CHHD Annual Research Day
November 6th, 2020

- Booklet -

Centre universitaire de santé McGill
Institut de recherche

McGill University Health Centre
Research Institute

CHHD
Child Health and Human Development

Welcome to the
6th Annual 2020 CHHD Research Day

Child Health and Human development Research Day is organized to reinforce and initiate collaborations between the program members and their guests through a virtual platform.

Please take note that all attendees, including presenters and judges should be registered prior to attending the event.

The registration will give you access to the full Fourwaves virtual poster platform that will be made available the day of the event, November 6th.

During the virtual poster sessions, attendees will be able to go through the abstract list, see the files the presenter uploaded and joint the conversation with the presenter (up to 8 people at the same time).

Registration deadline: November 5th, 5pm.

To register: https://event.fourwaves.com/chhd2020/

On the next pages, you will find:

- The Research day program including all the links
- The awards list
- A few important instructions to note during the day
- The participants abstract list

If at any moment during the day, you have a question or a problem, please contact Fanny Toussaint and Travis Moore by email.

(fanny.toussaint@muhc.mcgill.ca; travismoore.chhd@gmail.com)

Program

8:40 - 8:45	Login on Zoom: https://zoom.us/j/97665716006?pwd=bU5ZVHBWNkwvQXpRZk92U3krSDQ3Zz09
Welcoming Remarks and CHHD Updates	
8:45 - 9:00	Dr. Daniel Dufort
Oral presentations - Session 1: Chaired by Dr. Hugh Clarke	
9:00 - 10:00	**Junior Trainee Presentations**
9:00	Philippe Hwang, Master student, Dr. Hechtman's Lab
9:12	LeRon Best, Master student, Dr. Eppert's Lab
9:24	Jennifer Ladd, Master student, Dr. Nakhla's Lab
9:36	Samer Salameh, Medical Student, Dr. Daniel's lab
9:48	Sabrina Wimmer, Master student, Dr. Poenaru's lab
10:00 - 10:30	**Principal Investigator presentations**
10:00	**Dr. Zoua Vang**, PhD, associate investigator, RI-MUHC **Title:** Engaging with Indigenous communities to improve perinatal health
5 Minute Break	
Poster Session - Session 1 (Abstracts 11 to 27)	
10:35	Available though the event webpage, abstract tabs*: https://event.fourwaves.com/chhd2020/
10:35 – 11:50	Poster presentations
65 Minute Lunch Break	
12:55- 13:00	Login on Zoom: https://zoom.us/j/97665716006?pwd=bU5ZVHBWNkwvQXpRZk92U3krSDQ3Zz09
Oral presentations - Session 2: Chaired by Dr. Bethany Foster	
13:00 - 14:00	**Senior Trainee Presentations**
13:00	Sima Khazaei, PhD student, Dr. Jabado's lab
13:12	Lingxiao Chen, PhD student, Dr. Braverman's lab
13:24	Kim Noel, PhD student, Dr. Fontela's lab
13:36	Sabrina Alam, PhD student, Dr. Majeweska's lab
13:48	Yan Luan, PhD student, Dr. Rozen's lab
14:00 - 14:30	**Principal Investigator presentation**
14:00	**Dr. John Mitchell,** MD, Scientist, RI-MUHC **Title:** Clinical efficacy in rare disease: from bench to bedside

5 Minute Break	
Poster Session - Session 2 (Abstracts 28 to 49)	
14:35	Available though the event webpage, abstract tabs*: https://event.fourwaves.com/chhd2020/
14:35 - 15:50	Posters presentations
10 Minute Break	
Keynote presentation: Chaired by Dr. Meranda Nakhla	
16:00 -16:05	Login on Zoom: https://zoom.us/j/97665716006?pwd=bU5ZVHBWNkwvQXpRZk92U3krSDQ3Zz09
16:05	Introduction of the Keynote speaker
16:05 - 16:45	**Dr. Eric Benchimol**, MD, PhD, FRCPC, Senior Scientist, Child Health Evaluative Sciences, The Hospital for Sick Children, University of Toronto **Title**: Social Media: A Tool That Can Impact Pediatric Health Care and Science Policy
Winners Announcement, Closing Remarks	
16:45 - 17:00	**Dr. Daniel Dufort and Dr. Meranda Nakhla**
****Toasts and Cheers****	

**Registration prior the event required*

***We invite all the participants to grab a glass of their favorite beverage and to discuss!*

Awards

Best junior oral presentation: 250$

Best senior oral presentation: 250$

Junior poster presentations:

First position: 250$

Second position: 175$

Third position: 100$

Senior posters presentation:

First position: 250$

Second position: 175$

Third position: 100$

Good luck to all the presenters!

Tips prior to and during the day

✔ Test your camera and your audio

✔ Make sure you can sign in on the event website: https://event.fourwaves.com/chhd2020/

About the virtual poster platform:

Abstract and files will be available at any time during November 6th to the people who previously registered for the event.
The virtual poster platform features will be activated only during the official poster session time.
The virtual poster platform will be available through the event website (abstract tab).

Please consult the few links below to get more information about the virtual poster platform:

What to expect the day of the virtual poster session?
How to get ready for a virtual poster session?
How to give your browser access to the camera and microphone
An error message says I need to allow access to the Camera and Microphone. What should I do?

During the oral presentation:

✔ Please mute your microphone if you are not a presenter.

✔ Don't interrupt presenters during their presentation. Wait until the end of each presentation for questions.

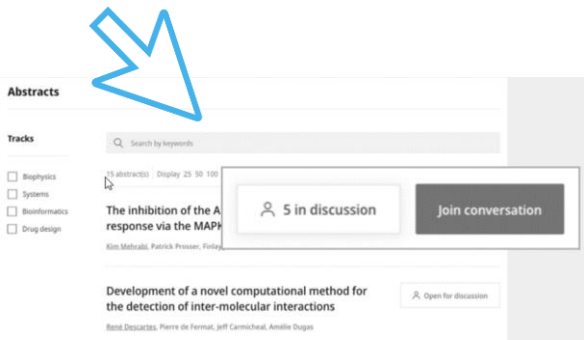
✔ **Attendees are asked not to write in the chat during the Trainee Oral presentations** as the chat notification number will be used to inform the presenter of the time progression.

During the poster session, when you joint a conversation:

✔ Wait and see if the presenter is already speaking

✔ Look if there is a judge in the room. If that is the case, wait until the presenter is finished their 5 minutes presentations

✔ If you are in a conversation with a presenter and a judge enters the room, please shorten your discussion and let the judge evaluate the presenter.



Abstracts

Abstract 1 to 10: Oral presentations
Abstract 11 to 49: Poster presentations
(11 to 27: AM poster session and 28 to 49: PM poster session)

1 - Characterizing How Age, Comorbidity, and Adverse Childhood Experiences Affect the Time to Reach Initial Treatment Stability of ADHD Patients in a Community Sample

Msc - Junior

Philippe Hwang[1], Lily Hechtman[2]

[1]Research Institute of the McGill University Health Campus, Montreal, Quebec, [2]Department of Child Psychiatry, Montreal Children's Hospital, McGill University, Montreal, QC

Background: Attention-Deficit / Hyperactivity Disorder (ADHD) may present with psychiatric comorbidity rates up to 77%, and early intervention is critical to mitigate adverse outcomes. Recent studies have suggested that comorbidities of ADHD are often missed, and that adverse childhood experiences (ACE) are related to ADHD severity. Our objective is to characterize the factors that increase the time to achieve initial treatment stability (TTS) of ADHD.

Methods: This study is a retrospective cross-sectional review of patients diagnosed with ADHD at a community pediatric clinic in Montreal. 161 charts were reviewed for information regarding the diagnosis and management of ADHD, psychiatric comorbidities, and ACE prior, concurrently, and following their diagnosis of ADHD.

Results: Prevalence of comorbidities was 53% with 15% diagnosed with 2 or more comorbidities. Learning disorders (43%), oppositional-defiant disorder (29%), and anxiety disorders (24%) were the most common comorbidities. Multiple regression analysis of age, comorbidity, and ACE significantly predicted TTS ($F(3,157)=7.411$, $p<0.0001$, $R2=0.124$). They each added significantly to the prediction at $p<0.05$ (age (inversely)-$p=0.037$, comorbidity-$p=0.014$, ACE-$p=0.004$)

Discussion: In our study, age at diagnosis was inversely associated with TTS. The presence of one or more comorbidities, as well as having two or more ACE independently predicted a significantly longer time to reach initial stability of ADHD treatment. These factors coupled with the high prevalence of comorbidities in the sample in line with current literature suggests that pediatricians should retain a high index of suspicion for these factors that may complicate the treatment of ADHD in their patients. Early detection and intervention for any comorbidities and other psychosocial factors present would likely aid in optimizing management of ADHD patients. Further study is indicated to investigate the interactions between ACE and comorbidities on treatment effectiveness.

2 - Identifying the Optimal Corticosteroids to Target Acute Myeloid Leukemic Stem Cells

Msc - Junior

LeRon Best[1], Isabella Iasenza[1], Andrea Neumann[2], Meaghan Boileau[1], Kolja Eppert[3]

[1]Research Institute of the McGill University Health Centre, Montreal, Quebec, Division of Experimental Medicine, Department of Medicine, McGill University, Montreal, Quebec., [2]Research Institute of the McGill University Health Centre, Montreal, Quebec., [3]Department of Pediatrics, McGill University, Montreal, Quebec, Research Institute of the McGill University Health Centre, Montreal, Quebec, Division of Experimental Medicine, Department of Medicine, McGill University, Montreal, Quebec.

Acute myeloid leukemia (AML) is a cancer of the blood characterized by an increase in the number of immature blood cells (blasts) in the bone marrow, which cause hematopoietic insufficiency. Chemotherapies used for AML have stayed the same for the last 40 years and involve extremely intense toxic treatment, yet approximately 40% of AML is resistant to initial treatment or eventually relapse. The survival rate 5 years after diagnosis of pediatric AML patients is poor (approximately 60%) and accounts for almost half of the leukemic deaths in children. This is partially due to the chemoresistant nature of the leukemic stem cells (LSCs) that sustain the disease. Compounds that specifically target LSCs while sparing normal hematopoietic stem cells (HSCs) may significantly improve patient outcome and lower toxicity across a broad leukemia spectrum in adolescent and young adult (AYA) and pediatric patients. After conducting an initial drug screen, our lab has identified corticosteroids as compounds that can target LSCs while sparing HSCs. Corticosteroids have been shown to trigger apoptosis in some AML that carry RUNX1-mutations. However, we observed that glucocorticoids can effectively eliminate LSCs in a large subset of non-RUNX1 subtypes of AML by driving them to terminally differentiate. The goal of this project is to identify other corticosteroids that will target LSCs more effectively than the compounds used for the initial screen, as well as gain insight into the optimal drug design and the mechanism by which corticosteroids target LSCs.

3 - Socioeconomic disparities in pump uptake among children with type 1 diabetes: findings from two parallel population-based retrospective cohort studies in Québec and Manitoba

Msc - Junior

Jennifer Ladd[1], Atul Sharma[2], Elham Rahme[1], Kristine Kroeker[2], Marjolaine Dube[3], Marc Simard[3], Céline Plante[3], Claudia Blais[3], Marni Brownell[2], Celia Rodd[2], Meranda Nakhla[1]

[1]The Research Institute of the McGill University Health Centre, [2]University of Manitoba, [3]Institut national de santé publique du Québec

Background: Insulin pump therapy has the potential to improve glycemic control, delay long-term complications, and improve quality of life for children with type 1 diabetes. Across Canada, all provinces have implemented universal pediatric insulin pump programs to improve access to pump therapy; however, these programs have not all been systematically evaluated. We hypothesized that socioeconomic (SES) disparities in pump therapy uptake would be reduced in Québec, in which pump therapy is fully funded, as compared to Manitoba, in which there is partial coverage.

Methods: Using multiple linked health administrative databases and a clinical diabetes registry, we conducted parallel population-based retrospective cohort studies of children with type 1 diabetes in Québec and Manitoba between 2011 and 2017. We used multivariable Cox regression analysis to determine the association between pump uptake and SES, defined by validated material and social deprivation indices.

