62nd Annual Meeting of the Canadian Association of Neuropathologists
Association canadienne des neuropathologistes (CANP-ACNP)

Meeting Abstracts

October 13–15, 2022
Saskatoon, SK
The Canadian Association of Neuropathologists – Association canadienne des neuropathologistes (CANP-ACNP) held their 62nd annual meeting at the Delta Bessborough in Saskatoon, SK from October 13th to 15th, 2022, under the leadership of Dr. Robert Hammond, President of the CANP-ACNP, Dr. Peter Schutz, Secretary Treasurer of the CANP-ACNP, and with technical support from CANP administrator, Colleen Fifield.

The academic program comprised 15 scientific abstracts, 9 unknown cases, a mini-symposium on competence based medical education in neuropathology, and the Presidential symposium on Multiple Sclerosis and Immune mediated Demyelinating Disease. Digital pathology images from the 9 unknown cases are available for viewing online (www.canp.ca). The unknown case sessions were moderated by Dr. Andrew Gao.

The Presidential Symposium 2022 on Multiple Sclerosis and Immune mediated Demyelinating Disease featured the Gordon Mathieson Lecture given by Dr. G. R. Wayne Moore entitled *Demyelination, multiple sclerosis, and MRI* and the David Robertson Lecture given by Dr. Michael Levin entitled *Multiple sclerosis and future therapies*. The program was completed by three invited presentations with Dr. E. Ann Yeh presenting on *Pediatric multiple sclerosis and immune mediated demyelination*, Dr. Tanja Kuhlmann presenting on *Neuropathology of MS and stem cells* and Dr. Pamela Kanellis presenting on *Outlook of patients and public on MS research and treatment in Canada*.

The Mary Tom Award for best clinical science presentation by a trainee went to Dr. Christopher Newell (Supervisor Dr. J. Joseph), and the Morrison H. Finlayson Award for best basic science presentation by a trainee was won by Dr. Erin Stephenson (Supervisor Dr. V.W. Yong).

The following abstracts were presented at the 62nd annual meeting of the Canadian Association of Neuropathologists – Association canadienne des neuropathologistes (CANP-ACNP) in October 2022.
Abstract 1: Effects of prenatal cocaine exposure on the human developing brain. A neuropathological study

Abstract 2: Utilizing neurodevelopmental time windows of hypoxic-ischemic pathology to infer brain maturity in patients with congenital cardiothoracic defects

Abstract 3: Spinal nerve root blood in pediatric autopsy cases is not necessarily a marker of trauma at that site

Abstract 4: Multifocal necrotizing leukoencephalopathy post-CoVID-19 infection: expanding the “neuro-CoVID” spectrum

Abstract 5: The international disseminated pediatric low grade glioma consortium: project goals and preliminary results

Abstract 6: Glioblastoma, IDH-wildtype with FGFR3-TACC3 fusion has unusual histologic, molecular and clinicoradiologic characteristics

Abstract 7: Infiltrative pattern in pediatric ganglioglioma

Abstract 8: Clinical implementation of methylation profiling: the SickKids experience

Abstract 9: Cerebral amyloidoma: pathological findings from diagnostic biopsy to autopsy

Abstract 10: Identification and validation of immunohistochemical antibodies against transcriptomically distinct human hippocampal astrocyte subtypes

Abstract 11: Cadherin-23 is essential for the normal organisation of cerebellar mossy fibre synapses

Abstract 12: The Extracellular Matrix Transcriptome Following Demyelination

Abstract 13: Nodding syndrome: characterizing the newest tau proteinopathy in Africa

Abstract 14: MRI-Pathological correlations show differential patterns of ex vivo texture in ALS

Abstract 15: Lymphoid and plasma-cell infiltrates with amorphous eosinophilic material deposition in the leptomeninges: a challenging case
Abstract 1

Free Neuropathol 3:25:4

Meeting Abstract

Effects of prenatal cocaine exposure on the human developing brain. A neuropathological study

Catherine Fallet-Bianco¹, Mubina Jovanovic², Dorothée Bouron-Dal Soglio¹

¹ Department of Pathology, Hôpital Sainte-Justine-Université de Montreal, Montreal, QC, Canada

Recent studies report that cocaine use among pregnant women continues to be a public health concern. Experimental studies have shown that prenatal cocaine exposure is responsible for disturbances affecting neurogenesis, neuronal migration and neurotransmitter systems. However, human-based studies are impacted by confounding factors: multi-drug use, lack of neuropathological studies.

