mutations of *PLA2G6*, in addition, suggests that the fetal NAD is a new entity, distinct from INAD, with different molecular basis. Associated malformations suggest a wide phenotypic spectrum and probable genetic heterogeneity. Finally, fetal NAD is an additional etiology of fetal akinesia.

Abstract A8

Motor neuron disease presenting with fetal akinesia

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By contrast to infantile spinal muscular atrophy, which usually links to deletions in the SMN genes, fetal onset motor neuron disease is poorly reported. We collected a series of twelve cases of fetal arthrogryposis (16-31 weeks gestational age) with fetal motor neuron disease and excluded infectious diseases, lysosomal storage disease and neuroaxonal dystrophy. Of these twelve, 3 were thought to be ischemic in nature with microvascular alterations and systemic or central nervous system ischemic injury. The remaining 9 all displayed marked reduction in anterior horn motor neurons. Of these 9, four demonstrated mineralised neurons, four demonstrated either neuronal loss or cavitation in the globus pallidus, and in two, degenerating neurons were detectable in the brainstem or globus pallidus. Specific sequencing of SMN1 was performed in 6 of 9 and was reported as normal. Whole exome sequencing was performed in 4 without definitive diagnosis. We conclude that fetal motor neuron disease can be distinguished from ischemic injury, is morphologically heterogeneous, may affect the globus pallidus and is rarely linked to SMN1 mutations.

Abstract A9

The central nervous system lesion in amniotic rupture sequence

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We review the central nervous system anatomy in nine cases of amniotic rupture sequence, all of which had neuropathological examinations. Of these, four had normal brains, and in none of these was the cranial vault involved, and one had cleft lip and palate. Of the remaining five, all had portions of the scalp, calvarium and dura replaced by amnionic membrane directly overlying arachnoid. In one, the membrane covered a narrow necked large encephalocele, and the contained brain demonstrated extensive disruption and degeneration. In the remaining four, one demonstrated cranioplacental adhesion, and in three there was a broad based encephalocele covered in large part by amnion. Two of these four cases demonstrated holoprosencephaly. One case with holoprosencephaly and one without demonstrated marked aqueductal stenosis, and two of the four demonstrated aqueductal occlusion or near occlusion by neuroglial excrescences. None demonstrated ventriculomegaly. Three of these four cases demonstrate varying degrees of mechanical distortion and secondary pathology. We conclude that brains with amnionic rupture sequence demonstrate both malformation and deformation, which likely points to the embryonic stage origin of the lesion.

Abstract A10

Chronic traumatic encephalopathy in contact sports: The Canadian experience

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Chronic traumatic encephalopathy (CTE) is suggested to be a progressive neurodegenerative disease, characterized by tau deposits in the depth of cortical sulci in neurons and in glioneuronal complexes around blood vessels. Few studies have suggested that it is caused by multiple concussions or subconcussive brain injuries. A recent publication showed that most American football players whose brain were donated to the Boston University concussion center had CTE (Mez et al. 2017). Over the last 6 years, with the help of neuropathologist colleagues across Canada, we have collected the brains of 33 high level professional and amateur athletes. These include 5 National hockey league (NHL) players, 15 Canadian football league (CFL) players, 3 College football players, 3 College hockey players, 2 professional boxers, 1 professional bull rider, 1 BMX champion, 1 rugby player and 2 skiers. All were male and the ages ranging from 15 to 87 years. Our results indicate that only a small portion of cases have CTE. Moreover, most cases are low stage (stage 1 or 2) and this pathology is mainly seen in some of the younger players. Older players either have no pathological findings or have other neurodegenerative diseases such as Alzheimer's disease. The disparity of results between the 2 groups will be discussed.

Abstract A11

Executive dysfunction and altered cerebrovascular activity in a rodent model of vascular cognitive impairment

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Most basic science research has focused on overt stroke caused by blockage of major blood vessels. Less attention has been paid to small vessel disease giving rise to covert stroke that often leads to vascular cognitive impairment (VCI). One reason for this may be the relative lack of relevant animal models. This talk will describe a model of VCI induced in middle-aged Sprague-Dawley rats exposed to a diet high in saturated fats, salt and refined sugar (HFSS). In Experiment 1, rats fed HFSS and subjected to a small mediodorsal (MD) thalamic stroke with or without concomitant cerebral hypoperfusion experienced significant executive dysfunction. In Experiment 2, dietary

influences on functional, physiological and anatomical parameters were assessed. We found significant hypertension, blockage of brain microvessels (2-photon microscopy) and white matter atrophy in HFSS diet animals. As in Experiment 1, profound, specific set-shifting executive dysfunction was noted following both small MD infarcts (0.332 mm^3) and the HFSS diet. In summary, these data describe a middle-aged animal model of VCI that includes clinically-relevant metabolic disturbances and small vessel disease and as such may be helpful in developing new cognitive therapies.

