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ONGOING RESEARCH STUDIES IN THE NEUROSCIENCES PROGRAM

Quarterly Report on the Research Activities Involving a Clinical Research Coordinator

April 1st, 2015 – June 30th, 2015

Prepared by

Mr. Ivan Despot

Clinical Research Coordinator
Division of Neurosurgery
Clinical Academic Campus of Vancouver General Hospital
University of British Columbia

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1. INTRODUCTION

This report contains up to date information on the ongoing research projects that are supported by the Clinical Research Coordinator (CRC) of the University of British Columbia's (UBC's) Division of Neurosurgery at the Clinical Academic Campus of Vancouver General Hospital (VGH) for the period of April 1st – June 30th, 2015. The main objective of the report is to familiarize the staff of the Division of Neurosurgery of UBC with the current research activities that are being supported by their CRC. The studies that are supported by the CRC in this report are divided into two categories of ongoing studies: prospective studies, and retrospective studies. Additionally, summer student research projects that have applied for funding are included as their own section. The number of studies per category is presented in the table below (Table 1).

Table 1. Number of studies per category.

Number of Ongoing Studies				Total
Prospective	Retrospective	Inactive or Complete Studies	Summer Studentships	
4 (1 new)	5 (4 new)	5	3	17 (5 new)

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

2. ONGOING PROSPECTIVE STUDIES

1. Timing of Mobilization After Burr Hole Drainage of Chronic Subdural Haematomas: a randomized study – PI: Dr. Akagami

Funding	Source	Amount	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
N/A	N/A	N/A	Sep '14 Sep '16	142	36	obtained	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.

There are 36 participants enrolled in the CSDH Study, 15 of them enrolled during the last quarter.

2. AHCRN REGISTRY: Characterizing Patient Population in the Adult Hydrocephalus Clinical Research Network (AHCRN) – AHCRN Registry– PI: Dr. Zwimpfer

Funding	Source	Amount	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
N/A	N/A	N/A	Nov '14 no end date	perpetual	22	obtained	active	N/A

A multicenter 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 Centers 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.

Accomplishments of Merit:

- VGH made UBC 1st site to have accomplish Neuropsychological Battery Administration Training
- VGH made UBC 1st site to complete Neuropsychological Battery Administration Quality Control

There are 94 participants enrolled in the AHCRN Registry at all participating sites. Of those, 22 are from the VGH site with 17 patients enrolled in the last quarter.

3. Resident Activity Tracker Evaluation Study - PI: Dr. Toyota

Funding	Source	Amount	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
N/A	N/A	N/A	Sep 15 - Aug 16	60	N/A	yes	not started yet	N/A

Medical resident work hour restrictions remains a large topic of debate in the Accreditation Council for Graduate Medical Education; and more importantly, also in the Royal College of Physicians and Surgeons of Canada.

An adequate number of hours of sleep play an important role in medical residents' performance, and quality of life. Factors associated with medical resident fatigue and prolonged work hours include the following: an increase in automobile accidents, negative effect on well-being, an increase in stress, relationship-related stress, and decreased performance in both simulated tasks and standardized tests. Formal changes to resident work-hours regulation have not been imposed for Canadian medical residents. On-call duties vary substantially across medical specialties further complicating the issue. The actual physical demands of resident on-call duties and the impact on sleep duration and number of interruptions have not been comprehensively investigated to date.

This study will be the first in literature to measure average and maximum heart rate, sleep duration and interruptions, and number of steps taken per day in medical resident trainees, across non-surgical and surgical specialties and when the residents are on or off call. Such novel results

will help advance and guide current discussion on resident work hour restriction towards a more comprehensive conclusion.

The RATE Study has yet to begin – no participants to report in this quarter.

4. TOCA 511 Study - A Phase 2/3 Randomized, Open-Label Study of Toca 511, a Retroviral Replicating Vector, Combined With Toca FC versus Standard of Care in Subjects Undergoing Planned Resection for Recurrent Glioblastoma or Anaplastic Astrocytoma – PI: Dr. Toyota, *new study this quarter*

Funding	Source	Amount	Study period	Anticipated enrolment	# of subjects enrolled	Approvals	Status	Abstract/ Paper/ Manuscript
N/A	N/A	N/A	01/10/15-30/09/19 (Enroll)	170 in Phase 2; 200 in Phase 3	N/A	pending	Not started yet	N/A

Name of Investigational Product: Toca 511, a retroviral replicating vector (RRV) expressing a yeast-derived, codon-optimized cytosine deaminase (CD) prodrug-activator gene, in combination with Toca FC (flucytosine) extended-release tablets.