We describe the neuropathological phenotype observed in two fetuses after prenatal exposure to cocaine. In a 34-year-old woman using cocaine for several years, ultrasonography at 24 gestational weeks revealed a severe microcephaly with a severe global disorganization of brain development. In the second case, a 19-year-old mother using cocaine, ultrasonography at 20 weeks showed a severe microcephaly with bilateral schizencephaly resulting from multiple hemorrhages.

A vasoconstriction of maternal-fetal arteries is, classically, the mechanism considered responsible for the disturbed brain development. A vascular disruption is probably the cause of the lesions in the second case. The changes in the first case are similar to those generated in experimental models and confirm that cocaine has direct toxic effects on the neurogenesis, gliogenesis and neuronal migration in the developing brain. The wide spectrum of brain lesions depends on multiple factors; the most important is probably the moment of exposure in gestation, as well as dose, frequency of cocaine use, and genetic susceptibility.
Abstract 2

Free Neuropathol 3:25:5

Meeting Abstract

Utilizing neurodevelopmental time windows of hypoxic-ischemic pathology to infer brain maturity in patients with congenital cardiothoracic defects

Karina Chornenka¹, Christopher Dunham²

¹ Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada
² Division of Anatomical Pathology, Children’s and Women’s Health Centre of BC, Vancouver, BC, Canada

Neuroradiologic investigations have demonstrated that cerebral development is delayed by 2-4 weeks in infants suffering from congenital heart defects and congenital diaphragmatic hernia (CHD/CDH). These estimates are based upon application of the “total maturation score” (TMS) system that evaluates brain development using magnetic resonance imaging (MRI) by assessing myelination, cortical gyration, insular development, T1 white matter signal intensity and the involution of the germinal matrix (N Engl J Med 2007;357: 1928-1938, J Pediatr Surg 2012;47:453-461). These infants often require surgical correction of their malformations shortly after birth, but unfortunately some do not survive. Of those coming to autopsy, it is not uncommon to encounter acute hypoxic ischemic injury (HII). We examined three individuals born at term with CHD/CDH, ranging in age from 3 to 5 months, who died shortly after surgery and displayed evidence of neuropathology that included acute HII characterized by periventricular leukomalacia (PVL) and pontosubicular necrosis (PSN). PVL and PSN are typically encountered in the context of prematurity and occur during specific developmental time windows (i.e., PVL: 24-32 weeks gestational age; PSN: 20 weeks gestational age – 2 months postnatal) (Acta Neuropathol 1995;90:7-10, Acta Neuropathol 2005;110:563-578). Given the ages of the affected individuals herein, we suggest that the presence of premature-type neuropathology in the form of acute HII could be used to support the hypothesis that infants with CHD/CDH incur delayed brain development. Moreover, based on our observations we propose that the delay in cerebral development could be longer than previous estimates using MRI.
Spinal nerve root blood in pediatric autopsy cases is not necessarily a marker of trauma at that site

Marc R. Del Bigio

Department of Pathology, University of Manitoba and Diagnostic Services Manitoba, Winnipeg, MB, Canada