Results: We identified 2,919 individuals with diabetes in Québec and 636 in Manitoba. Increasing material deprivation was associated with decreased pump uptake in both Québec (adjusted hazard ratio (aHR) 0.89 for each quintile increase in material deprivation, 95% confidence interval (CI) 0.85 – 0.93)) and Manitoba (aHR 0.70, 95% CI 0.60 – 0.82). SES disparities in pump uptake were greater in Manitoba as compared to Québec ($p < 0.01$).

Interpretation: Our results suggest that the Québec program of full financial coverage for pump therapy may partially mitigate the observed SES disparities in pump uptake and can be a model to improve access to pump therapy for all children with type 1 diabetes.

4 - A framework for including children's surgical care in National Surgical, Obstetric and Anaesthesia Plans

Msc - Junior

Sabrina Wimmer[1, 2], Paul Truché [3], Elena Guadagno[1], Emmanuel A. Ameh[4], Lubna Samad [5], Emmanuel Makasa[6], Sarah Greenberg[7], John G. Meara[3, 8], Tonnis H van Dijk[2], Dan Poenaru[1]

[1]Harvey E. Beardmore Division of Pediatric Surgery, The Montreal Children's Hospital, McGill University Health Centre, Montreal, Canada , [2]University Medical Center Groningen, University of Groningen, Groningen, the Netherlands, [3]Program in Global Surgery and Social Change, Harvard Medical School, Boston, MA, USA, [4]Division of Paediatric Surgery, Department of Surgery, National Hospital, Abuja, Nigeria, [5]Center for Essential Surgical and Acute Care, Indus Health Network, Karachi, Pakistan, [6]Wits Centre of Surgical Healthcare, Department of Surgery, School of Clinical Medicine, Faculty of Health Sciences, University of Witwatersrand, Republic of South Africa, [7]Division of Pediatric General & Thoracic Surgery, Seattle Children's Hospital, Seattle, Washington, US, [8]Department of Plastic and Oral Surgery, Boston Children's Hospital, Boston, MA, USA

Introduction: National Surgical, Obstetric, and Anaesthesia Plans (NSOAPs) have emerged as a strategy to strengthen and scale up surgical healthcare systems in low-and middle-income countries (LMICs). The aim of this study is to assess the inclusion of children's surgical care among existing NSOAPs and develop a framework based on the Global Initiative for Children's Surgery (GICS) Optimal Resources for Children's Surgery (OReCS) to guide inclusion of children's surgical care in future policies.

Methods: We performed two qualitative content analyses to assess the inclusion of children's surgical care among NSOAPs. We applied a conventional (inductive) content analysis approach to identify themes and patterns, and developed a framework based on the GICS OReCS document. We then used this framework to conduct a directed (deductive) content analysis of the NSOAPs of Ethiopia, Nigeria, Rwanda, Senegal, Tanzania and Zambia.

Results: Our framework for the inclusion of children's surgical care in NSOAPs included seven domains. We evaluated six NSOAPs with all addressing at least two of the domains. All six NSOAPs addressed "human resources and training" and "infrastructure", four addressed "service delivery", three addressed "governance and financing", two included "research, evaluation and quality improvement", and one NSOAP addressed "equipment and supplies" and "advocacy and awareness".

Conclusion: Additional focus must be placed on the development of surgical healthcare systems for children in LMICs. This requires a focus on children's surgical care separate from adult surgical care in the scaling up of surgical healthcare systems, including children-focused needs assessments and the inclusion of children's surgery providers in the process. This study proposes a framework for evaluating NSOAPs, highlights practice examples and suggests recommendations for the development of future policies.

5 - Peri-Operative Resonance Frequency Analysis and Skull Bone Characterization in Regard to Bone-Anchored Hearing Implant Stability

Md student - Junior

Samer Salameh[1], Aren Bezdjian[2], Sam J. Daniel[1]

[1]Department of Otolaryngology – Head and Neck Surgery, Montreal Children's Hospital, Faculty of Medicine, McGill University, Montreal, Quebec, Canada, [2]Department of Experimental Surgery - Faculty of Medicine, McGill University, Montreal, Quebec, Canada

Bone-anchored hearing implants (BAHI's) are osseointegrated devices that are effective for hearing restoration in patients with various forms of hearing loss. In the last two decades, BAHI's have been implanted with a low overall incidence of implant losses. However, loss of implant stability can sometimes occur without any identifiable cause. Resonance Frequency Analysis (RFA) is a non-invasive method that measures the stability of dental and orthopedic implants. The purpose of this project is to investigate the use of peri-operative RFA as a clinical, in-vivo, and non-invasive method to predict and prevent BAHI loss due to impeded stability, and to investigate BAHI stability in cadaveric skull bone using RFA and mechanical testing. The clinical side of this project is a prospective cohort study. Patients with an intra-operative baseline RFA measurement and at least one follow-up measurement were included. Threshold shifts were used to monitor the development of implant stability as they hold constant implant-related influencing factors. In the cadaveric side of this project, cadaveric specimens were implanted with BAHI's before undergoing RFA measurements and mechanical pushout tests. In total, 60 BAHIs were placed in 29 pediatric and 28 adult patients. RFA scores in adults were significantly greater at all time points of measurement compared to pediatric patients; however, significant increases in stability threshold shifts were more frequent in children compared to adults. Linear regression analysis of cadaveric implant properties showed a positive relationship between peak pushout load and mean RFA scores, as well as a non-linear relationship between mean RFA scores and age of donor. Our clinical and cadaveric data show that for pediatric and adult patients, the non-invasive RFA method has clinical relevance and could be an important tool added to BAHI surgery. Further assessment is needed to understand what bone- and patient-specific factors influence BAHI stability.

6 - H3.3G34W promotes growth and impedes differentiation of osteoblast-like mesenchymal progenitors in Giant Cell Tumour of Bone

PhD - Senior

Sima Khazaei[1], Nicolas De Jay[1], Shriya Deshmukh[2], Liam Hendrikse[3], Wajih Jawhar[1], Carol Chen[1], Livia Garzia[1], Claudia Kleinman[1], Nada Jabado[1]

[1]Department of Human Genetics, McGill University, Montreal, QC, Canada, [2]Department of Experimental Medicine, McGill University, Montreal, QC, Canada, [3]Cancer and Stem Cell Biology Program, The Hospital for Sick Children, Toronto, ON, Canada.

Glycine 34 to tryptophan (G34W) substitutions in H3.3 arise in ~90% of giant cell tumour of bone (GCT). Here, we show H3.3G34W is necessary for tumour formation. By profiling the epigenome, transcriptome and secreted proteome of patient samples and tumour-derived cells CRISPR/Cas9-edited for H3.3G34W, we show that H3.3K36me3 loss on mutant H3.3 alters the deposition of the repressive H3K27me3 mark from intergenic to genic regions, beyond areas of H3.3 deposition. This promotes redistribution of other chromatin marks and aberrant transcription, altering cell fate in mesenchymal progenitors and hindering differentiation. Single-cell transcriptomics reveals that H3.3G34W stromal cells recapitulate a neoplastic trajectory from a *SPP1*+ osteoblast-like progenitor population towards an *ACTA2*+ myofibroblast-like population, which secretes extracellular matrix ligands predicted to recruit and activate osteoclasts. Our findings suggest that H3.3G34W leads to GCT by sustaining a transformed state in osteoblast-like progenitors which promotes neoplastic growth, pathological recruitment of giant osteoclasts, and bone destruction.

7 - Efficacy of cholic acid therapy to treat liver disease in the PEX1-G844D mouse model of Zellweger Spectrum Disorder

PhD - Senior

Lingxiao Chen[1], Hong Choi[2], Erminia Di Pietro[2], Catherine Argyriou[1], Joseph Hacia[3], Zu-hua Gao[1, 2], Nancy Braverman[1, 2]

[1]McGill University, [2]Research Institute of MUHC, [3]University of Southern California

Individuals with the peroxisome biogenesis disorder, Zellweger Spectrum Disorder (ZSD), manifest chronic liver disease that is partially caused by bile acid synthesis defects and accumulation of toxic bile acid precursors due to peroxisome dysfunction. Cholic acid therapy for liver disease in ZSD is available in several countries, but its efficacy remains unclear. We conducted a short-term pilot study to evaluate dose and efficacy of cholic acid therapy in preventing/treating liver disease using a mouse model homozygous for PEX1-G844D allele, the murine equivalent of a common mutation in ZSD patients. This model recapitulates many hepatic features of mild to intermediate ZSD, including hepatomegaly, cholestasis, steatosis, liver fibrosis and hepatic cancer. We administered a cholic acid supplemented diet at different doses (0.5, 0.2, 0.1 and 0.01%) to our mice at 4 or 12 weeks of age for one month and examined the effect on liver pathology relative to animals on control diet using histology, immunohistochemistry and biochemistry. We found that cholic acid supplementation reduced C27-bile acid precursors accumulation and elevated serum levels of mature C24-bile acids in a dose-dependent manner. We also observed alleviated mitochondrial oxidative stress and reduced occurrence of hepatocyte necrosis in G844D mice after cholic acid supplementation. Nevertheless, cholic acid supplementation aggravated hepatosteatosis and increased ductular reaction in G844D mice at high dose. Moreover, liver function tests and poor growth indicated hepatotoxicity of high dose cholic acid. Overall, we found no improvement in peroxisome numbers or peroxisome import after cholic acid treatment at any dose. Remarkably, we observed cholic acid dose-dependent increase of C26:0 lysophosphatidylcholine, which is already elevated in our mouse model and in ZSD patients. In summary, our efficacy study suggests 0.1% cholic acid supplementation may have therapeutic potential, and we will test this dose in an expanded long-term study.

8 - A Prospective Cohort Study on the Evolution of Infection Markers in Children with Severe Bacterial Infections Treated with Antibiotics

PhD - Senior

Kim Noel[1], Jacques Lacroix[2], Elaine Gilfoyle[3], James McNally[4], Samara Zavalkoff[1], Patricia Fontela[1]

[1]McGill University, [2]Université de Montréal, [3]University of Toronto, [4]University of Ottawa

Background: Objective criteria are needed to guide antibiotic duration in pediatric intensive care units (PICUs). Inflammatory biomarkers have been successfully used to personalize treatment duration in adults and neonates, but their utility in children is unknown.

Objectives: To characterize the temporal behaviour of inflammatory biomarkers (C-reactive protein [CRP] and procalcitonin) in children with severe bacterial infections.

Methods: Ongoing prospective cohort study in 7 Canadian PICUs. Eligible patients are between 1 month and <18 years old admitted with suspected or proven severe bacterial infection (sepsis, pneumonia, and central nervous system and intrabdominal infections) and who received ≥1 antimicrobial. Aforementioned biomarkers are measured on days 1 to 7 and day 10 of antibiotic treatment.

Results: We have enrolled 208 patients. Median age was 56.0 months (interquartile range [IQR] 14.8 – 103.0). Median antibiotic duration was 9.5 days (IQR 6.0 – 14.0). Absolute levels of procalcitonin peaked on day 1, and descended over the course of treatment. By day 5, 82% and 43% of patients had ≥80% drop in procalcitonin and CRP levels, respectively. Patients with ≥50% drop in CRP levels from days 1 to 3 had, on average, shorter length of hospital stay (-6.4 days, 95% confidence interval [CI] -12.2, -0.8). The same trend was observed for procalcitonin (-4.6 days, 95%CI -11.9, 0.9). There was a strong correlation between mean daily multiple organ dysfunction scores with mean daily CRP (0.93, 95%CI 0.66, 0.99) and procalcitonin levels (0.98, 95%CI 0.88, 0.99).

Conclusion: Preliminary data suggest CRP and procalcitonin are promising biomarkers to guide antibiotic duration in children. Importantly, the majority of patients reached an 80% decrease from peak procalcitonin values by day 5, a published criterion used to stop antibiotics in adults.

