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# **Report on Research Activities in the Adult Neurosurgery Program supported by the Division's Clinical Research Coordinator**

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***\*\*This report only includes research supported by the Division's Clinical Research Coordinator. It does not include an exhaustive list of all of the projects being conducted by the Division of Neurosurgery faculty.***

# 1. INTRODUCTION

This report contains up to date information on the ongoing research projects that are supported by the Clinical Research Coordinators (CRC) of the University of British Columbia's (UBC's) Division of Neurosurgery at the Clinical Academic Campus of Vancouver General Hospital (VGH).

<i>Number of Ongoing Studies</i>			
Prospective	Retrospective	Newly Inactive or Complete Studies	Total
9 (1 new)	7 (0 new)	0	12

Detailed description of the purpose, objective, budget and sample size of each study is presented in the next four sections of this report.

\*\*This report does not encompass research projects in the Division's paediatric neurosurgery, functional neurosurgery and spine neurosurgery programs.

## 2. ONGOING PROSPECTIVE STUDIES

### 1. Timing of Mobilization After Burr Hole Drainage of cSDH:

PI: Dr. Akagami; Co-I: Drs. Tu, Chang, Honey, Makarenko, Fatehi, Sadr.

Funding	Source	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
N/A	N/A	Sep 2014 - Sep 2019	100	92	Yes	Active	N/A

This is a two treatment arm, randomized, prospective study to minimize re-do burr-hole drainage procedures and any other associated complications in patients with chronic subdural haematomas.

Primary Outcomes:

- Recurrence requiring re-do drainage within the 1<sup>st</sup> month post-operatively
- Recurrence requiring re-do drainage between the 1<sup>st</sup> and 3<sup>rd</sup> months post-operatively

The timing of when to mobilize patients after burr-hole drainage of chronic subdural haematomas remains controversial. Traditionally, patients have been subjected to delayed mobilization in order to allow for the theoretical re-expansion of the brain and to decrease recurrence. Timing of bed rest is not consistent among centres and varies from immediately after to 7 days after surgery.

The objective is to determine optimal timing of mobilization in CSDH patients following a burr-hole drainage.

*Enrolment has ended. A total of 92 participants were enrolled. Manuscript preparation is in progress.*

### 2. Adult Hydrocephalus Clinical Research Network (AHCRN):

PI: Dr. Zwimpfer

Funding	Source	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
N/A	N/A	Nov 2014 -	perpetual	505	Yes	Active	N/A

A multi-centre and multinational registry that collects data on adult hydrocephalus patients to characterize the etiology, understand variability, progression, and current treatment practices for hydrocephalus patients.

The overall purpose of the Registry is to establish and maintain a hydrocephalus patient event database for the Clinical Centres of the AHCRN, a research network newly established to investigate clinical management of adult hydrocephalus.

Primary Objectives:

- To describe the natural history and treatment response for adults with previously untreated congenital hydrocephalus
- To describe the assessment and treatment of patients with Normal Pressure Hydrocephalus (NPH)
- To describe the complications associated with shunt surgery

- To determine the role for treatment with Endoscopic Third Ventriculostomy (ETV)

The Registry will provide previously unavailable epidemiological information about hydrocephalus patients seen throughout the participating Clinical Centers. This information will provide the basis for multi-institutional studies to be carried out by the AHCRN that may ultimately improve the clinical care for adults with hydrocephalus throughout the world. The continuing collection of such information serves to provide data necessary for hypothesis generation and study design. Examples of preliminary study designs include, but are not limited to, the following: preliminary power analysis, sample size determination, and recruitment projections. Radiologic imaging data will provide a unique opportunity to assess aspects of adult hydrocephalus diagnosis, management, and outcomes.

