PLATFORM PRESENTATIONS

Grand Plenary Abstracts

GR.1

Different functional consequences result in different phenotypes in CLCN4-related developmental and epileptic encephalopathy

AN Sahly (Montreal) RE Guzman (Jülich) J Sierra-Marquez (Jülich) S Bungert-Plümke (Jülich) A Franzen (Jülich) L Mougharbel (Montreal) S Berrahmoune (Montreal) C Dassi (Montreal) M Srour (Montreal) KA Myers (Montreal)*

doi: 10.1017/cjn.2023.70

Background: Variants in *CLCN4* are implicated in neurodevelopmental disorder, X-linked intellectual disability, and epileptic encephalopathy. *CLCN4* encodes ClC-4, which is hypothesized to play a role in ion homeostasis and intracellular trafficking. ClC-4 relies on its formation of heterodimers with ClC-3, which possesses signals for target organelles. Methods: Case-Series. Then, we performed heterologous expression, patch-clamp electrophysiology, confocal microscopy, and protein biochemistry experiments to characterize our patients' ClC-4 variants. Results: All three male patients had developmental and epileptic encephalopathy. Patients #1 and #2 had normal-appearing brains on MRI and no dysmorphic features. Patient #3 had: microcephaly, microsomia, complete agenesis of the corpus-callosum; and, cerebellar and brainstem hypoplasia. Patient #1 had recurrent status epilepticus separated by months of seizure freedom, while Patient #2 and #3 had brief, daily seizures. The p.Gly342Arg variant impaired the heterodimerization capability of ClC-4. The p.Ile549Leu and p.Asp89Asn variants exhibited early transport-activation, with p.Asp89Asn favouring higher transport-activity of ClC-4. Conclusions: We extend the phenotypic spectrum of *CLCN4* variants and demonstrate the pathological functional-consequences of three previously unclassified variants. The p.Gly342Arg variant lead to a loss-of-function phenotype; however, the p.Ile549Leu and p.Asp89Asn variants likely caused gain-of-function phenotypes. Targeted animal or induced pluripotent stem-cell models are needed to further understand epileptogenic mechanisms of *CLCN4* variants.

GR.2

A deep intronic FGF14 GAA repeat expansion causes late-onset cerebellar ataxia

D Pellerin (London) MC Danzi (Miami) C Wilke (Tübingen) M Renaud (Nancy) S Fazal (Miami) M Dicaire (Montreal) CK Scriba (Perth) C Ashton (Montreal) C Yanick (Miami) D Beijer (Miami) A Rebelo (Miami) C Rocca (London) Z Jaunmuktane (London) JA Sonnen (Montreal) R Larivière (Montreal) D Genis (Girona) L Porcel (Barcelona) K Choquet (Boston) R Sakalla (Montreal) S Provost (Montreal) M Tétreault (Montreal) SJ Reiling (Montreal) S Nagy (London) V Nishadham (Bengaluru) M Purushottam (Bengaluru) S Vengalil (Bengaluru) M Bardhan (Bengaluru) A Nalini (Bengaluru) Z Chen (London) J Mathieu (Sherbrooke) R Massie (Montreal) CH Chalk (Montreal) A Lafontaine (Montreal) F Evoy (Sherbrooke) M Rioux (Sherbrooke) J Ragoussis (Montreal) KM Boycott (Ottawa) M Dubé (Montreal) A Duquette (Montreal) H Houlden (London) G Ravenscroft (Perth) NG Laing (Perth) P Lamont (Perth) MA Saporta (Miami) R Schüle (Tübingen) L Schöls (Tübingen) R La Piana (Montreal) M Synofzik (Tübingen) S Zuchner (Miami) B Brais (Montreal)*