Primary Objective:

To compare the overall survival (OS) of subjects treated with Toca 511 combined with Toca FC to subjects treated according to standard of care after tumor resection for recurrence of glioblastoma or anaplastic astrocytoma.

Methodology: This is a multicenter, randomized, open-label study of Toca 511 and Toca FC versus standard of care (SOC) that comprises Investigator's choice of either single agent chemotherapy (lomustine or temozolomide) or bevacizumab administered to subjects undergoing resection for first or second recurrence (including this recurrence) of glioblastoma or anaplastic astrocytoma. Subjects will be randomized at the time of surgery in a 1:1 ratio to receive either Toca 511 and Toca FC or control. Repeat scans will be obtained every 6 weeks for the first year and every 3 months after that.

Subjects may receive any standard of care treatment following progression or discontinuation from study due to toxicity. Crossover to the Experimental arm is not allowed, unless the primary endpoint is met and the Sponsor notifies the sites.

The ethics submission will start shortly.

3. ONGOING RETROSPECTIVE STUDIES

1. Thromboprophylaxis in Traumatic Brain Injury Study - an assessment of timing of treatment – PI: Dr Hameed

Study period	Approvals UBC CREB/VCHRI	Charts reviewed /sample size	Status	Abstract/Paper/ Manuscript	Funding
Apr. '15 – ongoing	pending	351	Not started yet	N/A	none

Timing of thromboprophylaxis following a traumatic brain injury (TBI) has been shown to be a contributing factor to complication rates and length of stay in TBI patients.

Objective:

- Determine optimal timing of thromboprophylaxis protocol implementation follow a traumatic brain injury

The results from this study will assist in guiding the continual improvement of health care protocols, such as the one for thromboprophylaxis use following TBI.

The study will be submitted for review and approval to CREB shortly.

2. Biomarkers in Malignant Brain Tumors Study - PI: Dr Toyota, *new study this quarter*

Study period	Approvals UBC CREB/VCHRI	Charts reviewed /sample size	Status	Abstract/Paper/ Manuscript	Funding
June 22, 2015 – August 1, 2016	obtained	151	active	N/A	Yes

Objective:

To conduct a retrospective clinical chart review of our institution's glioblastoma cases to compare the predictive and prognostic value of molecular markers to that of traditional histological diagnoses.

This will be a retrospective chart review involving charts of patients with glioblastoma treated at VGH between 2010-2014. We will create a database to register basic patient demographics, treatment protocols and outcome. Specific to our study, we will also classify the tumors by classic histologic description and grading as well as new cutting edge diagnostic molecular and genetic analysis.

Based on this database, we will then stratify the patients into outcome categories based on classical grading and newer molecular markers. A statistical analysis of this data will then be conducted in order to compare the predictive value of these classic histologic methods with the newer methods for patient outcomes.

Quinn Parker is a summer student who has obtained UBC SSRP funding for the summer.

3. Perioperative Quality of Life in Patients with Cushing's Disease – PI: Dr. Akagami, *new study this quarter*

Study period	Approvals	Charts reviewed	Status	Abstract/Paper/	Funding
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	UBC CREB/VCHRI	/sample size		Manuscript	
June 2015 – May 2017	Pending	60	Not started yet	N/A	none

Objective:

Our main objective is to investigate the cure rate for Cushing's Disease at Vancouver General Hospital. Because the recurrence rate is quite high, examining patient progress through the disease will elucidate the durability of surgical treatment. We will be indirectly measuring cure through patient quality of life. Examining quality of life will allow us to compare and contrast the efficacy of treatment with patient-centered outcomes.

Endogenous Cushing's Disease is a rare disorder with an annual incidence of 13 cases per million individuals. This rarity prevents medical centers from establishing universal management expertise in this disease. In particular, there have been no studies looking at patient quality of life as they progress through the disease. The quality of life is intricately affected by the complex nature of the disease. The project's implications will be the first of its kind, and will elucidate the cure rate, and the durability of the cure in the management of CD, and draw a distinction between treatment efficacy and patient-centered outcome.

