Meeting Abstracts

65th Annual Meeting of the Canadian Association of Neuropathologists Association canadienne des neuropathologistes (CANP-ACNP)

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October 23rd–25th, 2025
Banff, Alberta

Canadian Association of Neuropathologists
Association canadienne des neuropathologistes

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The Canadian Association of Neuropathologists – Association canadienne des neuropathologistes (CANP-ACNP) held their 65th annual meeting at the Banff Centre for Arts & Creativity – Banff, Alberta, from October 23rd–25th, 2025, under the leadership of Dr. Cynthia Hawkins, President of the CANP-ACNP, Dr. Veronica Hirsch-Reinshagen, Secretary Treasurer of the CANP-ACNP, and with technical support from CANP administrator Colleen Fifield.

The academic program comprised 23 scientific abstracts, 13 unknown cases, the Neuropathology in Practice Forum on *Immunohistochemical Markers for Inflammatory Myopathies*, and the Presidential Symposium. Digital pathology images from the 13 unknown cases were available for online viewing prior to the conference (www.canp.ca).

The David Robertson Lecture, *Pathomechanisms at the Interface of Neurological Infectious and Immune Disorders*, was delivered by Dr. Christopher Power. The 2025 Presidential Symposium, *Advanced Perspectives on Neurodegenerative Diseases*, featured the Gordon Mathieson Lecture by Dr. Ian Mackenzie on *New Approaches to Neurodegenerative Disease Diagnosis and Research*, and the Jerzy Olszewski Guest Lecture by Dr. Eric Smith entitled *Vascular Dementia*. The symposium also included three invited presentations: Dr. Rosa Rademakers discussed *The Role of Genetics in Understanding the Pathophysiology of Neurodegenerative Diseases*; Dr. Edward Lee presented on *The Role of Spatially Defined Omics in Understanding the Pathophysiology of Neurodegenerative Diseases*; and Dr. Julie Schneider spoke on *Insights from Population-Based Studies into the Pathological Determinants of Dementia*.

The Mary Tom Award for best clinical science presentation by a trainee went to Dr. Erin Stephenson (Supervisor Dr. Kristopher D. Langdon), and the Morrison H. Finlayson Award for best basic science presentation by a trainee was won by Dr. Karina Martin (Supervisor Harry V. Vinters).

The following abstracts were presented at the 65th annual meeting of the Canadian Association of Neuropathologists – Association candienne des neuropathologistes (CANP-ACNP) in October 2025.

Abstract 1

Free Neuropathol 6:23:4

Meeting Abstract

Decoding the diseased brain: using machine learning to gain comprehensive understanding of neurodegenerative diseases

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Neurodegenerative diseases are characterized by neuronal loss and deposition of misfolded proteins in the human brain. Since neuropathological evaluation remains the gold standard for definitive diagnosis, many efforts have been made to understand the complex neuropathological and molecular changes underlying neurodegenerative diseases using fully characterized post-mortem tissues. These include evaluating cytopathologies, morphologies of pathological inclusions, biochemical properties of misfolded proteins using seed amplification assays (SAA), and genotypic information. However, the results of these evaluations are not independent, but rather should be interpreted together. In order to integrate results from multiple disciplines and achieve a comprehensive understanding of the disease, a powerful and scalable tool is needed. We used machine learning, a branch of artificial intelligence, to learn latent patterns from high dimensional data and incorporate results from multiple disciplines. Machine learning-based analysis has allowed: i) the discovery of novel subtypes of multiple system atrophy based on morphological variables, ii) the integration of alpha-synuclein cytopathology and seeding behavior to describe cell type-specific seeding in synucleinopathies, iii) the understanding of differences in in inflammatory markers of distinct inheritable DNA sequence patterns, iv) the validation of subtype and staging in progressive supranuclear palsy, and v) the prediction of 4R-tauopathies using morphological differences in coiled bodies. Machine learning can be applied not only for diagnostic predictions in clinical settings, but also as a research tool to understand the comprehensive biological underpinnings of neurodegenerative disease.