9 - Modeling Cerebro-costo-mandibular Syndrome (CCMS) in mouse by mutating Snrpb

PhD - Senior

Sabrina Alam[1], Jacek Majewski[1, 2], Loydie Majewska[1, 2, 3]

[1]Department of Human Genetics, McGill University, Montreal, Quebec, Canada, [2]McGill University Health Centre at Glen Site, Montreal, QC, Canada, [3]Department of Pediatrics, McGill University, Montreal, Quebec, Canada

SNRPB, which codes for a core component of the spliceosomal small nuclear ribonucleoproteins is mutated in patients with a rare autosomal dominant disorder called Cerebro-Costo-mandibular Syndrome (CCMS). Though SNRPB is a core protein of the splicing machinery required in every cell, mutations in SNRPB causes abnormalities mostly in craniofacial bones and ribs in CCMS patients. The molecular etiology of how *SNRPB* mutation causes tissue-specific abnormalities is unknown. We hypothesize transcripts that are sensitive to the level of SNRPB during development are neural crest cell (NCC) specific, as these cells significantly contribute to craniofacial development. To test our hypothesis, we have generated a *Snrpb* conditional mutant mouse line with Loxp sequences and have mated the line with Wnt1-cre mice to ask if the deletion of *Snrpb* from NCCs causes craniofacial abnormalities that mimic CCMS. We have found that NCC-specific *Snrpb* heterozygous mutant embryos show mild midbrain, hindbrain, and pharyngeal arches hypoplasia at embryonic day (E)9.5. The phenotype becomes more severe at later embryonic days and becomes fully penetrant at E14.5, where no definite head and face structure is formed in 44 percent of the *Snrpb* heterozygous mutants. At weaning, no NCC-specific *Snrpb* mutant animal was found. Our skeletal analysis of the mutants reveals severe defects in the craniofacial structures ranging from the irregular formation of the middle ear bones to the complete absence of craniofacial components such as Meckel's cartilage, hyoid bone, and bones of the cranial base such as the frontal. Our preliminary data of whole-mount staining of E9.5 and E10.5 *SnrpbL/+; Wnt-1CreTg/+* embryos carrying the ROSA26R-lacZ reporter show reduced NCCs in the head and pharyngeal arches. We Aim to perform RNA sequencing of our *Snrpb* mutant NCCs to identify the transcripts affected due to the reduced SNRPB levels.

10 - Impact of high folate intake during pregnancy on embryonic development

PhD - Senior

Yan Luan[1], Daniel Leclerc[1], Marta Cosín-Tomás[1], Olga Malysheva[2], Brandi Wasek[3], Teodoro Bottiglieri[3], Marie Caudill[2], Rima Rozen[1]

[1]Departments of Human Genetics and Pediatrics, McGill University, and the Research Institute of the McGill University Health Center, Montreal, Canada, [2]Division of Nutritional Sciences and Genomics, Cornell University, Ithaca, USA, [3]Center of Metabolomics, Institute of Metabolic Disease, Baylor Scott & White Research Institute, Dallas, USA

Background: Some pregnant women have higher intakes of folic acid (FA) due to food fortification and increased use of multivitamins. We showed that diets containing 5-fold higher FA than the recommended intake for mice (5xFASD) during pregnancy, downregulated methylenetetrahydrofolate reductase (MTHFR), altered choline/methyl metabolism and led to neurobehavioral abnormalities in 3-week-old mouse pups. Folate and choline serve as methyl donors for S-adenosylmethionine (SAM)-dependent methylation reactions.

Hypothesis: Folate/choline/methyl metabolism disturbances may occur *in utero*, and neurobehavioral abnormalities may have their origin during embryonic development.

Methods: Female C57BL/6 mice were placed on control diet (CD) or 5xFASD for a month prior to mating and maintained on the same diet until embryonic day 17.5. Embryonic growth was evaluated; methyl metabolites and immunoreactive MTHFR were examined in maternal and embryonic tissues; microarray profiling and real-time qRT-PCR were used to assess expression of placental genes.

Results: No significant difference was observed for embryonic growth. Altered metabolite levels were observed in FASD embryos. The ratio of SAM to S-adenosylhomocysteine was decreased in embryonic livers and placentas in FASD mice. The concentration of glycerophosphocholine, an important storage form of choline, was decreased in embryonic livers and tended to be lower in placentas for FASD mice. FASD mothers showed increased phosphorylation of MTHFR protein in liver, an indicator of decreased activity, and decreased betaine in plasma. Placental microarrays showed 195 and 312 genes differentially expressed in FASD compared with CD group in males and females, respectively, as well as distinct patterns between male and female embryos. FASD altered expression of genes involved in vascularization, angiogenesis, embryonic and placental development, neurodevelopment and neurodegeneration.

Conclusions: 5xFASD during pregnancy results in metabolic disturbances in embryonic liver and placenta, as well as placental gene expression changes. These results are relevant for determining a safe upper limit for folate intake during pregnancy.

11 - Management of anorectal malformations in resource-limited settings: a systematic review

Undergraduate - Junior

Joseph Sayegh[1, 2], Felix Oyania [2, 3], Elena Guadagno [2], Dan Poenaru [2]

[1]Faculty of Medicine and Health Sciences, Department of Anatomy and Cell Biology, McGill University , [2]Harvey E. Beardmore Division of Pediatric Surgery, Montreal Children's Hospital , [3]Makerere University College of Health Sciences, Department of Surgery

Background: Anorectal malformations (ARMs) are common congenital anomalies treated in various settings with or without intestinal diversion. While many ARM patients in high-income countries are treated with a one- or two-staged approach, the effectiveness of these approaches in low- and middle-income countries (LMICs) is not clear.

Aim: To review the literature on the management and outcomes of anorectal malformations in LMICs.

Methods: Several databases (Africa-Wide Information, Cochrane, Embase, Global Health, Global Index Medicus, Medline, Web of Science) were interrogated up to May 27, 2020, resulting in 1269 studies. Two independent authors reviewed and selected abstracts based on preset criteria. Data from included studies were extracted, analyzed, and summarized. Risk of bias was assessed using the Methodological Index for Non-Randomized Studies (MINORS).

Results: Sixty-five articles were included for full-text analysis. One could not be obtained, and 21 others were excluded after full-text analysis. Final included studies originated from 11 different LMICs. The most common high, intermediate, and low ARM types were rectovesical fistula (n=72), rectovestibular fistula (n=693), and anovestibular fistula (n=207) respectively. Eighteen studies reported single-stage correction, 10 reported multi-staged correction, and 15 studies compared the previous two. Most commonly performed procedures were anterior and posterior sagittal anorectoplasty. Most studies reported positive outcomes following single-stage correction of ARMs.

Conclusion: The literature supports the effectiveness of single-stage correction for ARMs in LMICs. Further and multicentre studies are needed for single-stage repair for high ARMs.

12 - Comparison of retinal artery and vein measurements: a 30-year follow-up of a unilateral Retinitis Pigmentosa patient.

Md student - Junior

Anne Xuan-Lan Nguyen[1], Clara Tardif[1], Louis-Félix Berthiaum[1], Mercedes Gauthier[1, 2], Pierre Lachapelle [1]

[1]Department of Ophthalmology & Visual Sciences, Faculty of Medicine, McGill University / Research Institute of the McGill University Health Centre, [2]École de technologie supérieure

Background: Retinitis pigmentosa (RP) is a group of genetic disorders leading to progressive blindness. In a case of unilateral RP, that the first clinical sign of RP was only detected after 21 years in clinical tests. Comparing blood vessel arborizations in longitudinal patients can lead to better detection tools.

Methods: A 31-year-old woman initially presenting with unilateral (OS) RP and had four detailed fundus examinations (1984, 1995, 2002, 2006). The initially non-affected eye (OD) progressively developed RP. The scanned photos were processed into mosaics to visualize detailed blood vessel arborisations that were segmented and compared.

Results: When examining overlap percentages, both arteries and veins are progressively more displaced as we move away from the ONH, and veins have shown a more important absolute displacement than arteries. On average, the distance between determined vessel branching points and the centre of the ONH decreases with time, in both veins and arteries. The mean distances (from 1995, 2002m 2006) were all statistically different (p<0.05) from the initial reference visit (1984). The angle between these same branching points and the x axis, which was aligned with the fovea and ONH (0,0 coordinate), varied over time following similar clockwise-direction trends in arteries and veins. In 1984, 1995, 2002 and 2004, the mean angles varied between -11.1 o and 5.1 o for arteries and -34.3o and -29.2o for veins.

Conclusions: This is the first study to examine linear and angular retinal vessel displacements in a unilateral and longitudinal case of RP. In addition to the main vessels around the ONH, measuring branching vessel displacements is an efficient method to assess the displacements of the entire retinal blood vessel arborization. In this patient, veins seem to have a greater variability, but both veins and arteries follow similar directional displacement trends.

13- Side Effects and Perceived Benefits of Medications in Children with Chronic Noncancer Pain: A Retrospective Cohort Study

Undergraduate - Junior

Kacper Niburski[1], Nada Mohamed[2], Victor Hugo Gonzalez Cardenas[2], Rebecca Pitt[2], Pablo Ingelmo[2]

[1]McGill University, Faculty of Medicine, [2] Department of Pediatric Anaesthesia, McGill University Health Center.

Background: Pharmacological treatment of chronic noncancer pain in pediatric populations, has recently been shown to have little high-quality evidence and uncertain efficacy.

Aim: Evaluate the incidence of adverse effects and the perceived benefits of pharmacological treatment in children with chronic non-cancer pain conditions.

Design: Tabulated lists of common side effects (>5% incidence) were compiled. Incidence of adverse effects and of perceived benefit for each medication were self-reported by the patients within two weeks of treatment. Two reviewers independently screened the data. Data were collected from November 2018 until October 2019. A p-value less than 0.05 was considered significant. Chi-square and Mann-Whitney statistics were calculated with SPSS 25.

Results: Of the 145 children receiving medications, 60% reported taking 2 to 4 medications at one time. Of those, 73% reported some side effects and 52% reported between 1 and 4 side effects per medication. Taking more than five medications showed 100% prevalence of side effects. Fatigue (71%) was most frequently reported, followed by drowsiness (58%) and dizziness (55%). Sixty percent of patients reported some benefit, though only 48% of that was analgesic. There was a significant clinical efficaciousness reduction after three meds. Fifty-five percent of patients improved their insomnia related to pain when they took melatonin ($p<0.001$, OR 0.27 (0.16-0.44), RR 0.45 (0.34-0.60), NNT 3.29 (2.39-5.27)). Sixty-eight percent of patients receiving Celecoxib reported improvement (OR 0.36 (0.21-0.63), RR 0.64 (0.51-0.79), NNT 4.04 (2.68-8.24)).

Conclusion: The incidence of adverse effects associated with the pharmacological treatment of chronic non-cancer pain is significantly elevated and associated with a limited perceived analgesic benefit. Pain polypharmacy was associated with an increase in the incidence of adverse effects and decreased clinical efficaciousness after three meds.

14 - An interdisciplinary pain treatment program reduced the number of consults to the emergency department

Undergraduate - Junior

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[1]McGill University, [2]Montreal Children's Hospital, [3]The Alan Edwards Centre for Research on Pain

Background: There is currently a lack of information regarding the effects of chronic pain management on the number of chronic pain-related emergency department consults in the pediatric population.

Aim: This study aims to evaluate whether treatment of pediatric chronic pain conditions by an interdisciplinary team has an impact on the number of emergency department consults at the Montreal Children's Hospital.

Methods: This retrospective case control study analyzed the electronic charts of pediatric patients having received a chronic pain diagnosis by the Chronic Pain Service (CPS) between January 2016-December 2018. Emergency department visits, specialty consults, medications and admissions were all assessed in the time period of one year before the patient's first visit with the CPS and one year after.

Results: Of 327 patients diagnosed by the CPS during the study period, 315 patients were included in the analysis. Of these 315 patients, 155 patients consulted the emergency department within 1 year before their first CPS visit (396 total consults) and 105 patients consulted within 1 year after (250 total consults), demonstrating a net reduction of 16% of patients. Of these visits, 255 of the visits within 1 year before (64%) and 53 of the visits within 1 year after (21%) were chronic-pain related, showing a net reduction in chronic pain-related consults of 43%.

Conclusion: Pediatric patients with chronic pain conditions receiving services by an interdisciplinary pain treatment program were less likely to consult the emergency department within one year after being admitted in the CPS treatment program.

