

CNSS CHAIR'S SELECT ABSTRACT PRESENTATIONS

C.01

CNSS K.G. McKenzie Prize in Basic Neuroscience Research

Developmental phosphoproteomics identifies Casein Kinase 2 as a therapeutic target in medulloblastoma

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Background: The hedgehog pathway (Hh) is an important developmental signaling pathway that is commonly dysregulated in brain tumors, most notably in medulloblastomas. To identify novel therapeutic targets within the Hh pathway, we performed the first quantitative proteome-wide evaluation of phosphorylation events resulting from in vitro SHH administration and occurring throughout Hh-driven cerebellar development in vivo. **Methods:** Multiplexed quantitative mass spectrometry was done using Tandem Mass Tags 10-plex reagents, TiO₂ phosphopeptide enrichment and HPLC-MS/MS/MS. **Results:** Motif analysis of 2-fold changing phosphorylation events suggested casein kinase 2 (CK2) was responsible for mediating 45% of all changes in phosphorylation. Epistasis studies revealed that CK2 activity is necessary for hedgehog signaling and affects terminal signaling components, thereby circumventing challenges of emergence of resistance and a priori resistance that are commonly encountered with existing small molecule inhibitors in medulloblastoma. In vivo, mice harboring MB allografts resistant to current therapies showed near-complete cessation of tumor growth in response to a CK2 inhibitor. **Conclusion:** Our use of developmental phosphoproteomics revealed casein kinase 2 as a key regulator of hedgehog signaling and therapeutic target in medulloblastoma. Our success establishes a foundation for us, and others, to apply a similar approach in different tumor initiating pathways.

C.02

CNSS K.G. McKenzie Prize in Basic Neuroscience Research

Early treatment of HER2-amplified brain tumours with targeted nk-92 cells and focused ultrasound improves survival

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Background: Malignant brain tumors have a dismal prognosis, with residual after surgery necessitating adjuvant chemoradiotherapy. We previously demonstrated that targeted Natural Killer (NK-92) cells could be delivered to the brain using a combination of MRI-guided focused ultrasound and Definity microbubbles. Once in the CNS, they can track to malignant tissues without inflicting collateral damage. The HER2 receptor is expressed by epithelial tumours including both breast and glioblastoma; breast tumors with HER2-amplification have a higher risk of CNS metastasis, and poorer prognosis. **Methods:** We investigated whether multiple combined treatments of targeted NK-92 cells and focused ultrasound with

microbubbles could slow tumour growth and improve survival in an orthotopic HER2-amplified rodent brain tumour model using a human breast cancer line as a prototype. **Results:** Early daily treatments with targeted NK-92 cells and ultrasound improved survival and decreased tumour volumes compared with bi-weekly treatments, or either treatment alone. The intensive treatment paradigm resulted in cure in 50% of subjects. **Conclusions:** Many tumour proteins could be exploited for targeted therapy with the NK-92 cell line, and combined with the mounting safety evidence for transcranial ultrasound, this may soon provide a non-invasive and highly targeted treatment option for patients with brain tumours.

C.03

CNSS K.G. McKenzie Prize in Clinical Neuroscience Research

Timing of resumption of antithrombotic agents following surgical evacuation of chronic subdural hematomas: a retrospective cohort study

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Background: Antithrombosis (AT), with antiplatelets or anticoagulants, is a significant risk factor for the development of chronic subdural hematomas (cSDH). Resumption of AT following hematoma evacuation is variable, with scant evidence for guidance. **Methods:** We retrospectively analyzed 479 patients with surgically-evacuated cSDH at St. Michael's Hospital from 2007-2012. Collected variables included type of AT, indication for AT, timing and type of postoperative complications, and restart intervals for AT agents. Postoperative complications were classified as major or minor hemorrhages, or thromboembolism. **Results:** Among all patients, 14.8% experienced major hemorrhage, 23.0% minor hemorrhage, and 1.67% thromboembolism. Patients on any preoperative AT were at higher risk of major hemorrhage (OR=1.93, p=0.014), experienced earlier major hemorrhage (mean 16.2 versus 26.5d, p=0.052) and earlier thromboembolism (mean 2.7 versus 51.5d, p=0.036). The type of agent did not affect complication frequency or timing. Patients restarted on any AT postoperatively were at decreased risk of major rebleed following resumption, than those not restarted (OR=0.06, p<0.01). **Conclusions:** Patients on preoperative AT experienced thromboembolism significantly earlier, at 3d postoperatively, with no increase in rebleed risk following AT resumption. We provide cursory evidence that resuming AT early, at 3d postoperatively, may be safe. Larger prospective studies are required for definitive recommendations.