Abstract 2

Free Neuropathol 6:23:5

Meeting Abstract

The relevance of identifying limbic neuronal synuclein pathology in multiple system atrophy

Gabor G. Kovacs[1–6], Ivan Martinez-Valbuena[1], Shelley L. Forrest[1], Xiaoxiao Xu[6], Renato P. Munhoz[5], Jun Li[1], Ekaterina Rogaeva[1], Anthony E. Lang[5], Masahiro Enomoto[7]

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Two neuropathologically defined disorders that show consistently α-synuclein pathology include Lewy body diseases (LBD) and multiple system atrophy (MSA). MSA is characterized by predominantly oligodendroglial cytoplasmic inclusions and distinct synuclein protofilament folds. To compare literature observations on hippocampal neuronal synuclein pathology in MSA and to address the question whether brain regions showing unusual neuronal α-synuclein pathology are associated with distinct biochemical and structural profile of α-synuclein as a distinctive feature of atypical form of MSA. Literature overview of MSA with limbic neuronal synuclein pathology (atypical MSA). Report of a case and comparison with typical cases of MSA using α-Synuclein seed amplification assay (α-Syn SAA), immunoblotting, Proteinase K digestions, Conformational stability assay (CSA) and Electron cryo-microscopy. Neuronal cytoplasmic inclusions are thought to contribute to memory impairment when seen in the hippocampus in MSA and additionally large argyrophilic neuronal inclusions are detected in atypical MSA. In our case with atypical MSA, we demonstrate distinct biochemical characteristics of α-synuclein linked to cytopathological differences (e.g. neuronal or oligodendroglial) and a new Lewy-MSA hybrid fold brain regions showing neuronal inclusions. We propose that cell-specific protein pathologies can be associated with distinct filament folds and expand the current structure-based classification of α-synucleinopathies.

Abstract 3

Free Neuropathol 6:23:6

Meeting Abstract

Spinal cord α-synuclein mapping in Parkinson's disease

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It has been hypothesized that the etiology of Parkinson's disease (PD) lies outside the body via an inhaled/swallowed agent entering the body to cause protein-catalyzed misfolding of proteins akin to prion diseases. Early olfactory abnormalities and gut dysbiosis antedate a proposed march of α- synuclein misfolding through loci involving olfactory and autonomic systems in a body-first, not brain-first, sequence. Using anti-phospho-Ser129 α-synuclein antibodies and an immunohistochemical red readout, we mapped α-synuclein rostro-caudally, and at each level dorso-ventrally using Rexed's laminae. A semi-quantitative scale was used. Lewy bodies, Lewy neurites and granular α-synuclein in 35 spinal cords from a sequential series of patients deceased from 2016 to 2021 showed no caudo-rostral gradient along the length of the spinal cord. However, α-synucleinopathy was highest in the thoracic cord, lowest in the sacral cord. Intermediate autonomic lamina VII of Rexed showed the highest α-synuclein compared to dorsal sensory laminae I–IV ($p = 0.02$) and to ventral motor laminae VIII–IX ($p = 0.02$). Clinical stratification by Braak stage showed only that the autopsy cases with later, more severe Braak staging had earlier onset and longer disease duration. Our results show that directionality of spread within the spinal cord of PD is heterogeneous and does not correlate with Braak staging. The results lend no support for a gradient of α-synuclein within the spinal cord, neither along the neuraxis nor dorso-ventrally within any spinal level, while confirming the autonomic-predominant distribution of α-synuclein seen in the PD spinal cord.