15 - The role of Claudin-3 and glycoproteins in neural tube closure

PhD - Senior

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The neural tube is the embryonic precursor to the central nervous system, which is formed following elevation and fusion of the lateral edges (neural folds) of the neural plate. Our lab is investigating the role of the claudin (cldn) family of tight junction proteins in neural tube development. In chick embryos, depletion of Cldn3 causes neural tube defects at the final stage of neural tube development, neural fold fusion. The mechanism of chick neural fold fusion is still not fully understood. In scanning electron microscope (SEM) images, we identified a fibrous mesh between the closing neural folds of wild-type chick embryos which was absent in the Cldn3-depleted embryos. Research from the 1970s showed that the mesh is a glycoprotein cell-surface matrix, involved in temporary adhesion between the neural folds as they fuse. We hypothesize that Cldn3 is required for the formation of a glycoprotein mesh which is critical for neural fold fusion. Using fluorescently-tagged carbohydrate-binding lectin proteins, I am examining the pattern of expression of glycan chains along the neural tube. I will then determine whether this pattern changes in the Cldn3-depleted embryo and how the glycoprotein chains are involved in neural tube development. My preliminary results show that subsets of glycan chains are strongly expressed at the closing neural folds and that interrupting these glycan chains through lectin binding causes neural tube defects. This research is working towards a better understanding of the mechanisms in chick neural tube closure, and the role that Cldn3 is playing in this process.

16 - INVOLVEMENT OF PEROXIREDOXIN 6's PEROXIDASE AND CA2+-INDEPENDENT PHOSPHOLIPASE A2 IN SPERMATOZOA MOTILITY AND CAPACITATION

Msc - Junior

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Peroxiredoxins are antioxidant enzymes that protect spermatozoa against oxidative stress. PRDX6 has peroxidase and Ca2+-independent phospholipase A2 (iPLA2) activities. PRDX6-/- mice are subfertile, and their spermatozoa are highly sensitive to oxidative stress showing low sperm motility, high protein and DNA oxidation levels, and inability to produce viable embryos *in vitro*. Spermatozoa from idiopathic infertile men have low PRDX6 levels, impaired motility and high DNA fragmentation levels. The inhibition of iPLA2 activity promotes a dose-dependent decrease in sperm viability associated with increased ROS production, lipid peroxidation and DNA oxidation. We aimed to determine whether the absence of PRDX6 peroxidase or iPLA2 activities impairs fertility by affecting sperm motility and capacitation.

C47S and D140A knock-in mouse strains, lacking the peroxidase and iPLA2 activities (respectively), C57Bl6/J (wild-type) and PRDX6-/- male mice were used to compare fertility, sperm motility and capacitation levels. Two-month-old males from each strain were bred in separate cages with one age-matched wild-type female. The number of pups was recorded during three consecutive matings. Epididymal spermatozoa were incubated in PBS at 37°C for 2h to assess motility. Sperm samples were incubated in BWW medium with or without 5 mg/ml BSA and 20 mM bicarbonate at 37°C for 1h, and treated with 5 uM progesterone (acrosome reaction inducer). Capacitation was expressed as the percentage of acrosome-reacted spermatozoa, determined by Giemsa staining.

C47S and D140A mice produced a lower number of pups compared to wild-type, but similar to PRDX6-/- mice. Sperm motility was lower in C47S, D140A, and PRDX6-/- mice than wild-type at zero time, and severely reduced during the 2h incubation. Sperm capacitation was impaired in C47S, D140A, and Prdx6-/- mice.

In conclusion, PRDX6 peroxidase and Ca2+-iPLA2 activities are essential for male mouse fertility.

17 - Are the horizontal and amacrine cells of the retina injured in the context of bronchopulmonary dysplasia (BPD) and can stem cell therapy repair these injuries?

Undergraduate - Junior

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Background: Bronchopulmonary dysplasia (BPD) is a chronic lung disease that affects premature newborns who require prolonged mechanical ventilation and high levels of oxygen (hyperoxia). This prolonged hyperoxia may also cause retinal injuries in these infants.

Objective: To investigate whether the hyperoxia known to cause BPD-like lung injuries in a rodent model also causes horizontal and amacrine cell injuries in the retina of these animals, and whether these injuries can be repaired by stem cell therapy shown to repair the lung injuries.

Methods: Rowett Nude rat pups were exposed to hyperoxia (95% O2) or room air (21% O2) from postnatal day 4 to 14 (P4-14). At P14, the rats were injected with human-cord blood endothelial colony-forming cells (ECFCs) or a vehicle. From P14 to P28, all the rats were housed in room air. At P28, they were sacrificed and their eyes were extracted. The retinas were immunostained with anti-calbindin to label horizontal cells and with anti-calretinin to label amacrine cells. Number of horizontal and amacrine cells were counted at 0 µm, 1000 µm, and 3000 µm from the optic nerve and compared between the experimental groups.

Results: There was a significant decrease in horizontal cell density in the retina of hyperoxia-exposed rats compared to room air control group; the amacrine cell density was not different between the groups. Treatment with ECFCs did not result in an increased density of these cells in the retina of hyperoxia-exposed rats.

Conclusion: Hyperoxia exposure impaired the number of horizontal cells, but not the number of amacrine cells. Treatment with ECFCs did not improve the number of these cells, suggesting that ECFCs may not have a therapeutic effect on these cell injuries in the retina. Further studies are needed to investigate the impact of hyperoxia and ECFCs on the other retinal cells in this rat model.

18 - Odd-Skipped Related 1 (Osr1) Regulates Extracellular Matrix Deposition During Bladder Development and Disease

PhD - Senior

Vasikar Murugapoopathy[1], Philippe Cammisotto[1, 2], Abubakr Mossa[1, 2], Lysanne Campeau[1, 2], Indra R Gupta[1, 3]

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Collagens form a network of interwoven fibers in the bladder wall which mediate biomechanical properties that maintain low pressures during emptying and prevent over-distension during storage. When the bladder is obstructed, there is a marked increase in collagen that impairs its function. This raises the question: how is collagen deposition regulated during development and in disease? The transcription factor Odd-skipped related 1 (Osr1) regulates ECM formation and maintains mesenchymal cell progenitors in several organs. We hypothesize that Osr1 regulates mesenchymal cell progenitors that mediate the deposition of ECM in the bladder during development and in injury. Osr1 mRNA is initially expressed in epithelial and mesenchymal cells at the onset of bladder formation, but then it becomes restricted to a subset of mesenchymally-derived cells in the lamina propria and muscle layers of the adult bladder. Osr1+/- newborn mice have a decreased number of fibroblasts in the lamina propria accompanied by decreased collagen I and III. To understand the consequences of these ECM changes, bladder function was assessed. Adult Osr1+/- mice had lower bladder capacities, and they voided more frequently. Interestingly, adult Osr1+/- mice had an increase in collagen in the bladder suggesting injury. To determine if Osr1 regulates collagen deposition during bladder injury, we induced bladder obstruction in wild-type mice from spinal cord injury. Injured mice exhibited increased mRNA expression of Osr1 and collagen III. The results show that haploinsufficiency of Osr1 results in decreased collagen deposition. During bladder injury, there is an increase in collagen deposition and Osr1 is upregulated. These findings suggest that Osr1 demarcates a fibrogenic progenitor cell population during bladder development and disease.

19 - High-throughput screen of primary human acute myeloid leukemia stem cells identifies novel anti-LSC compounds

PhD - Senior

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For the past 40 years, the standard therapy for acute myeloid leukemia (AML), a blood cancer, consists of intense and toxic treatment targeting mainly the leukemia cells but also healthy cells. The long-term side effects associated with therapy include infertility and secondary cancers in children and adults, and the 5-year survival rate remains poor at 28.7% for all ages as a large portion of these individuals do not respond to therapy or the leukemia returns later. One of the main contributors to treatment failure in AML are the rare cancerous cells called leukemic stem cells (LSCs). These cells are the “root” of the disease and produce all the other leukemic cells. Hence, safer and novel therapies targeting the unique biology of LSCs are needed while sparing hematopoietic stem cells.

We isolated the CD34+ LSC containing fraction of a primary human AML sample (>90% purity) functionally validated to be enriched for LSCs in long-term xenotransplant assays, (Eppert, K., *et al*., 2011), and performed a high-throughput screen of 11,166 chemical molecules. We also counter screened against normal CD34+ cord blood (CB) hematopoietic stem and progenitor cells. From this, 93 highly effective anti-LSC compounds were identified including tyrosine kinase inhibitors, epigenetic modifiers, anti-apoptotic protein inhibitors and glucocorticoids. Glucocorticoids were also previously identified in our small scale screen of anti-LSC compounds performed using *in silico* and *in vitro* assays where they were found to specifically drive human LSCs to terminally differentiate, a similar mechanism to the highly effective all-*trans* retinoic acid treatment of childhood and adult acute promyelocytic leukemia (Laverdière, I. & Boileau, M., *et al*., 2018). We will now re-validate these hits *in vitro*, where the most efficient compounds will be chosen for anti-LSC validation in a panel of primary AMLs.

20 - Comorbid Psychiatric Disorders in Adults with Attention Deficit Hyperactivity Disorder With and Without Specific Learning Problems

Msc - Junior

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Background. Specific Learning Disorders (SLD) co-occur with Attention Deficit Hyperactivity Disorder (ADHD) in approximately 20% of cases. ADHD alone and SLD alone may also present with other psychiatric comorbidities, such as mood and anxiety disorders. There are conflicting findings about the risk of psychiatric comorbidities in adults with ADHD alone compared to those with ADHD+SLD. Our goal is to explore the risk of comorbidities in adults with ADHD alone and those with additional specific learning problems (SLP).

Methods: This retrospective chart review analyzed a clinical sample of 884 adults seen between 2001 and 2018. Patients underwent a comprehensive psychiatric evaluation including a systematic assessment battery, psychometric testing and a structured clinical interview. Patient charts were reviewed for information regarding ADHD, arithmetic and reading SLP, current and past DSM-IV Axis I and II psychiatric disorders.

Results: Patients were divided into four groups, ADHD alone (*N*=329), ADHD+SLP (*N*=317), SLP alone (*N*=87) and controls (*N*=141). The rate of current Axis I disorders did not significantly differ between groups. For past Axis I disorders, the ADHD alone group (28%) and ADHD+SLP group (32%) presented significantly higher rates of past substance use disorders versus controls (18%), *(p<.05)*. Group ADHD alone (53%) and group ADHD+SLP (45%) presented with significantly higher rates of Axis II disorders compared to group SLP alone (42%) and controls (32%), (*p<.05*). Specifically, group ADHD+SLP is at higher risk for obsessive-compulsive and antisocial personality disorders, whereas group ADHD alone is at higher risk for passive-aggressive, antisocial, borderline and obsessive-compulsive personality disorders *(p<.05*).

Conclusion: These results indicate that ADHD alone is a significant predictor for comorbid past Axis I and Axis II disorders among adults. In addition to ADHD, having SLP was associated with higher rates of comorbidity, namely past substance disorders, obsessive-compulsive and antisocial personality disorders.

21 - The role of the androgen blockade in alleviating GBS-induced innate immune response and subsequent neurobehavioral impairments

Msc - Junior

Seline Vancolen 1,2,Taghreed Ayash 2,Bernard Robaire 1,Guillaume Sebire 1,3

Will be presented in the PM session

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Background: Group B Streptococcus (GBS) is a leading cause of maternal infection during pregnancy. An exaggerated innate immune response leads to placental inflammation (chorioamnionitis). Chorioamnionitis is associated with an increased risk of autism spectrum disorders (ASD), a neurobehavioral disability that is more prominent in males than females. Although pre-clinical findings show that GBS-induced maternal immune activation occurs with more prominent inflammation and ASD- like behaviours in males than females, the mechanism underlying this sex difference is not understood. This knowledge gap raises the question of the role of sex steroids in the immune response. Our hypothesis is that testosterone up-regulates the placental innate immune response.

Methods: Lewis dams were injected every 24 h from G18 to G21 with corn oil (vehicle) or flutamide (anti-androgen) administered at a dose of 50 mg/kg body weight. On G19, dams were injected with saline or GBS serotype Ia suspended in saline. The four experimental groups were: (*1*) vehicle/saline, (*2*) flutamide/saline, (*3*) vehicle/GBS, (*4*) flutamide/GBS. Dams underwent C-sections on G22, with respect to their injection time. Maternal, fetal sera and placentas were collected for protein assays and *in-situ* analyses.

Results: Our preliminary results showed that the dose of flutamide we used counteracted the androgen effect as shown by a decreased anogenital distance of male pups from flutamide compared to vehicle dams. An expected trend of decreased maternal weight gain was associated with maternal GBS infection. A trend of decreased IL-1β and IL-6 concentration was observed in placentas of the male GBS/flutamide group compared to the GBS group only.