Increasingly, the forensic examination of suspected child abuse cases includes dissection of the entire cervical spine; hemorrhage along nerve roots is postulated to indicate forces exerted by shaking. Seventy pediatric spinal cords encased in dura mater were examined (including 12 en bloc cervical spines); age 0-58 months. The mechanism of deaths were: suspected abusive trauma 35; accident 13; undetermined or natural without head/neck trauma 12; forceps injury at birth 3; birth related intracranial hemorrhage 7. Prominent spinal subarachnoid hemorrhage was present in 30 cases; hemorrhage was detected along spinal nerve roots at the cervical level in 14/30 and at the lumbosacral level in 8/30 in the absence of definite injury to the spinal column. Two cases with definite evidence of bone/ligamentous injury to the spine and the 2 forceps injury cases had extensive epidural hemorrhage ± subarachnoid hemorrhage extending the entire length of the cord. Anatomical studies in humans, tracer studies, and experimental hemorrhage show direct communication of the cranial and spinal subarachnoid and subdural spaces with extension to the dorsal root ganglia. I conclude that the majority of spinal nerve root hemorrhages in pediatric trauma cases are simply markers of subarachnoid or subdural hemorrhage elsewhere. Additional work is needed to determine if en bloc spine dissection, which is invasive and time consuming, adds significant information to the autopsy.
Multifocal necrotizing leukoencephalopathy post-CoVID-19 infection: expanding the “neuro-CoVID” spectrum

Jacob A. Houpt¹, Lee Cyn Ang¹,², Qi Zhang¹,²

¹ Department of Pathology and Laboratory Medicine, London Health Sciences Centre, London, Ontario, Canada
² Department of Clinical Neurological Sciences, London Health Sciences Centre, London, Ontario, Canada

Multifocal necrotizing leukoencephalopathy (MNL), also known as disseminated necrotizing leukoencephalopathy (DNL), is a rare pathological phenomenon defined by numerous discrete foci of necrosis with predilection for ventral pontine white matter. While exact etiology and pathogenic mechanisms have yet to be elucidated, MNL is most often reported on post-mortem examination in the context of immunocompromised (ex: receiving chemotherapy or with untreated HIV-AIDS) or critically ill patients (ex: metastatic cancer, sepsis). Coronavirus disease 2019 (CoVID-19) is a viral respiratory illness with variable severity depending on host immune response and comorbid conditions. In its most serious cases, CoVID-19 can elicit both harmfully insufficient and excessive immune responses. We report on a case of CoVID-19 pneumonia which progressed to a clinical impression of sepsis, declining respiratory status, and death in an unvaccinated, previously well patient in which there were findings consistent with MNL throughout the midbrain and basis pontis. There was no encephalitis, microthrombi, infarcts, or other previously reported neuropathological findings. This index case was again compared and contrasted against four additional MNL cases examined at the London Health Sciences Centre. The neuropathological findings are examined and described for these 5 cases, all with clinical scenarios involving systemic critical illness and/or immune system compromise and with similar ventral pontine focal necrosis, myelin loss, and limited reactive glial response. Though numerous radiological studies have suggested a disseminated necrotizing leukoencephalopathic process underlying CoVID-19-associated encephalopathy, this case represents the first to offer pathological correlation supported by autopsy confirmation of MNL in a patient with CoVID-19 infection.
Abstract 5

Free Neuropathol 3:25:8

The international disseminated pediatric low grade glioma consortium: project goals and preliminary results

Adrian Levine1,4, Julie Bennett2, Joseline Haizel-Cobbina3, Liana Nobre2, Michael Dewan3, Uri Tabori2, Cynthia Hawkins1

1 Department of Pediatric Laboratory Medicine, Hospital for Sick Children, Toronto, ON, Canada
2 Division of Neuro-Oncology, Hospital for Sick Children, Toronto, ON, Canada
3 Department of Neurosurgery, Vanderbilt University Medical Center, Nashville, TN, USA
4 Clinician Investigator Program, University of British Columbia, BC, Canada

Although most pediatric LGG (PLGG) have excellent long-term survival, there is a subset of cases that disseminate (DPLGG) and have very poor outcomes. It is unknown why these tumors behave in such an aggressive way. We believe that biological mechanisms, distinct from those present in non-disseminated LGG, underlie this metastatic ability, but so far there has been no in-depth investigation of this.

To improve our understanding of this rare patient population, we have created a new consortium to compile DLGG cases across from across the world. We are collecting comprehensive clinical information, including the tumor presentation and pattern of dissemination, surgical outcomes and subsequent treatment courses, and quality of life outcomes. Cases with available tissue will be tested with our glioma NGS panel for the most common mutations and fusions, and methylation array for copy number and classification.