Abstract 4

Free Neuropathol 6:23:7

Meeting Abstract

Comparison of co-pathologies in CTE-NC and GGT and case report of an ex-football player

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To compare literature observations on the frequency and type of co-pathologies associated with chronic traumatic encephalopathy-neuropathological change (CTE-NC) and globular glial tauopathy (GGT). To report an ex-football player with primary progressive aphasia, and an unprecedented combination of degenerative pathologies, including CTE-NC. Mixed neurodegenerative pathologies are common but can be overlooked when there is a more obvious pathology. Literature review and summary of our observations in CTE and GGT cases. An 86-year-old male former Canadian Football player was longitudinally followed in the Cognitive Neurology Clinic at Toronto Western Hospital and underwent clinical assessments and MRI scans throughout the disease course. Paraffin-embedded sections from all brain regions available were immunostained with histological and immuno-histochemical stains. Mixed pathologies are frequently associated with CTE-NC associated also with ageing. In GGT the frequency is lower but unusual co-pathology constellations (e.g. TDP-43) may occur. In the case presented, multiple and rare constellations of degenerative pathologies observed: **1**) CTE-NC (high level); **2**) High level of ADNC); **3**) Lewy body disease (Braak stage 4 or limbic type); **4**) Cerebral Amyloid Angiopathy; **5**) Argyrophilic grain disease; **6**) Globular Glial Tauopathy Type II (Corticospinal tract involvement) with selective and asymmetric involvement of the corticospinal tract; and **7**) Neuronal intranuclear hyaline inclusion body disease. This study highlights the spectrum of proteinopathies that can be associated with multiple concussions and demonstrates that unusual constellations of rare neurodegenerative diseases beyond ADNC and Lewy body pathology can be observed as co-pathologies in the same individuals.

Abstract 5

Free Neuropathol 6:23:8

Meeting Abstract

Does the HLA locus have relevance in progressing supranuclear palsy?

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To investigate the role of human leukocyte antigen (HLA) haplotypes in progressive supranuclear palsy (PSP) and evaluate its relation to clinical and pathological diversity. PSP is a neurodegenerative 4-repeat tauopathy characterized by atypical parkinsonism and cognitive-behavioral changes. The HLA locus has not been investigated in PSP, but has been implicated in autoimmune and some neurological diseases. First, HLA haplotyping was performed in 44 PSP cases compared to a Canadian deceased donor pool. Binding predictions were used to explore relation of HLA molecules and tau peptides. Second, 32 autopsy-confirmed PSP cases were grouped by HLA haplotypes: and systematic analysis of inflammatory cells (T and B cells, microglia) and phosphorylated-tau was performed. Statistical analysis considering confounding factors and machine learning was used evaluate the effect of HLA haplotypes on pathology variables. The DQB106:01 allele showed an odds ratio of 2.94 (95 % CI 1.01–8.55, p = 0.047), and the narcolepsy-associated haplotype had an odds ratio of 2.59 (95 % CI 1.39–4.83, p = 0.0025). HLA-Tau peptide binding predictions confirmed strong tau peptide binding to alleles DQA101:02-DQB106:02 and DQA101:03-DQB1*06:01, but not to the PSP-protofilament fold. We observed differences of the constellations of neuropathological variables between HLA haplotype groups. Machine learning identified inflammatory markers and neuropathological ratios as strong predictors of HLA haplotypes (clustering accuracy: 86.96 % and 91.30 %), with clinical symptom sequences and neuropathological ratios achieving prediction accuracies of 80.00 % and 71.43 %, respectively. These findings highlight HLA haplotype-dependent neuroinflammatory and pathological variations in PSP, suggesting potential for patient stratification in immune-modulating therapy trials.

