRASPINAL PLEXUS REPAIR

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There is a 20 years' experience of intraspinal repair of plexus injuries in Stockholm. This surgery has been performed in obstetrical lesions, in children and adults with traumatic brachial plexus injuries as well as in lumbosacral plexus lesions. An obvious lesson from this experience is the narrow time window for the surgery to be successful. Expected outcome if surgery is performed within 1 month after trauma is a useful shoulder and elbow function with pain alleviation. The most successful case was a preadolescent boy who after surgery had return of useful arm as well as hand function together with elimination of serious pain. The worst case had a late operation that did not help in functional restoration or pain alleviation. Obstetrical cases had no benefit from late intraspinal repair. Repair of root ruptures in lumbosacral plexus injury has led to useful functional return in proximal hip and leg muscles.

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### CHITOSAN-BASED BIOMATERIALS FOR CLOSURE OF DURAL DEFECTS

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Closure of dural defects is a necessity after neurosurgical procedures to prevent cerebrospinal fluid leakage and to reduce the risk of perioperative infections. Reconstruction of the dura mater with endogenous material becomes very common. However, harvesting of periosteum or fascia lata may require extended surgical approach, additional incisions and time intensive suturing. A wide range of biomaterials, both of natural and synthetic origin, are being investigated for potential applications in dural defect repair.

Biocompatibility, nontoxicity and lack of antigenic activity represent the key determining criteria to create new biomaterials. Antibacterial properties and ability to stimulate regenerative processes are the desirable properties of new biomaterials. Chitosan is one of the high-promising bases for it.

Thus, the aim of our research is to create a biocompatible and non-toxic chitosan-based material to repair dural defects. Besides, we evaluate its biological properties.

The artificial membrane was prepared in 3% chitosan solution (molecular weight – 200 kDa, degree of deacetylation – 80 – 90%) with addition of chitin in ration 50:50. The film was made of it; then the

film was treated with 5% NaOH and glycerin solution to improve elasticity. We examined membranes for certain characteristics: tensile strength, rate of biodegradation and biocompatibility.

Our results appeared to confirm high strength properties that were slightly different from those of the native dura. Regarding to the rate of biodegradation this material can be applied as a permanent material to repair dural defects.

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#### ACUTE ANTAGONISM OF THE COMPLEMENT ANAPHYLATOXIN RECEPTOR C5aR IMPROVES THE OUTCOME FROM EXPERIMENTAL SPINAL CORD INJURY

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We investigated the role of the complement activation fragment C5a in secondary immunopathology following contusive spinal cord injury (SCI). Using *C5ar<sup>-/-</sup>* mice, which lack the G protein-coupled receptor for C5a, we show that C5a signaling during the acute phase of SCI is injurious as *C5ar<sup>-/-</sup>* mice displayed significantly improved recovery at 7 days post-SCI. Acute pharmacological blockade of C5aR with the selective antagonist PMX205 (1 mg/kg; day 0–7) similarly improved outcomes for up to at least 35 days post-SCI. Intriguingly, the early signs of improved recovery in *C5ar<sup>-/-</sup>* mice deteriorated in the post-acute phase (day 14 onward) and absence of C5aR ultimately led to worsened SCI outcomes, i.e., poorer functional recovery, greater lesion volumes and reduced white matter sparing, compared to wild type (WT) mice. Continuous treatment of WT mice with the C5aR antagonist PMX205 recapitulated the *C5ar<sup>-/-</sup>* phenotype, thereby confirming the dual nature of C5a signaling and indicating that C5aR serves a more reparative role in the post-acute phase of SCI. Experiments in bone marrow chimeric mice revealed that the dual and opposing roles of C5aR in SCI were mostly mediated via cells that are resident to the CNS and not infiltrating leukocytes. Additional *in vivo* and *in vitro* experiments showed that C5a signaling is required for astrocyte proliferation, suggesting that impaired glial scar formation may underpin the ultimately worsened recovery of *C5ar<sup>-/-</sup>* mice from SCI. Collectively, these findings highlight the complexity of the inflammatory response to SCI and stress the importance of optimizing the timing of therapeutic interventions.

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#### PIVOTAL ROLE OF VASOPRESSIN V1A RECEPTORS FOR BRAIN EDEMA FORMATION, SECONDARY BRAIN DAMAGE AND REGULATION OF CEREBRAL AQUAPORINS FOLLOWING TRAUMATIC BRAIN INJURY IN MICE

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Brain edema formation is well known to result in secondary brain damage and unfavorable outcome following TBI. Aquaporins, ubiquitous and highly specific water channels, mediate post-traumatic brain edema formation, but the mechanisms of their cerebral regulation remain still unclear. The current study was carried out to elucidate whether arginine-vasopressin V<sub>1a</sub> receptors mediate post-traumatic brain edema formation through regulation of cerebral AQP. WT and V<sub>1a</sub><sup>-/-</sup> mice were subjected to CCI (8 m/s, 1 mm). Brain water content (baseline/ 24 h), secondary contusion volume (15 min/ 24 h), neurological outcome, body weight and mortality were observed over 7 days. AQP1 and AQP4 mRNA were quantified by RT-PCR (baseline/ 24 h). AQP1 and AQP4 were localized and quantified by immunohistochemistry (+/- NeuN, GFAP) (baseline, 15 min, 1, 3, 12 or 24 h). AQP4 mRNA was constitutively expressed in astrocytes. AQP1 mRNA was up-regulated in neurons 24 h after trauma. V<sub>1a</sub> receptor-deficient mice had less post-traumatic brain water content, reduced secondary contusion volume, better neurological outcome and reduced weight-loss following TBI. Both AQP1 and AQP4 were regulated in a V<sub>1a</sub> receptor dependent manner after TBI. AQP1 immunoreactivity increased in the contralateral hemisphere, while AQP4 was mainly up-regulated in the traumatized brain. V<sub>1a</sub> receptor deficiency decreases post-traumatic brain edema and secondary brain damage. AQP1 was found on cortical neurons. Up-regulation of AQP1 and AQP4 is mediated by V<sub>1a</sub> receptors leading to post-traumatic brain edema formation. Thus, V<sub>1a</sub> receptors may represent novel therapeutic targets for the treatment of aquaporin-mediated brain edema formation.

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#### TREATMENT WITH ETIFOXINE IMPROVES FUNCTIONAL RECOVERY FOLLOWING TRAUMATIC BRAIN INJURY IN RATS

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*Biocodex*

Etifoxine (EFX) is a non benzodiazepine compound exhibiting anxiolytic properties in the treatment of adjustment disorders with anxiety in humans<sup>1</sup>. An enhancement of GABAergic neurotransmission underlies its anxiolytic profile directly after binding on the GABA<sub>A</sub> receptor or indirectly, involving the activation of translocator protein 18 kDa (TSPO) that leads to an increase in the synthesis of neuroactive steroids with GABAergic properties<sup>2</sup>. Considering that the GABAergic system is involved in the pathophysiology of traumatic brain injury (TBI), and also that TSPO is upregulated in response to injury<sup>3</sup>, we evaluated the effects of EFX on recovery of sensorimotor function in a rat model with mild TBI. Male Sprague-Dawley rats were treated with etifoxine (EFX; 50 mg/kg, i.p.) or saline (5 mL/kg) and received contusion injuries or sham injuries centered directly lateral to bregma over the left sensorimotor cortex. EFX treatment was administered 30 min following injury and every day during 7 days. Rats were tested on a variety of tests to measure sensorimotor performance (bilateral tactile adhesive removal test, limb-use asymmetry test and tapered beam walk test). Brain-injured rats exhibited significant sensorimotor function deficits compared to sham-injured rats. After two days of EFX treatment, behavioral impairments observed on the bilateral tactile adhesive removal test, the limb-use asymmetry test, and the tapered beam walk test were significantly reduced. The present results showed that the GABAergic compound EFX improved functional recovery following mild TBI in rats. These

current findings suggest that etifoxine may have therapeutic potential for the treatment of TBI.

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### **INTRACRANIAL HYPERTENSION MODEL IN PIGS: ASSESSMENT WITH TRANSCRANIAL DOPPLER AND INTRACRANIAL PRESSURE MONITORING**

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**Objective:** Intracranial hypertension (IH) develops in approximately 50% of all patients with severe traumatic brain injury (TBI). Therefore, it is very important to identify a suitable animal model to study and understand the pathophysiology of refractory IH to develop effective treatments. **Methods:** We describe a new experimental porcine model designed to simulate expansive brain hematoma causing IH. Under anesthesia, IH was simulated with a balloon insufflation. The IH variables were measured with intracranial pressure (ICP) parenchymal monitoring, epidural, cerebral oximetry, and transcranial Doppler (TCD). **Results:** None of the animals died during the experiment. The ICP epidural showed a slower rise compared with parenchymal ICP. We found a correlation between ICP and cerebral oximetry. **Conclusion:** The model described here seems useful to understand some of the pathophysiological characteristics of acute IH.

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### **MODERATE TRAUMATIC BRAIN INJURY: ACUTE PHASE COURSE AND DEVIATIONS IN PHYSIOLOGICAL VARIABLES IN THE INTENSIVE CARE UNIT AND AT THE WARD**

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Patients with moderate traumatic brain injury (TBI) have no guidelines for observation and treatment in the acute phase. The aim of this study was to describe the acute phase course in a cohort of moderate TBI patients. We also studied deviations in physiological variables based on guidelines for severe TBI the first three days post-injury. During a 5-year period (2004–2009), 119 adults (>16 years) according to the Head Injury Severity Scale were admitted to a level 1 trauma center. The cohort was divided into patients staying  $\geq 3$  days at an Intensive Care Unit (ICU patients) and patients who did not stay or stayed <3 days at an ICU (non-ICU patients). Injury-related and acute phase data were collected prospectively, while deviations in physiological variables (hypotension, hypoxia, hyperthermia, hyponatremia, hyperglycemia and

anemia) were collected retrospectively. 84% of the patients were admitted to an ICU the first day, and 52% stayed  $\geq 3$  days in ICUs. The ICU patients had lower median Glasgow Coma Scale score, higher median Injury Severity Score and more subdural hematomas than the non-ICU patients ( $p < 0.05$ ). Frequency of evacuation of intracranial mass lesions was similar in the groups (13%). More ICU patients had hypoxia (58%), hyperglycemia (65%), hyperthermia (60%) and anemia (53%) than non-ICU patients ( $p < 0.05$ ). More than 50% of moderate TBI patients stayed in ICUs  $\geq 3$  days due to intra- and extracranial injuries. The ICU patients had more deviations in physiological variables than the non-ICU patients, and lack of guidelines for moderate TBI patients may allow deviations to pass uncorrected.

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### **BRAIN EDEMA RESPONSE FOLLOWING EXPERIMENTAL FOCAL TRAUMATIC BRAIN INJURY**

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The pathophysiological course following traumatic brain injury (TBI) often involves development of brain edema. The therapeutic options are limited and few are targeting the mechanisms. Changes in the function of the blood brain barrier (BBB) and variations in the expression of aquaporins (AQP), allowing water movement between different compartments in the brain, have been suggested to be involved. In order to study these mechanisms and their dynamic response to TBI, rats were subjected to blunt controlled head trauma. We performed MR imaging, immunohistochemistry, immunohistochemistry and quantitative protein analysis on day 1 and 4 after trauma. Non-traumatized animals served as controls. The TBI resulted in a significant midline shift and a 12% decrease in ADC, indicating a hemispheric enlargement due to cytotoxic edema. The presence of IgG in the perilesional brain tissue was increased by 18%, which was associated with a 25% decrease of the anchoring tight junction protein zona occludens-1, both findings in accordance with a BBB breakdown. Immunohistochemistry and Western blot showed that the total amount of AQP4 protein decreased by 18%. The disruption of the BBB and the hemispheric enlargement were present at both day 1 and 4 after trauma while the decreased AQP4 protein levels were restored at day 4. In summary, the findings indicate that focal brain injury results in an edema response involving both cytotoxic and vasogenic types, a persistent BBB breakdown and a temporary decrease in AQP4 and suggests that both types of edema should be targeted in traumatic brain edema treatment.

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### **A MODEL FOR IN VITRO HIGH-ENERGY TRAUMA**

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A model for high-energy *in vitro* trauma designed and evaluated. The flyer-plate accelerates a metal fragment hitting cell-cultures and traumatises with good reproducibility. Glioma, caco2, and neuroblastoma are used to characterise post-trauma cellular events. The observations include micrographing, automated imaging (Cell IQ),

mitosis (BrdU-DAPI), and Gene Arrays. Cell-cultures were micrographed five times, up to 26 hr post-trauma. Significant regeneration was seen in all cell types (lesion-size change in time),  $P < 0.0001$ . Regeneration rate was different between cell-types,  $P < 0.0001$ . The cell-type specific regeneration also changed over time,  $P < 0.0001$ . Time-lapse imaging analysis 1<sup>st</sup>-26<sup>th</sup> hr post-trauma showed, that all cell-types underwent regeneration. Traumatized colonies' cell-growth was more pronounced than that of the controls. Lesion periphery makes us especially curious - a less cell-dense zone between the cell-free lesion and confluent zone. BrdU-DAPI stained neuroblastoma and glioma 24 hr post-trauma was employed to explore zonal differences. In both cell-types, mitosis percentage is higher in the lesion periphery than the confluent zone and in the controls. The mitotic activity differed between the cell-types. Distinct expression profiles were seen in 24 hr post-trauma neuroblastoma and glioma. These preliminary array data also reflected some pathophysiological responses to trauma. Regeneration in this model is cell-type specific. Mitosis level in lesion periphery differs from the confluent zone and controls, as well as between cell-types. We find the flyer-plate an advantageous cell model to explore high-energy trauma yet poorly understood.

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#### **TRAUMATIC AXONAL INJURY AND THE IMPORTANCE FOR REDUCTION OF GLASGOW COMA SCALE SCORE: AN MRI STUDY**

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In the common grading of traumatic axonal injury (TAI grades 1–3) thalamus lesions are classified as grade 1 and brain stem lesions as grade 3. We wanted to develop a modified TAI grading to investigate which TAI locations that had the most profound impact on consciousness.

98 patients with moderate to severe traumatic brain injury (TBI) without mass lesions were prospectively included and GCS scores were registered. Analyses of early MRI (FLAIR, T2\*GRE and DWI, median 8 days, range 0–28) were done blinded for clinical information. The modified TAI grading was: no TAI group ( $n = 15$ ), TAI group 1 (hemispheric lesions;  $n = 23$ ), TAI group 2 (corpus callosum, unilateral brain stem- and/or unilateral thalamus lesions;  $n = 46$ ), and TAI group 3 (bilateral brain stem- and/or bilateral thalamus lesions;  $n = 14$ ).

Median GCS score was 12 (IQR: 9–13) in the no TAI group, 10 (IQR 8–13) in TAI group 1, 9 (IQR 6–11.25) in TAI group 2, and 4 (IQR 3–6) in TAI group 3.

A linear decrease in GCS-score was found for these modified TAI-groups (Kendall's tau:  $-0.387$ ,  $p < 0.001$ ). Patients in TAI group 2 had significantly higher GCS scores than those in TAI group 3 ( $p < 0.001$ ), whereas the common TAI grading showed no differences between patients with TAI grade 2 and 3 ( $p = 0.521$ ). The modified TAI grading correlated with GCS score and differentiated between TAI groups 2 and 3. Hence, this new grading could be a purposeful way of grouping TAI lesions in patients with moderate to severe TBI.

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#### **INJURED SPINAL CORD PRESSURE EVALUATION (ISCoPE) STUDY: EXPANSION DUROPLASTY REDUCES SPINAL CORD PRESSURE IN ACUTE SPINAL CORD INJURY**

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We recently described a novel method to monitor intraspinal pressure (ISP) and spinal cord perfusion pressure (SCPP) after severe traumatic spinal cord injury (tSCI) at the level of maximal cord swelling<sup>1</sup>. High ISP in tSCI was not effectively reduced by laminectomy, suggesting cord compression against dura. We hypothesize expansion duroplasty lowers ISP and improves SCPP. 7 patients with severe tSCI (ASIA A-C) had open reduction of spinal fracture, posterior fixation and laminectomies within 72 hours of injury. The dura and arachnoid were incised posteriorly in the midline. A subdural pressure probe was inserted at the level of injury. Expansion duroplasty was done by suturing an elliptical collagen patch to the dural margin followed by fibrin glue. ISP and radial arterial blood pressure were monitored for 7 days. We calculated SCPP (mean arterial pressure, MAP, -ISP) and spinal pressure reactivity index (sPRx). AP dural diameter at the level of injury on T2W MRI increased after laminectomy and expansion duroplasty compared to laminectomy alone ( $58.7\% \pm 37.4\%$ ,  $n = 7$ , vs.  $21.0\% \pm 18.3\%$ ,  $n = 6$ ,  $p < 0.05$ ). In 3 patients the injured spinal cord expanded into the expansion duroplasty space. Compared with our non-duroplasty cohort, expansion duroplasty reduced mean ISP ( $20.3 \pm 6.2$  vs.  $13.3 \pm 6.7$  mmHg,  $P < 0.05$ ), increased mean SCPP ( $68.2 \pm 14.3$  vs.  $86.8 \pm 15.6$  mmHg,  $P < 0.05$ ) and improved sPRx ( $0.15 \pm 0.08$  vs.  $0.02 \pm 0.10$ ,  $P < 0.01$ ).

There was one CSF wound leak and one probe dislodgement. No patients deteriorated neurologically.

Expansion duroplasty reduces ISP and increases SCPP after tSCI without neurological deterioration.

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#### **COPING, COMPLAINTS AND WORK RESUMPTION THREE MONTHS AFTER MILD-TO-MODERATE TRAUMATIC BRAIN INJURY. PRELIMINARY RESULTS OF THE UPFRONT-STUDY**

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Investigate the incidence of complaints 3 months post trauma in relation to coping styles in a cohort of mild to moderate Traumatic Brain Injury (TBI) patients and to determine the rate of return to work (RTW).

Multicenter prospective longitudinal cohort study of mild to moderate TBI patients admitted to the Emergency Department. Patients received a baseline questionnaire 2 weeks post trauma covering complaints, RTW and coping styles. Coping styles were divided in passive and active coping styles. Three months post trauma, work resumption and complaints were assessed with a follow-up questionnaire.

The questionnaires were completed by 202 patients (mean age of 48.3 (19.7) years, range 16–91) and GCS scores ranging from 9–15 with 97% mild TBI). Three months post trauma 69% of all patients reported complaints.

Of those patients who were employed (n=87) at the time of the injury, 59% completely resumed their occupational activities 3 months post trauma whereas 21% worked on a lower level (or a less amount of hours) and 20% did not resume work at all.

The participants that resumed their work (completely and partly) reported significantly less complaints compared to the non resumers (4 vs. 9,  $t(55) = 2.81$ ,  $p = .007$ ). In both groups, the most frequent reported complaints were sleepiness, increased fatigability, dizziness and forgetfulness. Concerning the influence of coping style; a passive coping style was associated with the cluster of emotional complaints (irritability and anxiety) ( $r = .177$ ,  $p < .020$ ).

Three months after mild to moderate TBI 69% of all patients still has complaints that might intervene with successful resumption of work. Preliminary analysis suggests a relation with coping style.

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### MECHANISMS OF ENDOGENOUS INTOXICATION SYNDROME AT TRAUMATIC DISEASE IN BRAIN INJURY

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Object of our work is devoted to the problem of the decision of an actual scientific task in the field of traumatic brain injury. On the basis of complex dynamic research mechanisms that determined the progressive advance of four stages of syndrome of endogenous intoxication in traumatic brain injury: reaction-metabolic (hyperergic reaction of neuroendocrine system, hypermetabolism, hyperglycemia, and insulin resistance), inflammatory-toxic (hyper-fermentation, endogenous intoxication, generalized inflammatory reaction), the stages of systemic endogenous intoxication (progressive hypoxemia, sharp secondary worsening of metabolism, and accumulation of toxins) and the stages of multiple organ failure (development of systemic hypoxemia and intoxication, sharp accumulation of metabolism products and markers of brain damage and myocardium, arising of autoimmune reaction) have been studied. Predicted data were defined - multiple increase of absolute value of metabolism index; average molecular mass, the level of neuronal proteins (NSE and S100B), corticosterone, C-reactive protein and interleukin 1B. The study was conducted on 555 white rats, weighing between 190 grams to 200 grams, under the age of 6 months. Developed model for the study of pathological mechanisms development of endogenous intoxication in traumatic brain disease, which can reproduce a head injury with 0,516 joules of energy, and 82% mortality within 5 days after the injury. The maximum level of mortality was 48 hours and 5 days after injury, allowing time to consider these as critical. Based on the data key activities in the first stage are hypermetabolic warning, then intensive detoxification, preventing the development of acute inflammatory and autoimmune processes and intensification of lipid peroxidation.

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### EXTRACELLULAR N-ACETYLASPARTATE IN HUMAN TRAUMATIC BRAIN INJURY

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N-acetylaspartate (NAA) is regarded as a marker for neuronal health. A decrease in brain NAA, measured using *in vivo* 1H-MRS, is a characteristic of many neurological pathologies. MRS measures total intracellular and extracellular concentration only during the scan, while microdialysis measures extracellular NAA continuously and hence can detect change with time. It is unknown whether extracellular NAA can be used as a biomarker of neuronal health or injury. We therefore measured NAA in brain microdialysates from traumatic brain injury (TBI) patients.

Microdialysis catheters (CMA71, 100 kDa cut-off) were inserted into the cerebral parenchyma of 5 TBI patients and perfused with CNS perfusion fluid (0.3  $\mu$ l/min). Microdialysate collection vials were changed hourly, pooled into 8 h periods for each patient, and NAA concentrations measured by HPLC.

Microdialysate collection for NAA analysis started at a median of 50.4 h post-injury (minimum 26.1 h, maximum 82.2 h) and finished at a median of 142.3 h post injury (minimum 109.9 h, maximum 190.6 h). The median (inter-quartile range; IQR) concentration of NAA in the 62 pooled samples from the 5 TBI patients was 18.9(15.8–26.0)  $\mu$ M. There was a significant inverse correlation between microdialysate NAA concentration and time post-injury (n=62 data-points, Spearman  $r = -0.311$ ,  $p = 0.015$ ). Median (IQR) concentration of NAA in microdialysates before 72 h was 22.8(15.9–35.7)  $\mu$ M, compared with 18.5(15.6–21.3)  $\mu$ M after 72 h.

Extracellular NAA concentrations in TBI patients showed an overall pattern of decrease post-injury to reach a steady level of approximately 20  $\mu$ M. The study is ongoing, in a multimodality monitoring study determining whether extracellular NAA concentration correlates with secondary injury after TBI.

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### REMOVAL OF ACUTE SUBDURAL HEMATOMA IN PATIENTS WITH SEVERE CEREBRAL EDEMA WITH DISLOCATION SYNDROME BY DECOMPRESSIVE CRANIOTOMY, MULTIPLE INCISION OF THE DURA MATER

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Analyzed 22 case histories with acute subdural hematoma, urgent treatment admissions in the neurosurgical clinic in critical condition. The age group 18 to 72 years. In conducting imaging studies obtained informative parameters that characterize all of the components of intracranial contents, making it possible to trace the dynamics of severe head injury with acute subdural hematoma complicated by severe edema, swelling of the white and gray matter with the reduction of cerebral blood flow. In this regard, it was decided to conduct these patients decompressive craniotomy, removing acute subdural hematoma by *multiple incision of the dura mater*, which led to the passive removal of the hematoma and decompression through the sections of the brain substance without damage to the cerebral cortex. Intracranial pressure sensor installed to the correct tactics to further intensive care. Following the operations manual, imaging was performed, confirming the success of the intervention. In the postoperative period, significantly worsened the prognosis over 65 years, the postoperative level of intracranial pressure above 30. Postoperatively, 11 cases were positive, which is 26% higher in comparison with the test group, who underwent surgery conventional manner. The method of disposal of subdural hematomas in patients with severe edema, swelling of the brain by means of decompression craniotomy, evacuation of the hematoma by *multiple*

*incision of the dura mater* is a promising technique, which helps to minimize surgical trauma, prevents damage to the gray matter of the brain and improves treatment outcomes and survival rates.

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### **RILUZOLE PROVIDES NEUROPROTECTION AND ATTENUATES ISCHEMIA REPERFUSION INJURY FOLLOWING SURGICAL DECOMPRESSION IN EXPERIMENTAL CERVICAL SPONDYLOTIC MYELOPATHY**

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Cervical spondylotic myelopathy (CSM), which is caused by progressive compression of the cervical cord due to spondylosis, is the most common cause of spinal cord impairment worldwide. While decompression - the only treatment option for CSM - demonstrates efficacy, the physiological consequences of decompression have yet to be studied. Here, we used a preclinical rat CSM model to characterize the physiological changes in spinal cord after decompression and to examine the synergistic effects of decompression and riluzole administration.

Spinal cord blood flow (SCBF) and levels of oxidative damage were evaluated before and after decompression using MRI and fluorescent microspheres. Then using a novel experimental paradigm we examined the effects of combinatorial strategy consisting of decompression and riluzole. Immunohistochemistry were used to evaluate apoptosis and axonal integrity.

We demonstrated increased SCBF, clinical decline and oxidative damage soon after decompression indicating ischemia-reperfusion injury (IRI). *In vivo* and *in vitro* studies confirmed that decompression-mediated IRI could be prevented by riluzole administration. Moreover, combinatorial strategy markedly improves hand and gait function and attenuates below-level neuropathic pain compared to decompression alone. Finally, combined strategy reduces axonal damage, cellular apoptosis and motoneuronal injury in the cervical area as well as suppressing microglial and activation in the lumbar dorsal horns.

This work provides evidence of IRI development following decompression in CSM and mechanistic insights into the protective effect of riluzole. This study paved the way for CSM Protect clinical trial which examines the synergy of decompression and riluzole in human CSM.

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### **RESULTS FROM THE FIRST RANDOMISED CONTROLLED TRIAL OF SURGERY FOR TRAUMATIC INTRACEREBRAL HAEMORRHAGE [STITCH(TRAUMA)]**

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There have been a number of trials investigating surgery for spontaneous intracerebral haemorrhage but none of traumatic intraparenchymal haemorrhage (TICH). This study aimed to establish whether a policy of early surgery for TICH improves outcome compared with a policy of initial conservative treatment.

This was an international multicentre pragmatic randomised parallel group trial with primary outcome measured at six months. The study planned to recruit 840 adult patients. Patients had no more than two haematomas greater than 10ml and were within 48 hours of head injury. They did not have a SDH or EDH that required evacuation. Patients were randomised via an independent telephone/web-based randomisation service to early surgery within 12 hours or initial conservative treatment. Extended Glasgow Outcome Scale was measured at 6 and 12 months via a postal questionnaire.

Patient recruitment began in 2010 but was halted by the funding body for low UK recruitment in September 2012. 170 patients were randomised from 31 centres in 13 countries; 83 to early surgery and 87 to initial conservative treatment. Six and 12 month outcomes were obtained for 99%. Mortality was significantly higher in the initial conservative treatment group. Patients in the early surgery group were 10% more likely to have a favourable outcome but this did not reach statistical significance because of the reduced sample size.

This is the first ever trial of surgery for TICH and indicates that early surgery is a valuable tool in the treatment of TICH. Further research is warranted.

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### **THE CLINICAL PITFALLS AND POSSIBILITIES USING S100B MONITORING IN NEURO INTENSIVE CARE IN PATIENTS SUFFERING FROM TRAUMATIC BRAIN INJURY**

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With the growing frequency of traumatic brain injury (TBI) globally there is an intensifying need to develop clinical tools to facilitate and improve care. The protein S100B has been shown to increase in serum after injuries to the central nervous system (CNS). In moderate-to-severe TBI, S100B have been shown to correlate to the extent of the injury and to predict outcome.

In the neuro-intensive care unit (NICU) environment, frequent S100B sampling could be used to monitor patients suffering from cerebral lesions and hence facilitate decision making concerning radiological examination and neurosurgical interventions.

Due to the short half-life of S100B, 30–90 minutes, it is important to consider the sampling time as well as the temporal pattern of subsequent serum levels. The development of secondary peaks  $>0.05 \mu\text{g/L}$  of S100B, have also been shown strongly correspond to the development of secondary radiological deterioration following TBI.

Other pathologies may increase serum S100B, such as non-CNS trauma, recent surgery or malignancies, which will make the S100B contribution from the potentially affected CNS difficult to evaluate. Due to these extracranial sources, the specificity of S100B is not optimal, especially within the first 12 hours after trauma in affected patients.

In aggregate, S100B is an important biomarker in TBI care; however, knowledge of the protein dynamics and extracranial S100B sources is important to fully utilize this biomarker's clinical capabilities to predict outcome, display extent of CNS injury and monitor patients in the NICU.

### THE EFFECT OF CROSSOVERS IN THE FIRST RANDOMISED CONTROLLED TRIAL OF SURGERY FOR TRAUMATIC INTRACEREBRAL HAEMORRHAGE [STITCH(TRAUMA)]

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This study aimed to establish whether a policy of early surgery (ES) for traumatic intracerebral haemorrhage improves outcome compared with a policy of initial conservative treatment (ICT). Surgical trials are often associated with a high "crossover" rate because of the impossibility of blinding the treatment allocation together with changes in status after randomisation leading to changes in equipoise of the clinician, patient or relative.

An international multicentre pragmatic randomised parallel group trial with primary outcome measured at six months. Patients were adult with no more than two haematomas > 10 ml and were within 48 hours of head injury; with no SDH or EDH requiring evacuation. Patients were randomised to ES within 12 hours or ICT. Extended Glasgow Outcome Scale was measured at 6 and 12 months via a postal questionnaire.