Abstract A12

Clinical and neuropathological features of ALS/FTD with *TIA1* mutations

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Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) represent a disease continuum with common genetic causes and molecular pathology. We recently identified mutations in the T-cell restricted intracellular antigen-1 (TIA1) protein as a cause of ALS +/− FTD. TIA1 is an RNA-binding protein containing a low complexity domain (LCD) that promotes the assembly of membrane-less organelles, such as stress granules (SG). Whole exome sequencing of two family members with fALS/FTD revealed a novel missense mutation in the *TIA1* LCD (P362L). Subsequent screening identified five more *TIA1* mutations in six additional ALS patients, but none in controls. All mutation carriers presented with weakness, behavioral abnormalities or language impairments and had a final diagnosis of ALS +/− FTD. Autopsy on five *TIA1* mutation carriers showed widespread neurodegeneration with TDP-43 pathology. Round eosinophilic inclusions in lower motor neurons were a consistent feature. Cellular assays revealed abnormal SG dynamics in the presence of *TIA1* mutations. In summary, missense mutations in the LCD of *TIA1* are a newly recognized cause of ALS/FTD with TDP-43 pathology and strengthen the role of RNA metabolism in the pathogenesis in this disease.

Abstract A13

The Calgary Brain Bank

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With the financial assistance from two donors, we have established a neurodegenerative disease brain bank at the University of Calgary. At autopsy, tissues from anatomically specific regions are frozen in liquid nitrogen vapour and stored in small, bar-coded cryovials. Cases include patients with dementia, movement disorders, demyelinating diseases, and normal controls. We prepare additional FFPE blocks for diagnosis or banking. Sampling includes all major areas of cortex and most subcortical structures. All brains, including "normal" controls, are characterized with a basic set of stains and major classification schemata are used for Alzheimer and Lewy body diseases. These tissues are available to investigators with IRB-approved research on human tissues

Control tissue is important in the study of age-associated neurodegeneration. We preserve tissues from areas of brain that either are severely or minimally affected by neurodegeneration (e.g. in Alzheimer disease, Brodmann areas 9 and 17, respectively). In our "normal" aging cohort, which includes patients with no described neurodegenerative diseases, we find frequent evidence of low-stage Alzheimer or Lewy body related pathological changes. We also find relatively frequent small vessel disease, which in part relates to our preferential selection of patient's who died suddenly.

In preliminary studies, we have examined amyloid plaque structure with confocal microscopy using beta-sheet sensitive dyes and have studied the distribution of different chaperones in normal brain.

Abstract A14

The role of ATP and P2X purinoreceptor 7 in the pathogenesis of cerebral tau

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The tauopathies are a group of neurodegenerative diseases characterized by abnormal deposition of hyperphosphorylated-tau. The pathogenesis of these changes remains uncertain. In chronic traumatic encephalopathy, tauopathy is hypothesized to occur after repeated mild traumatic brain injury (TBI). Post-traumatic extracellular ATP release and signalling via the P2X purinoceptor 7 (P2RX7) has been shown to be important in mediating pathological changes in TBI. We hypothesized that ATP-P2RX7 is involved in the development of tauopathy.

We injected ATP analogue bzATP or vehicle intraventricularly into C57BL/6 mice, pre-treated with either intraperitoneal P2RX7 antagonist Brilliant Blue G (BBG) or vehicle. At 2 weeks and 3 months, behavioural change was assessed with the tail suspension test, accelerating rotatrod, and fear conditioning; mice were then sacrificed for immunohistochemistry and western blot.

We observed increased immobile time in the tail suspension test for mice treated with bzATP at 3 months. Similarly, for rotarod, mice treated with bzATP showed poorer performance at 3 months. These effects were diminished by BBG pre-treatment. Fear conditioning, however, did not demonstrate a significant difference between groups. Immunohistochemical staining for GFAP showed increased intensity at both 2 weeks and 3 months for bzATP-treated mice compared to those pre-treated with BBG. Levels of phosphorylated tau (AT8) were increased in bzATP-treated mice compared to controls.

In summary, ATP-P2RX7-mediated mechanisms may play a role in the development of behavioural deficits and tauopathy.