Abstract 6

Free Neuropathol 6:23:9

Meeting Abstract

Cognitive subtyping in schizophrenia reveals distinct clinico-pathologic signatures and a vascular-linked cognitive phenotype

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Cognitive impairment is a defining feature of chronic schizophrenia, but its underlying neuropathology remains unclear and treatment options are scarce. The contributions of Alzheimer's disease (AD) and cerebrovascular disease (CVD) pathology to cognitive decline in older patients are particularly understudied. This study examined the relationship between postmortem neuropathology and neuropsychological performance in 55 patients (mean age 78), representing, to our knowledge, the most detailed clinicopathologic investigation of late-life schizophrenia to date. Although 70 % met criteria for cognitive impairment, the prevalence of AD pathology (35.1 %) was comparable to that reported in age-matched controls. In contrast, CVD pathology was more frequent (84.2 %) and significantly associated with lower Mini-Mental State Examination (MMSE) scores ($B = –6.40$, $p < 0.001$), after adjusting for age and education. No other significant pathology-cognition associations were found. Notably, 42 % of cognitively impaired individuals lacked traditional neuropathological findings to explain their symptoms. k-means clustering of cognitive test scores revealed three cognitive subtypes with distinct clinical profiles, despite comparable degrees of neuropathological burden. The MMSE-CVD association

was specific to one group (NCOG_3), which showed domain-selective impairments, implicating vascular pathology in a distinct cognitive phenotype. NCOG_1 exhibited global cognitive deficits independent of all evaluated pathologies, while NCOG_2 demonstrated relatively preserved cognition and younger age at death. These findings reveal a novel, subtype-specific association between cognition and postmortem CVD pathology in chronic schizophrenia and suggest that cognitive subtyping may help stratify patients by underlying disease mechanism. Addressing cardiovascular risk may therefore represent a modifiable therapeutic target for cognitive symptoms in select patients.

Abstract 7

Free Neuropathol 6:23:11

Meeting Abstract

Mapping the digital divide: underrepresentation of neuropathology in large language model-driven diagnostic literature

Vladimir (Vova) R. Auer[1], Pramath Kakodkar[1], Daniel Markewich[1], Nooshin Shekari[2], Bryan Johnston[1], Viktor Zherebitskiy[1], Roland N. Auer[1], Jay Kalra[1]

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An LLM (Large Language Model) is an artificial intelligence (AI) trained on massive amounts of text to predict the next word, letting it generate and work with human-like language. The objective of this study is to assess the representation and diagnostic utility of LLMs in Clinical Neuroscience with a focus on neuropathology compared to other subspecialties. We performed a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) compliant review of 539 articles (ChatGPT (n = 508), Google Gemini (n = 14), Perplexity (n = 10), DeepSeek (n = 7)) spanning the years 2022–2025. Studies were categorized by subspecialty, input data type (admission note, radiological imaging, radiology report, pathology images, pathology report), and assessed LLM outcomes (diagnosis, grading, prognosis). Only 11.9 % (n = 64) of included studies focused on clinical neuroscience, and just 3 were dedicated to neuropathology. These studies targeted gliomas and neurodegenerative disorders. The other specialty that had the highest LLM utilization was Radiology (11.3 %, n = 61). Neuropathology-dedicated studies lagged in sample size, external validation, and model robustness, especially compared with other pathology (n = 37) subspecialties such as head and neck (n = 9), general surgical pathology (n = 7), gastrointestinal (n = 5) and gynecological pathology (n = 4). Neuropathology remains significantly underrepresented in the era of diagnostic AI. Given the distinctive morphologic and molecular complexity of CNS (central nervous system) lesions, there is an urgent need for dedicated model development and rigorous validation tailored to neuropathology.