170 patients were randomised from 31 centres in 13 countries; 83 ES and 87 ICT. Outcome at six months was available for 99%. Of those allocated to ES 26% did not receive surgery (24% died and 52% had a favourable outcome) and 74% did (11% died and 67% a favourable outcome). Of those allocated to ICT 37% had surgery, mainly for deterioration (22% died and 35% had favourable outcome) compared 27% died and 63% favourable outcome in those who did not cross-over. Logistic regression demonstrated that surgical patients were more likely to have a favourable outcome if they were younger and if the pre-surgery GCS was higher.

This analysis suggests that the beneficial results observed in the intention to treat analysis for the ES group are achieved by undertaking surgery prior to further deterioration.

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### EFFECTS OF EXPERIMENTAL TRAUMATIC BRAIN INJURY ON HIPPOCAMPAL SYNAPTIC SNARE COMPLEXES

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Traumatic brain injury (TBI) impairs neuronal function which can culminate in lasting cognitive dysfunction. Multiple reports indicate that TBI produces an impairment in evoked neurotransmitter release, but the mechanisms are unknown. Formation of the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex is a key step in vesicle fusion and synaptic neurotransmitter release. We hypothesized that TBI produced by controlled cortical impact (CCI) alters the levels of SNARE proteins (monomer and complexes) and cysteine string protein (CSP $\alpha$ ), a chaperone protein that promotes SNARE complex formation. Male Sprague Dawley rats subjected to sham surgery or CCI (2.7 mm deformation, 4 m/s) and sacrificed at either 6 hours, 1 day, 1, 2, or 4 weeks post-injury (n=6/group). Western blot analysis was used to measure changes in protein abundance in hippocampal homogenates compared to sham homogenates. The abundance of the synaptosome-associated protein of 25 kDa (SNAP-25) was elevated by 42% at 1 week (p<0.01), but was

reduced by 21% at 2 weeks post-injury (p<0.05). Synaptotagmin-1 levels were not altered by CCI. Vesicle-associated membrane protein (VAMP2) abundance was reduced by 29% and 63% at 1 week (p<0.05) and 4 week (p<0.01), respectively. CSP $\alpha$  was reduced by 20% at 1 day (p<0.05) and 26% at 1 week following CCI (p<0.01). Assessment of SNARE complex formation using SNAP-25 and Syntaxin-1 both revealed greater than 48% reductions in complex formation at 1 week (p<0.05) and 2 weeks (p<0.01) following CCI. Future studies will evaluate the role of TBI-induced alterations in SNARE complex formation on neurotransmitter release deficits. These results provide novel evidence that TBI alters SNARE protein abundance and impairs SNARE complex formation.

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### CT DENSITOMETRY TO PREDICT CONTUSION ENLARGEMENT IN TRAUMATIC BRAIN INJURY (TBI)

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Microvascular failure in the periphery of contusions is thought to be an important mechanism in driving lesion expansion. It remains unclear whether the mechanism that underlies this process is expansion of primary haemorrhage in the lesion core, or multifocal haemorrhage in the pericontusional tissue. Quantitative computed tomography (CT) variables can predict expansion of spontaneous intracerebral haemorrhage; we therefore explored whether the same was true for TBI contusions.

Images from 24 patients with TBI were analysed. Patients were included if they had two head CT scans within 5 days of injury and traumatic contusions. We defined the total mixed density contusion, the hyperdense core, and the hypointense oedema as separate regions of interest (ROI), and measured volume, mean voxel density, standard deviation, skewness, kurtosis and coefficient of variation of each ROI. We used non-parametric statistics (Spearman rank test) to examine the relationship between ROI metrics and cube root of change in volume. Growth dichotomised as greater than 30% was analysed by logistic regression.

Twenty-four patients with TBI were included, although 1 follow on scan could not be transferred for analysis. Spearman rank test for growth in lesion core was highly significant for core skewness (p=0.0085), with negative skewness correlating with core growth. No other measure of variance in any ROI was significant for core growth. This study suggests that measures of lesion variance in the contusion core may predict growth after admission. These data suggest expansion of the core, rather than multifocal haemorrhage in devitalised tissue. Further study is required to explore this.

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### QUANTITATIVE ASSESSMENTS OF TRAUMATIC AXONAL INJURY IN THE LIVING HUMAN BRAIN: COMBINED MICRODIALYSIS AND ADVANCED MRI APPROACHES

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Axonal injury is a major contributor to adverse outcomes following traumatic brain injury (TBI). The extent of axonal injury cannot currently be assessed reliably in living humans. We used microdialysis (MD) measurements of cytoskeletal protein tau and Diffusion Tensor Magnetic Resonance Imaging (DTI) to independently assess axonal pathology following TBI.

We studied 15 patients admitted to ICU for severe TBI. MD catheters were placed in normal appearing white matter (WM). Total tau levels were measured by ELISA in MD samples collected continuously for at least 72 hrs. Patients underwent DTI between 2 wks and 3 yrs after TBI. We used DTI to quantitatively assess WM integrity in brain regions of interest (ROIs) within 20 mm of the location of the MD catheters and in spatially matched ROIs in 5 age-sex-matched controls for each patient. Our primary outcome was the normalized difference in fractional anisotropy (FA) between each patient and the controls, defined in units of SD (z-scores). Abnormalities were defined as z-scores of FA < -2. We found that regions with reduced FA had initial tau levels higher than ROIs with normal anisotropy (p=0.036). Their tau levels ranged between 13,517 and 18,743 (median 13,747) pg/ml and 3,942–5,093 (median 4,612) pg/ml. A significant inverse correlation was observed between levels of tau and FA (r = -0.55, p=0.018).

This study shows a meaningful correlation between MD measurements of tau and DTI-based measurements of reduced brain WM integrity. We interpret this result to mean that both methods accurately reflect traumatic axonal pathology.

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#### DIFFERENT IMPLICATIONS OF MILD TRAUMATIC BRAIN INJURY – OUR EXPERIENCE

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Mild traumatic brain injury (mTBI) is the most common form of TBI with possible emotional, behavioral and cognitive consequences. Disturbing epidemiological situation requires multidisciplinary approach in order to identify patients with possible psychological disorder.

To reevaluate diagnostic criteria for mTBI, introduce contemporary imaging modalities and establish neuropsychological assessment as a part of treatment for mTBI.

One year ago prospective clinical study was started at Neurosurgery Clinic, Clinical Centre of Vojvodina in order to improve treatment of injured with mTBI using multidisciplinary approach. Patients underwent clinical observation, early MRI examination in first 72 hours after injury and neuropsychological assessment (Beck's Depression Inventory and MMSE) one month and seven months after injury.

Twenty men and ten female patients, mean age 33,27 year, mean GCS score of 14.57 were examined. 80% of patients had headache, 53,3%

vegetative disturbances, and 46,7% fatigue. Mean duration of retrograde amnesia was 15–30 minutes and mean duration of anterograde amnesia was less than 15 minutes. Most of patients were injured in traffic accidents (40%) and falls (40%). MRI head examinations were performed in 73% of patient. All patients had good results on MMSE. 90% of patients had minimal or no depression, 7% had mild and 3% moderate depression. We did not find significant correlation between clinical findings and presence of psychological disorders.

Great variety of cognitive, emotional and behavioral difficulties can be caused by mTBI so patients and medical professionals can benefit from better and faster diagnostic of these disturbances.

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#### EFFECT OF MANNOSE BINDING LECTIN PHARMACOLOGICAL INHIBITION IN CONTROLLED CORTICAL IMPACT BRAIN INJURED MICE

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We have previously shown that mannose binding lectin (MBL), one of the main activators of the lectin complement pathway, is expressed in the injured brain of patients and in that of mice subjected to controlled cortical impact (CCI) and that its deletion (as assessed in MBL-A and -C double KO mice) is protective (Longhi et al. submitted). We have now evaluated the effects of pharmacological MBL inhibition using Polyman-2, a compound that binds MBL-A with high (while MBL-C with low) affinity and endowed with neuroprotective properties (Orsini et al., Circulation 2012).

Eight-week old male C57Bl/6 mice were subjected to anesthesia with Pentobarbital (65 mg/kg) followed by CCI brain injury (parameters: velocity 5 meter/sec and depth 1 mm). At 10 minutes postinjury, mice (n=8) randomly received an intravenous infusion of either Polyman-2 (142 µg/mouse) or saline (equal volume, 100 µl). Additional mice received identical anesthesia, surgery, and saline/drug to serve as uninjured controls. Neurobehavioral outcome was evaluated weekly for four weeks by performing neuroscore and beam walk test; cognitive function was evaluated at four weeks postinjury using the Morris water maze.

All brain-injured mice showed sustained sensorimotor and cognitive deficits. Brain-injured mice receiving saline or Polyman-2 showed similar performance in neuroscore, beam walk and in Morris water maze.

Polyman-2 did not improve neurobehavioral performance after TBI. Since post-traumatic expression of MBL-C is greater than that of MBL-A, novel compounds with greater affinity for MBC-C should be investigated in the setting of TBI.

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#### IS N-ACETYLSPARTATE A MEASURE OF MITOCHONDRIAL DYSFUNCTION AFTER TRAUMATIC BRAIN INJURY?

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Energy metabolism is compromised following traumatic brain injury (TBI). Magnetic resonance spectroscopy provides non-invasive quantification of neurochemicals. Loss of N-acetylaspartate (NAA), a by-product of the Krebs cycle, suggests mitochondrial dysfunction. The current goal was to establish the relationships between NAA and other neurochemicals for better understanding brain metabolic dysfunction following TBI.

We used high-field 9.4T short echo  $^1\text{H}$ -MRS to quantify neurochemicals in cerebral cortex (lesion site) and hippocampus (perilesional) in 12 male F344 rats (3 mo) before and three days after a controlled cortical impact injury (5 mm tip, 3 m/s, 2 mm depth, 300 ms contact time). Animals were anesthetized with isoflurane during all experiments in accordance with institutional guidelines. We used LCModel to calculate absolute concentrations of NAA, glucose, lactate, alanine, and glutamate. The change in concentration of each neurochemical after injury and the correlations between changes in pairs of neurochemical were calculated. Data from both locations were combined to provide a range of injury severity.

NAA loss was highly correlated with lactate increase ( $r^2=0.76$ ) and lactate increase was correlated with glucose loss ( $r^2=0.29$ ). Increases in alanine and lactate were highly correlated ( $r^2=0.79$ ). Finally, loss of NAA and glutamate were highly correlated ( $r^2=0.69$ ).

These results provide quantitative non-invasive evidence of mitochondrial dysfunction, leading to elevated accumulation of lactate and alanine. The correlation between NAA and glutamate suggests that the glutamate observed by  $^1\text{H}$ -MRS is associated with brain energy metabolism. Thus, MRS biomarkers provide non-invasive assessment of brain metabolism that can be translated to humans.

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#### **CORRELATION BETWEEN CHANGES IN GREY AND WHITE MATTER RADIODENSITY WITH PROGNOSIS AFTER CRANIOPLASTY**

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Cranioplasty following decompressive craniectomy is reported to result in brain anatomical changes and concomitant neurological recovery. As attenuation measurement of brain nonenhanced CT scan (CT) can predict neurological prognosis in patients after cardiac arrest, we decided to perform a study to evaluate whether changes in radiodensity occur after cranioplasty and, if these changes may be related to neurological outcome. We prospectively evaluated patients with cranial vault defect by CT, before and after cranioplasty. We have measured the density in HU of WM and GM ipsilateral to bone defect. The neurological assessment was performed with the modified Rankin scale (mRs), the Mini mental state examination (MMSE) and the Barthel index (time frame: before and six months after cranioplasty). We evaluated 30 patients and observed an increased density of GM after surgery from  $28.7 \pm 8.02$  HU (mean and SD) to  $30.51 \pm 7.94$  (mean and SD) ( $p=0.144$ ), while for WM there was a reduction from  $27.08 \pm 3.80$  HU (mean and SD) to  $26.11 \pm 3.82$  HU (mean and SD) ( $p=0.052$ ). There was a significant increase in GM/WM ratio after cranioplasty from 1.05 to 1.18 ( $p=0.007$ ). We also have observed correlation between the increase on GM/WM ratio with improvement in postoperative MMSE ( $p=0.041$ ). Our study showed that attenuation changes in the brain occur after cranioplasty. Also, this changes seems to be correlated with cognitive outcome. Our work is the first to describe a GM/WM after cranioplasty may be related to better prognosis.

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#### **WHAT CAN WE REALLY EXPECT OF CEREBRAL BLOOD FLOW AFTER CRANIOPLASTY?**

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Cranial vault defects may be related with neurological deficits that can be associated with changes in cerebral hemodynamics. Our goal was to evaluate if cerebral blood flow (CBF) increases after cranioplasty using computed tomography perfusion (CTP). We prospectively evaluated patients with bone defect after decompressive craniectomy (DC) with CTP before and after cranioplasty. We performed neurological examination and evaluation of prognostic scales (mRs, MMSE and Barthel index) before and after six months. Of 30 patients, 15 (50%) had DC related to TBI and the remaining, due to cerebrovascular disease. The mean preoperative CBF was  $24.13 \pm 6.3$  ml/100 g / min (SD) ipsilateral to the bone defect and  $27.75 \pm 6.21$  ml/100 g / min (SD) contralateral to the bone defect. The mean postoperative CBF was  $22.63 \pm 8.2$  ml/100 g / min (SD) ipsilateral to the bone defect and  $26.23 \pm 5.73$  ml/100 g / min (SD) in the contralateral hemisphere. Although there's difference in CBF between both hemispheres that remains after cranioplasty ( $p=0.262$ ), this procedure did not cause significant changes in CBF (ipsilateral,  $p=0.31$ ; contralateral,  $p=0.24$ ). The absolute values of mean transit time (MTT) decreased in both hemispheres, being significant ( $p=0.02$ ) on the defect side. We also observed that there was significant improvement in all neurological parameters. Although all literature reports show CBF increment after cranioplasty and correlate this finding with clinical improvement, we observed that the best parameter to assess hemodynamics condition for these patients is MTT. After cranioplasty could occur a downregulation of the cerebral autoregulation curve, allowing suitable neuronal function with lower CBF.

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#### **MORPHOLOGICAL CHANGES ON CORTICAL SURFACE AND THEIR CORRELATION OF WITH NEUROLOGICAL OUTCOME IN PATIENTS WITH BONE DEFECTS AFTER DECOMPRESSIVE CRANIECTOMY**

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Deformity of cortex may occur with several lesions that compresses the cortical surface (tumors or hematomas). The purpose of our study was to evaluate if cortical deformity related to bone defect can be reversed after cranioplasty and its correlation with neurological improvement. We prospectively evaluated patients with bone defect after decompressive craniectomy (DC) using CT before and after cranioplasty. We estimated the degree of cortical sulci effacement, the amount of brain midline shift (MLS) and, the ratio of the cortical surface in two points (anterior and posterior) in the frontal and temporal lobes to the midline, between both hemispheres. We performed

the neurological assessment with the prognostic scales (mRs, MMSE, Barthel index) before and after six months. There was persistence of a normal condition (presence of cortical sulci) or returning to normal in 86.6% of patients after cranioplasty ( $p < 0.001$ ). We verified a MLS decrease from  $2.43 \pm 2.55$  mm (mean and SD) to  $1.16 \pm 1.93$  mm (mean and SD) ( $p = 0.004$ ). None of these parameters was correlated with neurological improvement. The difference of the anterior (frontal) distance decreased from  $9.04 \pm 7.04$  mm (mean and SD) to  $2.94 \pm 4.57$  mm (mean and SD)  $p < 0.001$ . The relation between the posterior (temporal) distances also decreased from 1.13 to 1.04 ( $p = 0.047$ ). This last measurement was the one which correlated with better prognosis according to Barthel index, ( $p = 0.035$ ). There are no papers in literature about cortical morphometric that correlate with improved prognosis after cranioplasty. Possibly this clinical improvement correlates with anatomical and functional restructuring of the cortical mantle being, a nonenhanced CT scan a simple and effective diagnostic tool.

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#### **PATTERN OF HEAD INJURY IN CYCLISTS**

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Oxfordshire has a higher percentage of population that cycles at least once a week at 28% compared with the rest of UK at 10% (1). Here we describe head injuries in cyclists over the period 2008 – 2013 that required admission to a major trauma centre.

Of the 786 patients admitted to Oxford University Hospital Trust during that period, 8.3% or 65 admissions were due to cyclists. Helmets were worn in 27.7% (18/65) of patients. There were 24.6% (16 patients) in which it was unknown if a helmet was worn or not. Of note, 47.8% (31/65) of patients did not wear a helmet. Alcohol was a factor in 10.8% of accidents.

The severity of head injury seen was quite high with 13/65 or 20% being a GCS 3–8 on admission. 29.2% (19/65) had a moderate head injury with GCS 9–13 and, 50.8% (33/65) were mild with GCS 14–15. Admission to Neuro Intensive Care Unit was required in 36.9% of presentations (24/65). Mortality during admission in this population was 6.2% (4/65) with only one of these deaths not directly attributed to head injury.

It is clear that cyclists are at risk of head injury and that this risk decreases with the number of cyclists on the road per capita. What remains contentious is the issue of bicycle helmets and whether these are significantly effective at reducing the morbidity and mortality to justify changes to legislation to mandate the legal requirement of wearing bicycle helmets.

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#### **HIPPOCAMPAL NEURON LOSS, WHITE MATTER DAMAGE AND BEHAVIORAL ALTERATIONS FOLLOWING A FLUID PERCUSSION INJURY IN MICE**

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We have previously shown gross histopathology and increased seizure susceptibility in a novel mouse model of fluid percussion

injury (Mukherjee et al. 2013). In that study, we demonstrated the pattern of neurodegeneration and neuron loss in the ipsilateral cortex between 1–30 days after injury. We also showed the pattern of ipsi- and contralateral astrocyte and microglial activation within these time points. While the previous study established the fundamental gross neuropathology in this model, we sought to further elucidate the pathological features in this mouse model of traumatic brain injury. To accomplish this goal, the current study examined hippocampal cell loss, white matter damage and behavioral performance between 1 and 30 days after a fluid percussion injury in our mouse model. The results demonstrate hippocampal cell loss, white matter damage and behavioral deficits following fluid percussion injury. The results further support the use of this mouse model of traumatic brain injury for future studies involving the central nervous system (CNS).

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#### **EMPLOYING BLOOD BIOMARKERS IN TBI CLINICAL TRIALS: FINDINGS FROM THE INTREPID2566 TRIAL**

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The multicenter INTREPID-2566 trial, which is investigating the safety and efficacy of NNZ-2566 in patients with traumatic brain injury (TBI), uses circulating brain damage markers to improve identification and characterization of patients and to monitor effects of therapeutic intervention. The study is examining whether changes in brain biomarkers over time are associated with clinical variables and outcomes in the trial.

Seventy-six moderate to severe TBI patients from the INTREPID-2566 trial were included. Glial (glial fibrillary acid protein [GFAP]), neuronal (ubiquitin C-terminal hydrolase [UCH-L1]) and axonal (αII-spectrin breakdown products 150 [SBDP150]) markers were measured by ELISA in serum on admission, at 12, 24, 36 and 48 hours and 3, 4 and 5 days after injury. Associations of initial Glasgow Coma Scale (GCS) score, age, gender, mechanism of injury and Glasgow Outcome Scale (GOS) score with biomarker profiles were investigated. Area under the curve (AUC) as a best estimate of the total amount of biomarker release was calculated for each marker in all patients.

RESULTS: All biomarkers were increased early after injury. UCH-L1, GFAP, and SBDP150 serum levels on admission strongly correlated with 1-month mortality ( $p = 0.001$ ,  $p = 0.008$  and  $p = 0.007$ , respectively) and UCH-L1 and GFAP with 3-months mortality ( $p = 0.002$  and  $p = 0.03$ , respectively), but not with age, gender, or GCS. UCH-L1 weakly correlated with CT findings ( $p = 0.047$ ). The greatest AUC values for UCH-L1, GFAP, and SBDP150 over 5 days of observation had the strongest association with 3-months mortality ( $p = 0.0006$ ,  $p = 0.006$  and  $p = 0.004$ , respectively). AUC values were also associated with 1-month mortality ( $p = 0.003$ ,  $p = 0.03$  and  $p = 0.02$ , respectively). These results suggest that determination of serum levels of brain damage proteins as well as their change over time may be useful in the characterization and stratification of patients with TBI, increasing the possibility of identifying a positive effect of the drug. These data emphasize the importance of including biomarker measurement in TBI trials.

### CHARACTERIZATION OF TBI MODELS AND EVALUATION OF EFFICACY OF NICOTINAMIDE, ERYTHROPOIETIN, AND CYCLOSPORIN A USING SERUM BIOMARKERS: RESULTS FROM OPERATION BRAIN TRAUMA THERAPY

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OBTT is a multicenter preclinical drug screening consortium for TBI. We measured serum glial fibrillary acidic protein (GFAP) and Ubiquitin C-terminal hydrolase (UCH-L1) in 3 rat models (parasagittal fluid percussion injury [FPI]), controlled cortical impact [CCI] and penetrating ballistic-like brain injury [PBBI]) treated with vehicle, or low or high doses of nicotinamide, erythropoietin [EPO] or Cyclosporin A [CsA]. At 4h after TBI UCH-L1 was significantly higher in CCI vs. FPI and PBBI, and GFAP lower in PBBI vs. CCI and FPI. Sham and TBI+Veh groups did not differ across experiments in the same model confirming intra-model reproducibility. But shams differed across models with highest UCH-L1 levels in CCI and lowest GFAP in FPI. High-dose nicotinamide reduced GFAP but not UCH-L1 in PBBI at 24h. High-dose EPO increased UCH-L1 at 4h and reduced it at 24h in CCI, but did not affect GFAP. CsA showed a dose-dependent increase in GFAP at 4h in CCI and PBBI but a reduction trend in FPI vs. Veh. CsA had no impact on UCH-L1. Different models produced distinct biomarker profiles replicable across experiments supporting use of biomarkers to characterize, standardize and refine TBI animal models. Importantly, this study demonstrates that drugs differently affect distinct types of lesions as reflected by distinct biomarker pathways. Taken together, these findings provide robust evidence for a potential application of biomarkers in TBI therapeutics thereby holding promise for personalized medicine. Support: US Army W81XWH-10-1-0623.

### AMNIOTIC FLUID DERIVED MESENCHYMAL STROMAL CELLS PROTECT ORGANOTYPIC BRAIN SLICES AFTER OXIGEN-GLUCOSE DEPRIVATION INJURY

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We established a model of cortical brain organotypic slices and oxygen-glucose deprivation (OGD) to assess the protective effects of amniotic mesenchymal stromal cells (AMSCs) or their conditioned medium (CM) on cortical ischemia, a critical component of brain

damage following traumatic brain contusion. Prefrontal cortex organotypic slices (P1-3 mice) were subjected to 2h OGD (hypoxic chamber: N<sub>2</sub>:95%, CO<sub>2</sub>:5%, O<sub>2</sub>:0.1%; DMEM without glucose). Control slices were maintained in culture medium in normoxic conditions. One hour post-OGD, the slices were cultured in: 1) culture medium; 2) co-culture with AMSCs; 3) 50% CM. Cell death evaluation: OGD increased propidium iodide (PI) incorporation both at 24h (mean ± SD: +2000 ± 459%) and 48h (+5000 ± 1588%) compared to controls. AMSC exposure following OGD significantly reduced PI incorporation both at 24h (-35 ± 19%) and 48h (-48 ± 23%) compared to OGD alone. CM exposure following OGD significantly reduced PI incorporation at 24h (-28 ± 23%) but no longer at 48h (-26 ± 42%) compared to OGD alone. Edema evaluation: OGD induced a marked slice swelling at 24h (137 ± 32%) and 48h (122 ± 10%) compared to pre-OGD. AMSC exposure following OGD significantly reduced slice swelling at 24h (122 ± 18%) compared to OGD alone resulting in the complete resolution of edema at 48h (99 ± 4%). Control slices co-cultured with AMSCs or CM never differed from those in culture medium. Our data show that AMSCs are able to protect cortical brain slices after ischemic injury and that CM from AMSCs confers transient protection. This model represents a reliable tool to investigate specific mechanisms associated with AMSC protection in the ischemic injury.

### BONE MARROW MESENCHYMAL STROMAL CELLS DRIVE PROTECTIVE M2 MICROGLIA POLARIZATION AFTER BRAIN TRAUMA

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Microglia/macrophages (M) are major contributors to post-injury inflammation but they may also promote brain repair in response to specific environmental signals that drive classic (M1) or alternative (M2) polarization. We investigated the activation and functional changes of M in mice subjected to controlled cortical impact (CCI) receiving human bone marrow mesenchymal stromal cells (MSCs) or saline infusion. MSCs up-regulated Ym1 and Arginase-1 mRNA (p < 0.001), two M2 markers of protective M polarization, at 3 and 7d post-injury and increased the number of Ym1+ cells at 7d post-injury (p < 0.05). MSCs reduced the presence of the lysosomal activity marker CD68 on the membrane surface of CD11b positive M (p < 0.05), indicating a reduced phagocytosis. MSC-mediated induction of the M2 phenotype in M was associated with recovery of neurological functions (assessed by composite neuroscore and beam walk) 7d post-injury (p < 0.01) and reparative changes of the lesioned microenvironment. *In vitro*, MSCs directly counteracted the pro-inflammatory response of primary murine microglia stimulated by TNF $\alpha$ +IL17 or by TNF $\alpha$ +INF $\gamma$  and induced M2 pro-regenerative traits, as indicated by the down-regulation of iNOS and up-regulation of Ym1 and CD206 (p < 0.01) mRNA. In conclusion we found evidence that MSCs can drive the M transcriptional environment and induce the acquisition of an early, persistent M2 beneficial phenotype both *in vivo* and *in vitro*. Increased Ym1 expression together with reduced *in vivo* phagocytosis indicates M selection by MSCs towards the M2a subpopulation, which is involved in growth stimulation and tissue repair.

### DIFFERENTIAL ACUTE AND CHRONIC RESPONSE OF CX<sub>3</sub>CR1 DEFICIENT MICE TO EXPERIMENTAL BRAIN TRAUMA

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We investigated the consequences of CX<sub>3</sub>CR1 fractalkine receptor deletion on neurobehavioral and histopathological outcome, and microglia/macrophage (M) phenotypical features in mice after traumatic brain injury (TBI) induced by controlled cortical impact (CCI). Four and seven days after injury CX<sub>3</sub>CR1<sup>-/-</sup> mice (n=12) subjected to CCI showed early significant reduction of sensorimotor deficits, evaluated using composite neuroscore, associated to lower cortical damage assessed by neuronal count and TUNEL staining compared to WT mice. Conversely, at 35 days they showed a delayed worsening of sensorimotor deficits and histological damage. M phenotypical features were assessed by immunohistochemistry for CD11b (% of stained area), CD68 (% of stained area), a marker of phagocytosis, and iNOS (numbers of positive cells/mm<sup>2</sup>), a marker of M1 phenotype. At early time points immunoreactivity for CD11b was increased (+25%, p<0.05) while that for CD68 and for iNOS was decreased (CD68: -33%, p<0.001; iNOS: -40%, p<0.001) in CX<sub>3</sub>CR1<sup>-/-</sup> compared to WT injured mice. In contrast, at 35 days a selective increase of iNOS (+189%, p<0.001) with no changes for the other markers was detected in CX<sub>3</sub>CR1<sup>-/-</sup> compared to WT mice. These data show an early protection followed by a chronic exacerbation of TBI damage in absence of CX<sub>3</sub>CR1. The different polarization of M observed at early and late stages in CX<sub>3</sub>CR1<sup>-/-</sup> mice suggests that fractalkine-mediated M activation may play a role in facilitating long-term recovery and repair after TBI.

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### THE FEATURES OF TRAUMATIC BRAIN INJURY WITH ACUTE DETERIORATION AFTER RECOVERY OF CONSCIOUSNESS

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In the last five years, we experienced four cases of traumatic brain injury which suddenly deteriorated despite recovery of consciousness. Therefore, we analyzed this and report the characteristics of the injuries.

1. A twenty-eight-year-old woman was injured in a traffic accident. Her consciousness was E3V2M6 (GCS) on arrival. A craniotomy and removal of the hematoma was performed. Her normal temperature (TEMP) was maintained. On the 7th hospital day (HD), her consciousness recovered to M6, but on the 12th HD acute deterioration occurred and she was dead on the 17th HD. AIS4 (head) ISS26 Ps0.955.
2. A seventeen-year-old boy was injured in a railway accident. His consciousness was E1V1M4 on arrival. A craniotomy and removal of the hematoma was performed followed by therapeutic hypothermia. On the 8th HD consciousness recovered to M6, but on the next day, acute deterioration occurred and he was dead on the 16th HD. AIS5 (head) ISS30 Ps0.830.

3. A twenty-five-year-old woman was injured in a crash. Her consciousness was E1V4M6 on arrival. Her normal TEMP was maintained. On the 5th HD consciousness recovered to M6, but on the 7th HD acute deterioration occurred and she was dead on the 19th HD. AIS4 (head) ISS21 Ps0.941.
4. A twenty-nine-year-old woman was injured in a crash. Her consciousness was E1V1M1 on arrival. Her normal TEMP was maintained. On the 4th HD consciousness recovered to M5 under sedation, but on the 7th HD, acute deterioration occurred and she was dead on the 18th HD. AIS4 (head) ISS21 Ps0.941.