*There are 1939 participants enrolled in the AHCRN Registry at all participating sites. Of those, 488 are from the VGH site with 12 patients enrolled in the last quarter.*

**3. Next Generation Sequencing for Rare Variants in Familial Intracranial Aneurysms:**

PI: Dr. William Gibson (UBC Medical Genetics; BCCHR), Co-I's: Drs. Redekop, Haw, Gooderham, Dandurand

Funding	Source	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
Yes	HSFC	Aug 2019 – ongoing	Perpetual	146	Yes	Approved	N/A

**Purpose**

Several genes that predispose to aneurysms of the large blood vessels like the aorta are already known, and there are some rare genetic syndromes that predispose to brain aneurysms when other medical features (such as kidney cysts) are also present. However, there are no genes yet known that cause non-syndromic brain aneurysms. Our goal is to identify the first human gene(s) for isolated intracranial berry aneurysms.

**Objectives**

Our two specific aims are to catalogue the spectrum of rare coding variants in families diagnosed with intracranial aneurysms, and to validate functional effects of the most promising variant(s) on cerebral vasculature using animal models.

*There are 187 participants currently enrolled in this study. 12 were enrolled this quarter. Manuscript is in preparation.*

**4. Variability in the concentration of antiepileptic agents in the cerebrospinal fluid of critically ill patients**

PI: Dr. Farzad Moien-Afshari (Neurology) Co-I's: Drs. Griesdale, Agha Khani, Redekop, Fatehi

Funding	Source	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
No	-	Nov 2019 – ongoing	100	0	Yes	Approved	N/A

### **Purpose**

Patients who are critically ill receive a multitude of medications, have metabolic disturbances and may also have renal or hepatic dysfunction. These factors influence the pharmacokinetics and pharmacodynamics of medications including AEDs. Consequently, previous studies have recommended using AEDs with easily measurable levels in the ICU. Again however, there is a paucity of studies that have addressed the CSF levels of these medications. Hence, there is a clear impetus to determine whether the serum level of AEDs is an effective surrogate of CSF concentrations and also to determine whether medications such as verapamil do in fact increase CSF levels.

### **Objectives**

The main goal of this study is to determine whether the concentration of phenytoin, levetiracetam, carbamazepine, lacosamide, and valproic acid remain therapeutic in critically ill patients. We propose a single-center study of patients admitted to the Vancouver General Hospital (VGH) ICU.

*Patients were consented for this study, though no data was collected with the onset of the COVID-19 pandemic.*

### **5. Identification of blood and cerebral spinal fluid factors involved in aneurysmal subarachnoid haemorrhage**

PI: Dr. Haw Co-I's: Drs. Sadr, Bernie, MacVicar

Funding	Source	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
No	-	Nov 2019 – ongoing	100	1	Yes	Approved	N/A

### **Purpose**

Ruptured intracranial aneurysms lead to subarachnoid haemorrhage (SAH), a form of intracranial bleed that is often associated with severe morbidity and mortality. One of the most feared complications of aneurysmal SAH (aSAH) patients is cerebral vascular constriction, or vasospasm. This vasoconstriction leads to decreased cerebral tissue perfusion and ischemic strokes, causing significant neurological sequelae and potentially lethal complications.

The current standard of care for aSAH patients in vasospasm include the administration of vasodilators such as intra-arterial verapamil and intra-venous milrinone. However, such treatments require invasive and highly specialised tools and personnel, are costly, and have limited efficacy.

The molecular mechanisms leading to post-aSAH vasospasm remain elusive. Therefore, better characterising such mechanisms could provide new avenues into tackling its devastating consequences.

**Objectives**

The aim of our research is to identify blood and cerebrospinal fluid factors that are involved in aneurysmal vasospasm. Characterising those molecular triggers of vasospasm would improve our understanding of the underlying pathophysiology. Ultimately, our goal is to predict and prevent vasospasm, or at least developing novel targets to manage it and prevent its devastating neuro-pathological manifestations.

*There are seven participants enrolled in this study. Six were enrolled this quarter.*

**6. Neuroscience of the human brain in health and disorder**

PI: Dr. Mark Cembrowski (UBC Dept. Cellular and Physiological Sciences); Co-I: Dr. Redekop

Funding	Source	Study period	# of subjects enrolled	Approvals	Status
No	-	Nov 2020 – ongoing	5	Yes	Recruitment ongoing

**Purpose**

(1) Understand organization and function of the healthy (i.e., pathologically unremarkable) human brain at molecular, cellular, and circuit levels; (2) use this understanding of the healthy brain to interpret dysregulation during epilepsy.