Abstract 8

Free Neuropathol 6:23:12

Meeting Abstract

OnSight: A real-time computational pathology companion for histopathology

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Precise microscopic examination of surgical tissue sections is a specialized skill critical for diagnosis and clinical care. While artificial intelligence (AI) shows promise for histological analysis, differences in slide digitization and proprietary software limit real-world deployment. We present OnSight, a platform-agnostic computer vision software providing real-time AI inferences to pathologists during digital slide review. OnSight is freely accessible as a single executable file, runs locally on consumer-grade computers, and requires no complex integration, enabling cost-effective and safe use in research and clinical workflows. OnSight was benchmarked on classification, mitosis detection, and immunohistochemical quantification. For tumor classification (glioma, meningioma, schwannoma, epithelial metastasis), a ViT-B/16 pretrained on the Kaiko foundation model was fine-tuned on 80,000 H&E tiles from UHN at 20×. Ki-67 nuclei were segmented with a YOLO model trained on QuPath-annotated patches from 10 cases. Mitotic figures were detected with a RetinaNet FPN (ResNet-50 backbone) trained on MIDOG++ at 40×. Validation used TCGA and UHN cases. Tumor classification accuracy was 95 % across public and institutional sets. Mitosis detection showed high area under the curve and agreement with manual review. Automated Ki-67 indexing showed closer agreement with neuropathologist counts than QuPath and is reported as a percentage. Median per-field latency was 0.3 s, enabling real-time use. OnSight provides accurate, SI-unit-standardized, low-latency pathology slide analysis with potential to reduce inter-observer variability, improve accuracy, and increase efficiency. Prospective multicenter evaluation is warranted for widespread use.

Abstract 9

Free Neuropathol 6:23:13

Meeting Abstract

Validation framework for an AI decision support tool in intraoperative neuropathology: protocol for a multi-phase evaluation

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Intraoperative consultations (IOC) for neurosurgical cases rely on rapid assessment of H&E-stained frozen sections and cytologic preparations, often under time pressure and with variable tissue quality. We describe a validation framework for evaluating OnSightPathology, an open and platform-agnostic artificial intelligence (AI) tool developed to classify intraoperative digital slides into five diagnostic categories: glioma, epithelioid, meningeal, schwannoma, and normal/reactive tissue. In the pilot phase, 10–20 representative cases from each class were selected from archival material, and 50–100 diagnostic tiles per case were extracted using an image feature-based clustering pipeline. Groups of tiles were assigned coarse labels (e.g., glioma, artifact) via visual histologic inspection. Ground-truth diagnoses were adjudicated on formalin-fixed paraffin-embedded sections through dual-review consensus. The annotated images will then be used to train a vision transformer model and will be deployed using OnSightPathology to provide "real-time" inferences to help with intra-operative frozen section analysis. The tool is designed to assist pathologists by highlighting diagnostically relevant regions, providing class probabilities, and flagging low-confidence areas for review. This approach is intended to augment IOC workflows by improving confidence, reducing turnaround time, and standardizing interpretation in time-sensitive settings. Subsequent phases will assess OnSightPathology's performance on external cohorts and in real-time clinical use.

Abstract 10

Free Neuropathol 6:23:14

Meeting Abstract

An internal audit of neuropathology consultation for autopsies at the London Health Sciences Centre – a quality improvement project

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In autopsy, neuropathological workups tend to be relatively extensive, requiring more tissue sampling, ancillary testing, and examination time compared to other body systems. As London Health Sciences Centre (LHSC) is a high-volume autopsy institution, in this quality improvement project we present the utility of a centralized neuropathology medical (hospital) / biobank autopsy database as an internal audit for laboratory management purposes. The database is a simple digital spreadsheet recording retrospectively, on all LHSC medical and biobank neuropathological autopsy consultations from 2005 to 2023, the following parameters: Case type (routine medical *vs.* biobank), in-house *vs.* externally referred, reason for neuropathology consultation, specimens examined (eg. brain, spinal cord, muscle), age at death, dates of autopsy / brain cut / sign-out, involvement of trainees, and final diagnosis. Once established, the database is easy to utilize, and multiple laboratory management statistics can be mined using basic spreadsheet functions. These include volume trends of case types over time, proportions of different reasons for consultation, and turn-around-time as a function of other parameters such as diagnosis, deceased age, trainee involvement, among others. The practical applications of an institutional neuropathology autopsy database for internal audit and laboratory management are many, including guidance on resource management based on consultation patterns, technical expertise based on specimen types, analysis of factors influencing turn-around-time, and guiding curriculum design in neuropathology education. Future directions include extending such strategy to forensic/medical-legal autopsies, which would also be useful in analyzing contributions of neuropathological consultations in addressing the forensic question.