C.04

Equestrian-related brain injuries presenting to emergency departments, Canada, 1990-2014

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Background: Horse riding is a hazardous activity with the potential for serious injury. Equestrian-related injuries account for a higher rate of injury per number of riding hours than motorcyclists and automobile racers. There is a lack of literature pertaining to equestrian-related brain injuries. The objectives of this study were to describe the incidence, characteristics, and mechanisms of equestrian-related

brain injuries sustained amongst Canadians between 1990 and 2014. *Methods:* Data were obtained from the Canadian Hospitals Injury Reporting and Prevention Program (CHIRPP) database. The study population consisted of individuals who sustained equestrian-related brain injuries between the years 1990 and 2014 and presented to one of 15 participating emergency departments. *Results:* Brain injuries accounted for 13.3% (N=1060) of all equestrian-related injuries. The greatest proportion of injuries occurred amongst individuals aged 15-19 years, followed by individuals aged 0-4 years. The predominant mechanism of injury was falls. 17.9% of individuals were admitted to hospital. Normalized rates of injury increased from 1990 to 2010. *Conclusions:* Brain injuries sustained while participating in equestrian are often of a greater severity than injuries sustained while participating in other recreational activities. A clear understanding of the epidemiology and mechanisms of equestrian-related brain injuries must be achieved in order to effectively implement prevention efforts.

C.05

A novel fusiform aneurysmal model in a rabbit carotid: a combination of pericarotid calcium chloride and elastase incubation

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Background: The purpose of this study was to develop a novel, simple and effective model of fusiform artery aneurysms in rabbits using a combination of periaortic calcium chloride (CaCl₂) and elastase incubation. *Methods:* Fusiform aneurysms were developed in three New Zealand White rabbits by exposing a 2 cm segment of the right carotid artery to CaCl₂ (0.5 mol/L) and pancreatic porcine elastase (75 U) for 20 minutes. The left carotid was used as a control. Vessel diameter was measured by serial digital subtraction angiography imaging at weeks 2, 4 and 6. Animals were sacrificed on week 6 and histopathological studies were performed. *Results:* All rabbits developed a fusiform aneurysm, with an average dilation ratio of 105% ± 10% by week 6. No mortality was reported. Histopathological studies revealed pathological features consistent with fusiform aneurysms. *Conclusions:* This novel rabbit model of fusiform carotid aneurysms is the first in the literature by using a combination of periaortic CaCl₂ and elastase incubation. This is a simple, reliable, and effective technique and results in a potentially valuable model for the study of fusiform aneurysms and possible therapeutic interventions, such as flow diversion.

C.06

Deficiencies in the reporting quality of RCTs in neurosurgery: How can we do better?

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Background: Deficiencies in design and reporting of randomized controlled trials (RCTs) limit their validity. The quality of recent RCTs in neurosurgery was analyzed to assess adequacy of design and reporting. *Methods:* A high-yield search of the MEDLINE and

EMBASE databases (2000-present) was conducted. The CONSORT and Jadad scales were used to assess the quality of design/reporting. A PRECIS-based scale was used to designate studies on the pragmatic-explanatory continuum. Spearman's test was used to assess correlations. Regression analysis was used to assess associations. *Results:* Sixty-one articles were identified. Vascular was the most common sub-specialty (37%). The median CONSORT and Jadad scores were 36 (IQR 27.5-39) and 3 (IQR 2-3). Blinding, sample size calculation and allocation concealment were most deficiently reported. The quality of reporting did not correlate with the study impact. The majority of studies (83%) had pragmatic objectives; while pragmatic studies had compatible design factors, trials with explanatory objectives were less successful. *Conclusions:* The prevalence and quality of neurosurgical RCTs is low. Many study designs are not compatible with stated objectives. Given the role of RCTs as one of the highest levels of evidence, it is critical to improve on their methodology and reporting. Alternative methodologies merit discussion.

C.07

Evaluation of the quality of life of patients with high grade subarachnoid hemorrhage following aneurysmal rupture

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Introduction: Patients presenting with high grade (HG) subarachnoid hemorrhage (SAH) from aneurysmal rupture may have persisting neurologic deficits which may lead to questioning the decision of treating aggressively. The objective of this study aims at analyzing outcome and long-term quality of life (QOL) of patients with HG SAH treated surgically. *Methods:* Retrospective study of patients with Hunt Hess (HH) grade IV or V SAH treated surgically at our institution. Long-term outcome was evaluated based on the modified Rankin Scale (mRS) at 3 years. Survivors were evaluated for QOL using various scales. *Results:* 63 patients (mean age of 52 year-old) were included. Intraparenchymal hemorrhage (IPH) was found in 85% of cases. 19 patients died. Predictive factors of poor prognosis and mortality were initial cerebral ischemia (p=0.003) and IPH (p=0.007). Favourable outcome (mRS 0-3) was found in 41% of patients. QOL questionnaires revealed that 80 % of responders showed more than 50% recovery. Mild or absent depression was observed in 78% of patients. *Conclusion:* In this surgical series, performed in an endovascular era, nearly all patients presented with SAH-associated IPH at admission. Despite the presence of such negative prognostic factor and the poor condition at admission, a high rate of favourable outcome and QOL was observed, therefore justifying aggressive surgical treatment.