All of the patients were young and had fractures in the posterior fossa and hemorrhage in the frontal lobe. There was no change of intracranial pressure (ICP) around the acute deteriorated area in all of the cases. There was acute deterioration 12 weeks after admission.

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### PATTERNS OF SEVERITY AND OUTCOME OF TRAUMATIC BRAIN INJURIES BY LOCATION OF TRAUMA IN AUSTRIA

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Traumatic brain injuries (TBIs) are a major public health problem. Although they are relatively well studied, information on some aspects, such as location, is limited. The aim of this paper was to describe patterns of TBI related to places where trauma occurred, analyse their causes and relations with severity and outcome.

1098 cases of TBI admitted to hospitals in Austria were analysed with respect to where they occurred. Primary populations at risk were identified for each location as well as demographic factors, patterns of injury severity, extent of injury and short and long-term outcomes.

TBIs at home occurred mostly in elderly after falls and had the worst outcome. TBIs on streets/public places were caused mostly by falls or traffic accidents. TBIs on roads/highways were the most common, especially in young ages. Outdoor/sports injuries were caused mainly by sports or falls. Workplace TBIs happened almost solely to men and were the most severe.

TBIs at different locations display distinctive patterns as to causes, severity, outcome and populations at risk. Location is therefore a relevant epidemiological aspect of TBI and we advocate its inclusion in future studies. Definitions of primary populations at risk at different locations could aid targeted public health actions.

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### DYNAMIC EVOLUTION OF ATROPHY AFTER MODERATE TO SEVERE TRAUMATIC BRAIN INJURY

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It is clear that many of the sequelae of Traumatic Brain Injury (TBI) are not just a direct consequence of the acute event, but represent a dynamic process, with changes occurring many years after the event. Here we investigate the temporal changes in regional volumes after TBI. Twelve patients who had sustained moderate to severe TBI, underwent serial MR imaging on at least three and up to five occasions. All were imaged within 1 week of injury as well as twice five or more months post injury which included 3D T1-weighted structural sequence. Eight controls underwent three imaging sessions over the same time period. Subject specific probabilistic segmentation estimates of regions of interest were derived using an atlas-based approach based on an expectation-maximization framework. Non-parametric statistics were used. The thalamus and cerebral white matter showed a significant volume loss over time for patients but not controls ( $P < 0.001$ ). The lateral ventricles showed a significant volume increase in the patient group ( $P < 0.001$ ). In contrast there was no significant volume change in the hippocampus for either patients or controls. The differential effects of volume change are consistent with progressive but selective damaging effects of TBI on the white and grey matter, indicating that individual regions have different resilience and/or vulnerabilities to the effects of injury. The volume changes seen are likely secondary to the influence of edema in the acute scans. Late changes in regional volume are attributable to a range of pathophysiological process, including Wallerian degeneration, metabolic changes, and inflammation.

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#### LONG-TERM CHANGES OF PERIVASCULAR MATRIX AFTER JUVENILE TRAUMATIC BRAIN INJURY: POSSIBLE RELATION WITH AMYLOID-BETA ACCUMULATION

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Traumatic brain injury (TBI) is a leading cause of long-term disability in the pediatric population. Juvenile (j)TBI induces phenotypic changes of the blood-brain barrier (BBB) and accumulation of amyloid- $\beta$  ( $A\beta$ ) at 2 months. Recently, we demonstrated emergence of cognitive dysfunctions up to 6 months after jTBI, suggesting that long-term changes of the BBB could participate in the establishment of neurodegenerative process. We hypothesized that early TBI induces changes in the neurovascular unit (NVU), associated with  $A\beta$  accumulation. We investigated NVU changes up to 6 months in a rat jTBI model, with a focus on the transporter P-glycoprotein (P-gp) and on the basement membrane proteins perlecan and fibronectin, known to be involved in  $A\beta$  clearance.  $A\beta$  staining is present and increased after jTBI around cerebral blood vessels, and the diameter of the cerebral microvessels is decreased by 25 and 34% at 2 and 6 months, respectively, without significant angiogenesis. P-gp staining in endothelium is decreased by 22% and parallels an increase of perlecan and fibronectin staining around cerebral blood vessels.

In conclusion, a brain injury occurring during childhood could accelerate neurodegenerative processes underlined by  $A\beta$  deposition and leading to cognitive dysfunctions. Associated with  $A\beta$  accumulation, the BBB

phenotype is changed with a decrease of P-gp and an increase of perlecan and fibronectin, both proposed to be involved in  $A\beta$  fibrillization and stabilization. These results strongly suggest that the emergence of behavioral dysfunctions observed in our model at long-term could be related to vascular dysfunctions such as a decrease of  $A\beta$  clearance.

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#### A SWINE MODEL OF INTRACELLULAR CEREBRAL EDEMA

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Large animal models of traumatic brain injury (TBI) provide a platform to study cerebral physiology but to date, few have succeeded in achieving raised intracranial pressure (ICP) above the 20–25 mm Hg threshold considered critical in human TBI. We describe a swine model of water intoxication and its cerebral histological and physiological sequale.

Female swine weighing 35–45 kg were anesthetized and continuously monitored with systemic and cerebral physiological monitors including ICP and Licox brain tissue oxygen tension (PbtO<sub>2</sub>) monitors. Four serum sodium intervals were designated: baseline (135–145 mEq/L), mild (130–134 mEq/L), moderate (125–129 mEq/L), and severe hyponatremia (116–124 mEq/L), and attained by infusing hypotonic saline. Both at baseline and at the end of the experimental protocol a wedge biopsy was obtained for pathological examination and electron microscopy.

We studied 8 swine that received a total of  $7.0 \pm 2.0$  liters of hypotonic saline over a mean of  $4.5 \pm 1.1$  hours. We found a substantial and consistent rise in ICP with decreasing serum sodium. Mean ICP rise from a baseline value of  $6 \pm 2$  to  $28 \pm 6$  mm Hg during severe hyponatremia, while cerebral perfusion pressure (CPP) decreased from a baseline of  $72 \pm 10$  to  $46 \pm 11$  mm Hg. We also found a decrease in PbtO<sub>2</sub> from a baseline value of  $18.4 \pm 8.9$  to  $5.2 \pm 3.0$ . Electron microscopy demonstrated substantial intracellular edema and astrocytic foot process swelling following water intoxication.

The swine model of water intoxication leads to elevated ICP, decreased PbtO<sub>2</sub>, and intracellular cerebral edema demonstrated on electron microscopy. This model may be a useful platform with clinical relevance to study intracellular cerebral edema in a setting similar to the modern ICU.

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#### DO PATIENTS WITH TRAUMATIC BRAIN INJURY AND GCS SCORE 13 HAVE DIFFERENT MRI FINDINGS OR OUTCOME THAN PATIENTS WITH GCS 9–12?

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There is no agreement whether a traumatic brain injury (TBI) with Glasgow Coma Scale (GCS) score 13 should be classified as mild or moderate. Objective was to compare MRI findings and functional outcome in patients with GCS score 13 and patients with GCS score 9–12. During 2004–2009, 119 patients (aged 6–94) with GCS score 9–13 were admitted to a level I trauma center, and 67 (56%) had early MRI (FLAIR, T2\*GRE and DWI) at median 8 days (range 0 to 28 days). Patients were divided into GCS score 13 (n=27; mean age 35) and GCS score 9–12 (n=40; mean age 36). Outcome was assessed with Glasgow outcome Scale Extended (GOSE) after 12 months. MRI was normal in 1 patient with GCS score 13 and in 1 with GCS score 9–12. Traumatic axonal injury (TAI) was found in 16 patients (59%) with GCS score 13 and in 30 patients (75%) with GCS score 9–12 (p=0.29). TAI in the brain stem (TAI grade 3) was more common in patients with GCS score 9–12; (28% vs. 7%; p=0.041). No difference was found regarding frequency of contusions (p=0.32). 78% of patients with GCS score 13 and 63% of patients with GCS score 9–12 experienced good recovery (GOSE 7–8) (p=0.19). Almost all patients with GCS score 13 exhibited MRI findings, and frequency of TAI or contusions was not different from patients with GCS score 9–12. Patients with GCS score 13 had less often TAI in the brain stem. Outcome did not differ significantly.

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#### DECOMPRESSIVE CRANIECTOMY VS HINGE CRANIOTOMY IN PATIENTS WITH SEVERE TRAUMATIC BRAIN INJURY – A PROSPECTIVE STUDY

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The problem of treatment of severe head injury neurosurgical patients with refractory intracranial hypertension (RIH) was dilemma for neurosurgical community for decades. Despite progress in understanding, monitoring and treatment the outcome of patients with intracranial hypertension and brain edema remains poor.

We have compared the effects of treatment and outcome of patients who have undergone to classical decompressive craniectomy (DC) and modified spared technique Hinge craniotomy (HC) in patients with severe traumatic brain injury (TBI).

In a prospective controlled randomized three-year study we followed 67 patients with RIH. In 41 patients the cause of the RIH was severe TBI. Of the 41 patients with TBI, 29 were treated surgically (29/41, 70%). Thirteen (44.8%) patients were treated with DC, 10 patients (34.5%) with HC, while 6 patients (20.7%) were treated with both DC and HC (bilateral craniectomy/craniotomy).

Results suggest that surgical treatment of patients with RIH as terminal treatment option is justified and superior compared to conservative treatment. The decision whether to make a DC or HC should be made intraoperatively depending on the findings and the condition of the brain, rather than preoperatively only on the basis of imaging. In both techniques it is crucial to make the basal decompression by removing the lateral wall and part of floor of middle cranial fossa in order to relieve compression of the brain stem and prevent uncal herniation.

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#### A LONGITUDINAL COHORT STUDY OF PATIENTS WITH MILD AND MODERATE TBI: A PILOT STUDY

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Outcome after mild and moderate traumatic brain injury (TBI) varies greatly. Prospective studies combining advanced MRI with a broad collection of predictors are needed. As preparation for a collaborative study with University of Cambridge, and participation in the EU study CENTER-TBI, a pilot study was conducted. The objective was to investigate the frequency of eligible patients, willingness to participate, feasibility of study procedures and also provide preliminary results.

Patients with TBI (18 to 60 years) and Glasgow Coma Scale (GCS) score 9–15 were prospectively included for 12 weeks from a regional Level 1 Trauma Center in Norway and the municipal outpatient clinic. All patients were asked to participate with basic information (cohort 1). Those without major premorbid medical conditions were selected to an in-depth study with repeated advanced MRI, questionnaires and cognitive computerized testing (CANTAB) (cohort 2). Outcome was assessed in all patients 3 months post-injury.

To date, after 8 weeks of inclusion, 38 patients satisfied inclusion criteria and 34 (90%) were enrolled. 19 of these (55%) were eligible for cohort 2, whereof 5 chose only basic registration. 66% had GCS score 15. CT was performed in 94% (abnormal in 22%). The completed pilot sample will be presented at the conference with CT and MRI findings, rate of post-concussion syndrome, emotional/somatic symptoms and premorbid factors.

Rate of participation was high. We recommend differentiating level of participation, since most patients were willing to report outcome, but several were excluded from the in-depth study.

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#### WHOLE BRAIN TRACTOGRAPHY – A PROGNOSTIC TOOL IN ACUTE PHASE OF TBI AND SAH – PRELIMINARY RESULTS

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Severe traumatic brain injury (TBI) and subarachnoid haemorrhage (SAH) are the most common pathologies on the neuro-ICU and are

associated with high mortality and morbidity. Diffusion tensor imaging (DTI) can provide useful information on the extent of damage in these conditions.

50 patients (28 SAH and 22 TBI) were included in an observation study. In these patients MRI with DTI analysis were performed on day twelve after admission. Due to various reasons (early death, haemodynamic instability, high oxygen requirements) some patients were not able to transport to the MRI, leaving 30 MRI scans (15 SAH, 15 TBI).

Fractional anisotropy (FA), average tract length, number of tracts, total tract length, axial diffusivity, radial diffusivity and mean diffusivity were measured in all patients. These results were compared between survivors and non-survivors at 6 months. The analysis was performed for the SAH and TBI group alone and the total group. Preliminary results show that DTI analysis on day 12 show significant differences between survivors and non-survivors at 6 months on FA, average tract length, total tract length and number of tracts. No differences were observed between patients with SAH and TBI. Preliminary results from MRI scanning with diffusion tensor imaging (DTI) show significant differences between survivors and non-survivors on day 12. No differences were observed between the SAH and TBI patients, which is important since both have different pathophysiological mechanisms. However these results are very promising, further research and validation in larger patient populations is needed.

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#### **RESCUE-ASDH STUDY – A RANDOMISED TRIAL OF PRIMARY DECOMPRESSIVE CRANIECTOMY VERSUS CRANIOTOMY FOR ACUTE SUBDURAL HAEMATOMAS**

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In the context of TBI, the bone flap can be left out when evacuating an acute subdural haematoma (ASDH) in the acute phase (primary decompressive craniectomy; DC).

The RESCUE-ASDH trial (Randomised Evaluation of Surgery with Craniectomy for patients Undergoing Evacuation of Acute Sub-Dural Haematoma) is a multi-centre, pragmatic, parallel group randomised

trial of primary DC versus craniotomy for head-injured patients with an ASDH.

RESCUE-ASDH aims to determine the effectiveness of DC versus craniotomy in 'the real world'; hence, following consent, surgeons will decide upon the suitability for randomisation of individual patients intra-operatively similar to routine practice.

The criteria which will be used to determine eligibility of individual patients are:

- *Inclusion criteria*

- Adult head-injured patients (aged >16 years)
- Acute subdural haematoma on CT
- The admitting neurosurgeon feels that the haematoma needs to be evacuated either by a decompressive craniectomy or craniotomy (bone flap >11 cm)

- *Exclusion criteria*

- Bilateral fixed and dilated pupils and/or brainstem injuries on CT
- Uncorrected coagulopathy
- Severe pre-existing physical or mental disability or severe comorbidity which would lead to a poor outcome even if the patient made a full recovery from the head injury.

The primary outcome measure will be the extended GOS at 12 months post-injury. The study will start with an internal pilot phase in July 2014, which, if successful will be followed by the substantive phase.

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**WITHDRAWN**

### SHOULD PATIENTS WITH GCS SCORE 13 BE CLASSIFIED AS MODERATE TRAUMATIC BRAIN INJURY?

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There is no agreement whether patients with Glasgow Coma Scale (GCS) score 13 should be classified as mild or moderate traumatic brain injury (TBI). The objective was to compare CT findings and functional outcome in patients with GCS score 13 versus patients with GCS score 9–12. During a 7-year period (2004–2011), 170 patients with TBI (aged 6–97) and GCS score 9–13 were admitted to a level 1 trauma centre. They were divided into patients with GCS score 13 (n=69; mean age 47) and GCS score 9–12 (n=101; mean age 44). Intracranial pathology on CT scan at admission was described and classified according to Rotterdam CT classification. Outcome was assessed with Glasgow Outcome Scale Extended (GOSE) 12 months after injury. No differences were found regarding intracranial CT findings in patients with GCS score 13 compared to those with GCS score 9–12 (77% vs. 80%, p=0.57). There were no differences in the frequency of subdural haemorrhage, epidural haemorrhage, sub-arachnoid haemorrhage or cranial fractures. Median Rotterdam CT score was 3 in both groups (interquartile range, IR 2–3 in both groups, p=0.77). Median GOSE score was 8 in GCS score 13 and 7 in GCS score 9–12 (IR 6–8 in both groups), (p=0.34). Frequency of good recovery (GOSE 7–8) was 66% and 62% (p=0.63). TBI patients with GCS score 13 did not differ significantly from patients with GCS score 9–12 with regard to CT findings and outcome, and hence might be classified as moderate TBI.

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#### CAN MAGNETIC RESONANCE SPECTROSCOPY SIMULTANEOUSLY PROBE LINKS BETWEEN EDEMA AND ENERGY DISRUPTION FOLLOWING TRAUMATIC BRAIN INJURY?

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Following traumatic brain injury (TBI) energy disruption, neurons and astrocytes exude organic osmolytes, including taurine and inositol, to maintain volume homeostasis. Recent high-field magnetic resonance spectroscopy (MRS) findings have documented that taurine and inositol changes can be quantified non-invasively after TBI. Other evidence showing post-injury N-acetylaspartate (NAA) loss in humans and animals after TBI is often interpreted as mitochondrial dysfunction. Our goal was to determine whether organic osmolyte loss, presumably indicating edema, was associated with energy disruption. We used high-field 9.4T short echo STEAM MRS to quantify neurochemicals in cerebral cortex (lesion site) and hippocampus in 12 male F344 rats (3 mo) before and three days after a controlled cortical impact (5 mm tip, 3 m/s, 2 mm depth, 300 ms contact time). Animals

were anesthetized with isoflurane for all surgery and scanning in accordance with institutional guidelines. We used LCModel to determine absolute concentrations of N-acetylaspartate, lactate, taurine, and inositol. We calculated the change in neurochemical concentration after injury and the correlations between changes in pairs of neurochemicals. Data from both locations were combined to provide a range of injury severity. Taurine and inositol fell gradually after TBI providing evidence of cell volume osmoregulation. Taurine and inositol changes were also correlated ( $r^2=0.84$ ). NAA fell and lactate increased rapidly. Moreover, NAA and lactate changes were strongly correlated ( $r^2=0.76$ ) suggesting disrupted mitochondrial energy production leading to upregulated glycolysis. The strong correlation of loss of each of taurine and inositol ( $r^2>0.85$ ) with NAA loss suggests that energy metabolism might play a role in osmoregulation.

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#### MATRIX METALLOPROTEINASE 9 LEVELS ARE INCREASED IN PERI-CONTUSIONAL BRAIN: A PAIRED MICRODIALYSIS STUDY

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Matrix metalloproteinases (MMP) are a family of extracellular enzymes that have important roles in the secondary injury cascade following traumatic brain injury (TBI). In particular, MMP-9 has been implicated as a key mediator of blood brain barrier disruption, lesion expansion, and brain oedema in experimental models. Clinical studies have suggested that cerebral MMP-9 levels are increased in TBI patients but it remains unclear if this is localised to sites of focal brain injury such as contusions. Twelve patients with severe TBI admitted to critical care were enrolled in the study. Microdialysis catheters (CMA 71, 100 kDa cut-off) were inserted in peri-contusional brain, either via a cranial access device or at the time of craniotomy. A second microdialysis catheter was placed in radiologically normal brain based on the presenting CT scan. Microdialysate was assayed in a multiplex ELISA for MMPs 1, 2, 7, 9, and 10 (Millipore/Luminex). Data were analysed with repeated measures analysis of variance. Levels of MMP-9 were significantly higher in peri-contusional brain compared with radiologically normal brain (p=0.03). There was also a significant reduction in MMP-9 levels from early (<72 hours) to later time points (>72 hours) following injury (p=0.04). In contrast, levels of MMP-1, 2, 7, and 10 were comparable at both sites and did not show similar temporal changes. MMP-9 expression is increased early following TBI and is principally localised to regions of injury. Inhibition of MMP-9 may be a promising target to reduce contusion expansion and peri-contusional oedema.

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**WITHDRAWN**

### MILD TRAUMATIC BRAIN INJURY: VESTIBULAR CONSEQUENCES

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A mild traumatic brain injury (mTBI) is often invisible, producing no gross pathological evidence like a hemorrhage, or structural damage to the skull or areas of the brain that can be seen via CT scan or MRI. Recent works indicates that over 90% of patients will have mTBI associated balance disorders. mTBI is a difficult diagnosis to prove in court. Proving a brain injury to a jury when there is visible evidence gives the defense a strong case to present. To verify vestibular disorders in patients with mTBI, computer stabilography (CS) has been successfully used since recently. This retrospective analysis included 22 patients (age =  $35,5 \pm 0,9$  years: 10 males, 12 females) with mTBI. A standardized clinical protocol for the examination was used. The average age of patients was years. Postural control function was assessed with "Stabiloanalyzer 01-03" ("Rhythm", Russian Federation), using open and closed eye Romberg test and dynamic stability test with active maximum body bent in a prescribed direction. For the control group 15 healthy persons were used. Symptoms from concussions and mTBI may not present themselves for 24-to-72 hours after the injury, and not during the first couple of hours when most victims go to the ER for evaluation. Due to our results, a moderate disturbances level of subjective vestibular disorders (average score =  $3,6 \pm 0,5$ ), according to the International classification of functional disturbances scale (WHO, 2001) was found. Almost at 54.5% of inspected patients, a spontaneous nystagmus during first days after trauma was exposed and also his complete disappearance by 10–13 day after a trauma was marked. All patients showed specific stabilography changes and among them the extension of statokinesiogram area over than  $200\text{mm}^2$  was marked as the most prominent. The fluctuations of pressure center was more significant in the sagittal plane. Values of "speed" and "quality of equilibrium function" were lower ( $p < 0,05$ ) in comparison with control group. Vestibular disorders are the most common manifestations ('sentinel finding') of mTBI. A concussion or a mTBI can seriously impact on the quality of life, ability to gainfully work, and developing stable personal and social relationships. The use of CS in patients with mild head injury opens new opportunities of medical-legal evaluation of vestibular dysfunction.

### INCIDENCE AND RISK FACTORS FOR SUICIDAL IDEATION AFTER MILD TRAUMATIC BRAIN INJURY

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Mild traumatic brain injury (mTBI) is highly prevalent and may be associated with risk of suicidal ideation (SI). Little attention is given to identification of possible risk factors for SI in ER assessment. A large cohort of mTBI patients was examined prospectively to investigate the prevalence and risk factors for SI. Prospective data was collected over 14 years. Over 50 demographic, outcome and psychometric measures were evaluated: radiological and clinical features collected at admission, psychiatric and social assessment at 3 and 6 months. Chi-square analyses were used to determine correlates of SI, logistic regression analysis to model the predictors. 2296 patients (mean age = 34.7) were seen, 82% suffered mTBI. The frequency of SI was high: 24% (3 months) and 53% (6 months). Altered level of consciousness ( $p = 0.008$ ) and female sex ( $p = 0.01$ ) was correlated with higher probability of SI. Radiological and clinical variables (GCS, amnesia length, CT findings) commonly assessed in the ER were not. In follow-up there was an increase in incidence of SI. At 6 months unemployment ( $p = 0.024$ ) and no past history TBI ( $p = 0.0008$ ) were predictive of SI, while initial clinical and radiological findings were not. Suicidal intent following mTBI is frequent and risk does not decrease with time from injury. Current routines for assessment of mTBI fail to identify patients at highest risk. Improvements in the ER assessment with inclusion of demographic, psychiatric and socioeconomic factors in the initial evaluation. Our observation of a delayed increase in SI indicates a time window for therapeutic intervention.

### SYMPTOMS AFTER MILD TRAUMATIC BRAIN INJURY CORRELATE WITH CEREBROVASCULAR REACTIVITY CHANGES IN BOLD MRI

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The aim of this study is to investigate the relationship between cerebrovascular reactivity (CVR) to  $\text{CO}_2$  measured with BOLD MRI and post concussion symptoms (PSC) following a mild traumatic brain injury (mTBI). Twenty-five patients (mean age = 42.6; 72% males) who sustained a recent mTBI were submitted to CVR testing using MRI blood oxygen level dependent (BOLD) images (average 63 days post-injury) and  $\text{CO}_2$  manipulation with the RespirAct™, a

custom built automated gas sequencer and breathing circuit combination. PSC was assessed using SCAT2 questionnaire. Mean CVR indexes were generated for whole brain, grey and white matter. Pearson coefficient was used to evaluate the correlation between global, White Matter (WM) and Grey Matter (GM) CVR and SCAT-2 scores. Global CVR and SCAT-2 showed a significant correlation ( $r=0.4$ ,  $p=0.048$ ), with patients with lower CVR indexes (indicating a state of vasoparalysis in response to CO<sub>2</sub>) more likely to have lower SCAT2 scores (more symptoms). A significant correlation was also found between GM CVR and SCAT2 scores ( $r=0.4$ ,  $p=0.044$ ). No significant relationship was found between gray matter WM CVR and SCAT2 ( $r=0.31$ ,  $p=0.13$ ). Severity of PSC correlates with impairment of CVR seen on BOLD MRI. Regional variations in CVR impairment can be detected by the technique. BOLD CVR needs to be investigated longitudinally as an imaging indicator of severity of injury in seemingly mild injuries, and may help to answer important questions such as time to return to work / play, and monitor response to treatment.

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### BLOOD BRAIN BARRIER DISRUPTION PERSISTS FOR YEARS AFTER A SINGLE TRAUMATIC BRAIN INJURY IN HUMANS

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Traumatic brain injury (TBI) is a recognised risk factor for dementia, with the associated pathology best described as a 'poly pathology'. However, the mechanism driving this late neurodegeneration remains elusive. Increasingly, blood brain barrier (BBB) disruption is recognised as a facet of a range of neurological disorders, including neurodegeneration. Whilst acute BBB disruption is recognised post-TBI, the longer term dynamics of this disruption remain to be described. From the Glasgow TBI Archive cases of single moderate/severe TBI with survival greater than 1 year ( $n=32$ ) and age matched controls ( $n=21$ ) were identified and sections of parasagittal cortex stained for fibrinogen and immunoglobulin G as markers of BBB disruption. These sections were then screened and assessed for pattern, distribution and extent of staining using a standard semi-quantitative scoring system.

Widespread extravascular fibrinogen immunoreactivity was present in a higher proportion of long-term TBI survivors (58%) in comparison to age-matched controls (9.5%). This increased staining was evident in all anatomical regions examined, including all cortical layers and at the crests of gyri and depths of sulci; though the greatest difference was noted in the deeper cortical layers (layers IV-VI). A similar pattern and distribution of immunoreactivity was observed in sections stained for immunoglobulin G.

These results provide evidence of widespread BBB dysfunction in a majority of long-term TBI survivors in comparison to more localised and limited disruption in a smaller number of age-matched controls. This post-TBI BBB disruption requires further characterisation and may serve as an anatomical substrate contributing to post-TBI neurodegenerative pathologies.

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### RECURRENT TRAUMATIC BRAIN INJURY (TBI) IN A NEW ZEALAND POPULATION-BASED INCIDENCE SAMPLE

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The impact of recurrent traumatic brain injury (TBI) is far in excess of what would be expected if the subsequent injury occurred in isolation. However, little is known about the prevalence, risk factors and long-term consequences of sustaining more than one (recurrent) TBI in the general population.

All new cases of TBI were identified over a one-year period as part of a population-based TBI incidence study using multiple, prospective, case ascertainment sources in the Hamilton and Waikato districts of New Zealand. All living cases of all ages were invited to participate in a follow-up assessment, one-year post-injury to assess the occurrence of recurrent brain injuries, post concussive symptoms, cognitive functioning, and community integration.

Prior to entry into the incidence study, 27% of the total sample ( $N=725$ ) of participants had experienced a previous TBI. Over the one year follow-up period, 8% had sustained at least one further TBI. Recurrent injuries occurred most frequently in males (60%), with highest peaks in prevalence in the under 5's and 18–25 year olds. The most frequent mechanisms of recurrent injuries were falls (47%) and assaults (16%). Children and young adults were at greatest risk of recurrent injury, increasing the lifetime impact of recurrent TBI. Given the mechanism of injury was frequently the same as the registering injury, the results suggest that greater efforts are needed to prevent recurrent TBIs.

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### INCIDENCE OF TRAUMATIC BRAIN INJURY ACROSS THE SPECTRUM: A POPULATION-BASED STUDY IN NEW ZEALAND (THE BIONIC STUDY)

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Traumatic brain injury (TBI) is a leading cause of disability in children and young adults. Yet despite the high frequency and impact of TBI, few population-based incidence studies have been conducted, potentially resulting in cases of TBI being missed from incidence estimates.

A prospective population-based TBI incidence study was conducted in the Hamilton and Waikato regions of New Zealand (173,205 residents). All new cases of TBI (in people of all ages) including hospitalised/non-hospitalised and fatal/non-fatal injuries that occurred over a 12-month period (2010–2011) were identified using multiple overlapping sources of information. Incidence rates per 100,000 person-years with 95% confidence intervals (CI) were calculated using Poisson distribution.

The total incidence rate of TBI was 790 (95% CI 749, 832) per 100,000. The majority of cases (95%) were classified as mild in severity, with 36% of cases not attending hospital immediately following injury. Nearly 70% of all TBI cases were aged <35 years. Males had a 77% (95% CI 58%, 97%) greater risk of sustaining a TBI than females. The most common mechanism of injury was due to a fall (37.7%).

The incidence of TBI, particularly mild TBI, is far greater than previously estimated. Case ascertainment methods need to include community sources of referrals to capture the full spectrum of TBI. The high proportion of people not attending hospital following injury is a concern and programmes to increase awareness of TBI and potential complications are urgently needed.

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**WITHDRAWN**

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#### **RIGHT MEDIAN NERVE ELECTRICAL STIMULATION IMPROVES THE OUTCOME OF TRAUMATIC COMA PATIENTS**

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To evaluate the clinical benefits of right median nerve electrical stimulation on traumatic coma patients. Coma patients following traumatic brain injury were recruited into clinical trial from 2005 to 2011. Patients were randomized to receive routine management or routine management plus right median nerve electrical stimulation (RMNS) according to the trial protocol. All patients received RMNS treatment 2 week or more and were followed up at the end of 6 months after injury, to the endpoint of level of consciousness. In right median nerve electrical stimulation group, 122 of 204 patients regained consciousness and 84 of 182 patients from control group were awakened. Both the brain stem auditory evoked potentials and blood perfusion in treatment group were improved significantly. The technique of right median nerve electrical stimulation shows effectiveness on unconsciousness and might be therapeutic choice which benefits the outcome of traumatic coma patients.