**Objectives**

(1) Characterize the molecular, cellular, and circuit properties of surgically resected discard human brain tissue in healthy cortex, (2) Compare this to analogous characterizations in brain tissue from epileptic foci to identify molecular, cellular, and circuit dysregulation in epilepsy.

**Research design**

Non-diagnostic discard brain tissue from Dr. Redekop and his staff, obtained via standard surgical resections from informed consenting participants, will be de-identified by Dr. Redekop or a member of VGH research staff, and via Dr. Hirsch- Reinshagen and VGH pathology, received by Dr. Cembrowski to be used in neuroscientific research examining molecular, cellular, and circuit properties. Acute experiments will involve:

- transcriptomics and epigenomics (tissue from n=12 participants needed for each of epileptic and non-epileptic datasets, in order to acquire sufficient statistical power based upon previously published results)
- whole-cell patch-clamp electrophysiology and morphological reconstructions (n=50 neurons needed for each of epileptic and non-epileptic datasets, likely requiring tissue from ~10 participants, in order to acquire sufficient statistical power based upon previously published results)

*There are six participants in this study. One participant was enrolled this quarter.*

**7. Aneurysmal Subarachnoid Hemorrhage - Red Blood Cell Transfusion and Outcome (SAHaRA): A Randomized Controlled Trial**

Funding	Source	Study period	# of subjects enrolled	Approvals	Status
Grant	CIHR	2017 – 2022	29	Yes	Recruitment ongoing

### **Purpose**

We propose a multicenter pragmatic randomized trial in patients with aSAH that will compare the effect of a liberal to a restrictive RBC transfusion strategy on the combined rate of death and severe disability at 12 months.

### **Hypothesis**

We hypothesize that in adult patients suffering from aSAH and anemia, a liberal RBC transfusion strategy as compared to a restrictive RBC transfusion strategy decreases the combined rate of death and severe disability at 12 months (using the modified Rankin Scale)

### **Justification**

Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating illness caused by the spontaneous rupture of an enlarged, weakened artery in the brain. It affects a young population and is a significant cause of premature death and loss of potential life years, similar in magnitude to ischemic stroke. It is a common neurologic reason for intensive care unit (ICU) admission and is associated with a mortality rate of 35% in North America. Less than one third of afflicted patients make a full recovery and 20% of survivors experience significant morbidity and impacts on daily living.

*There are 478 participants enrolled across 20 sites. 29 participants have been enrolled in Vancouver.*

### **8. A Placebo-Controlled Effectiveness in INPH Shunting (PENS) Trial (new this quarter)**

PI: Dr. Zwimpfer

Funding	Source	Study period	# of subjects enrolled	Approvals	Status
Grant	NIH	2021 – 2026	0	In progress	Not initiated

Although idiopathic normal pressure hydrocephalus (INPH) has been recognized for five decades, barriers still exist in recognition, referral and accurate diagnosis. Hesitance in referring elderly patients for surgical treatment of INPH results from an incomplete understanding of its pathophysiology, controversy over the appropriate diagnostic work up, and a significant concern about the effectiveness and complications of surgical treatment. The approach to screening, diagnosis and treatment of INPH varies throughout the world, though success rates in experienced centers are similar in uncontrolled studies.

The lack of consensus regarding tests predicting outcome of surgery in INPH,



and the skepticism of INPH in the neurology and neurosurgery communities reflect the limitations of INPH clinical research to support current INPH practices. INPH clinical research paradigms have not changed for over 20 years. A survey described the uncertainty surrounding the treatment of INPH and the need for a placebo-controlled study. Convincing proof of shunting effectiveness is likely to increase the number of INPH patients getting adequate treatment

The Placebo-Controlled Effectiveness in INPH Shunting (PENS) trial is a multi- center blinded, randomized, placebo-controlled design investigation of cerebrospinal fluid (CSF) shunt surgery.

**Primary Hypothesis**

The primary hypothesis of the PENS trial is that treatment of idiopathic normal pressure hydrocephalus (INPH) with an open shunt results in improved gait velocity.