Our data thus far on the first 53 cases demonstrates the DPLGG has much worse prognosis than the overall PLGG population. Virtually all DPLGG progress at 5 years, compared to a quarter of other PLGG, and the disseminated cases are approximately 5-times more likely to die at 10 years. This can affect children of all ages and does not carry a gender predilection. We observe three patterns of dissemination – 40% of patients present with a localized mass and have secondary dissemination, 35% with disseminated tumor and a clear dominant mass, and 25% with disseminated disease without a dominant mass. The most common molecular alteration is BRAF fusions.
Glioblastoma, IDH-wildtype with FGFR3-TACC3 fusion has unusual histologic, molecular and clinicoradiologic characteristics

Namita Sinha¹, Sherry Krawitz¹, Jai J.S. Shankar², Saranya Kakumanu³, Ken Aldape⁴, Marc R. Del Bigio¹

¹ Department of Pathology, University of Manitoba, Winnipeg, MB, Canada
² Department of Radiology, University of Manitoba, Winnipeg, MB, Canada
³ Cancer Care Manitoba, University of Manitoba, Winnipeg, MB, Canada
⁴ Laboratory of Pathology, National Cancer Institute, NIH, Bethesda, Maryland, USA

According to 2021 World Health Organization (WHO) classification, term ‘Glioblastoma’ is reserved for CNS WHO grade 4 astrocytic neoplasm that is IDH-wildtype. A small subset of glioblastomas may have unusual clinical, histological and molecular profiles that may need appropriate molecular work-up for definitive diagnosis, and some of them may be reported as high-grade glioma, not otherwise specified, if complete molecular work up is lacking. We present two cases: a 48-year-old female with imaging revealing right occipital solid, cystic, mass demonstrating nodular calcification; and a 53-year-old male with imaging revealing multifocal enhancing mass with extensive calcification in the right parietal, occipital and temporal regions. The cerebral tumors in both patients were relatively circumscribed high-grade glioma composed of GFAP immunoreactive monomorphic ovoid cells, with endothelial proliferation, predominantly infarct-type necrosis, and abundant calcospherites. Both tumors showed occasional mitosis with ki-67 of ~ 5-10%. Mass array analysis showed no IDH, H3F3A, BRAF V600E mutation in these two cases and revealed TERT promoter mutation in the second case. Because of unusual histology, methylation profiling was pursued in these two cases that matched to glioblastoma. Interestingly, NGS study showed FGFR3-TACC3 fusion in both the cases. Follow-up imaging showed tumor progression in these two patients, with recurrence at 9 months in the second patient. Both the patients are clinically well at 7 months and 15 months of follow-up. A few case reports are published with similar histologic and molecular findings. Our cases contribute to expanding histologic, molecular and clinical spectrum of FGFR3-TACC3 fused glioblastoma.
Abstract 7

Free Neuropathol 3:25:10

Meeting Abstract

Infiltrative pattern in pediatric ganglioglioma

Murad Alturkustani¹

¹ Department of Pathology, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

Ganglioglioma is a well-circumscribed low-grade glioneuronal tumor with a broad morphological spectrum. Diffuse glioneuronal tumors are used to describe cases with infiltrative growth. Molecular studies of some of these cases were consistent with ganglioglioma. This work aims to clarify the growth patterns in ganglioglioma. The available slides and clinical and molecular information for ganglioglioma cases under the open pediatric brain tumor atlas from the children’s brain tumor network database were reviewed to confirm the integrated diagnosis and to evaluate the growth patterns in these cases. Infiltration is defined as the presence of neoplastic cells among the nonneoplastic parenchyma. The diagnosis of ganglioglioma was confirmed in 16 of 46 cases (nine females and seven males; age ranges from eight months – 19 years with a mean of 9.9 years). The infiltrative pattern was identified in 5 cases as the predominant pattern and in another 5 cases combined with a circumscribed nodule, while only 6 cases had predominant circumscribed growth. This work confirms the presence of an infiltrative/diffuse variant of ganglioglioma. Awareness of this variant should help with infiltrative tumors, as the differential includes diffuse glioma, which is usually IDH wild type in this population.
Clinical implementation of methylation profiling: the SickKids experience