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#### **REGENERATION AND RELAYS IN THE INJURED SPINAL CORD**

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Over the last 20 years, major advances have been made in understanding the mechanisms limiting axonal regeneration in the injured adult mammalian CNS. Besides inhibitory signals and a lack of stimulatory influences in the environment of injured axons, a means to activate the regenerative capacity of injured neurons might be needed to achieve long-distance growth of injured axons. Regeneration of the dorsal column sensory axon system has been one focus of our experiments to achieve functional target reinnervation across a spinal cord lesion site using a combination of cellular graft, neurotrophin gradients and stimulation of the intrinsic growth competence of injured neurons. As an alternative approach, neural stem cells grafted to a lesion site might be able to serve as a neuronal relay that receives supraspinal input and sends projections to distal target neurons. This approach has recently been shown to partially restore some sensorimotor and cardiovascular parameters in rats with complete spinal cord transections. This talk will summarize some of these data highlighting the complexity of axonal regeneration for meaningful functional recovery.



assessment in specific axonal subdomains by using CypD<sup>-/-</sup> and CypD<sup>+/+</sup> mice expressing neuronal yellow fluorescent protein (YFP). Mice were exposed to either sham or cFPI with 3 or 24 h survival times. YFP positive axonal swellings were counted and categorized as localized within or exterior to the axon initial segment (AIS). Axonal varicosities, defined as an axon containing multiple adjacent swellings, were classified as callosal or cortical. The number of axonal swellings was not significantly reduced in CypD<sup>-/-</sup> animals compared to CypD<sup>+/+</sup> animals, regardless of location or time-point. Absence of CypD did, however, significantly decrease the numbers of both callosal (48%) and cortical (57%) varicosities at 24 h, but not at 3 h post-injury. Further, survival time point comparisons in CypD<sup>+/+</sup> mice revealed a statistically significant eight-fold reduction of AIS swellings over time while the callosal varicosities increased seven-fold and cortical varicosities increased two-fold. These results further support the role for CypD as a potential drug target for axonal injury although its effect may be restricted to specific axonal compartments. The striking difference in temporal dynamics between axonal swellings located in the AIS compared to the varicosities may suggest a difference in the underlying molecular mechanisms in these compartments.

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#### **AXONAL INJURY AND MICROGLIAL ACTIVATION FOLLOWING MILD DIFFUSE TRAUMATIC BRAIN INJURY IN THE PIG: A COMPONENT OF THE OPERATION BRAIN TRAUMA THERAPY CONSORTIUM**

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Traumatic brain injury (TBI) is a major health care concern. Although our knowledge of the complex pathologies associated with TBI has progressed and many therapeutics have shown promising results in rodent models of TBI, this efficacy has been limited when translated to humans. Recently there has been a call for higher order animal experimental models to better evaluate potential therapeutics prior to human translation. With this goal in mind we have begun characterization of a central fluid percussion injury (CFPI) model of mild diffuse TBI in the adult micro pig. In this model, macroscopic examination of the brain at six hours post-TBI was followed by quantitative assessment of diffuse axonal injury (DAI) achieved by computer assisted counting of axonal profiles exhibiting accumulation of amyloid precursor protein (APP). The CFPI employed did not result in contusion or hematoma formation and only minimal subarachnoid hemorrhage was apparent, consistent with mild diffuse TBI. Analysis of multiple brain sites revealed DAI, which was particularly abundant in the thalamus and corpus callosum. Increases in morphologically altered Iba-1 + microglia were also observed in areas associated with DAI, with the suggestion that these cellular responses are linked. The consistent spatial and temporal features of DAI in this animal model are reminiscent of those seen in humans, suggesting that this would constitute an excellent animal model for future drug screening. Supported by the US Army grant W81XWH-10-1-0623.

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#### **A TIME-COURSE OF HISTOLOGICAL AND BEHAVIORAL PATHOLOGY ASSOCIATED WITH INTRACRANIAL PRESSURE ELEVATION FOLLOWING MODERATE DIFFUSE TRAUMATIC BRAIN INJURY**

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The association between secondary elevations of intracranial pressure (ICP) above 20 mmHg following traumatic brain injury (TBI) and increased mortality/negative outcomes in humans has been well established. Apart from global ischemia caused by the impact of extremely elevated ICP on cerebral perfusion pressure (CPP), however, little is known about the pathology associated with modestly elevated ICP following TBI. The current study explores the histopathology and behavioral morbidity associated with elevated ICP over time post-TBI. We utilized a model of moderate TBI in rats followed by either intraventricular ICP monitoring or manual ICP elevation to 20 mmHg without reducing CPP below autoregulatory limits, precluding ischemia. Neuronal pathology was quantified via hematoxylin and eosin analysis. The degree of myelin pathology was semi-quantitatively analyzed via myelin basic protein immunohistochemistry. To evaluate the effect of elevated ICP on behavioral morbidity we utilized the whisker nuisance task, in which the whiskers were manually stimulated and responses to this normally innocuous stimulation were analyzed. All histological and behavioral analyses were assessed through 8 weeks following moderate TBI with or without secondary ICP elevations. These ongoing studies demonstrate that histopathology and behavioral morbidity are altered over time by modest ICP elevations following TBI, independent of global ischemia, as compared to animals sustaining TBI alone. Additionally the histopathology directly correlates to behavioral morbidity, specifically at 4 weeks post-TBI. Understanding these ICP-mediated pathologies could lead to better therapeutic management of patients with TBI and ICP elevation.

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#### **25 YEARS EXPERIENCE OF DC: THE QUESTION HAS BEEN REDUCED TO ONLY WHEN AND HOW INSTEAD OF DOING IT OR NOT**

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The debate around DC has lasted for 100 years. The top of the unbelievable process was the publication of DECRA published in NEJM (2011). Our aim was to certify the debate about when and how to do it instead of doing it or not. The question was examined not only from the scientific point of view, but of bioethics, as well. We examined the results of 43 DC including 4 very early DC in children. DC was performed above 25 mmHg ICP for 2–3 hours. The very early DC was performed above 20 mmHg ICP. Exclusion criterion was the fatal brain stem damage on CT. We performed a historical comparative study with a control group treated conservatively with the same method in 20 patients. The mortality rate within one month decreased by 60%. Severe disability within 1 year follow-up decreased by 35%. Good recovery increased by 50%. Death can be caused by hundreds of unknown factors so we must not examine the cases according to some well known constants like ICP, CT scan etc. Probably we are going to operate many times in vain, but we can avoid the mindless death of the patients especially in children caused by a reversible curative pathological process called brain oedema. We should continue the debate not about the performance of DC, but how to increase the efficacy of the DC.

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#### **THE CEREBROVASCULAR AND AXONAL RESPONSES TO REPETITIVE MILD TRAUMATIC BRAIN INJURY IN THE JUVENILE RAT**

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We have previously reported the damaging consequences of repetitive mild traumatic brain injury (mTBI) in adult rats while identifying various neuroprotective strategies. In this communication we revisit repetitive brain injury in the juvenile brain to determine if the threshold for injury and the intervals between repetitive injury needed for damage are comparable to those in adults and if they respond in a similar fashion to select therapeutic interventions including mild 35°C vs. moderate 33°C hypothermia. Juvenile rats were subjected to a subthreshold mTBI incapable of eliciting either axonal or vascular change, yet when repeated within a 3 h timeframe could evoke significant microvascular dysfunction and/or axonal damage. The potential for vascular function was assessed through the use of cranial windows, with the analysis of fixed tissue for APP immunoreactivity to assess the burden of axonal damage. Unlike adult rats, a significantly reduced level of subthreshold impact was needed to elicit significant vascular dysfunction when the TBI was repeated within 3 h. Unlike the adults, this repetitive injury did not evoke significant APP linked axonal damage. Further, unlike the adult situation, only the use of moderate hypothermia - but not mild hypothermia - provided significant cerebrovascular protection. These results illustrate that juvenile brains are significantly more vulnerable to lower threshold injuries and that their therapeutic attenuation requires more aggressive therapeutic approaches than those proving efficacious in adults.

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#### **CORTICAL REORGANISATION IN THE CHRONIC PHASE OF SPINAL CORD INJURY**

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Plastic changes within cortical areas occur after traumatic spinal cord injury (TSCI).

The aim of the study was to assess cortical activation in the chronic phase of TSCI using functional magnetic resonance imaging (fMRI). Ten right-handed patients with paraplegia and 18 age- and gender matched healthy controls were studied by fMRI. Individuals performed simple flexion/extension of the right hand fingers and the right ankle during fMRI. The activation volumes, maximum t values (Tmax) and centres of gravity (COG) were calculated. The extent of injury was estimated according to the American Spinal Injury Association (ASIA) classification scale.

The mean time since trauma was  $1848 \pm 1046$  days (range 388 – 4459). During hand movements the volume of activation (VOA) in the contralateral primary motor cortex was nonsignificantly larger among the TSCI patients (3650 vs 2777,  $p=0.09$ ). The VOA of the patients with complete TSCI who did not recover was significantly larger than the controls (4112 vs 2777,  $p=0.02$ ). The VOA did not enlarge during the ankle movement (2420 vs 1114,  $p=0.08$ ).

The Tmax values and COGs in BA4 were similar in both groups. There was a significant relationship between the VOA in BA4 and ASIA motor score ( $p=0.03$ ) during hand movements but no correlation was found during ankle movement (0.41). A positive correlation was also found during hand movement in the VOA of BA4 and time since injury ( $r=0.62$ ,  $p=0.05$ ).

The increased cortical activation in the chronic phase of thoracolumbar TSCI may be caused by increased use of upper limbs.

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#### **COMBINED TREATMENT OF SELF-ASSEMBLING PEPTIDES AND NEURAL PRECURSOR CELLS AFTER EXPERIMENTAL CERVICAL SPINAL CORD INJURY**

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The pathophysiology of spinal cord injury (SCI) involves inflammation and tissue scarring interfering with regeneration and recovery. A combined treatment approach with self-assembling peptides (SAP) and neural precursor cells (NPC) might improve this inhibitory environment and neuronal regeneration.

Following cervical laminectomy, rats were subjected to SCI. After randomization (NPC, SAP, NPC+SAP, vehicle, sham) SAPs and NPCs were injected into the spinal cord 1 day and 14 days after trauma. All animals received growth factors subdurally and immunosuppressive therapy. Neurological function was assessed on a weekly basis. 4 weeks after SCI rats were sacrificed and cryosections were prepared for immunohistochemical staining.

Animals treated with SAPs showed a larger amount of surviving NPCs ( $18.088 \pm 4.044$  vs.  $11.493 \pm 4.111$ ;  $n=6$ ;  $p=0.019$ ) and greater levels of differentiation: neurons (8.7% vs. 5.8%;  $p=0.015$ ) and oligodendrocytes (11.6% vs. 9.1%;  $p=0.005$ ). Furthermore, animals treated with SAPs alone or as a combined approach with NPCs had smaller intramedullary cysts ( $p=0.07$ ) and a larger percentage of preserved tissue. In the combined treatment group astrogliosis (GFAP density) and tissue scarring (CSPG density) were significantly reduced. Though the total number of motor-neurons was diminished, there was no significant difference between the groups. Synapt connectivity (Synaptophysin-density) was increased both in the NPC and in the combined treatment group. Behavioral assessments showed improvements favoring the animals treated combinatorially 4 weeks after SCI.

Shaping the inhibitory environment using SAPs reduces astrogliosis and tissue-scarring, supports NPC survival and differentiation, and reduces intramedullary cyst formation leading to an improved neurological outcome.

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#### **PITUITARY ADENYLATE CYCLASE-ACTIVATING PEPTIDE (PACAP) INDUCES AGE-DEPENDENT CHANGES IN VASOMOTOR RESPONSES ON ISOLATED RAT ARTERIES**

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PACAP is a potent vasodilator, but less is known about its organ specific and age related vasomotor effects. We hypothesized that

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vasomotor effects of PACAP depend on the origin of vessels and aging substantially modulates them.

Carotid (CA) and basilar arteries (BA) were isolated from young (2 month: 2 m, n=7) and senescent (28 months: 28 m, n=7) rats. Their vasomotor responses were measured with an isometric myograph (DMT-610M) in response to cumulative concentrations of PACAP 1-38 ( $10^{-9}$  M -  $10^{-6}$  M).

Isolated CAs and BAs were contracted by KCl (60 mM, CA: 2 m:  $6 \pm 0.51$  mN, 28 m:  $3.48 \pm 0.58$  mN and BA 2 m:  $5.43 \pm 0.35$  mN, 28 m:  $4.52 \pm 0.44$  mN, respectively). In 2 m CA, reduction in isometric force to increasing concentrations of PACAP were: ( $\Delta F$   $10^{-9}$  M:  $-0.37 \pm 0.07$  mN,  $\Delta F$   $10^{-8}$  M:  $-1.08 \pm 0.09$ ,  $\Delta F$   $10^{-7}$  M:  $-1.77 \pm 0.08$ ,  $\Delta F$   $10^{-6}$  M:  $-2.3 \pm 0.12$  mN;  $p < 0.05$ ), whereas in 28 m CA, there were only slight reduction in isometric force ( $\Delta F$   $10^{-9}$  M:  $-0.13 \pm 0.03$  mN,  $\Delta F$   $10^{-8}$  M:  $-0.2 \pm 0.04$ ,  $\Delta F$   $10^{-7}$  M:  $-0.36 \pm 0.06$ ,  $\Delta F$   $10^{-6}$  M:  $-0.83 \pm 0.12$  mN;  $p < 0.05$ ). In BA, relaxations to increases concentration of PACAP was minimal, both in 2 m and 28 m old rats (2 m:  $\Delta F$   $10^{-9}$  M:  $-0.26 \pm 0.08$  mN,  $\Delta F$   $10^{-8}$  M:  $-0.73 \pm 0.08$ ,  $\Delta F$   $10^{-7}$  M:  $-0.85 \pm 0.12$ ,  $\Delta F$   $10^{-6}$  M:  $-0.86 \pm 0.11$  mN;  $p < 0.05$ ; and 28 m:  $\Delta F$   $10^{-9}$  M:  $-0.23 \pm 0.08$  mN,  $\Delta F$   $10^{-8}$  M:  $-0.47 \pm 0.07$ ,  $\Delta F$   $10^{-7}$  M:  $-0.58 \pm 0.05$ ,  $\Delta F$   $10^{-6}$  M:  $-0.68 \pm 0.05$  mN;  $p < 0.05$ ), whereas responses of BA 2 m and 28 m did not differ from each other. Thus PACAP elicits dose-dependent relaxations in isolated CA and BA of rats, which were significantly greater in CA than in BA. Aging substantially reduces PACAP-induced relaxations in CA, but not in BA, which favor the idea that PACAP provides specific vasoprotection for cerebral vessels in older age.

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#### ROLE OF INTRACELLULAR CALCIUM-ION IN THE DEVELOPMENT OF HEMOLYSED-BLOOD INDUCED CEREBROVASCULAR CONSTRICTION

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Acute subarachnoid hemorrhage is followed by an early and delayed type of vasospasm, which severely reduces regional cerebral blood flow. However, the vasoconstrictor effects of whole hemolysed blood (HB) have not yet been characterized. We hypothesized that hemolysed blood reduces the diameter of cerebral vessels.

Basilar arteries (BA) were isolated from male Wistar-rats, cannulated at both ends and mounted into pressure-flow myograph chamber in the presence of zero flow and 80 mmHg of intraluminal pressure. Vessels diameter were measured by video-microscopy. The effect of extravasated blood was modeled by adding HB directly to the chamber. Changes of intracellular  $Ca^{2+}$ -ion concentrations were measured with ratiometric calcium-measurement at the wavelength of 340 and 380 nms using fura2-AM fluorescence dyes.

The AD of the BA was  $278 \pm 12 \mu\text{m}$ , whereas the passive diameter was  $392 \pm 8 \mu\text{m}$ . Perivascular HB ( $200 \mu\text{l}$  in 10 mL bath solution) reduced the diameter to  $164 \pm 11 \mu\text{m}$ . Presence of HB did not change the dilation to nifedipine ( $32 \pm 3$  vs.  $28 \pm 3$  BD%). HB increased the ratio of 340/380 nm from  $1.118 \pm 0.043$  to  $1.397 \pm 0.016$ . After washout the ratio returned to control level.

Thus hemolysed blood causes significant constrictions in isolated basilar arteries, which can be explained by the elevation of intracel-

lular  $Ca^{2+}$ -ion concentration in smooth muscle. These findings can contribute to the refinement of the treatment and better prognosis of patients with subarachnoid hemorrhage.

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#### THE $Ca^{2+}$ -BINDING PROTEIN S100B ELICITS A CONCENTRATION-DEPENDENT RELAXATION ON ISOLATED CEREBRAL ARTERIES

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The  $Ca^{2+}$ -binding protein-S100B (S100B) is expressed in the nervous system and in the extracellular space increased levels of S100B have been detected in several neurological disorders (e.g., brain injury and trauma). We hypothesized that S100B elicits dilation/relaxation of isolated rat basilar arteries.

Basilar arteries (BA) from 2 months-old rats were isolated and placed into an isotonic (diameter) or isometric (mN) myograph chamber, and responses to S100B ( $10^{-11}$  to  $10^{-6}$  M) were measured (isometric force and diameter). The maximal passive diameter and maximal relaxation of vessels were determined in the presence of nifedipine plus  $Ca^{2+}$ -free KREBS solution.

Basal diameter of BA was  $275 \mu\text{m}$  S100B significantly increased the diameter of BA in a dose-dependent manner (from  $280 \pm 7$  to  $317 \pm 8 \mu\text{m}$  at  $10^{-6}$  M,  $n=5$ ,  $p < 0.05$ ). Also, S100B elicited relaxation of BA (from  $0 \pm 0.02$  to  $-0.7 \pm 0.03$  mN,  $n=5$ ,  $p < 0.05$ ). Repeated administration of S100B elicited similar magnitude of changes. The ACh-induced vasomotor response did not change after S100B administration (diameter:  $92 \pm 15 \mu\text{m}$  vs.  $108 \pm 9 \mu\text{m}$ ,  $n=5$ ).

Thus the  $Ca^{2+}$ -binding protein S100B elicits dilation/relaxation of isolated basilar arteries without affecting endothelial function, suggesting that its mechanism of action relates to the smooth muscle  $[Ca^{2+}]_i$  level and we propose that S100B may provide neuroprotection in neurological disorders by increasing cerebral blood flow to the injured areas.

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#### "IMMUNE MARKERS OF INFLAMMATION IN TBI"

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Traumatic brain injury (TBI) is a complex disease to diagnose, treat and prognosticate. Much effort aims to identify biomarkers of brain injury to refine the diagnosis and prognosis of TBI. Biomarkers are defined as CNS proteins, released into blood and CSF following injury, which correlate with injury severity, neuroimaging findings and outcome. Although not brain-specific, inflammatory mediators have been investigated as potential biomarkers of TBI mostly due to their ability to exacerbate neurological damage or sustain repair. Cytokines are released within minutes following TBI to initiate, progress and terminate the inflammatory response. Several groups correlated cytokines measured in serum, plasma, CSF and microdialysates with GCS, ICP, TBI classification, GOS(E), mortality and BBB dysfunction. Although much endeavor exists to validate cytokines as biomarkers of TBI, the findings are sparse and often contradictory. Many groups have found no significant associations with clinical parameters, while others have shown that IL-6 and IL-8 and IL-10 correlate with mortality in both adults and pediatric TBI; Thresholds of IL-6 in plasma differentiate severe TBI whereas early IL-6 predicts ICP elevation. TNF was reported to correlate with higher ICP and lower CPP. IL-1 measured within 6 hours correlates with GCS and has been linked to poor outcome and increased ICP. The novel approach using IL-1/IL-1ra ratios in microdialysates revealed to predict favourable outcome; however the broad practicality of this method remains questionable. In this presentation, clinical studies on cytokine-related work will be discussed and related to experimental findings to highlight similarities and differences in cytokine research.

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#### REHABILOMICS RESEARCH: EXAMINING APPROACHES TO PERSONALIZED MEDICINE IN TBI

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The molecular mechanisms underlying TBI pathophysiology and recovery are both complex and varied. Further, the pathology and medical complications underlying many of the clinical sequelae observed in this population evolve over the acute injury period and encompass the subacute and chronic rehabilitation phases of recovery. This framework supports the contemporary concept that TBI is a chronic, yet temporally dynamic, state rather than a static insult from which limited recovery occurs. Despite ongoing neurodegeneration, and other chronic state pathology, the TBI recovery period is also characterized by a propensity for neuroplasticity and rewiring through multiple mechanisms. This Rehabilomics presentation summarizes key elements of how multidimensional and functional outcomes can be paired with genetic, proteomic, and hormonal biomarkers to inform chronic TBI pathology, to enhance early prognostication and screening measures, and to elucidate biosusceptibility markers for TBI relevant complications. In reviewing these concepts, implications for future research and theranostic principles for individualized patient care and comparative effectiveness studies are discussed.

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#### DECOMPRESSIVE CRANIECTOMY FOR REFRACTORY INTRACRANIAL HYPERTENSION OF SEVERE TRAUMATIC BRAIN INJURY IN CHINA

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Severe traumatic brain injured patients (GCS  $\leq$  8) were randomly divided into two groups: patients with standard trauma craniectomy group (n=241) got unilateral frontotemporoparietal bone flap (12 $\times$ 15 cm), and patients with limited craniectomy group (n=245) received routine temporoparietal scalp flap (6 $\times$ 8 cm). Refractory intracranial hypertension caused by unilateral massive lesions was confirmed on CT scan in all 486 cases. At 6 month follow-up according to Glasgow Outcome Scale (GOS), 96 cases in standard trauma craniectomy group had favorable outcome (39.8%), including 62 cases with good recovery and 34 cases with moderate deficit, other 145 cases got unfavorable outcome (60.2%), including 73 cases with severe deficits, 9 cases with persistent vegetative status and 63 cases with death. However, only 70 cases in limited craniectomy group got favorable outcome (28.6%), including 41 cases with good recovery and 29 cases with moderate deficit, other 175 cases had unfavorable outcome (71.4%), including 82 cases with severe deficits, 7 cases with persistent vegetative status and 86 cases with death (P<0.05). Furthermore, the incidence of delayed intracranial hematomas, incisural hernia and CSF fistulae in standard trauma craniectomy group was lower than that in limited craniectomy group (P<0.05). But the incidence of acute encephalomyelocele, traumatic seizure and intracranial infection was not significantly different between two groups (P>0.05). Our data confirm that Standard trauma craniectomy significantly improves the outcome of severe traumatic brain injured patients with refractory intracranial hypertension, which indicates that standard trauma craniectomy, but not limited craniectomy should be recommended for those patients.

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#### HEAD-INJURED PATIENTS WHO TALK AND DETERIORATE: ANALYSIS OF 192 CASES REGISTERED IN THE JAPAN NEUROTRAUMA DATA BANK

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The clinical course of talk and deteriorate (T&D) reflects serious progression of secondary brain injury. The treatment of traumatic brain injuries (TBI) is nothing but to prevent the secondary injury. It is important to understand the pathophysiology of T&D in establishing the treatment of the severe TBI. In order to clarify the clinical profile of TBI patients who T&D into coma, we reviewed 1091 patients with TBI who were registered in Japan Neurotrauma Data Bank from 2009 to 2011. One hundred ninety two (18%) patients presented T&D, and 160 deteriorated in to coma (GCS  $\leq$  8). In the majority of cases, CT scans revealed development of focal lesion(s) with mass effect and resultant midline shift. One hundred six patients (55%) had a subdural hematoma, 45 (23%) had an epidural hematoma, 26 (14%) had cerebral contusion / intracerebral hematoma and 15 (8%) had DBI. The GOS was GR in 26 (14%), MD in 27 (14%), SD in 50 (26%), VS in 27 (14%), and D in 62 (32%). The latent periods to deterioration were  $\leq$  3 hours in 110 (57%), 3–6 hours in 33 (17%), and > 6 hours in 49 (26%), demonstrating a shorter latency than those reported in previous studies. One hundred forty nine patients (78%) underwent surgery, i.e., evacuation of hematoma, and/or contusion necrotomy. The predictors for a poor outcome were a low GCS following deterioration, subdural hematoma, and being an elderly patient. In contrast, GCS during lucid intervals, and the length of time until deterioration or

until operative intervention did not influence the final result. A majority of cases showed deterioration within 6 hours post trauma, caused by a progressive mass effect. Deterioration into a low GCS resulted in a poor outcome, so early operative intervention is strongly recommended prior to the inevitable deterioration.

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### NEUROTRAUMA—THE ROLE OF THE RESIDENTS? THE CHANGING FACE OF TBI CARE

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Neurosurgical residents are the workhorses who are responsible for the primary care of neurotrauma patients. Neurotrauma is an important field within neurosurgery, but is often not perceived as challenging as vascular surgery. As a consequence residents lose interest in neurotrauma as they mature during training. Finding an appropriate balance between resident training and provision of the highest quality of care for these patients is challenging, especially outside of normal working hours. Limitations imposed by the EU Working Time Directive substantially impact on the quantity of exposure necessary for training, and variability between teachers can be confusing to residents. The extent of care the resident is allowed to perform with or without supervision is a factor for both training and quality of care. It might even, because of that, not get enough attention during training. In contrast, provision of the best quality of care requires knowledge of evidence-based medicine (and guidelines) and an experienced and interested doctor. In the care for neurotrauma roles are changing with an increased input of A&E and ICU doctors. Because of this, the risk exists that neurosurgeons take less interest in neurotrauma. Yet, neurosurgeons are the specialists with most knowledge of cerebral pathophysiology of neurotrauma and are best positioned to weigh the pros and cons of conservative versus surgical therapy. All that shifts the interest of neurosurgical residents away from neurotrauma and the question is: is this a good shift?

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### THE NEUROREGENERATIVE POTENTIAL OF S100B INDUCES SYNAPTOGENESIS FOLLOWING EXPERIMENTAL BRAIN INJURY

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We demonstrated earlier that the neurotrophic factor S100B increases hippocampal neurogenesis and promotes cognitive performance in a hippocampus-dependent learning task after traumatic brain injury (TBI). The objective of the present study was to elucidate cellular mechanisms mediating this positive effect on morphological and functional neuroregeneration. Rats were randomly subjected to lateral fluid percussion or sham injury and subsequent treatment (n=24). S100B (50 ng/hr) or vehicle was infused into the lateral ventricle for 7 days via an osmotic micropump. The expression of synaptophysin and ED1 (microglia) was quantified in the granular cell layer (GCL), CA3 region and hilus of the hippocampus and in the subcortical area in 5  $\mu$ m brain sections, 100  $\mu$ m apart (bregma -3.3 to -5.6 mm) on day 5 or 5 weeks post-injury.

While S100B induced a long-term synaptophysin expression in the GCL (p<0.05 on day 34) in non-injured rats, this effect was present only early

after TBI (p<0.05 on day 5). Microglial activation was widespread following TBI and S100B treatment (all areas: p<0.05 on day 34). The neurogenic activity of S100B induces a significant synaptogenesis in the germinative area of the hippocampus, the GCL, in non-injured rats. Following injury, the S100B-induced synaptogenesis is localized to the GCL only initially, while the subsequent migration of the newly generated neurons to injured brain regions dilutes the quantitative verification. The neuroregenerative process is monitored by activated microglia in this diffuse TBI model. The results also support our earlier findings indicating that better cognitive abilities are directly related to neuroregenerative effects of S100B.

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### DEVELOPMENT AND VALIDATION OF TWO ZEBRAFISH MODELS OF TBI

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Traumatic brain injury (TBI) is a leading cause of death and morbidity in industrialized countries with considerable associated direct and indirect health care costs. Zebrafish (ZF) are an emerging model organism for studies of disease and development owing to their unique advantages in genome manipulation, whole animal *in vivo* imaging, rapid rate of procreation and amenability to large scale preclinical drug validation. We developed a ZF model of chemically-induced brain injury in 4 dpf larvae using a 10 mM dose of glutamate. The NMDA receptor antagonist, MK-801, applied at of 62.5 nM, 125 nM, and 250 nM concentrations resulted in a dose-dependent delayed larval survival. We are currently evaluating other known neuroprotective compounds as validation of the larvae ZF model. Candidate compounds will be further evaluated in an adult ZF model. We use a targeted 1-MHz pulsed high intensity focused ultrasound (pHIFU) system applied to adult ZF to produce a non-penetrating head injury to the brain. Preliminary results indicate that pHIFU pressure amplitude at 10 MPa results in a 70.5  $\pm$  1% and 102  $\pm$  1% change in NF160 expression at 5,000 and 10,000 cycles respectively. Beta-III tubulin shows a 14  $\pm$  1% and 16  $\pm$  1% increase at the same parameters. We also found a 30  $\pm$  1% increase in cleaved caspase-3 in injured brains compared to controls. Post-injury recovery times show a linear increase with increasing injury severity. Our preliminary results indicate that the ZF response to brain trauma exhibits similar mechanisms of secondary injury to mammalian pathophysiology after TBI. Further refinement of the model is in progress with the aim to use the model to identify pharmacotherapeutic compounds via high throughput compound library drug screening.

