

a place of mind



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	Inactive or Complete Studies	Total
8	4	2	14

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 1st month post-operatively
- Recurrence requiring re-do drainage between the 1st and 3rd 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 (AHCNRN):

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 AHCNRN, 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 AHCNR 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 1901 participants enrolled in the AHCNR Registry at all participating sites. Of those, 505 are from the VGH site with 6 patients enrolled in the last quarter.

3. EVD Complications in Canada:

PI: Dr. Ryojo Akagami; Co-PI: Dr. Makarenko

Funding	Source	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
No	N/A	Jan 2018 –	500 (across Canada) 50 (VGH)	50	Yes	Approved	N/A

Context

Placement of external ventricular drain (EVD) catheters is a common neurosurgical procedure typically performed in emergent situations for the treatment of hydrocephalus and raised intracranial pressure (ICP). The procedure is associated with a number of complications resulting in significant morbidity. Comprehensive, prospective studies are lacking in describing the incidence of these complications and associated risk factors. A multi-centre prospective study is required in order to adequately investigate the complication profile of EVD catheter placement.

Design

This is a prospective multi-centre observational study to be conducted at 12 Canadian neurosurgical centres forming part of the Canadian Neurosurgery Research Collaborative (CNRC). The CNRC is a Canadian research network made up of 12 neurosurgery residents representing the participating sites, and supported by attending neurosurgeons. The CNRC is bound by an agreement signed by all residents to protect the confidentiality of data and privacy of patients.

Hypothesis

This study hypothesizes that in patients with EVD-catheters placed urgently (e.g. in the setting of intracranial hemorrhage or traumatic brain injury), the rates of EVD catheter-related complications including EVD catheter infection, hemorrhage and misplacement are influenced by patient, catheter and operator-related factors as described above.

There are 50 participants enrolled at UBC. Data collection has been completed across all Canadian sites. Manuscript has been submitted to the Journal of Neurosurgery.

4. Meningioma QOL Electronic Patient Reported Outcomes:

PI: Dr. Ryojo Akagami

Funding	Source	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
No	N/A	Jan 2018 – ongoing	Perpetual	20	Yes	Active	N/A

Purpose

This is a prospective study to collect information on quality of life before and after treatment for patients with meningioma. Knowing the expected quality of life associated with this diagnosis in the short and long term will not only help physicians and patients make a decision regarding treatment, but also, prepare the patient for the upcoming hardship. The goal of our study is to identify ways we can improve patient quality of life while they are undergoing treatment (surgery, radiation, or observation under the care of a neurosurgeon) for meningioma.

Objectives

The main goal of the study is to identify how does the diagnosis of meningioma and its subsequent treatment impact quality of life as measured by FACT-MNG in patients. We aim to establish a baseline for pre-operative quality of life in patients with meningioma and to determine the impact of surgical treatment and/or subsequent interventions on patient reported quality of life outcomes.

Hypothesis

Our hypotheses are the following: 1) we hypothesize that patient quality of life will improve after surgery for resection of meningioma compared to the observational group; 2) we hypothesize that VisionTree will be a feasible, well-tolerate and efficient tool for measuring objective and patient reported quality of life outcomes after meningioma treatment.

There are 21 participants currently enrolled in this study. None enrolled during the last quarter.

5. 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 175 participants currently enrolled in this study. 13 were enrolled this quarter. Manuscript is being prepared

6. 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. At the moment, recruitment is on pause and is expected to resume the following quarter.

7. 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.

Recruitment has begun this quarter, with currently one subject enrolled.

8. 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	3	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)

Recruitment has begun this quarter, with currently three participants enrolled.

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 (new this quarter)

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.

4. NEWLY INACTIVE OR COMPLETE STUDIES

1. Study of Biomarkers in the Blood and Cerebral Spinal Fluid of Aneurysmal Subarachnoid Hemorrhage Patients

PI: Drs. Redekop, Hanafy (Beth Israel Deaconess Medical Center), Co-I's: Drs. Haw, Gooderham, Dandurand

Funding	Source	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
No	-	Aug 2019 – ongoing	250	0	Yes	Approved	N/A

Purpose

The aim of this protocol is to study the biomarkers involved in the clinical consequences of aneurysmal subarachnoid hemorrhage (aSAH) in human subjects. The hypothesis is that a study of inflammatory biomarkers such as Toll-like receptor 4 (TLR4) and heme oxygenase (HO)-1 in aSAH patients, will allow for better prognostication following aSAH.

Objectives

The overall objective of this study is to collect blood and CSF samples from human subjects in order to study the biomarkers involved in the clinical consequences of patients who have been diagnosed with aneurysmal subarachnoid hemorrhage (aSAH). Samples will be studied using lab techniques such as molecular diagnostics, gene expression profiling, and blotting of factors that have been experimentally shown to have involvement in the clinical occurrences of aSAH. An attempt will be made to correlate results with the clinical time course of SAH. The long-term goal of this study is to increase management options for the clinical consequences of aSAH such as inflammation, vasospasm, and EBI, and work towards treatments that improve chronic aSAH neurological outcome.

This study has been put on pause.

2. The genetic and epigenetic basis of intracerebral aneurysms

PI: Drs. Redekop, Hanafy (Beth Israel Deaconess Medical Center), Co-I's: Drs. Haw, Gooderham, Dandurand

Funding	Source	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
No	-	Aug 2019 – ongoing	250	0	Yes	Approved	N/A

Purpose

The goal of this study is to delineate the underlying mechanism leading to aneurysm development, progression, rupture and vasospasm, which will help in identifying targets which are amenable to intervention.

We are aiming to discover genes and epigenetic influences on genes. Part of the project will be to identify these specific genes and epigenetic phenomena involved in the progression and rupture of aneurysms. There is no work to date on the epigenetic regulation of genes involved in these processes.

Objectives

The objective is to identify the biological functional pathways that were significantly over-represented by differentially expressed genes between aneurysm and control tissue samples as well as between ruptured and unruptured aneurysm samples

This study has been put on pause.