Adrian Levine1,2, Michelle Ku3, Scott Ryall1, Cynthia Hawkins1

1 Department of Pediatric Laboratory Medicine, Hospital for Sick Children, Toronto, ON, Canada
2 Clinician Investigator Program, University of British Columbia, BC, Canada

Over the past decade, methylation profiling and machine learning based classification has had a major impact on the diagnostic framework for CNS tumors, however there remains inconsistent and limited access to clinical testing for this analysis. At SickKids, we have implemented a clinically validated methylation assay using the Illumina EPIC platform for the Heidelberg CNS tumor classifier, copy number profiling, and MGMT promoter methylation status.

We have now run 136 samples for clinical use (plus additional samples for validation), which have been classified through both v11 and v12.5 of the Heidelberg classifier. Many external samples were not received with a histologic diagnosis, those that do have a diagnosis include 34 low grade gliomas (LGG), 19 high grade gliomas (HGG), 10 ependymomas, 4 pineal tumors, and 4 medulloblastoma/embryonal tumor.

Overall, only 34 samples (25%) classified with confidence score >0.85 on the v11 classifier and 77 samples (57%) on v12.5. The medulloblastomas all classified with high confidence scores, as did 7/10 ependymomas, and 2/3 papillary tumors of the pineal region. 9/19 HGGs classified with high confidence – most of which were methylation-defined subtypes of IDH-mutant and IDH-wildtype astrocytomas or glioblastomas, with unclear clinical significance. Notably, though 2 of the cases that were referred as HGG were in fact other tumor types, one being an ATRT, and the other an ependymoma with ZFTA-fusion. The classifier had particular challenge with LGGs, of which only 17 (50%) classified with high confidence, including one that was erroneously called “Control tissue, reactive tumor microenvironment”.

Meeting Abstract
Cerebral amyloidoma: pathological findings from diagnostic biopsy to autopsy

Shervin Pejhan¹, Adrian Budhram², Joseph Megyesi², Lee Cyn Ang¹,², Robert Hammond¹,², Qi Zhang¹,²

¹ Department of Pathology & Lab Medicine, University of Western Ontario, ON, Canada
² Department of Clinical Neurological Sciences, University of Western Ontario, ON, Canada

Amyloidoma is a rare condition defined by the aggregation of amyloid proteins forming a mass-like lesion. While brain-restricted amyloidomas have been reported, their course and pathogenesis are poorly understood.

We are reporting a case of multifocal brain amyloidoma in a 71-year-old man, which is significant for its protracted clinical course and progression of neurological symptoms. A pair of stereotactic biopsies revealed the underlying pathology.

The pathological findings were unusual with a dual picture of perivascular lymphoplasmacytic infiltration in the frontal area, accompanied by amyloid deposits in occipital white matter. Proteomic analysis of the amyloid protein by mass spectrometry was also curious as it characterised both lambda light chain and amyloid beta-protein without evidence of monoclonality. Further assessments found no involvement of other organ systems. With the progression of symptoms and lack of definitive treatment, the patient underwent palliative whole-brain irradiation, with no improvement, and passed away shortly thereafter.

Assessment of post-mortem brain tissue showed massive amyloid deposition in the periventricular white matter with sparse perivascular lymphocytes and fewer plasma cells than the biopsy samples. Special staining, immunohistochemistry, electron microscopy, and mass spectrometry confirmed multifocal cerebral amyloidoma, lambda light chain type. The collection of the biopsy and autopsy findings may be the result of lesions observed at different stages of progression, treatment effects, or a not-previously described pattern of brain amyloidoma.