doi: 10.1017/cjn.2023.71

Background: The late-onset cerebellar ataxias (LOCAs) have until recently resisted molecular diagnosis. Contributing to this diagnostic gap is that non-coding structural variations, such as repeat expansions, are not fully accessible to standard short-read sequencing analysis. Methods: We combined bioinformatics analysis of whole-genome sequencing and long-read sequencing to search for repeat expansions in patients with LOCA. We enrolled 66 French-Canadian, 228 German, 20 Australian and 31 Indian patients. Pathogenic mechanisms were studied in post-mortem cerebellum and induced pluripotent stem cell (iPSC)-derived motor neurons from 2 patients. Results: We identified 128 patients who carried an autosomal dominant GAA repeat expansion in the first intron of the *FGF14* gene. The expansion was present in 61%, 18%, 15% and 10% of patients in the French-Canadian, German, Australian and Indian cohorts, respectively. The pathogenic threshold was determined to be $(GAA)_{\geq 250}$, although incomplete penetrance was observed in the $(GAA)_{250\text{-}300}$ range. Patients developed a slowly progressive cerebellar syndrome at an average age of 59 years. Patient-derived post-mortem cerebellum and induced motor neurons both showed reduction in *FGF14* RNA and protein expression compared to controls. Conclusions: This intronic, dominantly inherited GAA repeat expansion in *FGF14* represents one of the most common genetic causes of LOCA uncovered to date.

GR.3

Socioeconomical disparities in acute ischemic stroke revascularization interventions in Ontario, Canada

F Taghdiri (Toronto) MV Vyas (Toronto) MK Kapral (Toronto) L Lapointe-Shaw (Toronto) P Tse (Toronto) J Porter (Toronto) Y Chen (Toronto) J Fang (Toronto) AY Yu (Toronto)*

doi: 10.1017/cjn.2023.72

Background: Lower socioeconomic status is associated with worse outcomes after stroke. We evaluated the differences in acute revascularization treatments in patients with acute ischemic stroke (AIS) who were materially deprived compared to those who were not. Methods: In a population-based cohort study, we used linked administrative data to identify community-dwelling adults hospitalized for AIS between 2017-2022 in Ontario, Canada. The main exposure was neighborhood-level material deprivation quintiles. Multivariable logistic regression was used to obtain the adjusted odds ratio (aOR) of receiving revascularization treatments

(thrombolysis or thrombectomy) for patients in each deprivation quintile compared to the least deprived quintile. Results: We identified 57,709 patients (median age 74 years; 45.9% female). Compared to patients in the least deprived quintile, those with higher deprivation were younger and more likely to have hypertension and diabetes, but less likely to have atrial fibrillation. Compared to patients in the least deprived quintile, fewer patients in the very deprived quintile (17.9% vs 19.6%, aOR 0.88, 95%CI [0.82,0.95]) and in the most deprived quintile (16.6% vs 19.6%, 0.77 [0.71,0.83]) received revascularization treatments. Conclusions: Our results suggest disparities in the use of acute ischemic stroke revascularization treatments by socioeconomic status despite access to universal health care.

GR.4

Neurophysiological and clinical effects of low-intensity transcranial ultrasound of the motor cortex in Parkinson's disease

T Cortez Grippe (Toronto) Y Oghli (Toronto) G Darmani (Toronto) T Arora (Toronto) C Sarica (Toronto) J Nankoo (Toronto) R Chen (Toronto)*

doi: 10.1017/cjn.2023.73

Background: Low-intensity transcranial ultrasound (TUS) is a non-invasive neuromodulation technique, which in theta burst mode (tbTUS) can increase cortical excitability. Parkinson's disease (PD) has altered cortical excitability of motor cortex (M1). We evaluated the neurophysiological and clinical effects of M1 tbTUS in PD patients. Methods: Sixteen PD patients (4F, 59.5±9.7 years) in ON and OFF dopaminergic medication states, and 15 controls (5F, 61.9 ±8.7 years) were evaluated. tbTUS was applied for 80 seconds at M1 with 20W/cm^2. Motor evoked potential (MEP) was recorded at baseline, at 5-minutes (T5), T30, and T60 after tbTUS. Motor (m) UPDRS was evaluated in PD at baseline and T60. Results: A linear mixed model on MEP amplitudes comparing PD-ON, PD-OFF and controls showed significant effect of time (F=4.83, p=0.003). Post-hoc analysis showed significant difference between baseline and T30 timepoints (p=0.0003). The MEP increase at T30 was higher in controls (66%), followed by PD-ON (41%) and PD-OFF (21%). PD-ON showed reduced mUPDRS at T60 when compared to PD-OFF, with significant effect of time (F=6.14, p=0.017) and group (F=5.39, p=0.025). Conclusions: tbTUS induced motor cortical plasticity is reduced in PD-OFF, that is partially restored by dopaminergic medications.Repeated sessions of tbTUS can be further investigated as a novel non-invasive treatment for PD.