Discussion: Flutamide appears to be effective in inducing the androgen blockade. Furthermore, our preliminary results suggest that the androgen blockade results in a reduced GBS-induced placental innate immune response. An increased sample size will determine whether these preliminary data are confirmed.

22 - Association of Social Jetlag and Sleep with Temperament in Healthy Canadian Preschool-aged Children

Md student - Junior

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Background: Social jetlag (SJL) measures the discrepancy between circadian and social clocks, which may lead to chronic sleep debt. The relationship between SJL with emotional and behavioural problems is well documented in adolescents and adults, however there are no studies evaluating SJL and temperament in children under 6 years of age using accelerometry-derived objective sleep data.

Methods: Cross-sectional study of a prospectively recruited cohort of children. We included children <6 years old attending primary care visits in The Applied Research Group for Kids (TARGetKids!) cohort, who wore an accelerometer for 7 days and had ≥1 valid weekend and weekday of accelerometry. SJL (difference in sleep midpoint between weekdays and weekend days) and sleep duration (total 24h and nighttime sleep) were measured. Parents completed the Rothbart Childhood Behaviour Questionnaires to quantify temperament dimensions: Surgency, Negative Affectivity, Effortful Control. Multivariate regression models were used to test the associations between sleep and temperament, adjusted for age, sex, ethnicity and daycare/school attendance.

Results: Of 78 children (39 girls (50%); mean age [SD]: 35.1[20.5] months), 20 children (25.6%) had SJL. Greater SJL was experienced in children who attended preschool/daycare (26.3[18.8]min;n=37) versus children who did not attend (17.6[14.8]min;n=35, $p<0.05$). There was no evidence of statistically significant associations between SJL and any temperament dimension. Longer 24h sleep (ß:0.347, 95%CI:0.182,0.512, $p<0.0001$) and longer night sleep duration (ß:0.413, 95% CI:0.163,0.663, $p=0.002$) were associated with higher Negative Affectivity scores.

Conclusion: SJL is highly prevalent in preschool-aged children (>25%), suggesting that early society start times may alter sleep habits of young children. In our cohort, there was a linear relationship between sleep duration and negative affect; the latter is associated with children developing internalizing behaviour such as low-self-esteem. Our study provides evidence that sleep quantity, but not SJL, is associated with temperament and may impact daytime behaviour of young children.

23 - The role of androgen and estrogen receptors in sex-biased DNA methylation in mouse liver

Msc - Junior

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We recently generated a catalogue of sex-biased differentially methylated regions (sDMRs) for mouse liver using whole genome bisulfite sequencing (WGBS) and showed that sex phenotype has a major impact on autosomal DNA methylation levels (Zhuang et al., 2020). Testosterone is known to affect DNA methylation in mouse liver (Reizel et al., 2015), however the impact of estrogen signaling has not been investigated. We hypothesized that both testosterone and estradiol signaling influenced DNA methylation through binding of their receptors and that androgen receptor (AR) or estrogen receptor (ESR) DNA binding sites overlapped with sDMRs. To test this hypothesis, we first examined sex-biased methylation in the liver of androgen receptor knockout (ARKO) (Notini et al., 2005) and estrogen receptor α knockout (ESR1KO) mice (Hewitt et al., 2010) using pyrosequencing methylation assays. Six sex-phenotype dependent sDMRs: three with lower methylation in males (male-biased) and three with lower methylation in females (female-biased) were assayed. Male-type methylation patterns were lost in ARKO XY female mice with androgen insensitivity, suggesting that testosterone signalling through AR contributed to demethylation of male-biased sDMRs and the higher methylation of female-biased sDMRs in wild type males. In ESR1KO male and female mice, sex-bias in methylation was lost, suggesting that ESR1 influenced the methylation levels of sDMRs in both, males and females. Next, we contrasted sex-phenotype dependent sDMRs with publicly available ChIP-seq data for AR and ESR1 binding in mouse liver (Li et al., 2012) and found that only 5.5% and 14.5% of sex-phenotype dependent sDMRs were located within 5kb of AR or ESR1 binding sites, respectively. These results show that signalling of testosterone and estrogen through their receptors contributes to sex-biased methylation in the mouse liver, however, the direct binding of the receptors to sDMRs is not the major mechanism.

24 - PEX1 Gene Augmentation Therapy Improves Retinal Functions and Peroxisome Metabolites in a Mouse Model for Zellweger Spectrum Disorder

Post-doc - Senior

Catherine Argyriou[1], Anna Polosa[2], Frederic Fournelle[3], Jenny Song[4], Erminia Di Pietro[5], Bradford Steele[6], Bruno Cecyre[7], Jean-Francois Bouchard[7], Joseph Hacia[6], Jean Bennett[4], Pierre Chaurand[3], Pierre Lachapelle[2], Nancy Braverman[1]

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Zellweger spectrum disorder (ZSD) is caused by mutations in any one of 13 *PEX* genes whose protein products are required for peroxisome assembly and function. Nearly all affected individuals develop a potentially blinding retinopathy. To test whether we could improve vision in these patients, we performed a proof-of-concept trial for *PEX1* retinal gene therapy using our mouse model homozygous for the murine equivalent of the common human PEX1-G843D mutation (G844D). This model exhibits diminished retinal function (electroretinogram, ERG), diminished visual acuity (optomotor reflex, OMR), and photoreceptor cell anomalies.

Adeno-associated virus 8 was used as a vector to deliver human *PEX1* (AAV8.HsPEX1). *In vitro* studies using *PEX1*-deficient mouse and human cell lines confirmed vector expression and recovery of peroxisome functions after *HsPEX1* delivery. The therapeutic vector was administered by subretinal injection to 2 mouse cohorts at 5 or 9 weeks of age; AAV8.GFP was used as a control in the contralateral eye. We found HsPEX1 protein expressed in the photoreceptor layer with no gross histologic side effects using immunohistochemistry. Screening at 8-20 weeks post injection showed improvements in ERG and visual acuity. At 6-7 months, the average ERG response in the *PEX1*-injected eyes was double that of GFP-injected eyes in both cohorts. *PEX1* gene augmentation also reduced the average C26:0 lysophosphatidylcholine in whole retinal lysates, which is elevated due to peroxisome dysfunction (measured by LC-MS/MS). Finally, a matrix-assisted laser desorption/ionization (MALDI)-imaging MS technique was developed to resolve the spatial distribution of peroxisome-mediated lipids along retinal sections. This provides a powerful new tool for studying the role of peroxisomes in retinal homeostasis and demonstrating metabolic recovery at distinct tissue regions following gene delivery, without contamination by non-transduced areas. Overall, our results support the clinical potential of retinal gene therapy to improve vision in patients with ZSD.

25 - MMACHC Methylation and Expression in Melanoma Cell Lines: A Potential Role in Methionine Dependence

Md student - Junior

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Background: The methionine dependence of tumour cell lines, the inability to grow in tissue culture media lacking methionine but supplemented with homocysteine, has been known for a long time. An understanding of the mechanism for this phenomenon in individual cancer cell lines remains incomplete. Recently, methionine dependence in the MeWo LC1 melanoma cell line was shown to be related to hypermethylation and reduced expression of MMACHC.Hypothesis: Hypermethylation of MMACHC leading to its reduced expression could explain the methionine dependence of various cancer cell lines and patient tumors.

Methods: The Cancer Cell Line Encyclopedia (https://portals.broadinstitute.org/ccle) (CCLE) was searched for MMACHC expression based on RNAseq data and MMACHC methylation based on CpG methylation.

Results: Out of 823 cancer cell lines in the CCLE with MMACHC methylation and RNA expression data, 52 (6.3%) were derived from melanomas. Seventeen of the melanoma lines (32.7%) had methylation values above the 97th percentile as compared to 8 of the non-melanoma lines (1.0%) (Odds Ratio 46.3; 95% CI 18.7-114.6). The odds of MMACHC expression being repressed, as measured by RNAseq, was higher in these 17 melanoma cell lines as compared to all other non-melanoma lines (Odds Ratio 15.5 ; 95% CI 4.5 to 53.1).

Conclusion: Seventeen melanoma cancer cell lines showed increased methylation patterns of MMACHC similar to those found in the MeWo LC1 cell line. These 17 melanoma lines showed an absence of MMACHC mRNA expression more frequently compared to all other cancer cell lines in the CCLE database. These findings predict that cells lines with hypermethylation and reduced expression of MMACHC would be methionine dependent. If true, disruptions in cobalamin metabolism might play a more general role in methionine dependence, and potentially in the pathogenesis of certain melanoma cell lines and tumours.

26 - Histone 3.3 K27M and K36M mutations perturbs antagonistic chromatin marks and disrupt development to promote tumorigenesis

Post-Doc- Senior

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Histone H3 Lysine-to-Methionine (K-to-M) substitutions on K27 and K36 occur in aggressive cancers and impair the deposition of major opposing chromatin methylation marks. We show that expression of H3.3K27M and H3.3K36M in *Drosophila* eye-primordia induces disorganized eyes and that H3.3K27M causes overgrowth and homeotic transformations. Notably, we observe increased H3K36me2 deposition in H3.3K27M-expressing eyes, and reciprocal increase of H3K27me2/3 in H3.3K36M-expressing eyes. We identify in K-to-M mutants locus-specific differences in the deposition of the repressive H3K27me3 and generally active H3K36me2. These lead to undue repression of genes involved in eye development, and aberrant expression of Piwi-interacting (piRNA) pathway and genes involved in body patterning such as *wg* and *Antp*. Reduction of H3K36me2 by *ash1* knock-down in H3.3K27M and of H3K27me2/me3 by *E(z)* knock-down in H3.3K36M restores eye growth and organization. We propose that, in addition to directly impairing methyltransferase activity, H3.3K27M and H3.3K36M promote oncogenic spread of antagonistic chromatin marks, enhancing transcriptomic deregulation and subsequent defective differentiation and tissue overgrowth.

27 - Histone H3.3 G34-mutant interneuron progenitors co-opt PDGFRA for gliomagenesis

PhD - Senior

Shriya Deshmukh*[1], Carol Chen*[2], Selin Jessa*[3], Djihad Hadjadj*[2], Veronique Lisi[2], Augusto Faria Andrade[2], Damien Faury[4], Steven Hebert[3], Nicolas De Jay[2], Michele Zeinieh[2], Mathieu Blanchette[5], Livia Garzia[6], Claudia Kleinman#[3], Nada Jabado#[7]

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Histone H3.3 glycine 34 to arginine/valine (G34R/V) mutations drive deadly high-grade gliomas in the temporo-parietal cortex of adolescents and young adults. This exquisite regional and temporal specificity implicates a developmental context permissive to gliomagenesis. Assembling the largest tumour cohort to date, we show that 50% of G34R/V tumours (n=95) bear activating *PDGFRA* mutations, with strong selection pressure at recurrence. While PDGFRA is a prototypical glial marker and G34R/V tumours are classified as gliomas, comparison of tumour transcriptomic signatures to reference single-cell forebrain atlases reveals that G34R/V tumours in fact arise in interneuron progenitors. G34R/V tumours express transcription factors (e.g. *GSX2*) that are normally restricted to interneuron progenitors, while repressing mature neuronal genes, likely through G34R/V-associated H3K27me3 deposition and differentiation blockade. Notably, *PDGFRA* and the interneuron-specifying factor *GSX2* are located immediately adjacent in the linear genome. By Hi-C chromosome conformation capture, we identify a chromatin loop connecting *PDGFRA* to active *GSX2* enhancer elements in G34R/V tumours, suggesting that the lineage-of-origin facilitates *PDGFRA* co-option to promote aberrant overexpression and mutation. Consistent with these findings, at the single-cell level, G34R/V tumours harbour dual neuronal/astroglial identity and lack oligodendroglial programs that are actively repressed by *GSX2*-mediated cell-fate specification. Expanded astroglial compartments in *PDGFRA*-mutant tumours suggest that mutant-PDGFRA potentiates gliomagenesis. In contrast, we show with CRISPR/Cas9-edited glioma cell lines that G34R/V mutations become dispensable for tumour maintenance. Collectively, our results suggest that G34R/V gliomas arise in *GSX2*-expressing interneuron progenitors, where G34R/V histone mutations impede differentiation to support a progenitor state that is permissive to *PDGFRA* co-option and gliomagenesis. These findings underscore the importance of lineage and cell-type context in neoplastic processes, and suggest *PDGFRA* signaling as a potentially targetable pathway in lethal G34R/V high-grade gliomas.