**9. Spatiotemporal Mapping and Decoding Oculomotion Functions in the Frontal Eye Fields (*New this quarter*)**

PI: Dr. Singhal; Co-I: Drs. Chang, Tamber, Haji, Redekop, Gooderham

Funding	Study period	# of subjects enrolled	Approvals	Status
n/a	2021 – Present	0	In progress	Not initiated

The planning and execution of eye movements likely relies on a complex and distributed system of interconnected cortical and subcortical brain regions. Of these regions, the frontal eye field (FEF) has been described in animals as an important network control node, located in the prefrontal cortical zone where low-threshold electrical stimulation can evoke and modulate contraversive eye movements. The location and exact function of the FEFs in humans is still controversial, with some microstimulation studies implicating the posterior middle frontal gyrus, while other stimulation studies and neuroimaging studies have identified sites as far posteriorly as the inferior precentral gyrus. A study of the functional localization of this region populations does not exist and may help understand the development of oculomotor function in humans, as well as provide important anatomo-functional information relevant to making resective epilepsy surgery safer for this population.

**Purpose**

The purpose of the study is to correlate eye movement data to neural recordings and stimulations from near the FEF in patients undergoing SEEG monitoring for epilepsy work up, to better understand the network function of this region.

**Hypothesis**

We hypothesize that neural activity patterns recorded from near the posterior middle frontal gyrus in humans will correlate most closely to eye movement patterns, representing the FEF.

### 3. ONGOING RETROSPECTIVE STUDIES

#### 1. Pituitary Adenoma Resection and Post-Operative Diabetes Insipidus:

PI: Dr. Makarenko; Co-I's: Dr. Akagami, Gooderham.

Study period	Approvals UBC CREB/VCHRI	Anticipated Charts to review	Status	Abstract/Paper/ Manuscript	Funding
Jun 2018 – Ongoing	Approved	300	Not started	N/A	N/A

#### **Objectives**

Our main objective is to characterize the rate of diabetes insipidus following endoscopic transsphenoidal resection of pituitary tumours and to analyze the amount of pituitary gland translation in the post-operative period. As our secondary objectives, we will assess clinical features and surgical outcomes among the cohort.

#### **Hypothesis**

We hypothesize the rate of diabetes insipidus following transsphenoidal pituitary surgery can be correlated with the distance travelled by the pituitary gland and subsequently the pituitary stalk following resection.

#### **Research Design**

This is a retrospective chart review of endoscopic transsphenoidal pituitary tumour resections by Drs. P. Gooderham and R. Akagami between January 1st 2010 and December 31st 2017 at Vancouver General Hospital. There is expected to be approximately 300 patient charts to be reviewed.

#### 2. Presentations of Ischemic Pituitary Apoplexy: A Case Series

PI: Dr. Akagami

Study period	Approvals UBC CREB/VCHRI	Anticipated Enrolment	Status	Abstract/Paper/ Manuscript	Funding
2019-Ongoing	Obtained	5	Active	N/A	N/A

#### **Research Objective**

This case series aims to illustrate and discuss five unique presentations of macroadenoma ischemic pituitary apoplexy, and direct physician attention towards specific symptoms that may warrant urgent surgical decompression despite little to no mass effect or changes on imaging.

#### **Research Design**

Charts from 01-January 2009 to 24-February-2019 will be reviewed. The collected data will be reported on for each case of ischemic pituitary apoplexy, describing salient and unique features of the history of presenting illness, imaging findings, lab results and management. A discussion section will summarize important learning points for clinicians and detail appropriate management in the context described.

### 3. Exploration of Potential Benefits to Radiation Therapy in Grade 2 Meningiomas

PI: Dr. Makarenko; Co-I: Dr. Rebchuk

Study period	Approvals UBC CREB/VCHRI	Anticipated number of patients reviewed	Status	Abstract/Paper/ Manuscript	Funding
Oct 2020- ongoing	Approved	800	Ongoing	N/A	N/A

#### **Purpose of research**

In this study, we will explore whether adjuvant radiation therapy (RT) provides overall survival (OS) and progression-free survival (PFS) benefit following resection of grade II meningioma in our local cohort. We will perform subgroup analysis to compare whether the extent of resection and timing of RT have a modifying effect on OS and PFS in this cohort. We also hope with subgroup analysis, to clarify if specific pathologic features of atypical meningiomas affect outcomes. Furthermore, we will explore whether the 2016 diagnostic change to grade II meningioma has affected the prevalence rate of these diagnoses. These results will guide local practice patterns in patients with grade II meningiomas.