Abstract 11

Free Neuropathol 6:23:15

Meeting Abstract

Ischemic stroke in hypereosinophilic syndrome: a clinico-pathologic study of two cases

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Ischemic stroke is a rare complication of hypereosinophilic syndrome (HES). Manifestations of stroke in HES have been described mainly in the radiologic literature; however, the pathologic characterization of central nervous system (CNS) involvement in HES is limited. We describe two patients who presented to hospital with systemic symptoms and were found to have peripheral blood hypereosinophilia. Thorough investigations for primary and secondary etiologies of hypereosinophilia were negative. Both patients subsequently suffered catastrophic strokes and died despite therapy and resuscitative efforts. Pertinent general autopsy findings in both cases included the presence of intraventricular cardiac thrombi. Post-mortem neuropathologic examination demonstrated a multi-territorial embolic infarct pattern in Patient 1 and a watershed infarct pattern in Patient 2. Microscopic features included the presence of microabscesses consisting of a disproportionately large number of eosinophils and infarcts associated with blood vessels showing occlusive thrombi with surrounding eosinophils. In summary, we present two post-mortem neuropathologic examinations of patients exhibiting CNS infarcts associated with HES, discuss potential pathomechanisms, and review the literature on this rare entity.

Abstract 12

Free Neuropathol 6:23:16

Meeting Abstract

Neuropathological correlates of serum biomarkers during the dying process in humans

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Neurocritical patients (NCPs) admitted to the intensive care unit (ICU) have severe neurological damage stemming from diverse causes including hypoxic ischemic brain injury (HIBI), intracranial hemorrhage (ICH), and traumatic brain injury (TBI), among others. Recently, blood-based neurologic biomarkers have emerged as a promising tool for prognostication, however, their utility for the diagnosis of tissue injury severity and the insights they provide into the pathophysiology of this brain injury are limited. We aimed to investigate the relationship of 120 blood-based systemic and neurologic biomarkers prior to the withdrawal of life-sustaining therapies (WLST) in humans with pre-mortem clinical measures and post-mortem neuropathological features in different neurocritical conditions. Clinical and demographic data, along with arterial biospecimens, were obtained from twenty-nine patients immediately prior to WLSM with subsequent post-mortem neuropathological evaluation. Proteomic analysis of plasma samples was performed using the ARGO HT platform. A standard neuropathological evaluation was performed followed by exploratory and advanced data analyses. Ten brain-enhanced markers were identified that exhibited significant positive associations with neuropathological features, most prominently selective neuronal death (SND) and reactive gliosis: ENO2, MAPT, NEFH, NEFL, NRGN, pTau-217, SNAP25, SNCB, and UCHL1. Notably, these associations were also successful in striating patients by their respective cause of injury. No significant correlations were present with chronic vascular, neurodegenerative, or

inflammatory neuropathology. Collectively, these results provide neuropathological demonstration of the brain tissue changes in neurocritically-ill patients and their immediate correlation with serum biomarkers. They also demonstrate that select brain-enhanced biomarkers likely possess diagnostic and prognostic utility.