28 - FATHERS MATTER: Blending patient-oriented and knowledge translation approaches to enhance healthcare experiences among fathers of children with developmental disabilities

Post-Doc - Senior

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Background: In addition to experiencing challenges of being a parent of a child with a developmental disability (DD), fathers of these children report feeling excluded and marginalized by healthcare providers (HCPs). We aimed to explore the barriers and facilitators to positive and empowering healthcare service experiences from the perspectives of both fathers of children with DD and HCPs.

Methods: We used a mixed-method design incorporating quantitative and qualitative approaches. Recruited from two Canadian provinces, participants were fathers of children with DD and HCPs working in childhood disability. Participants completed a Likert Scale questionnaire, measuring engagements/satisfaction in interactions, and a semi-structured interview exploring experiences, barriers and facilitators. Data were analyzed using descriptive statistics and inductive thematic approach.

Results: Fathers (n=7, 42.6 ± 8.2 years old) have 1-3 children with DD (age: 9.4 ± 5.3 years; 4 males). HCPs (n=13, 37.8 ± 13.0 years old [3 males]) are mostly working full-time (76.9%) for 11.5 ± 9.7 years, as Occupational Therapists (n=6), Neuropsychologists (n=1), Nurse (n=1), Pediatrician (n=1), Speech Language Pathologist (n=2), and Social Worker (n=1). Fathers reported to be *moderately-very much* involved in organizing their child's health-care services. They *often-all the time* advocate for child's needs and are involved in their child's care. While fathers are *moderately-very much* satisfied with their HCPs' interactions, they report that HCPs are only *sometimes* attentive to them. Emergent factors influencing these interactions were found to be: HCPs' attitudes/beliefs/experiences; Established parental roles; Logistics & communication (e.g. fathers' work schedule, language barrier, education level, time in interaction) & Fathers' attitude/beliefs/experiences (e.g. level of engagement, ability to share emotions/concerns, acceptance vs. denial).

Conclusion: We identified several barriers and facilitators to optimal interactions from the perspectives of fathers and HCPs. We further plan to integrate this information in designing and implementing e-learning knowledge translation modules targeting both populations.

29 - An approach to measuring retinal blood vessel movement in retinal degenerative patients.

Undergraduate - Junior

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Background: Retinal degenerations are the leading cause of childhood blindness worldwide. Exploring the movement of retinal blood vessels in patients can deepen our understanding of the pathophysiology of uncurable retinopathies.

Methods: 64 fundus photographs of 9 patients (17 eyes) with retinal degenerations taken over a minimum of 3 consecutive visits were compared. Time between the first and last visits varied from 6 to 19 years. During each visit, a fundus photo from each of the 17 eyes was selected from our database (N=1698 patients) and digitized. The scanned photos were processed to extract 128 vessel arborisations (64 arterial, 64 venous trees) that were segmented and compared for movement.

Results: Based on the decreasing overlap percentages (<95%), all 9 patients show evidence that retinal blood vessels were displaced as the retinal disease progressed. This displacement increased when moving further away from the optic nerve head. To further quantify small displacements, angular displacements have been calculated for these 9 right eyes and 8 left eyes. In 16/17 eyes, the angular displacement of arteries compared to veins was not significantly different. One eye showed a significantly different arterial displacement when compared to the veins following this pattern: while all the arteries moved in the same direction, the veins moved in the opposite direction at a slower pace ($P<0.05$).

Conclusions: To date, no study has tried to examine the deterioration of retinal arteries and veins separately in correlation with the progression of a retinal degeneration. Although preliminary, the vessel displacements (<95% overlap) observed in all our 9 patients is worth exploring as it might be correlated with clinical symptoms. Angular displacements should be calculated in patients who have a longer follow-up with multiple visits, as this method is proved to be robust in our ability to quantify small displacements, reproducibly.

30 - The role of claudin variants in the formation of kidney stones

Msc - Junior

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Genetic risk factors contribute to the formation of calcium-based kidney stones. The majority of calcium is reabsorbed via paracellular transport through tight junctions along the human nephron epithelium where Claudin proteins are expressed. Claudins determine the selectivity and permeability of different nephron segments. Studies have shown that *CLDN* gene sequence variants are associated with kidney stones. I hypothesize that sequence variants in Claudin genes that regulate paracellular transport of calcium in the nephron will be associated with the formation of kidney stones. Ninety adult patients (45 females, 45 males) with recurrent calcium-based kidney stones were recruited from one urologist's kidney stone clinic.Patient DNA was analyzed by Fluidigm Next Generation Sequencing. Sixteen rare non-synonymous variants were identified, and 13 were confirmed by Sanger sequencing. Four novel heterozygous missense variants were identified in the following: *CLDN11* S157F, *CLDN16* K29E, *CLDN17*A94V, and *CLDN18* H212D. Nine rare variants include *CLDN*4 A82T, *CLDN*4 A113T, *CLDN7* V55I, *CLDN*8 A94V, *CLDN*8 M97T, *CLDN*12 M98V, *CLDN*23 A90T, and *CLDN*24 V97I. *In silico* prediction software was used to predict the impact of the amino acid change. *CLDN4* A82T, *CLDN8* A94V, *CLDN11* S157F, and *CLDN17* A94V are predicted to be deleterious. For functional study, human claudin variants were generated by site-directed mutagenesis and cloned into a mammalian-expression vector, pEGFP. HEK293 cells were transiently transfected with *CLDN4* A82T and the mutant protein was unable to localize to the tight junction, unlike the WT *CLDN4* protein which did co-localize with ZO-1 by immunofluorescence as expected (n=3 independent experiments). Functional analysis showed that *CLDN4* A82T has an impact on the localization of the protein to the tight junction. Other claudin variants are under evaluation.

31 - Use of Bisphosphonates in a Retrospective Case Series of Children and Adolescents with Complex Regional Pain Syndrome

Undergraduate - Junior

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Background: There is increasing evidence for the use of bisphosphonates to treat Complex Regional Pain Syndrome in adults. However, there is scarce data for their use in children with Complex Regional Pain Syndrome.

Aim: This retrospective case series aimed to analyze the effects of bisphosphonates in children and adolescents with Complex Regional Pain Syndrome enrolled in a multidimensional pain treatment program.

Methods: We analyzed the data of 16 patients (15 females and 1 male, mean age 14±3 years) who received infusions of zoledronic acid (0.015±0.0044mg/kg), pamidronate (0.72±0.17mg/kg) or both depending on their initial response. The primary endpoint of the study was the patient's global impression of change. Secondary outcomes included pain intensity, physical function, role function (school attendance), use of pain medications, and adverse effects.

Results: Nine of 16 patients reported global impressions of change of 84% to 100% at a median follow up time of 16 (8-21) months after their last infusion of bisphosphonates. There were significant reductions in pain intensity and in need for pain medications. There was a significant increase in the proportion of patients with minimal or without physical disability and almost all patients normalized their school activities. Thirteen patients (81%) reported adverse effects, mostly flu-like symptoms, for a few days after the infusion.

Conclusion: The use of Bisphosphonate infusions may represent an effective treatment for children with CRPS not responding to multidisciplinary pain treatment programs.

32 - Developmental follow-up practices for children with congenital heart defects: A national environmental scan

PhD - Senior

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Will be presented in the AM session

Introduction: Developmental surveillance, screening and evaluation are central to early identification of developmental impairments. However, data is lacking on current developmental follow-up practices for children and adolescents with congenital heart disease (CHD) across Canada. Therefore, the objective of this study was to describe current developmental follow-up practices and to explore structural barriers to optimal developmental follow-up of children with CHD requiring open-heart surgery.

Methods : This is an embedded mixed methods study of current practices in the developmental follow-up of children and adolescents with CHD requiring open-heart surgery in Canada. All centers that perform pediatric open-heart surgery in Canada were approached. A questionnaire and telephone survey including both qualitative and quantitative questions were used.

Results: We collected data from 6/8 Canadian centers. These hospitals performed 80 to 600 pediatric open-heart surgeries annually. Three main developmental follow-up structures emerged from our data: 1) developmental surveillance during routine cardiology appointments (n=2), 2) a structured developmental follow-up program including screening and evaluation for a subset of children who had open-heart surgery (n=3), 3) referral to a neonatal developmental surveillance program for a subset of children who had open-heart surgery (n=1). While one professional surveyed described their current practices as optimal, the majority would like to develop a structured program or expand an existing one. Healthcare professionals in Canadian institutions described the lack of human and/or financial resources as important barriers to offering optimal follow-up programs.

Discussion : While developmental follow-up practices vary from one centre to another, only a small subset of children who had open-heart surgery benefit from a close developmental surveillance program within tertiary care centers in Canada, as recommended in the guidelines by the American Heart Association. Therefore, current surveillance practices may fail to promptly identify children and adolescents who experience developmental challenges.

33 - Endocrine and Growth Abnormalities in 4H Leukodystrophy Caused by Variants in POLR3A, POLR3B, and POLR1C

PhD - Senior

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Context: 4H or POLR3-related leukodystrophy is an autosomal recessive disorder typically characterized by hypomyelination, hypodontia, and hypogonadotropic hypogonadism, caused by biallelic pathogenic variants in *POLR3A*, *POLR3B, POLR1C* and *POLR3K*. The endocrine and growth abnormalities associated with this disorder have not been thoroughly investigated to date.

Objective: To systematically characterize endocrine abnormalities of patients with 4H leukodystrophy.

Methods: An international cross-sectional study was performed on 150 patients with genetically confirmed 4H leukodystrophy and pathogenic variants in *POLR3A, POLR3B,* or *POLR1C*. Endocrine and growth abnormalities were evaluated, and neurological and other non-neurological features were reviewed. Variables used to evaluate endocrine and growth abnormalities included pubertal history, hormone levels (estradiol, testosterone, stimulated LH and FSH, stimulated GH, IGF-1, prolactin, ACTH, cortisol, TSH, and T4), height and head circumference charts. Potential genotype/phenotype associations were also investigated.

Results: The most common endocrine abnormalities were delayed puberty (57/74; 77% overall, 64% in males, 89% in females) and short stature (57/93; 61%), when evaluated according to physician assessment. Abnormal thyroid function was reported in 22% (13/59) of patients.

Conclusions: Our results confirm pubertal abnormalities and short stature are the most common endocrine features seen in 4H leukodystrophy. However, we noted that endocrine abnormalities are typically under-investigated in this patient population. A prospective study is required to formulate evidence-based recommendations for management of the endocrine manifestations of this disorder.

34 - Family Risk Communication Preferences in Pediatric Surgery: A Systematic Scoping Review

Md student - Junior

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Purpose: Effective patient-surgeon communication is vital in pediatric surgical consultations. With families increasingly involved during such consultations, the treatment decision becomes difficult when a multitude of management choices are presented - thus rendering shared decision-making essential. However, a knowledge gap in patient communication preferences around surgical treatment exists in the literature. This systematic scoping review aims to detail the patient-preferred methods of risk communication in order to optimize information exchange in pediatric surgery.

Methods: The search strategy was prepared by a senior medical librarian, with 7 electronic databases searched for patient risk communication preferences. Two authors reviewed all titles and abstracts; conflicts were resolved by the senior author. A full-text screen was carried out on all included papers. Studies were excluded if patients were over 18 years of age, lacked mention of a risk communication modality or lacked patient input. All included publications were reviewed for data extraction, analyzed, and assessed for risk of bias using established tools.

Results: A total of 6380 publications were retrieved from the literature search. After duplicate removal 6037 articles remained, and 70 were finally included. By surgical specialty, studies were predominantly from ENT (30.0%), general surgery (15.7%), and urology (11.4%). Patient-preferred risk communication methods were classified as visual, verbal, technology-based, written, decision aids or other. Technological (32.4%) and written tools (29.7%) were most commonly preferred by patients as their preferred risk communication method. As seen in Figure 1, written tools were most frequently seen in general surgery and urology, while in ENT, technology-based tools were most common.

Conclusion: Eliciting patients' preferences for risk communication methods is of utmost importance in the pediatric surgical field. Different risk communication mediums appear best suited for specific surgical domains. However, there remains a need for the development of standardized validated risk communication tools.