Studying this case is beneficial to gaining insight into the pathobiology of this rare condition and to inform future studies and therapeutic interventions.
Identification and validation of immunohistochemical antibodies against transcriptomically distinct human hippocampal astrocyte subtypes

Brenden Joseph¹,², Kaitlin Sullivan³, Mark S. Cembrowski³, Veronica Hirsch-Reinshagen¹,²

¹ Department of Pathology & Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada
² Division of Neuropathology, Vancouver General Hospital, Vancouver, BC, Canada
³ Department of Cellular and Physiological Sciences, Djavad Mowafaghian Centre for Brain Health, University of British Columbia, Vancouver, BC, Canada

Our understanding of astrocyte function has steadily evolved from an early conceptualization as simplistic support cells to a current appreciation for their diverse and critical physiological roles. There is emerging evidence for the existence of distinct astrocyte subtypes with differential genomic expression, spatial localization, morphology, and physiological function. However, little is known about their specialized functions or the role of specific subtypes in human disease. A lack of established subtype-specific immunohistochemical markers represents a significant barrier to further investigation. To address this limitation, we aim to identify transcriptomically distinct human astrocyte subtypes and validate immunohistochemical markers for these. To identify distinct transcriptomic subtypes of human astrocytes, we used single cell nuclear RNA sequencing of 11,204 astrocytes in human hippocampal surgical samples from 5 patients with intractable mesiotemporal epilepsy. Canonical correlation and Seurat cluster analysis identified 6 distinct clusters of astrocytes with unique transcriptomes and revealed several candidate marker genes unique to each cluster. We are currently validating C8orf34 and NRG4 as subtype specific markers for Cluster 5, which was the most transcriptomically unique cluster. The study’s current and future directions include the selection of commercially available antibodies against candidate marker gene products and validation of these subtype-specific antibodies using double- and triple-label immunofluorescence microscopy with other established markers for various CNS cell types. Establishing validated antibodies will lead to the discovery of subtype-specific involvement of astrocytes in human neurological and psychiatric conditions and advancements in our understanding of human astrocyte physiology.
Abstract 11

Free Neuropathol 3:25:14

Meeting Abstract

Cadherin-23 is essential for the normal organisation of cerebellar mossy fibre synapses

Madison T. Gray1,2,3, Julie L. Lefebvre2,3

1 Department of Pathology and Laboratory Medicine, Western University, London, ON, Canada
2 Neuroscience and Mental Health, Hospital for Sick Children, Toronto, ON, Canada
3 Department of Molecular Genetics, Faculty of Medicine, University of Toronto, Toronto, ON, Canada

To understand the physiological basis of neurological disease, one must first identify which neurons are connected and how they form those connections. Here, we identify a novel cell adhesion molecule signature in Golgi cells, an inhibitory interneuron in the granular layer of the cerebellar cortex. Golgi cells receive excitatory input from both precerebellar mossy fibres and cerebellar granule cells, while providing inhibition to those same granule cells in a feedback loop. We show that both Golgi cells and their mossy fibre partners express cadherin 23 (Cdh23) – a pattern conserved in evolution.

Using explant cultures in vitro and ectopic viral expression in vivo, we demonstrate that Cdh23 is sufficient to induce the formation of synapses by mossy fibres. The known in vivo roles of Cdh23 depend on binding protocadherin 15 (Pcdh15) in trans. However, here we show that Pcdh15 is not expressed in mossy fibre neurons, Golgi cells, or their cerebellar targets. A Cdh23 mutant incapable of binding Pcdh15 nonetheless induces mossy fibre synapses in vitro and in vivo, confirming that the synaptic organiser function of Cdh23 is independent of Pcdh15 binding.

Finally, analysis of a Cdh23-null mouse reveals that Cdh23 is not necessary for anatomical synapse formation but mossy fibres. However, loss of Cdh23 results in enlarged, sparse mossy fibre terminals suggesting a role for Cdh23 in mossy fibre bouton development.
The Extracellular Matrix Transcriptome Following Demyelination

Erin L. Stephenson¹, Samira Ghorbanigazar², Charlotte D’Mello², Rajiv William Jain², V. Wee Yong²

¹ Department of Pathology and Laboratory Medicine, University of Calgary, Calgary, AB, Canada
² Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada

The extracellular matrix (ECM) of the central nervous system (CNS) is an interconnected network of proteins and sugars. The ECM has critical roles not only in homeostasis, but ECM remodeling in neurological diseases impacts both injury and repair.