#### **Research Aims**

- 1) Explore whether adjuvant RT following operative resection of grade II meningioma has an effect on PFS and OS
  - a) Explore any modifying effect by Simpson grade (Grade 1 v Grade 2-3)
  - b) Explore any modifying effect of RT timing (early [ $<6$ wks] v late [ $>6$ wks])
- 2) Determine whether grade of resection predicts OS or PFS in grade II meningiomas
- 3) Explore clinical and histopathological predictors of OS and PFS, and tumour recurrence in grade II meningiomas
- 4) Explore whether recent changes to histopathological diagnosis of meningiomas has affected prevalence rate
- 5) If possible, explore the effect of watch and wait versus operative +/- RT treatment for asymptomatic grade II meningiomas

#### **Design**

We will perform a single center retrospective chart review. Patient level data will be obtained from Vancouver General Hospital and BC Cancer Agency database between October 2007 and December 2020.

### 4. Retrospective Review of Patients with Temporal Lobe Low Grade Gliomas and Surgical Outcomes

PI: Dr. Makarenko; Co-I: Dr. Rizzuto

Study period	Approvals UBC CREB/VCHRI	Anticipated number of patients reviewed	Status	Abstract/Paper/ Manuscript	Funding
March 2021- ongoing	Approved	50	Ongoing	N/A	N/A

## Purpose

The study aims to define a resection strategy for optimal seizure control in patients with temporal low grade lesions.

## Objectives

The study aims to define a resection strategy for optimal seizure control in patients with temporal low grade lesions. The study will attempt to answer the following question:

Does the extent of resection in temporal low grade gliomas in adults, specifically gangliogliomas, DNET, and PXA, affect post-operative seizure control?

Seizure frequency will be assessed at 1 year and 2 year post operatively (from the follow up records) and compared to seizure frequency in the post operative period.

### 5. Review of Clinical Outcomes of Blister ICA Aneurysm over a twelve year Period. A Retrospective Study. (New this quarter)

PI: Dr. Haw; Co-I: Drs. Goodluck, Sadr, Redekop, Gooderham

Study period	Approvals UBC CREB/VCHRI	Anticipated number of patients reviewed	Status	Abstract/Paper/ Manuscript	Funding
Date range of charts: Jan 2010 - Jun 2021	Pending	20	Pending	N/A	N/A

## PURPOSE

Blister internal carotid artery aneurysms (BICAA) are difficult to treat whether via open or endovascular approaches. Over the years there has been an increase in the cases done via endovascular procedures. There are currently proponents for both approaches and as such both treatment options are utilized. A classification system to guide treatment would be beneficial and is currently unavailable to our best knowledge. A simplified classification based on anatomy and matched outcome may guide the approach to treatment. We propose to Review the VGH experience with BICAA, to propose a classification system to guide treatment.

## OBJECTIVES

To identify an anatomical classification of blister aneurysm location that can be used to guide treatment of blister aneurysms

- Identify other variables influencing clinical outcomes in blister aneurysms
- To show institutional outcome in open and endovascularly treated blister aneurysms

### 6. Surgical Resection for Insular Epilepsy: Systematic Review and Meta-Analysis

Dr. Fatehi

Study period	Approvals UBC CREB/VCHRI	Number of papers reviewed	Status	Abstract/Paper/ Manuscript	Funding
2021-present	Not required	20	Data collection in progress	In progress	N/A

7. **National Survey on the Clinical Utility of Artificial Intelligence for Grading Gliomas**  
Dr. Fatehi

Study period	Approvals UBC CREB/VCHRI	Number of surveys sent	Status	Abstract/Paper/ Manuscript	Funding
2021-present	Not required	232	Survey open	In progress	N/A

## **4. NEWLY INACTIVE OR COMPLETE STUDIES (PENDING PUBLICATION)**