Vincent Ye is a summer student who has obtained UBC SSRP funding for the summer. The study will be submitted for review and approval to CREB shortly

4. Timing of Incidence and Recovery of Delayed Facial Palsy after vestibular schwannoma resection: a retrospective review – PI: Dr. Akagami, *new study this quarter*

Study period	Approvals UBC CREB/VCHRI	Charts reviewed /sample size	Status	Abstract/Paper/ Manuscript	Funding
June 22 nd , 2015 – June 22 nd , 2016	Pending	60	Not started yet	N/A	none

Preservation of facial nerve function during resection of vestibular schwannomas (VS) remains one of the most important goals of surgery, with a significant impact on patient satisfaction and quality of life post-operatively¹. Delayed facial palsy (DFP) is a well-described, but incompletely understood phenomenon in which patients develop facial nerve palsy several days after surgical resection of VS². Several postulations have been made about the etiology of DFP, although none can satisfactorily explain all of the major features of this palsy. The purpose of this retrospective review is to examine our institution's large series of data regarding the timing of DFP onset and recovery, in order to draw inferences about the neural pathophysiology of this disorder.

5. LAANTERN Registry - PI Dr. Toyota, *new study this quarter*

Study period	Approvals UBC CREB/VCHRI	Anticipated Enrollment	Status	Abstract/Paper/ Manuscript	Funding
TBD	pre-submission	TBD	not started yet	N/A	Sponsor

Details to be released upon completion of the confidentiality agreement with the sponsor and completion of the Site Questionnaire.

4. INACTIVE OR COMPLETE STUDIES

1. Meningeoma Study - Review of Perisellar Meningioma Surgical Resection at Vancouver General Hospital – PI: Dr Akagami-*closed this quarter*

Study period	Approvals UBC CREB/VCHRI	Charts reviewed /sample size	Status	Abstract/Paper/ Manuscript	Funding
Sep '14-Mar '15	obtained	53	manuscript	Presented/submitted	none

This is a retrospective review of the perisellar meningiomas that were operated on by Dr. R. Akagami in Vancouver General Hospital between January 1st, 2001 – December 31st, 2013, with an open craniotomy approach, but may have been candidates for endoscopic treatment.

The treatment of perisellar meningioma intracranial tumours has remained a challenge over the past several decades, mainly attributed to the high risk of visual pathway involvement and vascular encasement. Surgical approaches have remained the mainstay of definitive treatment, with subfrontal, pterional, frontolateral, and orbitofrontal variants most commonly used.

Extended endoscopic transsphenoidal surgery is emerging as an alternative option for treatment of these lesions. Endoscopic transsphenoidal surgery provides wider access to the anterior skull base when compared to the classical microscopic transsphenoidal approach, with recent technological advances such as angled endoscopes and image guidance have extended the success rates of this novel approach.

Objectives:

- Characterize patients' suprasellar and meningioma anatomy
- Investigate their outcomes following transcranial resection of the meningioma tumour by Dr. R. Akagami

The aim is to have those patients who may have been candidates for endoscopic surgery identified based on radiographic tumour characteristics, and then compared against those patients who had perisellar meningiomas with anatomy not suitable for endoscopic treatment. A review of the cases that were operated on transcranially will then be established in an effort to compare the outcomes in lesions that have anatomy appropriate for endoscopic surgery. It is hypothesized that those patients that had perisellar meningiomas with anatomy suitable for endoscopic surgery will have more favourable post-operative outcomes from transcranial surgery.

The study was presented on the WB & MH Chung Research Day, Vancouver, B.C. '14 and at the North American Skull Base Society Meeting in Tampa, Florida '15. The study was closed this quarter.

2. Case Study – Ipsilateral Lateral Corticospinal Tract Innervation; an Anatomic Variant – PI: Dr Akagami - *closed this quarter*

Study period	Approvals UBC CREB/VCHRI	Charts reviewed /sample size	Status	Abstract/Paper/ Manuscript	Funding
Apr. – Aug. '15	approved	1	completed	N/A	none

Ipsilateral lateral corticospinal tract innervation is a rare but recognized anatomical variant of motor innervation.