Multiple sclerosis (MS) is a chronic inflammatory and degenerative disease of the CNS. Here, we evaluated ECM changes in MS lesions compared to controls using databases generated in-house through spatial RNA-sequencing, and through a public resource of single-nucleus RNA sequencing. Our results found widespread changes in ECM molecules and their interacting proteins, including alterations to proteoglycans and glycoproteins within inactive and active MS lesions. Some highly upregulated members, including serglycin and SPARC-related proteins, have not previously been investigated and their role on MS lesion evolution and disease course remains unknown. Our results emphasize that there are profound changes to the ECM following demyelination.
Abstract 13

Free Neuropathol 3:25:16

Nodding syndrome: characterizing the newest tau proteinopathy in Africa

Kenneth G. Kodja1,2,3, Sylvester Onzivua4, David Clutterbuck2, David L. Kitara5, Amanda Fong2, Michael S. Pollanen1,2,3

1 Department of Pathobiology and Laboratory Medicine, University of Toronto, Toronto, ON, Canada
2 Ontario Forensic Pathology Service, Toronto, ON, Canada
3 Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, ON, Canada
4 Department of Pathology, College of Health Sciences, Makerere University, Kampala, Uganda
5 Department of Surgery, Gulu University, Gulu, Uganda.

Nodding syndrome (NS) is an acquired tau proteinopathy plaguing the remote rural communities in Eastern sub-Saharan Africa. It has been proposed that infection with the nematode parasite Onchocerca volvulus triggers an autoimmune attack against the human protein leiomodin-1. This theory is dependent on the constitutive neuronal expression of leiomodin-1. We tested this hypothesis by exploring the histologic distribution of this protein in the normal human brain. Subsequent immunostaining of cerebellar tissue and C. elegans (a proxy for Onchocerca volvulus) using an antibody recognizing the N-terminus of leiomodin-1 was conducted. Our study failed to identify the presence of leiomodin-1 immunoreactivity in neurons or glia. Our results also suggest the possibility of leiomodin-1 antibody cross-reactivity between human Purkinje cell membranes and the body wall of C. elegans; a finding explained by the homology between leiomodin-1 and tropomodulin. This outcome does not support the hypothesis of autoimmunity involving Onchocerca volvulus and leiomodin-1. We also investigate the signature laminar distribution of cortical tau pathology in NS. Through morphometric analysis, our current study, in agreement with the literature, suggests that primary tauopathies (the likes of progressive supranuclear palsy, corticobasal degeneration, Pick’s disease and globular glial tauopathy) are associated with severe lower layer (IV-VI) pathologic burden, independent of clinical symptomology. Interestingly, we found predominant involvement of the upper layers (I-III) in NS; a laminar profile similar to the amyotrophic lateral sclerosis and parkinsonism-dementia complex of Guam. The present study lays the foundation for future work investigating potentially unique mechanisms of propagation and neurodegeneration in NS.
MRI-Pathological correlations show differential patterns of 
ex vivo texture in ALS

Avyarthana Dey1,2, Collin Luk1, Abdullah Ishaque1,2, Peter Seres3, Dennell Krebs5, Yee-Hong Yang4, Julia Keith5,6, Sumit Das1,7, Ekaterina Olkhov-Mitsel5, Sanjay Kalra1,2

1 Neuroscience and Mental Health Institute, University of Alberta, Edmonton, AB, Canada
2 Division of Neurology, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB, Canada
3 Peter S. Allen MRI Center, University of Alberta, Edmonton, AB, Canada
4 Faculty of Science – Computing Science, University of Alberta, Edmonton, AB, Canada
5 Laboratory Medicine and Molecular Diagnostics, Sunnybrook Health Sciences Centre, Toronto, ON, Canada
6 Department of Laboratory Medicine & Pathobiology, University of Toronto, Toronto, ON, Canada
7 Department of Laboratory Medicine & Pathology, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB, Canada