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### REMOTE-ISCHEMIC PRECONDITIONING AS A PROPHYLACTIC TREATMENT FOR MILD TRAUMATIC BRAIN INJURY

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Mild traumatic brain injury (mTBI) accounts for the largest proportion of brain injury cases. Sports injuries and military trauma in particular have high incidences of repetitive mTBI occurrences. Treatments to reduce the secondary cellular injury mechanisms associated with mTBI remain elusive. We previously developed a model of mTBI using a shock wave generating device which demonstrated hallmark features of white matter pathophysiology and persistent neurobehavioural deficits relevant to mTBI. Remote ischemic preconditioning (rIPC) has been shown to provide benefit to tissues in instances of cardiovascular stress such as ischemic stroke and cardiac surgery. In the current study we evaluated the use of rIPC as a potential prophylactic treatment for mTBI. Anesthetized adult male Sprague-Dawley rats were subject to 4 cycles of hind-limb ischemia applied for 5 minutes followed by 5 minutes of reperfusion. A control group consisted of rats subjected only to anesthesia. 48 hours after treatment, rats were subjected to a ~38–40kPa primary blast exposure. Preliminary results indicate a reduction in  $\alpha$ II-spectrin breakdown in the corpus callosum of rIPC treated rats, independent of protective effects exerted by isoflurane preconditioning. rIPC also modulated the heavy neurofilament response to primary blast trauma. Immunoblotting for HIF-1 $\alpha$  indicated a lack of expression in all injury groups suggesting that ischemia did not play a role in the blast mTBI model. The current results suggest that rIPC may reduce pathophysiological response after mTBI, independent of ischemic signalling pathways.

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#### A STUDY OF CONCUSSION INHIBITORY EFFECT OF RECOMMENDATIONS ON SPORTS HEAD INJURIES

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Recommendations on sports head injuries is composed of evaluation for concussion, Medical imaging, and GRTP (Graduated return to play protocol). This recommendation aimed to common recognition for corresponding to sport-concussion in Japanese neurosurgery. This study was made to elucidate the concussion inhibitory effect of recommendations on sports head injuries. X University American football team was subjected to this examination. This team's team doctor is entrained three seasons from 2010 to 2012. Total number of players registered in this period is 221 people. Similarly, the total number of games registered in this period is 25 games. We reviewed the incidence of concussion from 2010 to 2013 in this team. During these 4 years, there were 8 cases / 7 players of concussions. Overall concussions occurred most frequently among senior players, most frequently during Kicking game, and most frequently be blocked. Comparing the earlier 2 years (2010~2011; Pre recommendations period) with the later 2 years (2012~2013; Post recommendations period), there was a slight decrease in the incidence of concussions in the later period. In particular, no recurrence case has occurred in the later period. Our results suggest that reduction the risk of recurrence by the GRTP. Finally, Inhibition of chronic traumatic brain injury is expected. So, put the recommendations to practical use for examination & management of sports concussion. Further research to evaluate the timing to RTP, and the long-term outcome of rest, is needed.

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#### TRAUMATIC BRAIN INJURY MORTALITY IN THE SLOVAK REPUBLIC IN 2009–2012

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Traumatic brain injuries (TBI) are the most common cause of death among all injuries. Knowledge on causes and mortality trends is essential for effective prevention. The aim of this study was to describe mortality data due to TBI in the Slovak Republic in 2009–2012.

Death certificate data on TBI-related deaths in 2009–2012 were obtained from the Statistical Office of the Slovak Republic. ICD-10 codes for TBI deaths were used to select TBI-related deaths.

We have analyzed all 2327 deaths caused by TBI in the Slovak Republic in the years 2009–2012. This number represents 20% of all trauma deaths in the Slovak Republic in the given period. Out of TBI mortality cases, 80% are men and 20% are women. Mean age of men is 9 years less than of women (54 versus 63 years). Mortality rates in individual age groups differ widely. For men, the mortality rate increases rapidly, from 2 in age group 0–4 to 80 in 85+ per 100,000. The steady incline is interrupted by a peak of 12 per 100,000 in age group 20–24, it is lower in the next age groups and rises steadily again. The increase after the age of 65 is rapid, with additional 10 per 100,000 for each 5-year age group. Increase in mortality rates in consecutive age groups in women is much less rapid than in men, starting with 1 per 100,000 in 0–4 and reaching as high as 46 per 100,000 in 85+. Again, the steepest increase is after the age of 65. The most common mechanisms of injury for all population are falls in 48% followed by traffic accidents in 26%. This distribution differs when looking at individual genders.

In men, 47% of all TBI deaths is caused by falls, 26% by traffic accidents and 12% by suicide by firearm. In women, 56% all TBI deaths is caused by falls, 29% by traffic accidents and 8% by assault. When looking at mechanisms of brain injury in individual age groups, at highest risk of death by TBI in traffic accident are age groups 1–34 years. Falls are the most common cause of death by TBI in children 0–4 and above 40 years of age. Suicide by gun is also a common cause of TBI death, especially in age groups 25–64. We see gender differences in the distribution of mechanisms of death. Apart from falls and traffic accidents, assault is also a common mechanism of TBI death for women, especially in age groups 30–59.

To conclude, our basic description of TBI mortality rates between 2009 and 2012 in Slovakia shows several facts. The TBI mortality increases in men and women across the age groups with the steepest increases after 65th year of age. The most common causes of injury are falls and traffic accidents. In the future we will focus on more detailed analysis of TBI mortality rates according to regions and other variables.

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#### TRAUMATIC BRAIN INJURY MORTALITY IN AUSTRIA IN 1980–2012 IN OLDER ADULTS

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Traumatic Brain Injury (TBI) is a serious problem in elderly adults, causing high hospitalization and mortality rate. Old age is recognized as an independent predictor of worse outcome after TBI.

**Methods:** Information on all deaths in Austria between January 1, 1980 and December 31, 2012 was obtained from the Statistical Office of Austria. These data are based on information from death certificates. To filter the deaths caused by TBI we have used the International Classification of Diseases (ICD). The codes of the 9th edition of the ICD were used to classify deaths between 1980 and 2001 and the codes of the 10th edition of ICD were used in deaths occurring in 2002 and onwards. The Centers for Disease Control and Prevention (CDC) definition of TBI was used.

We have reviewed mortality caused by TBI in Austria in people of 65 years of age and older in the time period 1980–2012. Overall, TBI mortality in the studied group was in slight decline from 1980 till 2000, and then it started to rise. In the given time period, we identified 16,204 fatal TBI cases, out of which 39% were women and 61% men. Overall mortality in Austrians of 65 years of age and older in the time period 1980–2012 was 40 per 100,000 inhabitants.

In the given age group, the most common cause of TBI were falls (47%) followed by traffic injuries (22%) and suicides (17%). The pattern differs by gender and in individual age groups. In women, falls cause 57%, traffic 25% and suicides 7% of mortality causes. In men, falls cause death by TBI in 42%, traffic in 21% and suicides in 23%. TBI mortality in Austria in citizens of 65 years of age and older has over past 30 years stable trend, with rising increase in the oldest age groups.

hypothesize that the breach of this threshold is one mechanism for seizure termination.

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WITHDRAWN

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#### **INTRAPARENCHYMAL ELECTRODE RECORDINGS OF CORTICAL SPREADING DEPOLARISATION AND CONTINUOUS SEIZURE ACTIVITY - NEUROVASCULAR DISRUPTION AND SEIZURE OXYGEN THRESHOLDS**

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Work is in press from our group detailing methods for the detection of cortical spreading depolarization (SD) with intraparenchymal electrodes. Here, we describe the recording of SD and epileptic seizures using a Spencer type depth electrode inserted into the cortex of a patient following traumatic brain injury.

This single patient case report details the dynamic brain tissue oxygen changes that occur as a result of clustered SD waves (n=106) and the electrophysiological progression from repeated SDs to intermittent and then continuous seizure activity. In addition to documenting the changes in neurovascular response to repeated episodes of SD, we found consistent falls in pbO<sub>2</sub> following the onset of seizure. We submit that this represents evidence for the loss of neurovascular coupling to seizure activity in metabolically compromised tissue.

Consistent temporal relationships were found between the onset of ictal activity and time to reduction in tissue pbO<sub>2</sub> (med. 37 sec IQR 23–41) and the termination of seizure activity and the start of tissue pO<sub>2</sub> recovery (med. 28 sec IQR 13–34.5). A median fall in pbO<sub>2</sub> of 19% (IQR 14–23%) was found at seizure termination with a median total pbO<sub>2</sub> reduction following seizure of 22% (IQR 18–25%).

A significant negative correlation between seizure intensity and pbO<sub>2</sub> (n=28, p<0.05) was found, indicating that in these data, an oxygen threshold exists for the maintenance of ongoing ictal activity. We

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#### **A REPORT OF 93 CASES OF TRAUMATIC PROGRESSIVE EPIDURAL HEMATOMAS**

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To investigate the clinical characteristics and methods for early diagnosis and treatment of traumatic progressive epidural hematoma (TPEDH). The clinical and radiological data and outcome of 93 patients with TPEDH were reviewed retrospectively. Having reviewed the literature, the results of these cases were analyzed. Among the 93 cases, 72 were male and 21 female, with an average age of 33±12 years. The average interval time from injury to the confirmed diagnosis of TPEDH was 8±13 hours. TPEDH was formed by the enlargement of small hemorrhage on initial CT scanning in 41 cases, and in the other 52 cases, the TPEDH oc-

curred in the location of no hemorrhage on initial CT scanning. Among them, TPEDH in 28 cases was found after initial decompressive craniectomy. The most common locations of TPEDH were tempo-parietal region and fronto-temporal region, followed by the frontal, parietal, parieto-occipital and occipital regions. The TPEDH was unilateral in 83 cases and bilateral in 10. Deterioration of consciousness was the most common manifestation and increased ICP after operations was the dominating manifestation in the cases who received initial decompressive craniectomy. Conservative therapy was used in 5 cases and surgery in the other 88. Primary decompressive craniectomy was made in 33 cases. Skull fracture was confirmed in 83 cases of TPEDH. The following Glasgow Outcome Scale (GOS) scores of 5-4-3-2 and 1 were experienced in 56-20-10-3 and 4 patients respectively on discharge. Most TPEDH occurred within the first 12 hours after injury and located at the impact site. Skull fracture at the impact site was the basic risk factor for the occurrence of TPEDH. Dynamic evaluation and repeated CT scanning of the head would contribute to the early diagnosis, and improvement of the outcome for such cases could be enhanced if the occupying TPEDH was evacuated promptly.

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#### CRANIOPLASTY, A TRIVIAL PROCEDURE? INTENT AND DETAILS OF THE GERMAN CRANIAL RECONSTRUCTION REGISTRY (GCRR) PROPOSAL

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Cranioplasty is conceived as a standard neurosurgical procedure which is important to restore the integrity of the skull, to protect the brain, maintain or improve cosmesis and to prevent the sinking skin flap syndrome. Despite being a standard procedure, it is performed with large technical variety and is associated with a significant spectrum of complications, such as wound healing disorders, intracranial bleedings or biological incompatibility of the cranioplastic material. While appropriate studies on cranioplasties are not available at present, profound data collection is the overarching principle of the GCRR to finally improve the clinical course of these patients.

The GCRR is a project initiated by a consortium of individual members of the Section for Neurotrauma and Intensive Care in Neurosurgery of the Deutsche Gesellschaft für Neurochirurgie (DGNC). Every neurosurgical unit in Germany conducting cranioplasties is/will be invited to join the registry. With the help of a specially designed questionnaire, patients receiving a cranioplasty will be recorded in a multicenter and prospective database. Patient specific risk factors, surgical details, materials for cranioplasty and intra- and postoperative complications will be recorded. The investigation period will cover acute complications as well as subsequent problems and long-term outcome. All results of the GCRR including epidemiological data, surgical techniques, material for cranioplasty, complications, risk factors and long-term outcome will be published and/or reported at forthcoming trauma meetings.

The structural details of the GCRR and the prospective questionnaire are presented to launch data acquisition and to encourage other institutions or similar consortia to participate in the registry.

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#### PLATELET AGGREGATION INHIBITION OF INTRAVENOUS ADMINISTRATION OF NSAIDS AFTER HERNIATED DISC SURGERY

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The perioperative pain management is an essential component of shared responsibility between anaesthetists and surgeons. The rationale of using non-steroidal anti-inflammatory drugs (NSAIDs: metamizol, diclofenac or paracetamol) as analgesic adjuvants is to reduce opioid use and consequently alleviate opioid-related adverse effects. However, it is less known whether NSAIDs possess any antiplatelet effect in a timely fashion after operation of spinal disc herniation.

The aim of this *in vivo* study was to examine if intravenously administered metamizol, diclofenac and paracetamol have an effect on COX-dependent platelet aggregation after surgical intervention.

In our *in vivo* study intravenous metamizol, diclofenac and paracetamol were selectively administered intravenously during the surgical intervention. The epinephrine-induced platelet aggregation was determined by Multiplate<sup>®</sup> optical aggregometry. Blood samples were taken before and 1, 4 and 6 hours (h) after drug administration.

Diclofenac induced an immediate platelet aggregation inhibitor which could not be observed after 6 h (0 h: 73 ± 6 AUC, 1 h: 21 ± 8 AUC, 4 h: 51 ± 11 AUC). Metamizol also induced an immediate platelet aggregation inhibition that lasted for longer than six hours (0 h: 96 ± 14 AUC, 1 h: 25 ± 9 AUC, 4 h: 22 ± 5 AUC, 6 h: 31 ± 8 AUC). Paracetamol did not show any antiplatelet effect (0 h: 116 ± 12 AUC, 1 h: 97 ± 1 AUC).

The findings of the present study show that intravenously administered metamizol and diclofenac but not paracetamol exhibited a time-dependent inhibition of platelet aggregation. Further elucidation of the underlying mechanisms of platelet aggregation inhibition could contribute to a better understanding of this process and might affect the treatment of perioperative hemorrhage.

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#### CRANIOPLASTY WITH INDIVIDUALLY PREPARED CRANIAL IMPLANTS USING THE CAD/CAM TECHNIQUE

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Facts support that decompressive craniectomy alleviates life-threatening acute high intracranial pressure and it is performed worldwide. Less attention has been paid to the late negative consequences of the widely open intracranium. Although the missing protection of the brain and cosmetic setback would be enough indications for a timely closure of the skull, the insufficient regional blood flow and consecutive

neurological symptoms are more compelling to schedule the cranioplasty as soon as the intracranial pressure normalized. Recent investigations demonstrated improved cerebral blood perfusion in the brain area following reconstructive surgery of cranial defects.

Results of cranial reconstruction after head trauma (63%), or decompressive craniectomy for middle cerebral artery occlusion (37%) were analyzed. A series of 204 consecutive patients were operated on with cranioplasty. Following CT bone scans the implanted cranial prosthesis were formed individually for every patient from polyethylene material using computer-aided design and computer-aided manufacturing (CAD/CAM) technique. Cranioplasty was performed at 4 months after the head trauma in patients without primary dural injury and at 6 months in the group with dural injury. Follow-up period was at least 6 months up to 10 years. Precise coverage of the defect and acceptable aesthetic results were achieved in every case. Neurological improvement appeared immediately after cranioplasty in 12%, or at a later stage of rehabilitation (54%). Neurological deterioration was not detected. Transient minor complications, like subgaleal hematoma developed in 20% of the patients. Skin necrosis necessitated removal of the implant in two patients.

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#### QUANTITATIVE ASSESSMENT OF CORTICAL ATROPHY AND AXONAL DEMYELINATION IN SEVERE TRAUMATIC BRAIN INJURY USING MULTIMODAL NEUROIMAGING

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Cortical atrophy and axonal demyelination are prominent neuro-anatomic sequelae of traumatic brain injury (TBI), and their extent can have appreciable repercussions for patient recovery and rehabilitation. To perform a preliminary assessment and mapping of gray matter (GM) atrophy and axonal demyelination in the white matter (WM) for a cohort of 20 human adults across the first 6 months post-TBI, with a focus on feasibility and proof-of-concept analysis. The study was implemented in accordance with the Declaration of Helsinki and with approval from the UCLA Institutional Review Board. Neuroimaging data were acquired from TBI patients admitted to the Neurointensive Care Unit of the UCLA Medical Center. A Siemens Magnetom Trio Tim scanner was used to acquire  $T_1$ - and  $T_2$ -weighted magnetic resonance imaging (MRI) volumes both acutely and chronically (several days and ~6 months post-injury, respectively). After affine co-registration of all acquired volumes within each subject, segmentation and cortical thickness calculations were performed using FreeSurfer software. Manual corrections were implemented by three experienced users with training in neuroanatomy. The extent of axonal demyelination was estimated based on the ratio of voxel intensities between  $T_1$  and  $T_2$  volumes following Glasser & Van Essen (Journal of Neuroscience, 2011, vol. 31, p. 11597). Cortical atrophy and demyelination measurements obtained from voxels exhibiting pathology-related alterations in image intensity were discarded from the analysis. Bilateral cortical atrophy was identified consistently across subjects over extensive portions of healthy-appearing cortex (mean thickness change over cortical

locations and subjects:  $-0.55$  mm; standard error of the mean over subjects:  $0.20$  mm). Cortical regions exhibiting mean atrophy over subjects greater than 1 mm were in the temporal lobe (middle and inferior temporal gyri, lingual, fusiform and parahippocampal gyri, temporal pole), frontal lobe (orbital gyri, straight gyrus, transverse frontopolar gyri), and limbic lobe (anterior cingulate gyrus and sulcus). WM demyelination was found to be distributed diffusely throughout the cerebrum, with predominance in frontal and temporal regions.

Discussion. The atrophy and demyelination patterns identified here occur in regions which are involved in memory formation and retrieval (lateral and medial temporal lobe), speech (ventromedial temporal lobe), personality and temperament (prefrontal cortex), and cognitive control (anterior limbic areas), all of which are often impacted by TBI. These preliminary findings may contribute to elucidating the relationship between neuropsychological deficits and structural brain changes due to TBI, with potential relevance to personalized treatment and rehabilitation.

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#### INFLAMMASOMES IN THE CENTRAL NERVOUS SYSTEM

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The inflammasome is a multi-protein complex involved in the activation of the inflammatory caspase, caspase-1. Caspase-1 is responsible for the processing of the pro-inflammatory cytokines interleukin- $1\beta$  (IL- $1\beta$ ) and IL-18. We have previously shown that the inflammasome in the central nervous system (CNS) is involved in the generation of an innate immune inflammatory response through the activation of caspase-1 and the maturation of IL- $1\beta$  and IL-18. The inflammasome also contributes to a cell death mechanism known as pyroptosis. Here we describe the role of the NLRP1, NLRP2 and AIM2 inflammasomes in the inflammatory response in neurons and astrocytes and the mechanisms of inflammasome activation involving DNA, ATP and potassium in cells of the CNS after brain and spinal cord injury.

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#### PREDICTING OUTCOME AFTER TBI: CURRENT STATUS AND FUTURE PERSPECTIVES

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Traumatic brain injury (TBI) is a heterogeneous condition that encompasses a broad spectrum of disorders. Accurate outcome prediction is relevant both for clinical practice and for research purposes. We aim to provide an overview of the current state of affairs with respect to assessment and prediction of outcome after TBI.

*Moderate and severe TBI*

For TBI patients with Glasgow Coma Score  $\leq 12$ , the IMPACT and CRASH models have been developed on large datasets with state-of-the-art methods. These models have been externally validated in

multiple recent patient cohorts from different countries including the US, the UK, Austria, Italy and the Netherlands. These validation studies show adequate performance for both models. Furthermore, the simple models perform close to more complex variants, indicating that the main prognostic information in moderate and severe TBI patients is captured by age and TBI severity as represented by the Glasgow Coma Scale and pupillary reactivity.

#### *Mild TBI*

For those with Glasgow Coma Score 13–15, a recently published prognostic model was of limited methodological quality and performed poorly at external validation. Currently available cohorts are of insufficient size or quality to develop valid prognostic models. Exploratory analyses in the TRACK-TBI pilot study indicate that socioeconomic and psychosocial factors are more discriminative between good and poor outcome than injury severity in mild TBI.

Large international collaborative studies, such as CENTER-TBI and TRACK-TBI, will collect high quality data on large numbers of patients across the full injury severity spectrum, including mild TBI. These data will allow for further improvement of prediction of various outcomes, up till 24 months after injury, by including better predictors such as more advanced imaging parameters and biomarkers, and by using a more dynamic approach to prediction using information from baseline to the first days and weeks after trauma.

For moderate and severe TBI, basic but solid predictions can well be made. Improvements may come from new biomarkers and imaging. These new predictors may also enhance our insights in prognostic processes and provide further opportunities for personalized medicine. For mild TBI the prognostic effects of more basic predictors still need to be determined.

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### **THE INTERNATIONAL TRAUMATIC BRAIN INJURY RESEARCH (INTBIR) INITIATIVE**

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The European Commission, the National Institute of Neurological Disorders and Stroke and the Canadian Institutes of Health Research set up the International Traumatic Brain Injury Research (InTBIR) Initiative, a global effort to coordinate clinical research activities across the full spectrum of Traumatic Brain Injuries (TBI). The long-term goal is to improve clinical outcomes and lessen the global burden of TBI by 2020 through the discovery of causal relationships between treatments and clinically meaningful outcomes. InTBIR specific objectives are: (i) to establish data sharing and collaboration; (ii) to further establish and promote the use of the TBI Common Data Elements as standards for TBI clinical data collection; (iii) to develop and apply analytical tools to enable comparative effectiveness research (CER) for TBI treatments, diagnostic tools and outcome measures. EU is supporting with EUR 35 M two InTBIR projects: (i) CENTER-TBI collects a prospective observational dataset of 5,400 patients for CER and better characterization of TBI. The conceptual approach is to exploit the heterogeneity in biology, care, and outcome of TBI, to discover novel pathophysiology, refine disease characterization, and identify effective clinical interventions; (ii) CREATIVE builds on the PROSAFE intensive-care unit network to enrol 7,000 to 9,000 moderate to severe TBI patients. CREATIVE aims at better describing the epidemiology of moderate-severe TBI, building a prognostic model, and identifying most effective clinical interventions for treating TBI patients.

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### **EXERCISE DEPENDENT PLASTICITY IN THE INJURED SPINAL CORD**

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Anatomical, biochemical and functional reorganization of the spinal cord occurs after a traumatic insult and subsequent secondary tissue degeneration. Various spinal cord injury (SCI) models and interventions have shown the adaptive potential of the spinal cord and its limitations with limited supraspinal influence. Leading opinions indicate that meaningful recovery of function will most likely result from a combination therapy approach, comprised of regenerative/neuroprotective transplants and neurotrophic factors, elimination of inhibitory molecules and functional sensorimotor training. We routinely use: peripheral nerve grafts to support and direct axonal regeneration across an incomplete cervical level injury or a complete thoracic transection injury, matrix modulation with chondroitinase (ChABC) to facilitate axonal extension beyond the distal graft-spinal cord interface and exercise (forced wheel walking, bicycling or step training on a treadmill) to provide muscle stretch and loading and rhythmic sensory input to the spinal cord. Functional recovery due to synaptic connections made by axons growing into and out of the grafts is tested by evaluating kinematic data, EMG activity, spinal cord field potentials and c-Fos levels after stimulation of the PNG. We (and others) have demonstrated an increase in spinal cord levels of endogenous neurotrophic factors with exercise, which may facilitate neuroprotection, axonal elongation beyond a nerve graft and a return of functional activity below the level of injury. We will present additional evidence for a role of acute exercise in preventing the onset of neuropathic pain, in reducing spasticity and in promoting axonal regeneration by thoracic and lumbar propriospinal neurons.

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### **VENTRAL C1-C2 TRANSARTICULAR FIXATION FOR COMBINED C1-C2 FRACTURES**

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Most of the combined C1-C2 fractures are potentially life-threatening, meaning that they have to be fixed. Fractures without dislocation and no signs of ligament rupture can be immobilized with external collars. Some cases need HALO fixation, but there are some cases, which have to be fixed by a surgical method. There are a lot of techniques of posterior fixation and some for anterior approach. Since 2008, we have been using the ventral C1-C2 transarticular fixation.

Retrospective analysis of the 9 operated patients data was done. Except one case, all of them suffered a combined C1-C2 fracture, with atlantoaxial instability. In cases with dislocating dens fracture preoperative and intraoperative Crutchfield traction was used for repositioning. During the operation we used cannulated screw technique controlled by biplanar image intensifier. After the surgery CT control was mandatory to evaluate the screw position. Screw malposition or vertebral artery injury was not detected. The mobilization was done at first day after surgery in Miami collar. We did not have hardware failure.

The anterior C1-C2 transarticular fixation is a safe option in combined C1-C2 fractured cases, especially when they are complicated with dens fracture. For those who are familiar with the dens screw fixation it is very easy to perform this type of surgery. The use of biplanar fluoroscopy control is mandatory. We think that the vertebral artery injury risk is lower than in the posterior fixation. On the other hand, the rehabilitation is very fast because the posterior cervical muscles are not affected.

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#### **TREATMENT OF TRAUMATIC SPINAL COMPRESSION FRACTURES WITH VERTEBROPLASTY AND FACET THERMAL ABLATION AT THE DEPARTMENT OF NEUROSURGERY OF SZEGED**

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Thoracic and lumbar spinal compression fractures are rather frequent injuries and often cause the patient considerable pain. Therefore analgesic neurosurgical interventions are often required in these cases. The aim of our presentation is to summarize and compare the efficacy of these interventions.

Between 01/01/2006 and 12/31/2013, kyphoplasty, vertebroplasty and facet thermal ablation for traumatic spinal compression fractures were performed in 157 cases at our department. As the indication of the surgery is drug-resistant pain, the efficacy of surgery was measured by the changes in the subjective complaints of the patients.

Patients who previously underwent kypho- or vertebroplasty reported similar results: 69% of them considered the pain relief significant, while 26% reported moderate effect. After facet thermal ablation, these data were 75% and 20%.

In most cases, drug-resistant pain caused by traumatic spinal compression fracture can be considerably relieved by neurosurgical intervention. Vertebroplasty, kyphoplasty and facet thermal ablation all proved to be very effective, patients reported reduced pain in almost all cases. An argument for facet thermal ablation is that although both interventions can be carried out under local anesthesia, facet thermal ablation is less invasive, while vertebroplasty also provides partial or, in some cases, complete anatomical reconstruction and, last but not least, it also provides prevention of later compression.

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#### **EFFICACY AND SAFETY OF LUMBAR CEREBROSPINAL FLUID DRAINAGE AS A SECOND LINE THERAPY FOR INCREASED ICP IN SEVERE TBI PATIENTS**

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Early treatment of elevated ICP is a cornerstone of therapy in severe TBI patients. There is an increasing number of evidence that controlled lumbar drainage is an efficient and probably safe method in lowering of ICP. Our center has been using this intervention for 10 years. Here we present our data about controlled lumbar drainage as a second line therapy.

Retrospective analysis was performed using demographic, clinical and outcome data of severe TBI patients admitted in the last 5 years. We performed 6–7 lumbar drainage interventions in a year. They were used as a second line therapy in salvageable patients with normal haemostasis and discernible basal cisterns on the pre-intervention CT scan. Data of 30 interventions were analyzed. Patients were young, comatose and with multiple injuries (median age: 28, GMS: 4, ISS: 25). Lumbar drain was inserted mainly on the first week and maintained for 5 days. Episodes of ICP > 20 Hgmm within one day (13 vs 1) and the peak ICP measured (31 mmHg vs 23 mmHg) were decreased after intervention ( $p < 0.001$ ). The need for additional second line therapies (barbiturate, hyperventilation, surgery) decreased (28 vs 10 interventions,  $p < 0.001$ ). No anisocoria or brain stem herniation was experienced during insertion and only 5 cases of bacterial meningitis were identified. The 28 day mortality was 10% compared with our total TBI population, where mortality was 20–33% in this period. These results reinforce that lumbar drainage is an efficient and relatively safe method as an ICP lowering second line intervention.

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#### **LONG-TERM OUTCOME OF SEVERE TBI PATIENTS ADMITTED TO THE LARGEST NEUROTRAUMA CENTER IN BUDAPEST**

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Long-term outcome of severe TBI patients differs between countries and centers. Follow-up of patients is important to each center for the assessment of their work and to give prognosis for patients' relatives. Péterfy Hospital and Trauma Center is the largest neurotrauma center in Budapest with extended imaging and neurosurgery/neurointensive care facilities. Here we present our result from the last 5 years.

Demographic, clinical/neurological parameters and CT scans were collected at admission. Mortality (short – 28 day; long – 6 and 12 months) and functional status (GOS, DRS, FIM scales at 12 month) were followed by the hospital information system and telephone interviews by trained personnel.

The number of admitted patients per year didn't change during this 5 year period (70–80 patients/year). The median age was 48 years (76% male) and 58% of patients suffered from co-existing diseases. The 28-day mortality varied between 26%–35%, the 12-month mortality was 44–55%. We lost 15–25% of the patients for long-term follow-up. Only 20–33% of the survivors reached rehabilitation care. Full recovery was found (GOS 5) in 11–20% of the cases, rates of minor disabilities were within 6–9%, severe disabilities were found rarely (3–5%). We could not identify any obvious trends in parameters following this 5-year dataset. Follow-up of our severe TBI patients is an informative research concerning our daily practice and development of the health care system. The ratio of patients recovered with good functional outcome among survivors is acceptable, the mortality rate is higher than in Western European centers.