Objective of the study is to report a case of ipsilateral lateral corticospinal tract innervation discovered during intra-operative monitoring for a neurosurgical procedure.

To further characterize this anatomic variant by magnetic resonance (MR) tractography

Current research published around ipsilateral lateral corticospinal tract innervation consists of case reports of ipsilateral motor defects following stroke or literature surrounding congenital tract malformations. We will report a case of ipsilateral lateral corticospinal tract innervation discovered incidentally during intra-operative monitoring for a neurosurgical procedure, which was further characterized by magnetic resonance (MR) tractography. This has never been previously reported in the literature, and may help in providing better understanding upon this condition as well as how to manage patients with this anatomic variation.

The study was completed this quarter.

3. Frequent Recurrence of Pilocytic Astrocytomas in Adults: a retrospective review - PI: Dr Toyota

Study period	Approvals UBC CREB/VCHRI	Charts reviewed /sample size	Status	Abstract/Paper/ Manuscript	Funding
Aug 11 – Dec 15	obtained	35	completed	N/A	none

Pilocytic astrocytomas (PAs) are well circumscribed, slow-growing WHO grade I tumors of the CNS that generally follow a benign course (88%-100% survival at 5 years), and are rare in adults. Recent studies have shown however, PAs in adults not only show recurrence rates of 30%, but also malignant transformation in half of the cases that repeat surgery.

Objectives:

- Perform a cohort analysis of an adult patient population with PAs
- Identify any associations between adult PA features and a decrease in progression free survival and overall survival
- Relate immunohistochemistry to patient outcome

Current literature of similar studies has the limitation of small sample sizes, and further research needs to be completed. The authors plan to provide said needed research.

4. Case Report and Review of the Literature - Urgent Lateral Canthotomy Post-Percutaneous Cavernous Sinus Superior Orbital Fissure Puncture For Endovascular Obliteration of Cavernous Dural Arteriovenous Fistula – PI: Dr. Haw *closed this quarter*

Study period	Approvals UBC CREB/VCHRI	Charts reviewed /sample size	Status	Abstract/Paper/ Manuscript	Funding
Nov. 14 – Mar. 15	obtained	1	completed	N/A	none

A carotid-cavernous fistula case study, treated with a percutaneous transorbital cavernous sinus puncture via the superior orbital fissure puncture, and a subsequent coil embolization, is presented.

Objectives are to discuss technique of direct superior orbital fissure puncture of the cavernous sinus for embolization of CCFs and management of a potentially serious intra-procedural complication.

Arteriovenous shunts between the internal and or external carotid arteries and the cavernous sinus are called carotid cavernous fistulas (CCF). Morbid signs and symptoms of CCFs include proptosis, ophthalmoplegia, chemosis, and decreased visual acuity and or visual loss. What has become the mainstay approach is transvenous endovascular embolization. Coil embolization by transfemoral-inferior petrosal (IPS) approach is used in the majority of cases. An alternative approach includes direct puncture of the inferior ophthalmic vein or cavernous sinus through the superior orbital fissure. The different techniques available, and potential untoward ramifications of said techniques are discussed with example of case at Vancouver General Hospital.

5. SUMMER STUDENTS

1. Deep Brain Stimulation for Spasmodic Dysphonia Secondary to Essential Tremor

PI: Dr. Chris R. Honey
Student Ms. Vivian Braithwaite, Y3 B.Kin.
Funding UBC Summer Studentship Research Program, – Accepted SSRP

2. Collection and Submission of Clinical, CSF and Radiological Data of Patients Being Assessed at Vancouver General Hospital Adult Hydrocephalus Clinic as Part of the Adult Hydrocephalus Clinical Research Network (AHCRN)

PI: Dr. Charles Haw
Student Mr. Nicholas Salterio, Y1 B.Sc.
Project Supervisor: Dr. Thomas J. Zwimpfer
Funding VGH Foundation Hydrocephalus Fund

3. Collection of clinical, CSF and radiological data of patients being assessed at the Vancouver General Adult Hydrocephalus Clinic as part of the Adult Hydrocephalus Clinical Research Network (AHCRN)

PI: Dr. Thomas J. Zwimpfer
Student Ms. Michelle Tran, Y5 Unclassified
Funding VGH Foundation Hydrocephalus Fund