In vivo magnetic resonance imaging (MRI) has provided a reliable biomarker for amyotrophic lateral sclerosis (ALS). However, lack of pathological specificity of these biomarkers impedes their integration in clinical investigations. To address this lack of specificity and establish their relationship with disease pathology, the aim of the current study was to examine the associations between ex vivo neuroimaging and histopathological features. We hypothesized that histopathology of the cervical spinal cord (cSC) and precentral gyrus (PCG) shows associations with texture of the posterior limb of internal capsule (PLIC).

Formalin-fixed brains of 13 ALS patients underwent excision of the PCG, PLIC, and cSC. T1-weighted MRI was performed for PCG and PLIC from which texture features – namely autocorrelation (autoc), energy (energ), inverse difference normalized (inDnc) – were extracted. Quantitative histological assessments were performed using QuPath to assess the density of axons in the corticospinal tract on NF immunolabeling, and extent of macrophage infiltration of the corticospinal tract on CD68 immunolabeling in the cSC. Qualitative assessments were performed to assess superficial spongiosis and presence of TDP-43 inclusions in the PCG. Pearson’s r correlational analysis was performed between texture and histological features. Statistical significance was set at p < 0.05.

A negative correlation was observed between PLIC autoc and presence of TDP-43 inclusions (r = -0.652, p = 0.022) as well as superficial spongiosis (r = -0.585, p = 0.046) in the PCG. A positive correlation was observed between PLIC energ and CD68 density (r = 0.714, p = 0.009).

The PCG and cSC demonstrate patterns of histopathological changes associated with PLIC texture features in ALS.
Lymphoid and plasma-cell infiltrates with amorphous eosinophilic material deposition in the leptomeninges: a challenging case

Gianluca Lopez1,2, Karam Han1, Shino D. Magaki1, Sophie X. Song3, Noriko Salamon4, Kanwarpal S. Kahlon5, Inna Keselman6, Ausaf A. Bari7, Harry V. Vinters1

1 Section of Neuropathology, Department of Pathology and Laboratory Medicine, Ronald Reagan UCLA Medical Center and David Geffen School of Medicine, Los Angeles, CA, USA
2 University of Milan, Milan, Italy
3 Section of Hematopathology, Department of Pathology and Laboratory Medicine, Ronald Reagan UCLA Medical Center and David Geffen School of Medicine, Los Angeles, CA, USA
4 Department of Radiology, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA
5 Division of Hematology-Oncology, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA
6 Department of Neurology, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA
7 Department of Neurosurgery, David Geffen School of Medicine, Los Angeles, CA, USA

A 65-year-old female presented with recurrent seizures. She had a history of intractable epilepsy after a motor vehicle accident, which was treated several decades ago with left anteromedial temporal lobectomy and hippocampectomy; hippocampal sclerosis was noted at the time. At the time of her last hospital presentation, she underwent magnetic resonance imaging, which showed a leptomeningeal enhancement in the left parieto-occipital lobe. She underwent a biopsy for diagnostic purposes, which showed a diffuse lymphoid infiltrate predominantly involving the leptomeninges, with extension into the Virchow-Robin spaces and with deposits of amorphous eosinophilic material. The lymphoid population comprised small atypical lymphocytes, scattered plasma cells, and plasmacytoid lymphocytes. With immunohistochemistry, the lymphoid infiltrate was positive for CD20, CD19, and BCL2; a subset of cells were positive for CD138 and MUM1; lambda light chain restriction was noted on RNA in situ hybridization. Negative stains included CD3, CD5, CD10, CD21, CD23, and BCL6. The Ki-67 proliferative index was estimated at 5%. On Congo red stain, the amorphous material showed green birefringence under polarized light. MYD88 mutation was not detected. The patient had no evidence of systemic amyloidosis, monoclonal IgM gammopathy, urinary Bence Jones protein, or bone marrow or other organ sites involvement.