35 - Lysophosphatidic acid signaling in human sperm viability

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Msc - Junior

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The lysophosphatidic acid (LPA) signaling is important to maintain germ cell viability during spermatogenesis. However, the presence of an active LPA signaling pathway in mature spermatozoa is unknown. The PI3K/AKT pathway is involved in the maintenance of human sperm viability. Peroxiredoxin 6 is an antioxidant enzyme with peroxidase and calcium-independent phospholipase A2 (iPLA2) activities. The inhibition of iPLA2 activity impairs viability and phosphorylation of PI3K and AKT, and promotes oxidative stress in human spermatozoa. The exogenous addition LPA in the incubation medium, prevented these damages.

We hypothesize that the LPA signaling is active in spermatozoa and regulated by kinases. Our objectives are: 1) To determine the presence of LPA receptors (LPAR) in human spermatozoa and whether LPAR signaling activates the PI3K/AKT pathway; 2) To study the regulation of the PI3K/AKT pathway by kinases; and 3) To determine the LPA species involved in sperm viability.

Triton X-100-soluble and sperm plasma membrane preparations will be used to determine the presence and location of LPAR in human spermatozoa by immunoblotting and immunocytochemistry using anti-LPAR antibodies. Spermatozoa will be incubated for 4h at 37°C with or without Ki16425 (LPAR1-3 inhibitor), H89, chelerythrine, and U126 (PKA, PKC, and MEK inhibitors, respectively). Then, phosphatidylserine externalization and DNA oxidation, and sperm viability will be assessed by flow cytometry using Annexin V, 8OHdG, and calcein AM, respectively. We will identify LPA species by mass spectrometry in human sperm samples treated with or without MJ33, specific inhibitor of iPLA2 activity.

The inhibition of LPAR or kinases will lead to apoptotic-like changes and sperm cell death. The inhibition of PRDx6 iPLA2 activity will impair LPA species production. These studies will help to understand the molecular mechanisms involved in the maintenance of sperm viability, to understand causes of sperm dysfunction associated with male infertility.

36 - Reproductive decline across generations due to paternal MTHFR deficiency and linked to demethylation of young retrotransposons

Post-Doc - Senior

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Methylenetetrahydrofolate reductase (MTHFR) is a crucial enzyme in one-carbon metabolism with an important role in production of S-adenosyl methionine and methyl groups for cellular processes including DNA methylation. As mouse and human studies have shown that MTHFR deficiency can impact male fertility and sperm DNA methylation, there is the potential for the intergenerational passage of epimutations. Here, our aim was to determine whether the effect of MTHFR deficiency on the testis or sperm DNA methylation was similar or exacerbated from one generation to the next.

While F1 *Mthfr* -/- fathers had minor effects on testis weights and sperm counts with a small increase in abnormal tubules (20%) in the testis; F2 *Mthfr* -/- sons showed a further deterioration in reproductive parameters with more decrease in testis weights, sperm counts and increase in abnormal tubules. Genome-wide DNA methylation analysis revealed that F1 sperm DNA methylation was dramatically affected, with nearly 30,000 CpGs affected, most (99.2%) showing a loss of methylation. Compared to their fathers, >80% of F2 sperm DNA methylation defects overlapped with regions affected in F1 sperm suggesting that there are regions consistently susceptible to MTHFR deficiency. These regions were coincided with genomic loci that late methylated during prenatal germ cell development and highly enriched in young retrotransposons.

The worsening of reproductive parameters in MTHFR-deficient sons versus their fathers suggests that epigenetic defects can accumulate across generations and loss of methylation at retrotransposons could contribute to this effect, findings reminiscent of epigenetic inheritance.
(Supported by CIHR).

37 - Natural History Study of Intermediate-Severe Salla Disease

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Msc - Junior

Context: Sialic acid storage disease (SASD) is an autosomal recessive neurodegenerative disorder with a spectrum of severity characterized by accumulation of free sialic acid in lysosomes. Pathogenic variants in *SLC17A5* are associated with three different forms of SASD: Salla disease (SD), intermediate-severe Salla disease and infantile sialic acid storage disease (ISSD). Intermediate-severe Salla disease is the most recently characterized form and describes individuals with a phenotype severity between those with Salla disease and ISSD. Disease-onset occurs at an early age and clinical features include hypotonia, global developmental delay and ataxia.

Objectives: To report the first longitudinal characterization of intermediate-severe Salla disease progression in two sisters with the same pathogenic variants but differing phenotypes and to determine the splicing implications of the c.819+1G>A variant.

Methods: Retrospective medical records review was performed for both patients with biallelic mutations in *SLC17A5*: c.406A>G and c.819+1G>A. Functional studies on patients' blood samples are ongoing to determine the role of the c.819+1G>A variant in aberrant splicing.

Results: Hypotonia and developmental delay was noted in both patients with intermediate-severe SD, shortly after birth for patient A and at 6 months of age for patient B. Developmental plateau was reached in late childhood in both patients and developmental regression was noted in both patients during adolescence with increasing spasticity, dystonia and sialorrhea, with an earlier onset in patient A, compared to patient B. The effect of the splicing variant will be determined by cDNA sequencing.

Conclusions: The clinical course outlined here provides a framework for intermediate-severe Salla disease progression, which differs drastically from other forms of SASD. This is the first study to analyze the clinical course and progression of intermediate-severe Salla disease and to determine the effect of the c.819+1G>A splice site variant.

38 - Epilepsy in children with cerebral palsy: a data linkage study

Undergraduate - Junior

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Cerebral palsy (CP) and epilepsy are the most prevalent conditions among children hospitalized with neurologic impairment. The reported prevalence of epilepsy in children with CP is highly variable across populations, from 15-60%. Little is known about healthcare utilization patterns in children with co-existing epilepsy and CP, compared to children with CP or epilepsy alone. Using provincial data from the Canadian CP registry and administrative health datasets from Quebec we sought to determine the prevalence of epilepsy and trends in healthcare utilization for children with CP compared to the general population. Our sample consisted of 302 children from The Registre de Paralysie Cérébrale du Québec (REPACQ), 370 children with CP identified using ICD9 codes from the Régie de l'assurance maladie du Québec (RAMQ) and 6040 children from the general population, who were age and sex matched to the REPACQ cohort. The prevalence of epilepsy was determined using two different administrative case algorithms. The prevalence of epilepsy was 34.44-43.24% in children with CP compared to 0.75-1.39% in the general population. Among children with CP, children with epilepsy were more likely to have triplegic/quadriplegic CP subtype, function at GMFCS level IV/V, be born at term and have a diagnosis of neonatal hypoxic ischemic encephalopathy. Healthcare utilization including frequency of hospital admissions, emergency department (ED) visits, and length of hospitalization was highest in children with CP and epilepsy, compared to children with a single diagnosis of CP or epilepsy and the general population. Epilepsy accounted for a similar proportion of hospitalizations and ED visits at approximately 10% and 5% respectively for children with epilepsy and CP, and epilepsy alone. Children with co-existing epilepsy represent a unique subset of the population of children with CP who have increased medical complexity and increased usage of healthcare services.

39 - Neonatal Screening for Surgical Congenital Anomalies in Low- and Lower-middle Income Countries: A Systematic Review

Md student - Junior

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Background: A significant contributor to the burden of disease in children from low- and lower-middle-income countries stem from congenital anomalies amenable to surgery. Screening programs represent a crucial step towards better management of these surgical conditions but are not well described in the current literature. We aim to outline existing fetal and neonatal screening methods used for surgically correctable congenital anomalies in low and lower-middle-income countries.

Methods: A systematic review was completed using Medline (Ovid), Embase (Ovid), Cochrane (Wiley), Global Health (Ovid), Web of Science (Clarivate Analytics), Africa Wide Information (Ebsco) and Global Index Medicus (WHO). Inclusion criteria included articles discussing neonatal screening methods for surgically correctable congenital anomalies in low and lower-middle-income countries. Articles were screened by title and abstract by two independent contributors using Rayyan software. Conflicts were resolved through discussion and by a third contributor when no consensus was reached.

Results: In total, 3473 articles were identified, and 19 included in the full-text review. The majority of articles were prospective (57.9%) or cross-sectional studies (26.3%). A total of 153,265 patients from 13 low-income and lower-middle-income countries were involved. The most frequent surgical specialties discussed were cardiac surgery (63.2%), urology (52.6%) and general surgery (47.4%). Although most articles discussed a single screening method (73.7%), others combined two (21.1%) or three (5.3%). Clinical examination of the newborn, ultrasound and pulse oximetry were the most popular methods of screening, accounting for 36.8%, 31.6% and 21.6% of the articles, respectively.

Conclusion: Screening for surgically correctable congenital anomalies in neonates in low and lower-middle-income countries relies on cost-efficient, validated methods. These methods seem efficient in low-resource settings, and combined screening methods increase the certainty of eventual diagnosis and decrease delays to proper management.

40 - Development and validation of a multiplex method to quantify polar and nonpolar sphingolipids by LC-MS/MS

Msc - Junior

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Lysosomal storage disorders (LSDs) are a group of inherited metabolic disorders characterized by the accumulation of undegraded material within the lysosome because of the malfunctioning or absence of specific enzymes. One such disease caused by the accumulation of glycosaminoglycans (GAGs) is mucopolysaccharidosis IVA (MPS IVA), a multisystemic progressive disorder with the primary impact being on the skeletal system along with several other clinical manifestations. Mutation in the gene encoding the enzyme N- acetylgalactosamine- 6-sulfate sulfatase (GALNS) results in the accumulation of GAGs, mainly, keratan sulfate (KS), and chondroitin sulfate (CS). Accumulation of GAGs has been associated with multifold damage with an increase of inflammation and initiation of sphingolipid metabolism. Sphingolipids are a diverse group of bioactive lipids. They are involved in several cellular activities like signal transduction, inflammatory responses, apoptosis, and cell proliferation. Polar sphingolipids, such as sphingomyelin, induce inflammatory cytokine expression in cells. Currently, the only biomarkers used in the clinic to diagnose and follow therapies of MPS disorders are the GAGs. However, the methods used to quantify GAGs are not robust and have resulted in many false-positive and false-negative results. Our study focuses on identifying sphingolipids that can act as biomarker(s) for early diagnosis and follow up of MPS diseases. This is achieved by developing an effective and sensitive method(s) to identify and quantify these biomarkers using LC-MS/MS. In this study, we developed a new multiplex LC-MS/MS (MRM) method to separate and quantify various polar and nonpolar species of sphingolipids such as sphingomyelin, sphingoid bases, and ceramides. MRM MS/MS methods were developed to measure sphingolipids using purchased standards. New extraction methods were explored to extract polar and nonpolar sphingolipids from serum samples. Work is in progress to identify new biomarkers in the serum of MPS IV patients.

41 - Targeting extracellular vesicle-mediated intercellular (angiocrine) communication in the vascular stem cell niche of Glioblastoma Multiforme

Post-Doc - Senior

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Glioblastoma multiforme (GBM) represents the most frequent and lethal form of primary brain malignancy which is subdivided into mesenchymal (MES), classical, and proneural (PN) subtypes. GBM cell populations exhibit a hierarchical structure composed of tumour initiating glioma (stem) cells (GSCs) and their progeny. While GSCs resemble neural stem cells, they also exhibit significant heterogeneity such as MES-like and PN-like GBM GSC subtypes.

Extracellular vesicles (EVs) are spherical membrane structures that cells release to communicate with one another. These packets of molecular cargo can be taken up by various 'recipient' cells resulting in reprogramming of the cellular content and function. EV release, cargo and uptake of EVs in cancer are regulated by *oncogenic* drivers and *epigenetic*cellular differentiation states. Thus, webs of different EV 'donor' and 'recipient' cells may communicate over distances in the brain leading to an integration of cellular responses and disease progression.

Vasculature represents a support system, infiltration 'highway' and, possibly, a unique point of vulnerability for GSCs. GSCs are highly angiogenic, produce endothelial growth factors (e.g. VEGF), and stimulate new blood vessel recruitment and growth, and also *respond* to vascular cues. GSC tend to home proximally to tumour capillaries, migrate toward (angiotropism) and surround blood vessels (vascular cooption), and infiltrate the neuropile along vascular channels. Moreover, GSCs can also activate differentiation programs resulting in adoption of either endothelial- or pericyte-like phenotypes and contribution to the vessel wall (vasculogenic mimicry).