GR.5

Incidence of orbital infarction syndrome following endovascular thrombectomy

M MacMillan-Wang (Winnipeg) J Shankar (Winnipeg) S Alcock (Winnipeg) A Trivedi (Winnipeg) D Jain (Winnipeg)*

doi: 10.1017/cjn.2023.74

Background: Orbital infarction syndrome (OIS) is a rare entity defined as acute ischemia of intraorbital structures. Three case reports of OIS post-endovascular thrombectomy (EVT) have recently been published, two demonstrating absent choroid blush (CB) on digital subtraction angiogram (DSA). Our goals are to determine the true incidence of OIS post-EVT and to identify imaging findings (e.g. CB) that may alert neurologists to potential cases. Methods: A retrospective cohort study including all EVT patients from Health Sciences Center (HSC), Winnipeg in 2019-20 was performed. Patient charts were reviewed to determine the incidence of OIS. Pre- and post-EVT DSA images were reviewed, and the sensitivity and specificity of absent CB for OIS was calculated. Results: Out of 248 patients, 13 were excluded for incomplete charts, and 4 cases (1.7%) of OIS were discovered. During sensitivity/specificity analysis of absent CB for OIS, 51 patients were excluded for inadequate imaging. There were 4 true positives, 0 false-negatives, 113 true-negatives, and 67 false-positives; resulting in a sensitivity of 100% and worst-case scenario specificity of 63% (assuming all 51 indeterminate cases were false positives). Conclusions: OIS is rare post-EVT with an incidence of 1.7%. Absent CB is very sensitive for diagnosing OIS with lower specificity.

GR.6

Harnessing the endogenous regenerative potential of the injured spinal cord

LD Hachem (Toronto) J Hong (Toronto) A Velumian (Toronto) AJ Mothe (Toronto) CH Tator (Toronto) MG Fehlings (Toronto)*

doi: 10.1017/cjn.2023.75

Background: The adult spinal cord contains a population of ependymal-derived neural stem/progenitor cells (epNSPCs) with the potential to enhance endogenous regeneration. However, little is known about the mechanisms that regulate the activation of these cells after injury. Recently, we discovered that glutamate excitotoxicity, a hallmark in the pathophysiology of acute SCI, promotes epNSPC proliferation/survival. Here, we characterize the downstream signaling pathways involved in this response and target this mechanism *in vivo* to enhance the endogenous regenerative capacity of these cells. Methods: epNSPCs were isolated from the central canal region of the adult spinal cord. *In vitro* pathway analysis was conducted using immunohistochemistry, RNAseq and Western Blot. *In vivo*, rats underwent SCI and at 1-week post-injury were randomized to receive CX546 (positive AMPAR modulator), or vehicle-control. Animals underwent behavioural testing and spinal cords were extracted for analysis. Results: Glutamate excitotoxicity leads to calcium influx in epNSPCs via AMPARs and together with Notch signaling drives proliferation and astrocytic differentiation. Positive modulation of AMPARs subacutely after SCI enhances epNSPC proliferation, astrogliogenesis, neurotrophin production, neuronal survival and functional recovery. Conclusions: We uncover an important mechanism by which AMPARs regulate the growth/phenotype of epNSPCs which can be targeted therapeutically to harness the regenerative potential of the injured spinal cord.