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#### **PRE- AND POSTOPERATIVE CEREBRAL PERFUSION ASSESSMENTS IN CHRONIC SUBDURAL HEMATOMA**

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Chronic subdural hematoma (cSDH) constitutes one of the most frequent posttraumatic neurological disorders in the elderly, still bearing by poor prognosis. The pathophysiology of signs and symptoms is related to compression of the underlying cortical areas and putative reduced regional perfusion. <sup>99m</sup>Tc-HMPAO SPECT allows to semiquantitatively analyze cerebral blood flow (CBF) redistribution. To date, few studies have been addressed to evaluate preoperative cerebral perfusion and its changes after cSDH evacuation. We examined 21 patients underwent unilateral cSDH evacuation and submitted to preoperative (day 1), early (days 2–3) and late (days 7–8) postoperative cerebral <sup>99m</sup>Tc-HMPAO SPECT. Ipsilateral vs contralateral cortex CBF value was assessed by using the Asymmetry Index ratio. Among the parameters evaluated, sex, age, hematoma side and volume, preoperative neurological examination, type of operation and anesthesiology, time of surgery, and outcome did not show any statistical correlation. Although 13 patients showed a relative hyperperfusion at the first postoperative SPECT control, the CBF tended to homogenize at the consecutive neuroradiological examination. Interestingly, we found a significant chi-square result ( $p < 0.04$ ) between the preoperative and the first postoperative time when stratifying the patients according to the time between the beginning of the symptoms and the operation (+ 60 days). We conclude that local brain perfusion autoregulation is active in the cortical area below the cSDH and is influenced by the compression time. The postoperative late redistribution of the CBF affects the cerebral cortex globally, confirming that the vessel autoregulation remains unaltered after surgery even in the presence of a compressive mechanism.

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#### **A PRELIMINARY STUDY SERUM $\beta$ -ACTIN AS POTENTIAL BIOMARKER OF DIFFUSE AXONAL INJURY IN SEVERE TRAUMATIC BRAIN INJURY**

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Actins are essential components of mammalian cytoskeleton, playing critical roles in a wide range of cellular processes.  $\beta$ -Actin is the only isoform locally translated in the CNS. Recent studies identify roles for  $\beta$ -actin in promoting CNS tissue architecture, demonstrating its importance in neuronal growth and migration, axonal guidance and synaptogenesis. However, the unique contributions of  $\beta$ -actin in CNS are not fully understood yet. To date,  $\beta$ -actin has never been related to TBI secondary damage and diffuse axonal injury (DAI). We studied the timeline levels of serum and CSF  $\beta$ -actin in severe TBI patients and related the values with the clinical outcome. Seven men affected by severe TBI ( $n=4$ ) and polytrauma including TBI ( $n=3$ ) were submitted to ICP monitoring for a minimum period of 3 days. Serial withdrawals of serum and CSF with a specific timeline (T0 and each 6 hours) were performed. The GCS and ICP values at these time points were related with the levels of serum and CSF  $\beta$ -actin. The preliminary results indicate the presence of higher levels of both serum and CSF  $\beta$ -actin in the polytraumatized and TBI patients with dismal outcome. In the good outcome group, the serum and CSF levels of  $\beta$ -actin are reducing within 6 hours post-TBI. Although the small number of patients doesn't allow to attribute a statistical power, this study shows a correlation between  $\beta$ -actin CSF and serum concentrations in severe

TBI patients and their outcome.  $\beta$ -actin as biomarker of DAI-related outcome in severe TBI should be considered.

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#### **CADAVER MODELS TO EVALUATE THE TWO MAIN TYPES OF DC**

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Despite large leaps in methods and indications for decompressive craniectomy in treating malignant post-traumatic brain edema, controversy still remains about different methods and mortality and morbidity remain high. Therefore a cadaver method for comparing the bifronto-temporal and bifronto-temporo-parieto-occipital craniectomies might provide useful data for clinical decision making and treatment. The authors created a fresh cadaver model for mapping intra-cranial pressure change at the level of tentorium during bifrontal and fronto-temporo-parietal decompressive craniectomies. Other characteristics were also observed like the size of surface for ICP reduction and the location of bridging veins which are under the danger of occlusion. The cadaver model that was created is in no way exact compared to *in vivo* pressure monitoring and only provides approximate data. Cadavers were used 1 to 2 days after passing away. 3 different cadavers were used to acquire pressure mapping data during a simulated 35 mmHg ICP. Pressure sensor catheters were inserted into the uncus. The ICP models were created by inflated ventricles. Firstly, a wide bifrontal craniectomy was made and classical fish-mouth dura incision was made. Dura sutures were made. The frontal bone crest above the sinus was reattached with plates and both sided fronto-temporo-parietal craniectomy was made. Wide dura incision was made. With the before mentioned model, the pressure reduction seems to be better at a bifronto-temporo-parietal fashion. The position of veins are better at bifrontal fashion if we do not protect the veins by tunnels. Considering the ICP at uncus level, further observations are needed. It seems to be better the bifronto-parieto-temporo fashion as well.

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#### **ENDOVASCULAR TREATMENT OF TRAUMATIC AND SPONTANEOUS CAROTID-CAVERNOUS FISTULAS**

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Carotid-cavernous fistula (CCF) is the most common arterio-venous fistula in the head and neck region which has characteristic ophthalmic findings and threat of visual loss. An analysis of clinical records was done on 18 CCF patients who visited the Department of Neurosurgery, University of Pécs from 2000 to 2013. Fifteen cases were of the direct or post-traumatic type, and 3 cases were of the indirect or spontaneous type (due to the rupture of infraclinoidal aneurysm). Fifteen patients of the direct type had a definite history of head trauma. Clinical symptoms on the first visit included exophthalmus in 16 cases, conjunctival injection in 16 cases, visual disturbance in 8 cases, which included amaurosis in 3 cases, noise in cranial cavity in 12 cases, diplopia in 12 cases, epistaxis in 1 and ocular pain in 7 cases. In 14 cases vascular bruit was heard with auscultation on the eyelid. CT of the orbit or brain, and DS angiography were used as a diagnostic procedure in all patients. In 6 patients detachable balloon occlusion was done at the time of angiography, and the other 12 fistulas

were successfully embolized by using a polyurethane based liquid polymer and with the help of detachable coils and stents. In 3 patients the permanent occlusion of the internal carotid artery was performed in the other 15 patients the reconstructive disjunction of the fistula was achieved. The fistulas were successfully closed in all of our patients and this lead to the regression of symptoms except for the complete visual loss.

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#### **DYNAMIC VISCOSITY AS A MEASURE OF THE STATE OF CRANIAL COMPLIANCE IN A SWINE MODEL OF BRAIN EDEMA**

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A large animal model is well suited to study intracranial physiology as it allows for intensive cerebral monitoring. We used a swine model of brain edema induced by water intoxication to study intracranial pressure dynamics following injections of normal saline at different levels of brain edema.

Adult female swine weighing between 35 and 45 kg were anesthetized and continuously monitored with systemic and cerebral physiological monitors. Four serum sodium intervals were designated: baseline (135–145 mEq/L), mild hyponatremia (130–134 mEq/L), moderate hyponatremia (125–129 mEq/L), and severe hyponatremia (116–124 mEq/L), and attained by infusing hypotonic saline. Two cc of normal saline were injected over 15 seconds into the intracranial compartment. Following bolus injections of saline the resultant area under the intracranial pressure curve was measured over 6 minutes. The area under this curve is expressed in units of mmHg x seconds which corresponds to the dynamic viscosity of the intracranial system. With 2 cc injection of normal saline measured system dynamic viscosity increased from a baseline of  $6688 \pm 2324$  at baseline to  $10890 \pm 2637$  at mild hyponatremia to  $15,425 \pm 4092$  at moderate hyponatremia, and  $22,461 \pm 3603$  at severe hyponatremia, indicating a non-linear rise in system dynamic viscosity with increasing brain edema.

Dynamic viscosity of the intracranial system expresses the amount of pressure exerted over time to maintain intracranial CSF flow and increases in a non-linear manner with increasing brain edema. Increasing brain edema leads to a sharp rise in system dynamic viscosity that likely reflects the non-linear rise in resistance to CSF flow and may thus serve as a useful correlate of the state of the intracranial compliance.

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**WITHDRAWN**

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#### **ESTIMATION OF THE PROGNOSTIC VALUE OF BRAIN STEM SEGMENTATION BY PROBABILISTIC TRACTOGRAPHY IN SEVERE TRAUMATIC BRAIN INJURY AND ITS VERIFICATION BY ANATOMICAL DISSECTION**

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Diffusion tensor imaging (DTI) and probabilistic tractography are powerful tools to quantitatively examine white matter integrity and create probabilistic connectivity (PC) maps. Previous studies showed that subcortical areas can be segmented by their cortical connections. Techniques, which reliably identify irreversibly injured brain areas would allow us to predict the long-term outcome of severe TBI patients. Our aim was: 1, to examine if the major brain stem pathways could be segmented by probabilistic tractography in healthy subjects; 2, to identify structural abnormalities as biomarkers in severe TBI patients.

Magnetic resonance imaging (MRI) scans were performed using the following sequences: T1, FLAIR, SWI, T2 and DTI. From the DTI images fractional anisotropy (FA) and PC (connection to the medial and sensory thalamus and the internal capsule) maps of the brain stem were reconstructed.

In healthy controls (n=20) there was a high correlation between the FA and PC maps of the brain stem and the anatomical structure. Sixteen severe TBI patients were tested. There was no significant correlation between the outcome and the T1, T2, FLAIR and SWI abnormalities. In patients who remained unconscious (n=6) we observed disorganization of the FA and PC maps in the upper pons. The dissection verified the results of the brain stem segmentation (n=2). In those who regained consciousness (n=10) the brain stem was intact.

According to our results, the FA and PC maps highly correlate with the clinical state. DTI and probabilistic tractography may be clinically

useful methods to predict long-term outcome of severe TBI patients. This research forms part of the Development of the Analytic Healthcare Quality User Information (AHQI) framework.

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#### MODELING SPINAL CORD INJURY IN THE PRIMATE

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Recent studies show that plasticity of the corticospinal tract (CST) in the primate after hemisection is substantial and significantly greater than that observed in the rodent (Rosenzweig et al, 2010). This plasticity positively correlated with recovery of a variety of forelimb functions, suggesting that the primate may have a higher degree of plasticity than rodents. Contusion/compression injuries are the most common in humans. This paper will describe the early results on the development of a unilateral contusion injury model in the primate, and compare both recovery of function and CST plasticity in this model to the hemisection model. (Supported by the VA, The CH Neilsen Foundation, and NIH NS042291)

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#### CORRELATION BETWEEN INTRACRANIAL PRESSURE AND MEASUREMENT OF OPTIC NERVE SHEATH IN A SWINE MODEL OF INTRACRANIAL HYPERTENSION

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Some studies have shown that the measurement of the optic nerve sheath (ONS) is correlated to invasive ICP monitoring. However, no studies have shown to date, if ONS can be useful to monitor oscillations of ICP. Therefore, we aimed to evaluate the correlation of parenchymal ICP monitoring and the measurement of ONS in a swine model of intracranial hypertension. Nine piglets were evaluated. After insertion of a 8Fr urinary catheter in the right parietal lobe and a parenchymal intracranial pressure monitoring in the right frontal lobe, a continuous infusion of 0,9% saline through the urinary catheter was performed to inflate the balloon at the distal tip. In Group A, we infused 4 ml saline in 15 min; in Group B, an additional 3 ml was infused over 15 min, 30 min after the first infusion; and in Group C, 7 ml was infused over 15 min. The final stage was the deflation of the balloon. Along the procedure, 8 measurements of the ONS were made. In group A, mean ICP was 6.2 (range: -4.6 - 32 mmHg). In group B, mean ICP was 19.8 (range: -2.9 - 50.9 mmHg). In group C,

mean ICP was 42.8 (range: 2.2 - 86.4 mmHg). The mean right ONS was 3.9 mm + - 0.5 (SD) when ICP below 20 mmHg and 4.6 + -0.65 (SD) when ICP above 20 mmHg (p<0.0001). The mean left ONS was 3.9 mm + - 0.3 (SD) when ICP below 20 mmHg and 4.6 + -0.65 (SD) when ICP above 20 mmHg (p<0.0001). There was a moderate correlation between ICP with left and right ONS (r=0.39, p=0.004 and r=0.38, p=0.006). This study showed that the measurement of ONS is associated with parenchymal ICP monitoring in a experimental model. The discovery of a moderate correlation suggests that measurement of ONS may be useful in monitoring ICP noninvasively, which may be translated to the clinical setting.

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#### CT PERFUSION IN TRAUMATIC ACUTE SUBDURAL HEMATOMA: A NEW TOOL TO PREDICT OUTCOME?

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Studies in brain hemodynamics are scarce in the emergency setting, but the use of CT Perfusion is an alternative tool to assess the hemodynamics in brain trauma. As traumatic acute subdural hematomas are severe lesions commonly associated to poor outcome, we aimed to evaluate the brain hemodynamics in such patients.

Five patients admitted at the emergency department sustaining traumatic acute subdural hematoma were evaluated. Preoperative CTP was performed immediately after nonenhanced head CT scan. Postoperative CTP was performed in four patients. The outcome was assessed 6 months after surgery using the extended Glasgow Outcome Scale.

4 male and 1 female were evaluated. Mean age was 46 + - 8.1 y (SD). Mean preoperative midline brain shift (MLS) was 10.1 + - 1.8 mm (SD). The main mechanism of trauma was fall (four patients). There was a significant reduction in MLS after surgery (p=0.003). There was an overall improvement in cerebral blood flow after surgery (from 23.9 + - 6.1 to 30.7 + - 5.1 ml/100 g/min) and in mean transit time (from 7.3 + - 1.3 to 5.8 + - 1 seconds), although not statistically significant (p=0.06 and p=0.06, respectively). Spearman correlation test of postoperative and preoperative CBF ratio with outcome was 0,94 (p=0.054). Only one patient died (three days after surgery). This patient was victim of car crash and had the highest preoperative mean transit time (9.97 seconds) and cerebral blood volume (4.51 ml/100 g).

This pilot study is the first to evaluate brain hemodynamics through CTP in patients with acute subdural hematoma. Although there were only five cases in this series, it suggests that the hemodynamic amelioration is correlated with outcome.

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#### SKULL FRACTURE: INDICATOR DANGEROUS TO LIFE OR PREDICTOR OF INTRACRANIAL INJURY?

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**Introduction:** In forensic science as well as in the scales (AIS, ISS) of assessment of the severity of injury based on anatomical principles a skull fracture is assessed as a life-threatening injury or a severe injury, which may conflict with clinical observations.

The purpose of the work is to identify a skull fracture as an indicator of the severity of traumatic brain injury or as a predictor of intracranial lesions.

**Materials and methods:** A retrospective analysis of cases treated in the institute of neurosurgery (280 patients) and autopsy material (131 autopsies) of patients with traumatic brain injury was conducted. All patients underwent CT and craniography. Statistical processing of the results was done using  $\chi^2$ .

**Results:** Analysis of the obtained data showed that the incidence of skull fractures depends on the sample of material being analyzed. Skull fractures were diagnosed in 102 cases (77.9%) at autopsy and in 85 cases (30.4%) in the clinic ( $\chi^2 - 79.3$ ,  $P=0.0000$ ). According to the sample of hospitalized patients, 57.6% of all skull fractures were observed in patients with mild traumatic brain injury. This can be explained by the fact that patients with mild traumatic brain injury outnumbered those with severe traumatic brain injury in the sample (208 vs. 29). Comparison of the incidence of fractures among patients with mild traumatic brain injury and those with severe traumatic brain injury yielded reliable statistical data showing that skull fractures were predominant in patients with severe traumatic brain injury ( $\chi^2 - 13.9$ ;  $P=0.0001$ ). Patients with mild traumatic brain injury had skull fractures predominantly in the cranial vault ( $\chi^2 - 7$ ;  $p=0.008$ ) and one bone ( $\chi^2 - 5.8$ ;  $p=0.016$ ) as compared with patients with severe traumatic brain injury. A reliable statistical connection was established between skull fractures and intracranial lesions ( $\chi^2 - 3.8$ ;  $p=0.051$ ) in patients with mild traumatic brain injury.

**Conclusion:** It can be concluded that a linear fracture of the cranial vault is a risk factor for potential intracranial lesions, but not a predictor of the severity of traumatic brain injury. It is proposed that a skull fracture be regarded as life-threatening only when it directly causes a potentially dangerous injury (open, penetrating TBI, multiple and comminuted fractures of the cranial vault, fractures of the skull base, pneumocephalus, liquorrhea).

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#### NEUROCOGNITIVE TESTING IN THE EMERGENCY DEPARTMENT USING AN IPAD: FEASIBILITY & IMPLEMENTATION

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Collection of neurocognitive data in the acute phase after mild traumatic brain injury (mTBI) presents distinct challenges. The environment in the emergency department (ED) is often busy and noisy, and time constraints mean that traditional pen and paper tests or more comprehensive computerised testing can be difficult to administer. However, robust cognitive behavioral metrics may provide a useful basis for triage and stratified management of patients. In this study we explored the feasibility of using cognitive testing battery embedded in a tablet computer platform for patients who presented to a busy ED with mTBI. These tests, based on the CANTAB battery of tests (<http://www.cambridgecognition.com/>) and implemented on an iPad, included paired associates learning and spatial working memory tasks. We collected data during their emergency department presentation from 21 patients after mild head injury and 20 patients who had sustained a traumatic injury but no head injury. The testing was well tolerated by patients with all consenting patients completing the full battery. The total testing time was 20 minutes, and the test results provided metrics regarding motor reaction time, and in the cognitive domains of attention, memory, executive function and learning. All patients were followed up at 2 weeks and 3 months with repeat neurocognitive testing and magnetic resonance imaging being performed, using an expanded panel of tests implemented in the same platform, but based on a tablet PC (Paceblade™). Serial assessments in the same testing environment allowed us to assess changes over time and relate these to neuroimaging findings.

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#### EFFECT OF TWO DIFFERENT TYPES OF ENRICHED ENVIRONMENT PRECONDITIONING ON FUNCTIONAL OUTCOME OF RATS AFTER EXPERIMENTAL HEAD INJURY

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There is an ongoing debate on the efficacy of enriched environment (EE) in rehabilitation: experimental data are rather controversial. The aim of our present study was to investigate the effects of early post-natal EE and auditory stimuli preconditioning on functional outcome in case of severe TBI.

In the 1<sup>st</sup> experimental setting 15 male Wistar rats were traumatized with lateral fluid percussion head injury model with 2.6 atm injury severity. Eight animals lived within EE conditions on their first 35 post-natal days. Functional outcome was measured by the open field and beam balance tests on the 1<sup>st</sup>, 4<sup>th</sup> and 8<sup>th</sup> post injury days. While the EE animals performed better at each time points in the beam balance test the number of grooming and rearing in the open field test were increased in case of control animals related to the EE. The difference was significant in case of grooming in the 1<sup>st</sup> post-injury day ( $p=0.047$ ).

In the 2<sup>nd</sup> experimental setting 31 male Wistar rats were traumatized with impact accelerational head injury model with 450 g weight from 1.5 m. Pre-injury, 17 of them lived in an enriched auditory stimuli environment which involved listening of 60 dB loud music 12 h per day. Surprisingly, rats that had received the auditory stimuli performed significantly worse in the beam balance test independently of the TBI (even in pre-injury setting). In the open field test we found significantly more rearing activity on the 1<sup>st</sup> day post-injury of the auditory preconditioned animals  $p=0.018$ .

In conclusion while we have proven at least partial beneficial effects of early post-natal EE our study revealed controversial effects of auditory stimuli preconditioning most probably due to noise-induced labyrinth-injury.

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#### PROGNOSIS OF SEVERE TRAUMATIC BRAIN INJURY IN HUNGARY - ANALYSIS OF THE FIRST TEN YEARS OF THE PÉCS SEVERE HEAD INJURY DATABASE

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The “Pécs Severe Head Injury Database” has been established in the Department of Neurosurgery, University of Pécs in July 2002 in an attempt to provide better insight to the region-specific characteristics and challenges of the pathogenesis, therapy and prognosis of severe traumatic brain injury (TBI).

Inclusion criteria included documented head injury and GCS ≤ 8 during hospitalization. Relevant clinical parameters and monitored data were collected from patients’ records, and divided into three groups: prehospital state, primary and prolonged treatment categories. For statistical analysis single and multiparametric logistic regression were utilized applying SPSS 20.0 software.

Between 1<sup>st</sup> of July 2002, and 30<sup>th</sup> of June 2012, 414 consecutive severe TBI cases were treated, 100 (24.15%) female and 314 (75.85%) male patients. The mean age was 54.56 ± 20.16 years. Average GCS on admission was 5.79 ± 2.99. During the hospitalization 223 patients survive and 191 patients died out of the 414 cases; the overall in hospital mortality was 46.14%. From the 414 cases, 299 were treated with the utilization of ventriculostomy (mortality: 40.47%) and 115 cases were managed without it (mortality: 60.87%). The prognostic analysis of the database proved the predictive power of several well-known prognostic factors in severe head injury - among others the age, GCS on admission, coagulopathy and elevated ICP. Mortality rate was found significantly lower in those patients whose treatment complied with the international guidelines.

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#### SEVERE TRAUMATIC BRAIN INJURY AND THE YOUNG MALE SYNDROME: PSYCHOLOGICAL AND EVOLUTIONARY REASONS BEHIND ETIOLOGY?

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In choosing mates, both genders are interested at the age of 15–35 years, hence males in this term rather take part in dangerous situations to get access to fertile females. Evolutionally “willingness for risk-taking” may serve as a signaling device of male physical displays during choosing mates, defined by Wilson and Daly in 1985 as “young male syndrome”. We hypothesized that this “syndrome” can be correlated with accidents which lead to severe traumatic brain injuries (sTBI).

Our sample consisted of 374 patients suffering sTBI (females: 90; males: 284) who were investigated concerning age, risk taking behavior, sex ratio, mortality and alcohol intoxication at injury. We created three groups of injury circumstances according to levels of risk with K-Means Cluster Analysis: 1. low risk, 2. moderate risky, 3. high risk; furthermore we defined 4 age groups: 1. under 15 years, 2. 15–35 years, 3. 36–65 years, 4. above 65 years. Incidence rates have been analyzed with Chi-square tests and T-tests.

Our results indicate that males at the age of 15–35 y acquired sTBI while exhibiting riskier behaviors than the other age groups of males

and any age groups of females, therefore it may be a manifestation of “young male syndrome”.

Acute alcohol intoxication played a dominant role in head traumas in young males, most probably escalating their risk-taking propensities. These findings not only provide an explanation on the predominance of young males among the injured but also highlight the importance of specific age group targeted injury-prevention strategies.

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#### A RETROSPECTIVE STUDY OF PATIENTS AGED OVER 70 YEARS WITH SUBDURAL HAEMATOMA

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A retrospective study was performed on 225 patients aged over 70 years of age who operated on with acute or chronic subdural haematoma (SDH) at Department of Neurosurgery, University of Szeged between 2005 and 2013. The outcome of SDH of elderly patients taking anticoagulants or platelet aggregation inhibitors, moreover the efficacy of lumbar subarachnoid infusion after surgery are investigated.

The following parameters were recorded: medical history, coexisting systemic diseases, usage of anticoagulant or antiplatelet therapy, clinical condition, radiological findings, the method of surgical treatment, lumbar subarachnoid infusion, outcome (reoperations).

The group analyzed consisted of 225 patients aged over 70 years with subdural haematoma. Between 2005 and 2009, 91 patients had chronic and 14 patients had acute subdural haematoma, 19 patients took acetylsalicylic acid, 6 patients took clopidogrel and 15 patients took Syncumar in the period of 3 months before admission; we used lumbar subarachnoid infusion at 10 patients, the brain re-expanded in 15 patients during the operation; we reoperated 15 patients. In the group of patients taking anticoagulants the reoperations were three times higher and the mortality rate was two times higher than in the group of patients not taking anticoagulants. The results of patients who were operated between 2010 and 2013 are currently being processed. The postoperative lumbar subarachnoid infusion can help the brain expand, and taking anticoagulants involve a high risk of rebleeding and presumes reoperations.

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#### EFFECTIVENESS OF GUIDELINE ADAPTION WITHOUT LAUNCHING AUDIT ON PROGNOSIS OF HEAD INJURY – HUNGARIAN EXPERIENCES

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The disease burden of intracranial trauma is high in Hungary. The adherence to guidelines relying on well characterized effectiveness of certain clinical interventions is the most effective approach to diminish this health loss. The serious head injury guideline had been adopted in 2006 in Hungary, without launching audit for its application. Our study aimed to describe the case fatality ratio (CFR) for intracranial injury in Hungary to describe the effectiveness of guidelines' application.

Hospital discharge records of 7070 patients admitted between 01/01/2004 and 31/12/2010 with diagnosis of intracranial injury (S06 by ICD10) from every inpatient institutions of Hungary has been involved by the processed database. The CFRs were calculated for 1 week and 6 months.

The 1-week CFRs were 21.2% among male and 23.6% among female, which were elevated up to 47.0% and 50.4% by 6 months. There was no association between age and 1-week CFR ( $p=0.485$ ). The 6-month CFRs was positively correlated with age ( $p<0.001$ ). The log-transformed number of patients treated by institutions was not correlated with 1-week CFR ( $p=0.069$ ), but was inversely correlated with 6-month CFR ( $p=0.028$ ). The CFRs were not decreased after enacting guidelines in 2006. (1-week CFR was 23% before 2006 and 22% after 2006, 6-month CFR was 47% and 49%).

The adaption of guidelines did not improve the prognosis of serious head injury in Hungary most probably due to the low adherence of its application. This experience demonstrated that the guideline potential cannot be exploited without proper auditing.

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#### **CT AND MRI FINDINGS ARE NOT PREDICTIVE OF LONG-TERM OUTCOME FOLLOWING MILD TRAUMATIC BRAIN INJURY**

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Identification of mild traumatic brain injury (mTBI) relies on imaging and clinical exam, with positive findings on CT or MRI considered a more serious injury. For certain patients, mTBI results in lasting symptoms and incomplete recovery. MRI findings can help identify mTBI patients with prolonged recovery, however it is unclear whether positive imaging is related to long-term outcomes. Therefore, we examined the relationship of imaging to 6 and 12-month outcomes following mTBI. Enrolled through the prospective, multicenter Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) study, 133 mTBI patients (GCS 13–15) evaluated at a Level 1 Emergency Department within 24 hours from injury, receiving both a head CT and MRI, were included. Outcomes measured included the Glasgow Outcome Scale Extended (GOSE) score, the Brief Symptom Inventory 18 Item (BSI-18) score and the Post-Traumatic Stress Disorder Checklist (PCL) score. T-test and Chi-squared testing was performed as well as logistic regression modeling. Mean age was  $40 \pm 16$  years old, 71.2% male with 79% having a GCS of 15. 30.1% had positive findings on CT and 36.8% had positive MRI. Neither positive CT nor MRI was significantly related to outcome at 6 or 12 months. Controlling for injury severity and demographics, CT and MRI findings failed to be significant predictors of worse outcome at either time point. Though imaging is an important diagnostic tool

immediately following mTBI, with more detailed imaging identifying patients with prolonged recovery, positive findings may not be useful in determining long-term outcomes and other factors should be considered.

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#### **BENEFICIAL EFFECTS OF MEMANTINE THERAPY AFTER CONTROLLED CORTICAL IMPACT INJURY IN ADULT RATS**

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In these preclinical experiments we assessed the therapeutic effectiveness of administration of the moderate-affinity noncompetitive glutamate receptor antagonist, memantine hydrochloride, in adult rats after controlled cortical impact (CCI) injury. We hypothesized that post injury administration of memantine would reduce CCI-induced neuronal and synaptic loss and result in better cerebral blood flow (CBF). Memantine (10 mg/kg) or vehicle was administered daily for 3 weeks starting one hour after CCI injury, by intraperitoneal injection during the first 4 days and thereafter per os over an additional 17 days period. Measured variables included cell number (Nissl stain) and synapse density (synaptophysin immunoreactivity) in the hippocampus. Additionally, rats were evaluated for CBF by arterial spin-label MR imaging and for performance on vestibulomotor (beam balance and beam walking) and memory acquisition and retention (Morris water maze test, fear conditioning) testing. The injury level in the current study was not sufficiently severe to produce significant behavioral differences between vehicle-treated injured and sham animals, however positive trends were detected in the memantine treated injury group. Compared to injured vehicle treated rats, memantine treatment reduced hippocampal neuronal and synapse loss and attenuated impairments in CBF ipsilateral to injury site. Together, these results suggest that in the adult rat CCI model, post injury treatment with memantine is effective in reducing cell and synapse loss and attenuating deficits in cerebral blood flow. These data are consistent with reports of beneficial effects of memantine treatment in a rat model of stroke and in patients with vascular dementia. The effect of memantine treatment on behavioral performance after traumatic brain injury is currently being investigated in rats exposed to more severe CCI injury.

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#### **EARLY SURGERY FOR FRONTAL DEPRESSED SKULL FRACTURE IS NOT ASSOCIATED WITH BETTER OUTCOME**

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Frontal Depressed Skull Fractures (FDSF) increase the rate of unfavourable neurological outcomes, central nervous system (CNS) infection, smell and taste disturbances (STD) and epilepsy. By convention, FDSF are treated surgically and early operation is recommended to reduce the incidence of infection. There is, however, only class III literature addressing the efficacy of this approach, and it argues against the automatic surgical treatment of all cases of depressed skull fracture. Retrospective review of all consecutive patients who underwent surgical treatment of FDSF from January, 2010 to January, 2013. Patient's information during hospitalization were collected from patient's electronic records and tomographic evaluation were done with digital images by two neurosurgeons. We found 41 patients with FDSF who underwent surgical treatment with a mean age of 28.02 years (SD: 16.03) and ranged from 2 to 81. The median Glasgow Coma Score (GCS) at admission was 12. Sixteen patients (39%) underwent neurosurgical procedure at the first 24-hour-period (Early surgery group – ESG) and 25 (61%), were operated after the first day of trauma (Delayed Surgery Group – DSG). Tomographic analysis showed that intracranial focal lesions (IFL) were found in 37 (90,2%); 4 (9,8%) had Epidural hematoma (EDH), 14 (34,1%) had Cerebral Contusion (CC) and 19 (46,3%) had combination of two or more types of IFL. The median of days from traumatic brain injury (TBI) to surgery was 2 (two), and ranged from the first day of hospital admission (D1) to the seventeenth day (D17). Five patients died during the hospital stay, mounting 12,2% of in-hospital mortality. Twenty-six patients (63,4%) completed follow-up with a mean time of 17 months (+ -9). There was no difference of the mortality rate (MR) between the ESG and DSG (22% vs 17,7%,  $p=0,58\%$ ) as well as in the outcome analyzed by the Glasgow Outcome Scale extended – GOS<sub>e</sub> ( $p=0,12$ ). Patients with isolated lesions on CT scan had a MR of 0% against 38,4% on patients with multiple intracranial lesions (MIL) ( $p=0,02$ ): FDSF is a peculiar and distinct type of skull fracture. We found that more than 90% of patients had associated IFL. Most of patients had tomographic signals of dural tear (70,7%) which represents an increased risk of cerebrospinal fluid (CSF) leakage and CNS infection, specially when left untreated. However, we found no difference on MR or bad outcome (analysed by GOS<sub>e</sub>) between the ESG and DSG. The only variable identified as a risk factor for mortality was the presence of MIL on CT scan. The delayed surgical treatment might be a safe and effective approach.