Abstract 13

Free Neuropathol 6:23:18

Meeting Abstract

Brainstem cap dysplasias: pathology and novel descriptions

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Brainstem cap dysplasias are characterized by heterotopic axonal tracts coursing peripherally in the brainstem, identified by magnetic resonance imaging. However, there is a paucity of neuropathological descriptions of cap dysplasias. We therefore aimed to review the histopathology and expand the morphological spectrum of cap dysplasias. Three forms are described, including pontine tegmental cap dysplasia (PTCD), medullary tegmental cap dysplasia (MTCD), and anterior mesencephalic cap dysplasia (AMCD; a component of the Joubert syndrome). We describe a series of seven brainstem dysplasias with "cap" features from our autopsy practice: Two PTCD, one MTCD, two AMCD, and two undescribed forms. Both PTCD cases demonstrated hypoplasia of rhombic lip derivatives and a dorsal pontine tegmental tract. The MTCD case demonstrated hypoplastic rhombic lip derivatives, large axonal tracts in the medullary fourth ventricle and coursing along the ventrolateral medulla, post-necrotic tegmental calcifications, and spinal cord anomalies. The two AMCD cases demonstrated Joubert syndrome features with axonal bundles crossing the interpeduncular fossa as leptomeningeal heterotopias. The two additional cases of undescribed "cap" forms have a prominent tectal cap. In one case, this is formed by aberrancy in the pathway of the inferior colliculi brachia, and in the other it is formed by incomplete duplication and fusion of midbrain with cerebellar elements, and heterotopic dorsal and lateral medullary tracts, in the context of a complex supratentorial malformation. In summary, "cap dysplasia" should be considered a morphological descriptor rather than limited to axonal pathology or a particular disease entity, as a diversity of pathological developmental processes are evident.

Abstract 14

Free Neuropathol 6:23:19

Meeting Abstract

Keratan sulfate proteoglycan is not expressed in the human fetal cerebellar system except in pontine nuclei and transitory vermal septa; not in corticospinal fasciculi caudal to internal capsule

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We determined spatial and temporal expression of keratan sulfate (KS) proteoglycan in the cerebellar system, dysgeneses and in white matter fasciculi. KS proteoglycan is an extracellular matrix molecule secreted by astrocytes. KS forms an early template of neuroblastic migration to the cortical plate and some axonal fascicles before axons enter. KS immunoreactivity was studied in sections of cerebellar cortex and in deep cerebellar, inferior olivary and red nuclei and white matter in 18 human fetuses 14–41 weeks gestation at autopsy, 6 infants to 2 years, and 9 cerebellar dysgeneses. Synaptophysin expression was compared. Dentate, inferior olivary and red nuclei are nonreactive at all ages, but pontine nuclei are positive from early 2nd trimester. Cerebellar white matter pathways remain non-reactive throughout fetal and postnatal life. Bergmann glia are nonreactive at all gestational ages. Transitory parasagittal KS septa demarcate vermis/hemispheric boundary. KS is not expressed in Dandy-Walker, Joubert or Chiari malformations, pontocerebellar hypoplasia or cerebellar heterotopia. Axonal fascicles of the corticospinal tract caudal to the internal capsule do not exhibit KS reactivity. Synaptophysin in cerebellar system was normal. Absence of hindbrain KS contrasts with strong forebrain reactivity. Lack of KS expression in normally developing cerebellum and associated brainstem nuclei except pontine, and its absence in cerebellar dysgeneses implies that KS does not contribute to pathogenesis in cerebellar system malformations. Transitory KS septa define early vermal margins, similar to septa of neuromeric segmentation. The intense KS template of the internal capsule does not extend caudally to brainstem fascicles.

Abstract 15

Free Neuropathol 6:23:20

Meeting Abstract

Chromogenic in situ hybridization for detection of *CDKN2A/B* homozygous deletion

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The presence of *CDKN2A/B* homozygous deletion (HD) denotes a higher WHO grade and more aggressive behavior in gliomas and meningiomas. The gold standard assays for detecting copy number variation (CNV) include chromosomal microarray, next generation sequencing, and fluorescence in situ hybridization (FISH). However, these methods are costly, time consuming, and have limited availability in resource-sparse centers. Thus, an inexpensive and time-efficient assay for detecting *CDKN2A/B* HD would be helpful for routine neuropathology cases. Chromogenic in situ hybridization (CISH) combines DNA hybridization techniques utilized in FISH with conventional peroxidase reactions utilized in immunohistochemistry to interrogate CNV with brightfield microscopy. We hypothesize that CISH is a sensitive and specific method for detecting *CDKN2A/B* HD. We performed *CDKN2A* CISH on a retrospective cohort of whole slide tissue sections of 5 gliomas and 10 meningiomas using the ABNOVA CDKN2A/CEP9 CISH probes and implementation kit. Two pathologists independently counted and scored 100 cells from each case showing any CEP9 (red/control) signals and no CDKN2A (green) signals as HD, and cells showing both red and green signals as *CDKN2A/B* intact. The pathologists' scores were averaged and compared to the *CDKN2A/B* status for each of the glioma and meningioma cases, acquired via FISH testing and methylation profiling, respectively. Our results demonstrate that detection of *CDKN2A/B* HD with CISH showed high concordance with *CDKN2A/B* locus interrogation with orthogonal assays. CISH is a sensitive and specific method for detecting *CDKN2A/B* HD in glioma and meningioma and is a more cost-effective and practical alternative to traditional CNV detection methods.