We reasoned that in GBM EVs mediate reciprocal tumour-endothelial interactions. We wished to examine whether endothelial EVs may exert paracrine (angiocrine) influence on GSCs and their progeny in a manner that influences the stem cell hierarchy and disease aggressiveness, and that these angiocrine responses are specific to the molecular subtype *of GBM GSCs (MES vs PN).*

Here we show that the effects of placing conditioned media from primary and immortalized endothelial cells (ECM) over the PN and MES cell types display an obvious phenotypic change. Specifically, the sphere-forming ability of PN GSCs and cluster-forming abilities of MES GSCs was reduced after coming in contact with ECM. The phenotype was reproduced when GSCs came in contact with EVs of primary endothelial cells (EEVs). Interestingly, at a molecular level, EEV exposure to PN cells caused GSCs to express reduced levels of NOTCH1, NES and SOX2 (hallmarks of PN GSCs), and gained MES GSC hallmarks such as CD44 and VIM. This proneural to mesenchymal-like switch was also observed in vivo, when GSC157 cells were xenografted into mice. Finally, the EEV proteomics revealed EMT pathway in the top ten pathways enriched in the protein clusters.

Taken together, our study offers new understanding of the EV mode of angiocrine effects on tumour stem cell hierarchy, which may have both diagnostic and therapeutic significance in GBM.

42 - Neural Crest Specific Deletion of Mouse Sf3b4 Leads to Abnormal Craniofacial Phenotype

PhD - Senior

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Nager and Rodriguez syndromes are two rare disorders that have been attributed to the haploinsufficiency of SF3B4, a core component of the U2 complex of the splicing machinery. Patients of both syndromes have craniofacial as well as limb abnormalities with variable expressivity including small jaw bones, small cheek bones, downward slanted eye lids, radial-ulnar defects, and thumb abnormalities. Using in situ hybridization, we showed that in mouse embryos, Sf3b4 was expressed ubiquitously from embryonic day (E)9.5 – E11.5. From E11.5 – E12.5, enriched expression of this gene was found in the maxillomandibular region, limb, and tail bud. To study the craniofacial abnormalities caused by haploinsufficiency of Sf3b4, we generated a conditional mutant mouse line using CRISPR/Cas9 and mated it to Wnt1-Cre2 transgenic mice to delete Sf3b4 specifically in cranial neural crest cells. Although heterozygous mutant embryos from these matings were normal, homozygous mutants have hypoplasia of the midbrain and abnormalities in the frontonasal prominence with variable severity. Thus, it appears that Wnt1-Cre2:Sf3b4-/- mutants mimic craniofacial phenotypes observed in Nager/Rodriguez syndrome patients. In the future, we will use this mutant mouse line to uncover the etiology of these two syndromes.

43 - Chronic pulmonary hypertension in the extreme premature newborn – an era with screening and without PDA treatment

Fellow - Senior

Gabriela de Carvalho Nunes[1, 2], Punnanee Wutthigate[1, 2], Jessica Simoneau[1, 2], Claudia Renaud[1, 2], Adrian Dancea[1, 2], Marc Beltempo[1, 2], Gabriel Altit[1, 2]

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Extremely premature infants are at risk for pulmonary hypertension (PH). Since 2015, guidelines recommend PH screening at 36 weeks postmenstrual age (PMA). Patency of the ductus arteriosus (PDA) may worsen PH, but interventions to accelerate its closure were abandoned in 2015. Our objectives were to assess: PH prevalence, echocardiographic parameters, and associated outcomes.

Methods: Retrospective cohort of infants <29 weeks admitted from 2015 to 2019 at our center. Data from charts and echocardiography images done closest to 36 weeks PMA were extracted. PH was defined as; estimated systolic pulmonary pressure 40mmHg or abnormal septal curvature by eccentricity index (>1.3).

Results: 222 infants were included, 78 (35%) with PH. Those with PH had lower birth weight (781±230 vs 850±221 grams, p=0.03), with no difference in gestational age. PH was associated with late onset bacteremia (51% vs 49%, p=0.03), moderate/severe bronchopulmonary dysplasia (51% vs 49%, p=0.03) and death (8% vs 1%, p=0.02). PH infants required longer mechanical ventilation (median 25.5 [IQR 5-35.5] vs 16 [IQR 2-32.5] days, p=0.03) and hospitalization (127 ± 61 vs 107 ± 36 days, p=0.005), and had more PDA at 36 weeks (47%, vs 16%, p=0.01). Those with PH had increased systolic to diastolic tricuspid regurgitation ratio (1.52 ± 0.59 vs 1.35 ± 0.47, p=0.03) and right ventricle (RV) end diastolic area (3.32 ± 0.93 vs 3.05 ± 0.73, p=0.02). Other markers of RV function were similar.

Conclusion: A third of our population was affected by PH at 36 weeks, requiring more medical resources. The mortality rate was less compared to previous cohorts described, possibly secondary to screening detecting milder cases and the non-PDA interventional approach allowing for unloading the RV.

44 - **Cancelled**

45 - Characterization of somatic mutations in mTOR pathway genes in focal cortical dysplasias

PhD- Senior

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Background: Focal cortical dysplasias (FCDs) are congenital structural abnormalities of the brain, and represent the most common cause of medication-resistant focal epilepsy in children and adults. When possible, surgical resection of affected tissue is performed as treatment. Recent studies have shown that somatic mutations (i.e. mutations arising in the embryo) in genes of the mTOR pathway, an intracellular signalling pathway important for cell cycle regulation and migration, underlie some FCD cases. Specific therapies targeting the mTOR pathway are presently available, allowing for potential personalized treatment. However, testing for somatic mTOR pathway mutations in FCD tissue is not performed on a clinical basis, and the contribution of such mutations to the pathogenesis of FCD remains unknown.

Aim: To investigate the feasibility of screening for somatic mutations in FCD tissue and determine the proportion and spatial distribution of FCDs which are due to low-level somatic mTOR pathway mutations.

Methods: We performed ultra-deep sequencing of 13 mTOR pathway genes using a custom HaloPlexHS target enrichment kit in 24 resected histologically-confirmed FCD specimens.

Results: To date, we identified causal variants in 58.3% (14/24) of patients at an alternate allele frequency of 0.62–33.7%. Distribution of the mutation loads correlated with the FCD lesion's size and histopathological severity.

Conclusions: Screening resected FCD tissue using a custom panel results in a high yield, and should be considered clinically given the important potential implications regarding surgical resection, medical management and genetic counselling.

46 - Investigating the effects of histone H3.3 point mutations in neural crest cells and craniofacial development

Msc - Junior

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Patients with mutations in histone remodellers that alter methylation patterns in both cell and animal models present with craniofacial abnormalities, suggesting that altered methylation of histone N-terminal tails may affect neural crest cell (NCC) development. Incorporation of H3.3 into nucleosomes is necessary for expression of genes essential for cranial NCC specification, whereas the role of modification of the H3.3 tail in NCC development remains to be determined. We postulate that

To test this hypothesis, we used CRISPR/*Cas9* to generate a mutant mouse line that expresses a missense mutation previously shown to alter the methylation of H3K27 and H3K36. In this poster, we present preliminary data using the *Wnt-1 Cre2* mouse line to drive expression of this mutation in NCCs. Alcian Blue and Alizarin Red staining will be used to analyze cartilage and bones in heads of E14.5 and E17.5 embryos, respectively. Our result will enable us to begin to address the role if any of H3K27 or H3K36 methylation in NCC development.

47 - Partial loss of function mutations in C2CD3 as a potential novel cause of an isolated renal ciliopathy

Msc - Junior

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Nephronophthisis (NPHP) is an autosomal recessive renal ciliopathy and is the most common genetic cause of end-stage renal disease in the first three decades of life. Ciliopathies are caused by defects and perturbations involving the primary cilium, which is an antenna-like organelle with established mechanosensory roles that are crucial for embryonic patterning, organ development and maintenance. Disorders of the cilium commonly present with multi-organ involvement, leading to a wide range of phenotypic effects, including neurological, retinal, facial, skeletal, digital, and renal defects; however, some individuals with mutations in ciliopathy genes present with an isolated organ-specific phenotype (e.g., brain, renal, retinal). Based on clinical observations, it has been suggested that this phenotypic difference could be explained by the severity of the underlying mutation, with complete loss-of-function mutations manifesting with an early-onset multi-organ phenotype and partial loss-of-function mutations resulting in a milder single-organ phenotype. Using whole exome sequencing, we identified compound heterozygous partial loss-of-function mutations in the ciliopathy gene, *C2CD3* (OMIM# 615944), from a proband presenting with isolated NPHP without extra-renal manifestations. Notably, complete loss-of-function mutations in *C2CD3* have previously been reported in patients with a severe systemic phenotype (Orofaciodigital syndrome IV, OMIM# 615948); however, no known cases of isolated renal disease have yet been described. Using patient-derived fibroblasts, we demonstrate a ciliogenesis defect in the proband, with significantly shortened cilia and abnormal cilia length distribution when compared to age-matched healthy controls. Interestingly, there was no difference in the percentage of ciliated cells. Based on these observations, we propose partial loss-of-function mutations in *C2CD3* as a potential novel cause of NPHP. Future work will further characterize the effects of these mutations on ciliary-specific pathways to fully elucidate the role of *C2CD3* in ciliogenesis.

48 - Telemedicine in a chronic pediatric pain service: A retrospective cohort study

Employee

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Background: Chronic pain is common in childhood and is associated with school absenteeism, emotional distress, depression, and family problems. Telemedicine, especially during COVID, has been seen as one means of providing care directly to the patient.

Aim: Evaluate the effectiveness of a telemedicine clinic in Pediatric Chronic Pain.

Design: Participants in the retrospective cohort study were selected starting in March 2020 to May 2020. Inclusion criteria included children and adolescents less than 18 years , with chronic pain and who could fill out survey. Initial contact was held via email.

Results: 146 patients were selected to receive a survey, Patients perceived that physicians cared about their problems (average (AVG) 4.75, standard dev (SD) 0.67), were comfortable discussing problems (AVG 4.47, SD 1.05), that physicians wanted to know about the condition (AVG 4.65, SD 0.70), good understanding of the condition with telemedicine (AVG 4.54, SD 0.81). Patients not feeling more connected to their care because of telemedicine (AVG 2.38, SD 1.28), believed their pain was not better managed (AVG 2.27, SD 1.01).

If the telemedicine was convenient (p=0.0012), patients reported a statistical difference in perceiving that their pain was better managed (p=0.000012), they felt more connected to their physician through telemedicine (p=0.000074), it provided the same quality of care as in-person (p=0.000063).

Conclusion: Telemedicine in Pediatric CPS as a convenient option, however, most do not believe pain is better managed because of it. Further work needed for optimization of telemedicine for CPS patients.

49 - Investigating the role of Snap29 in motor function in P1 pups.

Employee

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Synaptosomal-associated protein 29 (*SNAP29*) encodes a member of the SNARE family of proteins which is implicated in numerous intracellular protein trafficking pathways. *SNAP29* is deleted in 90% of patients with 22q11.2 deletion syndrome (22q11.2DS). In addition, homozygous mutations in *SNAP29* in patients with intact chromosome 22q11.2 are responsible for the developmental syndrome called CEDNIK (cerebral dysgenesis, neuropathy, ichthyosis, and keratoderma) and have recently been linked with a type of leukodystrophy; Pelizaeus-Merzbacher-like disease (PMLD). We generated a mouse model that recapitulates many abnormalities found in these syndromes including impaired motor skills in adult *Snap29* mutant mice. To identify the earliest time point at which impaired motor skills can be detected, we subjected P1 pups to motor assays and found that *Snap29* mutant pups have a greater difficulty to return to the supine position when placed on their backs. We next sought to identify which tissues are affected in these mutant mice. More specifically, we focused on whether the corpus callosum was properly formed since agenesis of the corpus callosum has been reported in CEDNIK patients. We also investigated if the number of motor neurons in the spinal cord are properly specified at this stage. We also investigated if these neurons are properly myelinated given the link to PMLD. Finally, we investigated if the neuromuscular junction (NMJ) was properly established in *Snap29* mutant P1 pups. Although, these investigations are still ongoing, we found that the corpus callosum and the number of motor neurons are properly specified in the *Snap29* P1 pups. Interestingly, the NMJs seem abnormal in these mutant pups, although more work will be required to identify which step of NMJ formation is impacted. Importantly, our work will contribute to our understanding of how SNAP29 impact motor function as well as its role outside of the brain.