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### COMPLEX SURGICAL TREATMENT OF SKULL BASE INJURIES

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Increasing number of skull base fractures and associated injuries of the surrounding anatomical structures are diagnosed nowadays, mainly as consequences of high energy traffic accidents. Five years retrospective survey of cases treated with skull base traumas in our department were reviewed. Trauma of the anterior skull base is often associated with injuries of the orbit or paranasal sinuses. Frontobasal fractures can result in CSF rhinorrhoea, olfactory or optic nerve injury. Laterobasal injuries may cause CSF otorrhoea and peripheral facial nerve palsy. Skull base fractures can result in also direct bony injury of the internal carotid artery or formation of carotid-cavernous fistula or posttraumatic an-

eurysm. Even venous sinuses can be affected by skull base trauma, resulting in a huge amount of bleeding. Injuries of the posterior skull base can cause instability of the craniocervical region. Fractures involving the foramen magnum are often associated with C 0 - C 2 injuries.

Early diagnosis, complex and definitive surgical solution is very important in the case of these life-threatening injuries, needing a multidisciplinary surgical cooperation during the whole treatment procedure.

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### OPTIMAL CEREBRAL PERFUSION PRESSURE – TOWARDS INDIVIDUALISED TREATMENT IN SEVERE TRAUMATIC BRAIN INJURY

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Optimal CCP (CPP<sub>opt</sub>) refers to a narrow CPP target where cerebrovascular reactivity is optimal. The routine use of CPP<sub>opt</sub> in the management of patients with severe TBI requires an automated methodology for its continuous bedside calculation.

We have sought to develop and validate such a methodology based on monitoring of cerebrovascular pressure reactivity (PR<sub>x</sub>). Prospectively collected data from 327 TBI patients managed in the neurosciences ICU, Addenbrooke's Hospital were retrospectively analysed. Mean arterial pressure (MAP), intracranial pressure (ICP), and CPP were continuously recorded and PR<sub>x</sub> was calculated online (ICM+ software). Glasgow outcome scale was assessed at 6 months.

An automated curve fitting method was developed to determine CPP at the minimum value for PR<sub>x</sub> which corresponds to the level of optimal cerebrovascular reactivity. Minute-by-minute time trends of CPP<sub>opt</sub> were created using a moving 4-hr window. A CPP<sub>opt</sub> curve was on average present during 55% (range 1–91%) of the whole recording period. Mortality increased steadily with the median CPP shifting below the threshold of CPP<sub>opt</sub>. Higher mortality was associated with relative 'hypoperfusion' (CPP < CPP<sub>opt</sub>), severe disability with 'hyperperfusion' (CPP > CPP<sub>opt</sub>), while favourable outcome with smaller deviations of CPP from the individualised CPP<sub>opt</sub>. Deviations from individualised CPP<sub>opt</sub> were more predictive of outcome than deviations from a fixed threshold of CPP (60 or 70 mmHg).

Real-time calculation of CPP<sub>opt</sub> is possible in severe TBI patients. The feasibility of using CPP<sub>opt</sub> for guiding patient management needs to be tested in the context of a prospective multi-centre study.

### CONICOTOMY OF THE BRAIN – IS THE DC/DECOMPRESSIVE CRANIECTOMY/AN ELECTIVE OR EMERGENCY REFUGEE?

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I could get an inside look to the daily routine of different departments and the intensive units as a resident doctor. I astonished as a neurosurgical doctor how great debate exist around the usage of the decompressive craniectomy. There are a lot of studies against and a lot of them supporting of the DC. After reading many studies and articles, I noticed that the DC is an “ultimum refugium” in many cases. It raises many questions. Is the decompressive craniectomy like the conicotomy a lifesaving method? Is the survival rate higher by using the DC? What are the risks and sequelae of their use? In the emergency care we can not follow the well-known rules of the prospective, randomised trials known in the elective care. The rules of the emergency care follow the rules of the simple, logic turn of mind. In simple words, we use conicotomy if we see a suffocating person.

In our study we compare the scientific methods of crisis states used in emergency care and conclusions with the current status of DC.

The result shows that the current life-saving techniques are not studied with methods of prospective randomized controlled trials (RCT). The result in consonance with opinions of the bioethics in this states.

The question is: “Is there any possibility that the clinical trials of the decompressive craniectomy are studied by the rules of the prospective randomized controlled trials like in the emergency care?”

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#### NIH PARTICIPATION IN THE INTERNATIONAL TRAUMATIC BRAIN INJURY RESEARCH (INTBIR) INITIATIVE

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The National Institutes of Health (NIH) is one of the founding members of the INTBIR initiative and enthusiastically supports the common goal of creating a knowledge network to improve outcomes after traumatic brain injury (TBI). NIH contributes approximately \$80M toward TBI research annually, which funds dozens of basic, preclinical and clinical research studies.

Two large, multicenter projects have been identified as being highly relevant to the INTBIR initiative. TRACK-TBI, led by Geoff Manley at UCSF, is a prospective, observational study of 3,000 subjects of all ages across the range of concussion to coma to develop a more precise and predictive classification system for TBI and to validate neuroimaging and biomarkers.

ADAPT, led by Mike Bell, Univ. Pittsburgh, will study 1,000 children with severe TBI to compare management and treatment effectiveness for TBI in intensive care units.

In addition to supporting these clinical studies, NIH also played a major role in the development of Common Data Elements for TBI research (TBI-CDEs).

The Federal Interagency TBI Research (FITBIR) informatics system, a U.S. Department of Defense and NIH collaboration, uses the TBI-

CDEs for its data dictionary and provides a platform for collaboration and data sharing.

FITBIR will be used by NIH-funded TBI research teams and is also available for other studies. Developing an INTBIR data sharing policy to enable fair and reasonable access is an important goal for the coming year.

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#### ‘SOLID RED LINE’ – AN OBSERVATIONAL STUDY ON DEATH FROM REFRACTORY INTRACRANIAL HYPERTENSION

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Cerebrovascular pressure reactivity has been showed to be independently correlated with outcome after TBI. However, as an index plotted in time domain, PRx is rather noisy. To ‘organize’ PRx and make its interpretation easier, colour coding of values, with green, when PRx < 0 and red when PRx > 0.3 has been introduced as horizontal colour bar in the ICM+ screen. After ten years of use, we realized that in rare cases of deaths from refractory intracranial hypertension, rise of ICP above 20 mm Hg (before CPP falls below 50 mmHg) is commonly preceded with values of PRx > 0.3, appearing on a screen as a ‘solid red line’.

20 patients after TBI and one after traumatic SAH from 6 centres in Europe and Australia have been studied. All of them died in a scenario of refractory intracranial hypertension. In majority of cases the initial ICP was below 20 mm Hg and finally rising to values well above 60 mmHg, resulting in CPP less than 20 mm Hg. In 3 cases initial ICP was already elevated at start of monitoring. ‘Solid red line’ was observed in all cases preceding rise of ICP above 25 mmHg by minutes to hours and in two cases by two and three days.

‘Solid red line’ is a mathematical consequence of mean ICP being strongly than usual and persistently positively correlated with MAP. It may indicate deteriorated autoregulation. If such a state is observed over a prolonged period, it should be considered as an indicator of deep cerebrovascular deterioration.

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#### PATIENT-SPECIFIC THRESHOLDS OF INTRACRANIAL PRESSURE AFTER PATIENTS WITH TRAUMATIC BRAIN INJURY

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Based on continuous monitoring of the pressure reactivity index (PRx) we defined individualized intracranial pressure (ICP) thresholds by graphing the relationship between ICP and PRx. We hypothesized that an "ICP dose" based on individually assessed ICP-threshold would correlate closer with 6-month outcome when compared to fixed doses. 327 severe traumatic brain injury (TBI) patients have been studied. Individualized thresholds were visually identified from graphs of PRx versus ICP over the total monitoring time for each patient; PRx > 0.2 was the cut-off. ICP doses were then computed as the cumulative area under the curve (AUC) above the defined thresholds in graphing ICP versus time. The term, Dose20 (D20), is used to refer to an ICP threshold of 20 mm Hg. The markers D25 and DPRx were calculated similarly. Separate logistic regression models were fit with mortality as the outcome and each dose as the predictor, both alone and adjusted for covariates. A clearly identifiable PRx-based threshold was possible in 224 patients (68%). DPRx (0.81, CI 0.74-0.87) was found to have the highest AUC over both D20 (0.75, CI 0.68-0.81) and D25 (0.77, CI 0.70-0.83).

We found that individualized doses of intracranial hypertension were stronger predictors of mortality than doses derived from the universal thresholds of 20 and 25 mm Hg. The pressure reactivity index could offer a method towards individualizing the ICP threshold.

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#### **TACKLING CONCUSSION: NEUROMECHANICS AND NEUROPATHOLOGY**

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Over the past 70 years, diffuse axonal injury (DAI) has emerged as one of the most common and important pathological feature of traumatic brain injury (TBI). Axons in the white matter appear to be especially vulnerable to injury due to the mechanical loading of the brain during TBI. As such, DAI has been found in all severities of TBI and may represent a key pathologic substrate even of mild TBI (concussion). Pathologically, DAI encompasses a spectrum of effects from primary mechanical breaking of the axonal cytoskeleton, to transport interruption, swelling and proteolysis, through secondary physiological changes. Depending on the severity and extent of injury, these changes can manifest acutely as immediate loss of consciousness or confusion and persist as coma and/or cognitive dysfunction. In addition, recent evidence suggests that TBI may induce long-term neurodegenerative processes, such as insidiously progressive axonal pathology. Indeed, axonal degeneration has been found to continue even years after injury in humans, and appears to play a role in the development of Alzheimer's disease-like pathological changes. Supported by NIH grants, NS38104 and NS056202.

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#### **PAROXYSMAL AUTONOMIC INSTABILITY IN TRAUMATIC BRAIN INJURIES AT NEUROSURGICAL INTENSIVE CARE UNIT**

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Paroxysmal autonomic instability after severe brain injury is a syndrome of marked agitation, diaphoresis, hyperthermia, hypertension, tachycardia, and tachypnea accompanied by hypertonia and extensor posturing. We evaluated to autonomic symptoms-seven criteria and also exclusive criteria (infection, side effects of drugs, other metabolic diseases) with the clinical data of post traumatic brain injury 117 dead patients from January, 2007 to March, 2011. Male and female ratio was 92:25. Mean age of patients was 53.5 (2~94) years. The mean initial GCS score was 6.36, GOS score was 1. The number of patients applied to our autonomic symptoms seven criteria was divided 8 groups (seven criteria : 4, six criteria : 4, five criteria : 5, four criteria : 4, three criteria : 10, two criteria : 42, one criteria : 32, no criteria : 16. A 28-year-old man started several bipolar rhythms of autonomous dysfunction with the hyperactive and the hypoactive stage. It might accelerate the 24kg loss of weight. He was treated with baclofen, sedatives, antihypertensives for the hyperactive stage and the sympathomimetic drugs were adjusted for the hypoactive stage with ventilator. There were not abnormal laboratory findings except supranormal catecholamines. The SPECT (Single Photon Emission Computed Tomography) showed the hypoperfusion during the autonomic dysfunction. The bromocriptine made him stable. The current evidence base does not allow the development of empirical criteria of autonomic instability. The dopamine agonist may has a complex cascade of neuromodulation for the autonomic instability.

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#### **SUBDURAL HYGROMA AFTER DECOMPRESSIVE CRANIECTOMY IN TRAUMATIC BRAIN INJURY**

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Subdural hygroma (SDG) is a complication occurring after head trauma that may occur secondary to decompressive craniectomy (DC). However, the mechanism underlying SDG formation is not fully understood. Also, the relationship between the operative technique of DC or the decompressive effect and the occurrence and pathophysiology of SDG has not been clarified. Purpose of this study was to investigate the risk factors of SDG after DC in our series. From January 2004 to December 2008, DC was performed in 85 patients who suffered from traumatic brain injury. We retrospectively reviewed the clinical and radiological features. For comparative analysis, we divided the patients into 2 groups: one group with SDG after craniectomy (19 patients; 28.4% of the total sample), the other group without SDG (48 patients; 71.6%). The risk factors for developing SDG were then analyzed. The mean Glasgow Outcome Scale (GOS) scores at discharge of the groups with and without SDG were 2.8 and 3.1, respectively ( $p < 0.0001$ ). Analysis of radiological factors showed that a midline shift in excess of 5 mm on CT scans was present in 19 patients (100%) in the group with SDG and in 32 patients (66.7%) in the group without SDG ( $p < 0.05$ ). An accompanying subarachnoid hemorrhage (SAH) was seen in 17 patients (89.5%) in the group with SDG and in 29 patients (60.4%) in the group without SDG ( $p < 0.05$ ). Delayed hydrocephalus accompanied these findings in 10 patients (52.6%) in the group with SDG, versus 5 patients (10.4%) in the group without SDG ( $p < 0.05$ ). On CT, compression of basal cisterns was observed in 14 members (73.7%) in the group with SDG and in 18 members of the group without SDG (37.5%) ( $p < 0.007$ ). Furthermore, tearing of the arachnoid membrane, as observed on CT, was more common in all patients in the group with SDG (100%) than in the group without SDG (31 patients; 64.6%) ( $p < 0.05$ ). GOS showed

statistically significant difference in the clinical risk factors for SDG between the group with SDG and the group without SDG. Analysis of radiological factors indicated that a midline shifting exceeding 5 mm, SAH, delayed hydrocephalus, compression of basal cisterns, and tearing of the arachnoid membrane were significantly more common in patients with SDG.

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#### VASCULAR COMPROMISE IN CONTUSION EXPANSION

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The magnitude of damage to cerebral tissues following traumatic brain injury (TBI) is determined by the primary injury plus numerous secondary injury responses that inevitably worsen the primary injury. When TBI results in a cerebral contusion, the hemorrhagic lesion typically progresses during the first several hours after impact, either expanding or developing new, non-contiguous hemorrhagic lesions, a phenomenon termed “hemorrhagic progression of a contusion” (HPC). Since a hemorrhagic contusion marks tissues with essentially total, unrecoverable loss of function, HPC is among the most feared types of secondary injury encountered following TBI. Recently, a novel molecular mechanism was postulated to account for HPC that involves activation of the mechano-sensitive transcription factors, Sp1 and NF- $\kappa$ B, and transcriptional upregulation of Sur1-Trpm4 channels in endothelial cells of penumbral microvessels. Unchecked opening of Sur1-Trpm4 channels results in accidental necrosis of endothelial cells, resulting in progressive microvascular failure, delayed capillary fragmentation, and expansion of the hemorrhagic contusion, i.e., HPC. Here, we review emerging evidence on the role of Sur1-Trpm4 channels in TBI. We show upregulation of Sur1-Trpm4 channels in TBI in both animal models and in humans, and we confirm the co-association of the 2 subunits, Sur1 and Trpm4, *in vivo* with co-immunoprecipitation and with Förster resonance energy transfer (FRET). We review the role of the channel in accidental necrotic cell death *in vitro*, and in capillary fragmentation *in vivo*, with the latter shown to be blocked by gene silencing and gene suppression as well as by pharmacological inhibition of Sur1 and Trpm4.

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#### ANTIBIOTIC USE: A POTENTIAL DETERMINANT OF PENETRATING SPINAL CORD INJURY OUTCOMES

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The management of penetrating spinal injuries in patients with partial neurological deficit has seen various eras historically, and been the source of controversy generally. The apathy with which some practitioners view “futile” intervention (especially in those with total fallout) has alternated with the aggressive surgical approach. The vast majority of available literature points to a single digit rate (although one study showed a 76% rate) of improvement of neurological deficit

in patients who are managed conservatively, relative to the 39–71% rate in the post-laminectomy group.

The patients in our unit were treated (all but several cases) conservatively. However, we encountered a variation, but with the administration antibiotics vs no antibiotics as the tipping point. Is it possible that the exposure to prophylactic antibiotics generally administered to surgical patients may play a more significant role in the positive outcomes than previously thought?

Objectives:

- to elucidate the rate of improvement of patients with penetrating spinal injuries, and exposure to antibiotic treatment (prophylactic or therapeutic)
- to define the potential link between improvement and specific antibiotics
- to investigate whether the initial neurological state of a patient impacted the outcome of those who received antibiotics

The information is derived from a retrospective cohort of the relevant patients.

Study population: The people under investigation were patients admitted to our neurosurgical unit with penetrating spinal injury.

Study period: 2009–2012

The study demonstrated the need of a multi-centre randomised control trial of the potential benefit of antibiotics with/without laminectomy.

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#### THE EFFECT OF MILD TRAUMATIC BRAIN INJURY (MTBI) ON THE STRUCTURAL PLASTICITY OF THE AXON INITIAL SEGMENT (AIS)

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The AIS is a crucial subdomain regulating action potential firing and undergoes activity-dependent structural plasticity to modulate neuronal excitability. Previously, we demonstrated in mTBI-mice dramatic alterations in the electrophysiological status of intact neocortical pyramidal neurons, consistent with AIS-specific changes. The purpose of the current study was to determine if mTBI induces AIS structural plasticity within intact neocortical pyramidal neuron populations. Thy1-YFP mice exposed to either sham or central fluid percussion injury ( $1.7 \pm 0.2$  atm) were perfused after a 2-day recovery period. Immunoreaction with ankyrin-G, a scaffolding protein for axonal voltage-gated sodium-channels, was used to fluorescently label the AIS. Confocal microscopy was used to identify intact YFP<sup>+</sup> pyramidal neurons in neocortical layer 5, whose axons were continuous from the soma of origin to the subcortical white matter. Immunofluorescent profiles of ankyrin-G were superimposed on traces of YFP<sup>+</sup> axons to determine, with respect to the somas of origin, their starting and termination points, as well as the point of maximal signal intensity of the AIS reported as mean  $\pm$  SEM. In sham animals, the AIS started  $2.1 \pm 0.4$   $\mu$ m from the soma with maximum signal intensity seen at  $11.7 \pm 1.7$   $\mu$ m, and termination occurring at  $27.4 \pm 0.9$   $\mu$ m. While mTBI animals had similar AIS start and maximal signal intensity points ( $2.3 \pm 0.4$   $\mu$ m,  $9.9 \pm 1.1$   $\mu$ m; p-value = 0.7676, 0.4502, respectively), the AIS termination point was significantly different ( $22.8 \pm 0.9$   $\mu$ m; p-value = 0.0053), resulting in a decrease of AIS length. Such a change in AIS structure may explain some of the electrophysiological abnormalities seen in intact neocortical pyramidal neurons after mTBI.

### LATERAL VENTRICLE VOLUME ASYMMETRY PREDICTS MIDLINE SHIFT AND 6-MONTH OUTCOME IN SEVERE TRAUMATIC BRAIN INJURY

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Early CT scan findings play an important role in the management of patients with severe traumatic brain injury (sTBI). We hypothesized that lateral ventricular volume asymmetry is an earlier sign of developing asymmetric pathology than midline shift and is an indicator of poor outcome.

This retrospective analysis was performed on 84 adults with blunt sTBI requiring a ventriculostomy presenting to a Level I Trauma Center. 76 patients underwent serial CTs within 3 hrs and an average of 3 scans within the first 10 days of sTBI. Six-month outcome data as Disability Rating Scale (DRS) and Glasgow Outcome Scale-Extended (GOS-E) were available for 64 patients. Lateral ventricle volumes were quantified by computer assisted manual volumetric measurements. Lateral ventricular volume ratios (LVR) were determined on the initial CT to evaluate ventricular asymmetry. Relationships between the initial LVR values, midline shift development and outcome scores were tested.

Sixty percent (15 of 25) of the patients with a LVR > 1.8 had 0–5 mm midline shift on initial CT. These patients had an odds ratio of 6.47 ( $p < 0.01$ ) to develop a subsequent > 5 mm midline shift. Surviving patients at 6 months with an initial LVR of > 2.2 had significantly ( $p < 0.05$ , Mann-Whitney U-test) worse DRS and GOS-E scores than patients with an initial LVR of < 2.2 (mean scores for LVR > 2.2: DRS = 10, GOS-E = 4; for LVR < 2.2: DRS = 5, GOS-E = 6).

We propose that LVR captures ventricular asymmetry and may predict midline shift, be an early indicator of poor outcome and a useful sign in the clinical management of sTBI.

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### PROGNOSTIC RELEVANCE OF LONGITUDINAL BRAIN ATROPHY ESTIMATION IN POST-TRAUMATIC DIFFUSE AXONAL INJURY

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Diffuse axonal injury is a well comprehended kind of post-traumatic brain lesion characterized by widespread disruption of cerebral white matter bundles. Recovery trajectory, if the patient recovers his consciousness, is mainly characterized by neuropsychological sequelae such as attention and memory deficit. Brain atrophy as assessed by quantitative measurements on serial MRI volumetric scans may represent a challenging biomarker, useful to predict the prognosis of these kind of patients because data coming from recent observations of some authors, show relevant correlations between white matter cerebral atrophy and cognitive post-traumatic performance as assessed by neuropsychological tests. We set up a longitudinal study including patients in post-traumatic coma being hospitalized with a DAI pattern revealed by MRI. Patients presenting with DAI in addition to any focal brain lesion, such as subdural hematoma, are excluded. Patients undergo MRI scan (T1 3D MPRAGE, isotropic voxel 1 mm 3) at 4 time points (1,7,13,25 months) and neuropsychological evaluation (FAB, TMT A and B, RAVLT, Rey figure, Raven's CPM, WCST) at the same time. Purpose was to study the atrophy phenomenon with respect to its timing, and to patient outcome. We included 10 patients; only 4 have already completed the 4 time points observation. WM atrophy is grossly influencing the early seven months period (range 0.51%–16.4%) We observed an initial statistically significant trend of correlation (Pearson) between WM volume loss and memory (–0.820) and attention (0.813) scores.

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### CONVENTIONAL VS QUANTITATIVE APPROACH IN ASSESSING POST-TRAUMATIC VENTRICULOMEGALY AND ITS RELATION TO 6-MONTH OUTCOMES IN SEVERE TRAUMATIC BRAIN INJURY

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Post-traumatic ventriculomegaly is a known complication of severe traumatic brain injury (sTBI) associated with poor clinical outcome.

Subjective assessments leave the relationship of ventriculomegaly and outcome measures elusive. We hypothesized that ventricular volumetric based identification of ventriculomegaly could add to subjective radiologic assessment of ventriculomegaly in predicting outcome. This retrospective analysis was performed on 84 adults with blunt sTBI requiring a ventriculostomy presenting to a Level I Trauma Center. Serial CTs within 3 hrs and an average of 3 additional scans within the first 10 days of sTBI and 6-month outcome data, Disability Rating Scale (DRS) and Glasgow Outcome Scale-Extended (GOS-E), were available for 64 patients. Subjective assessment for ventriculomegaly and quantified ventricular volumes were determined. Relative enlargement to initial volume was calculated. The relationship to 6-month outcome was assessed between patients without ventricular enlargement and each of the following groups: (A) Subjective radiological diagnosis of ventriculomegaly. (B through E) Quantitative measurement groups: (B) any, (C) overall, (D) bilateral, (E) unilateral enlargement. Mann-Whitney U-test determined significance ( $p \leq 0.05$ ). Ten surviving patients with unilateral enlargement (E) had significantly worse DRS and GOS-E scores than all other 19 surviving patients (mean scores for group E: DRS=10, GOS-E=4; for non-unilateral enlargement group: DRS=4, GOS-E=6). Other groups (A-D) did not differ in outcome from non-enlargement patients. Quantitative approach identified a subgroup of sTBI patients with unilateral ventricle enlargement indicating poor outcome while other types or subjective-diagnosed ventricle enlargement did not.

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#### CONTRALATERAL AND THIRD VENTRICULAR COMPRESSION ARE EARLY CT SIGNS HERALDING SECONDARY INFARCTS IN NON-PENETRATING SEVERE TRAUMATIC BRAIN INJURY

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Posttraumatic secondary infarction (PTCI) is a common secondary injury following severe traumatic brain injury (sTBI). Several risk factors for PTCI have been identified including low admission GCS, raised ICP, herniation and decompression surgery but no known early CT signs predicting PTCI have been identified yet. Existing CT classifications (e.g., Marshall Classification and Rotterdam Score) predict overall prognosis, but have not been validated for predicting PTCI. We aimed to identify early CT signs as risk factors of PTCI. A prospective convenience controlled cohort study enrolled 131 adult patients with sTBI. CT scans were evaluated retrospectively for the presence of secondary infarcts, third ventricular compression, contralateral ventricular compression in relation to primary mass lesion, intra-ventricular hemorrhage, basal and cortical subarachnoid hemorrhage in patients with and without secondary infarcts. Fifteen of 131 patients (11.4%) developed secondary infarcts. Third ventricular compression and contralateral ventricular compression on initial CT scan was seen more frequently in patients with PTCI: 14/15

vs 55/116 (OR=15.5; 95%CI 1.98-121.98  $p < 0.01$ ) and 10/15 vs 20/116 (OR=9.6; 95%CI 2.96-31.14  $p < 0.01$ ), respectively.

Contralateral and 3<sup>rd</sup> ventricular compression were found to correlate with the development of PTCI. These CT signs can be considered as surrogate markers of CSF volume loss, an early compensatory step in intracranial swelling often seen in sTBI. Subsequent rise in ICP can lead to herniation, vessel compression and ultimately secondary infarcts. Identification of these early CT signs may lead to intensified treatment and to reduced risk of secondary infarcts.

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#### LATERAL VENTRICLE VOLUME ASYMMETRY IS RELATED TO SPECTRIN BREAKDOWN

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Biomarkers of neuronal injury together with neuroimaging could be used to better evaluate sTBI severity.

The relationship between early lateral ventricle volume asymmetry, Rotterdam score, Marshall CT Classification and cerebrospinal fluid (CSF) biomarkers were assessed.

This retrospective study included 84 adults with blunt sTBI requiring ventriculostomy presenting to a Level I Trauma Center. 64 patients had an initial CT done within 3 hrs after TBI and quantitative CSF biomarker data (UHCL-1, SBDP145, SBDP150, SBDP120, MAP2, MBP, S100B) available within 24 hrs after injury. Lateral ventricle volumes were quantified by computer-assisted manual volumetric measurements and their ratio (LVR) was calculated to capture ventricular asymmetry. Marshall and Rotterdam scores also were determined. Non-parametric tests were used to assess the correlations. LVR values were significantly correlated with the Rotterdam score ( $\rho = 0.45$ ,  $p < 0.001$ ) and Marshall CT classification ( $\rho = 0.29$ ,  $P = 0.008$ ). There were 68 patients who had both LVR and biomarker levels available. The only biomarker that was significantly associated with LVR was SBDP145 ( $\rho = 0.30$ ,  $p = 0.023$ ). In those with  $LVR \leq 1.8$ , mean SBDP145 values taken at the earliest time point within 24 hours was 64.6 (SD97.6) and in those with  $LVR > 1.8$  was 103.0 (SD 81.4) ( $p = 0.02$ ). SBDP145 was also correlated with the Rotterdam score ( $\rho = 0.38$ ,  $p < 0.001$ ) and with Marshall Classification ( $\rho = 0.23$ ,  $p = 0.017$ ).

Our results suggest that asymmetric distortion is an important component of brain pathologies in sTBI and is associated with both

Rotterdam and Marshall Classifications. These CT findings are associated with early elevations of SBDP145, suggesting SBDP145 is an important indicator of sTBI severity.

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#### **A NEW FMRI APPROACH FOR ESTABLISHING CONSCIOUS AWARENESS AND COMMUNICATION IN BEHAVIOURALLY NONRESPONSIVE PATIENTS**

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The interpretation of human thought from brain activity, without recourse to speech or action, is one of the most provoking and challenging frontiers of modern neuroscience. In particular, patients who are fully conscious and awake, yet, due to brain damage, are unable to show any behavioural responsiveness, expose the limits of the neuromuscular system and the necessity for alternate forms of communication. Although it is well established that selective attention can significantly enhance the neural representation of attended sounds, it remains, thus far, untested as a response modality for brain-based communication. Functional magnetic resonance imaging (fMRI) data were acquired as healthy participants (N=15) and behaviourally non-responsive patients (N=10) were asked to answer binary questions by selectively attending to the appropriate word ('yes'/'no'). 90% of the answers provided by healthy participants were decoded correctly based on activity changes within each individual's attention network. Moreover, formal comparison with the current best-established fMRI technique for binary communication, revealed improved individual success rate, and scanning times required to detect responses. Six patients demonstrated their ability to follow commands by selectively paying attention according to instructions. Three patients were also able to guide their attention to repeatedly communicate correct answers to several questions. These results demonstrate that behaviourally non-responsive patients can use selective auditory attention to convey their ability to follow commands and to communicate. This technique may be useful in establishing basic communication with patients, who appear to be unresponsive with bedside examinations, as well as existing neuroimaging methods.

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#### **EFFECT OF MILD HYPOTHERMIA TREATMENT ON RAT RIPK-1 EXPRESSION FOLLOWING TRAUMATIC BRAIN INJURY**

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To investigate the relationship between mild hypothermia treatment and gene transcription and protein expression of receptor-interacting protein kinase-1 (RIPK-1) following by traumatic brain injury (TBI) in rats. Forty adult male Wistar rats were randomly divided into 5 equal groups (normal, sham, sham+hypothermia, TBI, and TBI+hypothermia). After TBI induced by fluid percussion injury (FPI), group TBI remained at normal temperature (37°C), and group (TBI+hypothermia) underwent mild hypothermia (32°C) for 4h. Neurological severity scores (NSS) were then assessed. All rats were sacrificed after 48h and brain tissues were harvested, stained with

hematoxylin and eosin (HE). mRNA and protein expressions of RIPK-1 were analyzed by reverse transcription-polymerase chain reaction (RT-PCR), real-time PCR, Western-blot, and immunohistochemistry (IHC), respectively. Significantly decreased NSS scores were observed in group TBI+hypothermia compared to group TBI ( $P < 0.01$ ). Additionally, group TBI increased RIPK-1 levels compared to group sham ( $P < 0.05$ ). Reduced expression of RIPK-1 were apparent in group TBI+hypothermia compare to group TBI ( $P < 0.05$ ). However, no statistically significant difference was observed among groups normal, sham, and sham+hypothermia in NSS scores and the expression of RIPK-1 ( $P > 0.05$ ). Mild hypothermia treatment significantly reduced NSS score and RIPK-1 upregulation after TBI, which may provide a better understanding of the mechanisms by which hypothermia reduces secondary brain injury in TBI patients.

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#### **ESTABLISHMENT OF TRAUMATIC BRAIN INJURY-INDUCED STRESS ULCER MODEL IN RATS WITH AN ELECTRIC CORTICAL CONTUSION IMPACTOR**

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The application of electric cortical contusion impactor (eCCI) caused traumatic brain injury (TBI)-induced animal model of stress ulcer (SU) in rats and lay the foundation for further study on the pathogenesis and treatment of SU. A total of twenty Sprague-Dawley rats were subjected to impact injury at 4 mm depth of penetration, for a sustained depression of 200 ms, at 4 m/s velocity for TBI using the eCCI device. The brain and gastric mucosal blood flow were measured for 48 h following TBI, and then the brain and gastric tissues were removed for observing histopathological changes. After 48 h of TBI, the mucosal blood flow in the brain surface of rats were reduced, oozing surface of red blood cells. The number of neurons was decreased with structural disorder. The structure of gastric mucosal tissue surface was disordered, with mucosal surface cells and glandular stomach cell degeneration, loss, accompanied by red blood oozing. Eosinophilic infiltration of inflammatory cells in the submucosa of gastric were observed. There is existence of SU following TBI induced by electric cortical contusion impactor. The SU animal model induced by TBI in rats was established successfully, which may serve as a suitable platform to provide experimental evidence for the pathophysiological of SU following TBI.

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#### **NEUROPROTECTION: PRECLINICAL/TRANSLATIONAL DISCOVERY**

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Despite the neuroprotective success of various pharmacological interventions in experimental models of CNS injury, none have successfully translated to the clinical arena. While a number of factors have been proposed to account for this failure, our own studies have highlighted the importance of species selection as well as dosage and timing of drug administration. We will use two case studies to illustrate these points. The first examines the use of substance P receptor

antagonists for the treatment of elevated ICP following TBI. The temporal dynamics of ICP and brain oxygenation changes after clinical TBI are poorly reflected in rodent models of TBI, while large animal models better mimic the human condition. Moreover, the data from large animal models allows simultaneous analysis of all of the parameters that contribute to brain oxygenation (ICP, MABP, CPP), thereby providing a more advanced understanding of their interrelationships and thereby potential treatment targets. The second case study examines the efficacy of pharmacologic aquaporin modulators to reduce edema after traumatic CNS injury. We demonstrate that the effect of the modulators depends not only upon the model being used, but also upon the timing of drug administration, with the effects of late administration sometimes being diametrically opposed to the effects of early administration. While problematic in terms of simplistic translation, these types of results do provide an insight into the mechanistic complexity of CNS injury and the factors that must be taken into account in the quest for successful clinical translation.

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#### **CANADIAN PARTICIPATION IN THE INTERNATIONAL INITIATIVE FOR TRAUMATIC BRAIN INJURY RESEARCH (INTBIR)**

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Led by the Canadian Institutes of Health Research - Institute of Neurosciences, Mental Health and Addiction (CIHR-INMHA), Canada is one of the three founding members of the IntBIR initiative. INMHA and several national partners including Defense Research Development Canada, le fonds de recherche du Québec santé, the Hotchkiss Brain Institute, the Ontario Brain Institute and the Ontario Neurotrauma Foundation have partnered to support \$10M in new funding for TBI research in Canada aligned with the goals and vision of IntBIR. In November 2013 Canada's Minister of Health Rona Ambrose officially announced \$7.4M funding of 5 new teams focused on the early diagnosis and management of mild TBI or concussion in children and youth and 14 Catalyst grants focused on the early diagnosis and management of mild TBI across the lifespan.

INMHA hosted the second IntBIR meeting in Vancouver in October 2013 with a key objective being to encourage scientific exchange and networking among members of newly funded TBI research programs undertaken in the EU, the United States and Canada. Invited participants learned first hand about existing and planned resources, including infrastructure, databases, Common Data Elements and their promotion/internationalisation. Discussion at the meeting also focused on data sharing policies and technologies, and a dedicated session was intended to foster progress towards standardized data collection, sharing and meta-analyses.

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#### **FACTORS OF INFLUENCE ON SURGICAL DECISION MAKING AND OUTCOME IN PATIENTS WITH ACUTE SUBDURAL HEMATOMA: A RETROSPECTIVE STUDY OF 109 PATIENTS WITH EVALUATION OF QUALITY OF LIFE**

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The acute subdural hematoma (ASDH) due to traumatic brain injury (TBI) often leads to severe disability despite neurosurgical treatment. Therefore, whether to operate or not, and with or without a bony decompression, i.e. decompressive craniectomy (DC), pose ethical dilemmas. In this study patients were retrospectively analyzed for whom neurosurgical consultation was requested between 2008 and 2012 in order to determine which factors might be of influence on surgical decision making and outcome. Outcome was assessed with mortality on discharge, the Glasgow Outcome Scale (GOS) and the Quality of Live after Brain Injury (QOLIBRI) scale.

Included were 109 patients. In mild TBI and ASDH, operated patients more often had focal signs (75 vs 25 %;  $p = .01$ ) and had more midline shift (10 vs 3 mm;  $p = .001$ ). Comparing DC with craniotomy alone, the DC group was younger (53 vs 67;  $p = .004$ ), less often used anticoagulants (53 vs 28;  $p = .05$ ), had thinner hematoma (13 vs 17 mm;  $p = .03$ ), more accompanying intracranial pathology (71 vs 34 %;  $p = .03$ ) and had worse functional outcome ( $GOS \leq 3$ : 80 vs 56 %;  $p = 0.05$ ). QOLIBRI was the same for mild and moderate/severe TBI (69 vs 64;  $n = 9$ ;  $p = .63$ ).

The study shows factors that might be of influence on surgical decision-making in ASDH. Interestingly, QoL did not differ between mild and moderate/severe TBI. These results should strengthen the call for a comparative effectiveness study on surgery for ASDH.

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#### **BLAST-INDUCED CEREBRAL VASCULAR DYSFUNCTION**

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Concussive traumatic brain injury (TBI) is associated with cerebral vascular dysfunction comprised of impaired compensatory responses to changes in arterial pressure, oxygen and carbon dioxide levels and hematocrit, as well as increases in blood-brain barrier (BBB) permeability. Traumatic cerebral vascular injury likely contributes to the increased mortality/morbidity observed in humans and experimental animals when concussive TBI is accompanied by arterial hypotension or hypoxemia. Although cerebral vascular dysfunction is an established consequence of concussive TBI, the effects of blast-induced neurotrauma (BINT) on the cerebral vasculature are unknown.

Blast injury is the most prevalent source of mortality and morbidity among combatants in Operations Iraqi (OIF), Enduring Freedom (OEF) and New Dawn. While TBI has been a significant cause of mortality and morbidity among combatants in past conflicts, the incidence of TBI among war fighters in OIF and OEF is higher than past conflicts. Although these reports indicate that there is a high incidence of blast exposure and TBI among military personnel in Iraq and Afghanistan, the degree to which primary blast injury, that is, blast over- and underpressures, contributes to BINT is not clear and the degree to which BINT contributes to cerebral vascular dysfunction is unknown. Whereas the effects of BINT on neuropathological and behavioral outcomes have been studied for decades, there has been very little research on the cerebral vascular effects of BINT.

Using two experimental models of rodent blast injury, one that models primary blast exposure followed by impact injury and the other primary blast exposure alone, we have observed significant reductions in cerebral blood flow, increases in cerebral vascular resistance and reductions in dilator responses to reduced intravascular pressure in isolated middle cerebral arterial segments. These results indicate that BINT, like concussive TBI, is associated with cerebral vascular dysfunction.

### VARIABILITY IN SURGICAL DECISION MAKING FOR ACUTE SUBDURAL HEMATOMA: RESULTS OF AN ONLINE QUESTIONNAIRE

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Currently, there is only class 3 evidence for the treatment of traumatic acute subdural hematoma (ASDH). This lack of evidence leads to uncertainty regarding the optimal management approach, possibly resulting in a variable view among neurosurgeons in managing ASDH. The aim of this online questionnaire was to study the variable view on treatment of the ASDH in the Netherlands and Belgium.

An online questionnaire, involving treatment decisions on 6 cases of patients with a traumatic ASDH, was sent to 7 Dutch and 3 Belgian neurosurgical centers. Clinical and radiological variables differed per case and were based on real-life conditions.

Fifty-six neurosurgeons responded (response rate 60%). For cases of severe TBI and an ASDH there was a modest variation for the decision to evacuate the hematoma or not and a large variation for the decision to combine the evacuating with a decompressive craniectomy. The main reasons to operate were 'neurological condition' and 'mass effect'. For ASDH and mild/moderate TBI there was large variation for operating or not and 'hematoma size' was the predominant reason to operate.

Intercenter variation was seen, most notably, between two centers for the decision to evacuate the hematoma or not (14 vs 90% 'yes' answers,  $p < .001$ ).

This study suggests a variation in surgical management of the traumatic ASDH. Specifically, decisions varied more for moderate/mild cases than for severe cases, possibly reflecting more uncertainty with regard to mild/moderate TBI and ASDH. This treatment variation offers the opportunity to perform a comparative effectiveness study into surgery for ASDH.

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#### STATE-OF-THE-ART LECTURE ON TRAUMATIC BRAIN INJURY

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The past decade has witnessed unprecedented growth in our understanding of traumatic brain injury (TBI). Buoyed by technical advances in the clinical setting utilizing advanced imaging, biomarker discovery and genomic evaluation, together with similar advances in the basic sciences incorporating advanced bioimaging, molecular biology and targeted electrophysiology, our understanding of TBI across the spectrum of severity has increased exponentially. Clinical research has moved from the once singular concept of traumatically-induced brain edema and ICP elevation to a more global appreciation of the complex metabolic, electrophysiological, and blood flow abnormalities that impact outcome. These clinical discoveries have been strengthened by an improved understanding of genetic variation and the influence of complex secondary posttraumatic factors in determining outcome. In the laboratory, equally

impressive accomplishments have been made with new insights into the cell and molecular biology of neuronal and axonal injury together with a better appreciation of the responses of the related brain microenvironment including its glial and vascular elements. Novel neuroprotective strategies have been identified and their benefits have been critically evaluated in multiple model systems. Together with those themes emerging from the clinical setting, basic science discovery suggests that TBI's dominant consequence is one of CNS circuit disruption wherein the brain's normal excitatory and inhibitory balance is either functionally or structurally perturbed, leading to a less than optimal recovery. While TBI remains the most complex disease known to man, the research and clinical community should be encouraged by the remarkable progress made to date.

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#### OUTCOME PREDICTION IN PERSISTENT POST TRAUMATIC COMA

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Existing methods to predict recovery following severe traumatic brain injury (TBI) lack accuracy. This study determines the value of quantitative diffusion tensor imaging (DTI) to predict functional outcome one year after severe TBI. In a multicenter study including 12 centers, we prospectively enrolled 185 patients who remained comatose at least 7 days after TBI. Patients underwent brain MRI, which included DTI analyzed in 20 preselected white matter tracts. White matter was divided in two areas: axial (including anterior and posterior brainstem, cerebral peduncles and splenium of the corpus callosum) and hemispheric (genu and body of the corpus callosum, anterior and posterior limbs of the internal capsule, sagittal stratum, superior longitudinal fasciculus and corona radiata). Patients were evaluated at one year with a modified Glasgow Outcome Scale extended (GOSE). A prognostic model was constructed according to the axial and hemispheric DTI injury expressed in values normalized to controls per center. GOSE at one year was unfavorable (UFO,  $GOSE \leq 4$ ) in 126 patients (68%) and favorable (FO,  $GOSE \geq 5$ ) in 59 patients (32%).

All patients with a hemispheric FA score below 80% and all but one patients with an axial mean FA score below 80% had an unfavorable outcome.

TBI outcome depends on both axial and hemispheric injuries as can be assessed by DTI.

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#### THE PATHOLOGY OF DIFFUSE AXONAL INJURY

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Diffuse axonal injury (DAI) is recognised as one of the most common pathologies in traumatic brain injury (TBI), described in all severities from mild to severe. Over the past 7 decades, from early accounts reporting diffuse white matter pathology following TBI in isolated cases and short series of human autopsy material, through the more formal

neuropathological descriptions of cohorts derived from the Glasgow TBI Archive, the apparently stereotypical pattern and distribution DAI are now readily recognised. Pathologically DAI encompasses a spectrum of abnormalities including primary disruption of the axonal cytoskeleton, transport interruption and axonal swelling and proteolysis coinciding with clinical presentations reflecting injury severity and extent, such as confusion, loss of consciousness and coma. With the growing recognition that TBI is associated with increased risk of neurodegenerative disease, such as Alzheimer's disease (AD) and chronic traumatic encephalopathy (CTE), attention has focussed on TBI related pathologies which may have a role in influencing longer term outcomes. Recent evidence suggests that, in a proportion of survivors from TBI, there remains an insidious, progressive axonal pathology, which may continue even years after the original injury and may serve as a substrate for development of late, TBI-associated neurodegenerative pathologies. As such, DAI is now considered not only a key pathology in acute TBI, but also an important potential contributor to post-TBI neurodegenerative disease.

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#### OUTCOME ASSESSMENT AFTER ACQUIRED BRAIN INJURY

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The ultimate goal of health care and rehabilitation following traumatic brain injury (TBI) is to return a person to full health or to enable him/her to maintain as high a functional and health-related quality of life (HRQoL) level as possible (Berger et al., 1999; Koskinen, 1998). TBI can result in lifelong physical, cognitive, emotional, and behavioral impairments, activity limitations and participation restrictions, affecting the person's self image and coping strategies. An overview on the European and American state of the art concerning outcome assessment (psychological, psychosocial and neuropsychological assessments) after TBI will be presented. The QOLIBRI and its short form (QOLIBRI-OS) will be exemplarily depicted as a new outcome instrument in HRQOL.

There are manifolds medical, health economic, social and ethical implications to improve outcome assessment. This may enhance disease characterization, clinical and care interventions and neuropsychological rehabilitation.

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#### AN iPad CASE REPORT VIEWER FOR HIGH-DEFINITION FIBER TRACKING FOR TBI PATIENTS AND THEIR CLINICIANS

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We have developed a tablet-based application, the HDFT Report App, to enable clinicians and patients in research studies to see and understand probable damage from Traumatic Brain Injury (TBI) by viewing 2- and 3D images of their brain, focusing on white matter tracts and quantification of their axonal projections. The overall goal

is to visualize white matter fiber tract injury by making the "invisible wounds of TBI" as understandable for patients as an X-ray of a bone fracture. Using mobile computing technology, imaging data for individual patients can be downloaded remotely onto an iPad within hours of an MRI brain scan. Clinicians and patients can view the data in the form of images of each tract, rotating animations of tracts, 3D models, and graphs. Ten major tracts can be examined for asymmetry, gaps in axonal projection fields, or reduced branching and volume. Novice users can effectively navigate and interact with the application (generally explain images and graphs representing normal tracts and tracts showing evidence of reduction), within fifteen minutes of orientation, with high accuracy (96%). The architecture supports extensive graphics, provides an intuitive, attractive interface with a smooth user experience, and allows for securely serving cases from a database. Patients and clinicians have described the application as providing dramatic benefits in understanding their TBI.

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#### QUANTIFYING WHITE MATTER STRUCTURAL INTEGRITY WITH HIGH DEFINITION FIBER TRACKING IN TRAUMATIC BRAIN INJURY

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There is an urgent, unmet demand to biologically quantify and pinpoint the location and extent of damage in traumatic brain injury (TBI). We have developed High Definition Fiber Tracking (HDFT), a 3T MRI-based diffusion spectrum imaging (DSI) and tractography analysis pipeline, to quantify axonal injury in military and civilian TBI patients. A novel homologue correlation methodology quantified tractography to estimate white matter integrity in patients and healthy controls. Forty-one subjects (23 TBI, 18 controls) were scanned with the HDFT DSI protocol. After reconstruction, bilateral hemisphere homologues of eight major tracts were segmented. Integrity of segmented tracts was estimated by calculating homologue correlation and tract spread. Both groups showed high correlations for all tracts. TBI patients showed reduced homologue correlation and tract spread and increased outlier count (correlations  $>2.32$  SD below control mean). On average, 6.5% of tracts in the TBI group were outliers, with substantial variability among patients. Number and summed deviation of outlying tracts correlated with initial Glasgow Coma Scale (GCS) score and 6-month Glasgow Outcome Scale – Extended (GOS-E) score, suggesting that correlation metrics can detect heterogeneous damage affecting a low proportion of tracts, presenting a potential mechanism for advancing TBI diagnosis.

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#### THERAPY OF TRAUMATIC OPTIC NEUROPATHY (TON): WHEN? HOW? MONO AND/OR COMBINED THERAPY? TRADITIONAL AND/OR SURGICAL TREATMENT FOR TRAUMATIC OPTIC NEUROPATHY?

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Time factor is extremely important in the efficiency of TON therapy - by early diagnosis of ON lesion with consecutive neurological trauma, as soon as it is possible, in cases of closed traumatic optic neuropathy.

Reasons for late recognition of closed TON could be e.g. unconsciousness, respiratory and circulatory disorders, other neurological deficits, urgent neurosurgical and/or traumatological operations.

Neurosurgical treatment is necessary in both cases of primary cranial trauma (multiple fractures of the cranial base, direct damage of the brain tissue &/or cranial nerves) or in cases developing secondary cranial trauma (epidural-, subdural hemorrhage, SAH, IC hematoma, higher intracranial pressure (HIP).

Attributes of secondary closed TON are swelling edema of the pre-chiasmal optic nerve, vascular degeneration of retinal ganglion cells, neurosurgical exploration of optic canal with/out steroids. On the basis of this pathophysiological theory, our proposal for therapy in closed TON cases is: complex treatment, namely steroids, diuretics and medication to improve microcirculation of small vessels of CNS as a combined and parenteral therapy.

We would like to emphasize the importance of early recognition and complex (traditional and neurosurgical) treatment of TON, and to demonstrate it by two instructive neurotraumatological case reports of children.

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#### LACK OF STANDARDIZATION IN APPLYING PAINFUL STIMULI FOR ASSESSING THE GCS

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Since its first description (Teasdale and Jennett, Lancet 1974) the Glasgow Coma Scale (GCS) has been widely accepted for assessment of the level of consciousness. In patients not obeying commands, this assessment requires application of a painful stimulus, which should be standardized to facilitate reliable interpretation. Nail-bed pressure and stimulation to the head and neck were recommended in 1974, but other locations have been suggested subsequently. To gain understanding of the current variation in evaluating the GCS, we conducted surveys among neurosurgical residents and junior neurosurgeons. A total of 100 questionnaires were returned at international training courses (response rate 93%) and a web-based survey was conducted in the UK (n=38), asking how painful stimuli are applied. Responses to the questionnaires showed that 72% performed a standardized approach, but that the type of painful stimulus applied varied substantially. Nail-bed pressure was often used by about 70% of responders and sternal rub by 56%. Overall, substantial variation was noted and other locations often used are: supra-orbital pressure 51%, trapezius or pectoralis major pinch 38%, retromandibular stimulation 17% and earlobe pressure 15%. The web-based survey showed a similar preference for supraorbital pressure (58%) and trapezius or pectoralis pinch (31%), but nail-bed pressure was never used by 54% of UK trainees. These results illustrate a general lack of standardization in assessment of the GCS in patients with reduced level of consciousness. This is likely to confound consistency in findings, to limit their reliability in clinical care and in research. New standard guidance is required.

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#### RECOVERY OF SENSORY-MOTOR FUNCTION OF THE LOWER LIMBS AFTER COMPLETE PARALYSIS: HOW, WHY AND WHAT IS TO FOLLOW?

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It is well known that the sensory input representing the timing and level of loadbearing on the lower limbs is an important source of input to the central nervous system in sustaining postural and locomotor control. The degree to which this source of input is critical, however, continues to be not fully realized in effort, to recover motor function after neural trauma. Experiments will be described which demonstrate that after complete paralysis, the return of the experience of bipedal and quadrupedal load-bearing in response to lumbosacral stimulation can be used to restore standing after complete paralysis due to spinal cord injury in humans. Similar results have been achieved in rats, but in addition, full weight-bearing stepping can also be recovered in the presence of spinal epidural stimulation and pharmacological modulation largely involving serotonergic agonists. Finally we have observed that a progressive increase of the level of loadbearing on a daily basis in rats and humans further enhances the level of recovery of standing potential. The mechanisms of the recovery of motor function with these interventions are gradually being formulated from the perspective of how spinal networks can be fine-tuned to facilitate the performance of a wide range of complex motor tasks. This fine tuning can be accomplished using a combination of neuromodulatory interventions, including multiple forms of electrical stimulation, sensory modulation and pharmacological modulation.

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#### CORRELATION BETWEEN INTRACRANIAL PRESSURE AND MEASUREMENT OF OPTIC NERVE SHEATH IN A SWINE MODEL OF INTRACRANIAL HYPERTENSION

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Some studies have shown that the measurement of the optic nerve sheath (ONS) is correlated to invasive ICP monitoring. However, no studies have shown to date, if ONS can be useful to monitoring oscillations of ICP. Therefore, we aimed to evaluate the correlation of parenchymal ICP monitoring and the measurement of ONS in a swine model of intracranial hypertension. Nine piglets were evaluated. After insertion of a 8Fr urinary catheter in the right parietal lobe and a parenchymal intracranial pressure monitoring in the right frontal lobe, a continuous infusion of 0.9% saline through the urinary catheter was performed to inflate the balloon at the distal tip. In Group A, we infused 4 ml saline in 15 min; in Group B, an additional 3 ml was infused over 15 min, 30 min after the first infusion; and in Group C, 7 ml was infused over 15 min. The final stage was the deflation of the balloon. Along the procedure, 8 measurements of the ONS were done. In group A, mean ICP was 6.2 (range: -4.6 - 32 mmHg). In group B, mean ICP was 19.8 (range: -2.9 - 50.9 mmHg). In group C, mean ICP was 42.8 (range: 2.2 - 86.4 mmHg). The mean right ONS was 3.9 mm + - 0.5 (SD) when ICP below 20 mmHg and 4.6 + - 0.65(SD) when ICP above 20 mmHg (p < 0.0001). The mean left ONS

was 3.9 mm + - 0.3 (SD) when ICP below 20 mmHg and 4.6 + - 0.65 (SD) when ICP above 20 mmHg ( $p < 0.0001$ ). There was a moderate correlation between ICP with left and right ONS ( $r = 0.39$ ,  $p = 0.004$  and  $r = 0.38$ ,  $p = 0.006$ ). This study showed that the measurement of ONS is associated with parenchymal ICP monitoring in a experimental model.

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### CT VENOGRAPHY IS A USEFUL IMAGING MODALITY FOLLOWING TRAUMATIC BRAIN INJURY

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Multislice CT scanners have made possible the acquisition of venographic studies that offer an excellent overview of the intracranial venous sinuses. Post-traumatic dural venous sinus thrombosis (DVST) is associated with the presence of skull fractures that extend to a venous sinus or jugular bulb.

In our institution, CT venography is undertaken routinely for head-injured patients with a skull fracture extending to a venous sinus or jugular bulb. This policy started in late 2010. Here, we report our initial experience with 15 consecutive ventilated head-injured patients.

DVST was identified in 5 patients (prevalence 33%). Three patients had occlusive thrombosis. The lateral sinuses (transverse and sigmoid) were implicated in all cases. The CRASH (basic) predicted risk of mortality ( $0.21 \pm 0.1$  vs  $0.18 \pm 0.04$ ;  $p = 0.81$ ) was not different between the DVST and the non-DVST group; this indicates that the 2 groups were similar with respect to injury severity. Four out of the 5 patients with DVST required advanced measures for ICP control compared to 4 out of 10 without thrombosis. Digital recordings of multi-modal neuro-monitoring were available for 10 patients (3 with DVST). In the DVST group the proportion of total monitoring time with ICP > 25 mmHg was  $0.18 \pm 0.11$  compared to  $0.03 \pm 0.06$  in patients without DVST. Cerebrovascular pressure reactivity was impaired in patients with DVST as indicated by higher PRx values (DVST  $0.32 \pm 0.11$ , non-DVST  $0.05 \pm 0.03$ )

Post-traumatic DVST is an under-recognised problem that is potentially associated with raised ICP and disturbed cerebrovascular pressure reactivity. Appropriate management strategies need to be defined.

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### NATIONAL STUDY OF CHRONIC SUBDURAL HAEMATOMA IN THE UNITED KINGDOM

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Chronic subdural haematoma (CSDH) represents one of the commonest disorders in neurotrauma. The BNTRC—a research network for neurosurgical trainees in the UK ([www.bntrc.org.uk](http://www.bntrc.org.uk))—has undertaken a prospective study in order to establish contemporary management and outcomes of patients with CSDH.

All adult patients aged > 16 years with a CSDH are eligible for inclusion. Data are submitted directly by participating neurosurgical units (NSU) to the ORION online secure platform.

Prior to launching the study, national standards were agreed on the basis of best available evidence. These standards include: 60-day recurrence rate < 20%; unfavourable modified Rankin Scale (mRS; 4–6) at discharge from NSU < 30%; morbidity rate in NSU < 10% and mortality rate in NSU < 5%. As of 30 November 2013, data have been collected on over 800 patients. Preliminary results indicate that approximately two-thirds of all patients referred to a NSU are symptomatic and/or have significant mass effect; management of this group of patients takes place in a NSU. Almost 90% of these patients have a presenting GCS of 13 – 15. However, approximately 60% have a presenting mRS of 3 – 5. Burr-hole evacuation is the most frequently performed operation. Approximately 60% have a mRS 0 – 2 at discharge. Complete results will be presented at the INTS2014.

The neurotrauma community needs to focus its research efforts on this increasingly common condition. Moreover, trainee research networks are feasible and we welcome international collaboration to facilitate development of such networks in other countries ([ak721@cam.ac.uk](mailto:ak721@cam.ac.uk)).

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### TREATMENT OF MILD TRAUMATIC BRAIN INJURY BY EPIDURAL SALINE AND OXYGEN INJECTION; PROPOSAL OF A NEW TREATMENT AND A NEW CONCEPT OF PATHOGENESIS

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Mild traumatic brain injury (mTBI) is still common complication of minor head injuries. We have reported the limited effectiveness of epidural blood patching for chronic post-traumatic headache (Eur J Med Res 12; 249, 2007). We have developed epidural saline and oxygen injection (ESOI) treatment. We investigated the effectiveness of ESOI for mTBI. We have treated 18 cases fulfilling the diagnostic criteria of mTBI. They received brain MRI. Lumbar puncture was performed to measure the intracranial pressure (ICP) and remove cerebrospinal fluid (CSF). ESOI was performed at lumbar level. The effectiveness was evaluated 3 months after the treatment subjectively in 6 categories; Complete cure (C; return to normal life without headache), Excellent (E; return to normal life with occasional headache), Good (G; diminished symptoms but still disturbed normal life), Fair (F; diminished symptoms with recurrence), No (N; no effectiveness), and Poor (P; worsened). Mean age was 37.8 years old and 17 cases suffered from traffic accident. MRI did not show responsive abnormalities. Mean ICP was 160.0 mmH<sub>2</sub>O. In 14 patients, CSF removal ameliorated their symptoms such as headache and blurred vision and in one case improvement of hand movement was observed. The treatment outcome was as follows: C = 6, E = 4, G = 6, F = 2. No patients worsened. ESOI can be a new and safe treatment for mTBI. Our results indicate that the signs and symptoms of mTBI may not derive from brain damage itself but from disturbed CSF circulation dynamics.