Abstract 16

Free Neuropathol 6:23:21

Meeting Abstract

Routine immunohistochemical assessment of mismatch repair proteins in high-grade gliomas: retrospective analysis and clinical implications

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Testing for deficiencies in mismatch repair (MMR) proteins (MLH1, PMS2, MSH2, and MSH6) via immunohistochemistry (IHC) has become a widely-adopted means of screening for tumour predisposition syndromes and for informing potential immunotherapeutic treatment options. While some centres rely on IHC for all 4 MMR proteins, others have relied on a more cost-effective means of screening only the secondary partner proteins PMS2 and MSH6 (as losses of MLH1/MSH2 are expected to result in degradation of PMS2/MSH6S). Just under 2 years ago, Cancer Care Ontario (CCO) began to fund routine MMR IHC testing on all high-grade gliomas (HGGs). London Health Sciences Centre has thus far tested 132 of these tumours for all 4 MMR proteins via IHC. Of these, 4 (approximately 3 %) were found to have a loss of MMR immunopositivity (2 for MSH6, 2 for PMS2). These cases had particularly elevated nuclear pleomorphism when compared to most other HGGs and involved sporadic loss of MSH6 (with negative germline testing for Lynch syndrome), loss of MSH6 secondary to temozolomide chemotherapy (with intact MMR in the original tumour), and biallelic loss of PMS2 in the context of 2 cases of congenital mismatch repair deficiency syndrome (CMMRD). This IHC approach has been efficacious in contributing towards the diagnosis of tumour predisposition syndromes, identifying monoallelic versus biallelic loss of MMR proteins, and providing potential targets for immunomodulatory therapies. Furthermore, these results support the use of a two-antibody MMR IHC screening approach relying solely on MSH6 and PMS2.

Abstract 17

Free Neuropathol 6:23:22

Meeting Abstract

Malignant transformation of craniopharyngioma with spinal metastasis: a case report and comprehensive literature review

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Malignant transformation of craniopharyngioma is exceedingly rare with few cases characterized by systemic spread or molecularly confirmed clonal progression. We present a pediatric case of adamantinomatous craniopharyngioma that evolved over 12 years into a high-grade epithelial neoplasm with clival extension and spinal metastases causing vertebral fracture and spinal cord compression; to our knowledge, this is the 3rd case of spinal dissemination in the literature. The transformed tumor demonstrated high-grade epithelial morphology (Ki-67: 100 % vs 5 % initially), strong pancytokeratin and vimentin expression, partial H3 K27me3 loss, and absence of glial or neuroendocrine differentiation. Molecular profiling confirmed the same CTNNB1 p.S33C mutation in both the initial and transformed tumor, along with a segmental 1p deletion acquired in the latter, supporting molecularly confirmed clonal evolution. A systematic review (n = 35) on craniopharyngioma cases with malignant transformation revealed consistent epithelial immunophenotype, frequent p53 overexpression (89 %, n = 17), high mean Ki-67 (41 ± 21 %). More surgeries were significantly associated with longer time to transformation (r = 0.49, p = 0.005), suggesting that multiple surgical interventions delayed progression, while no significant correlation was observed with radiation dose (r = 0.01, p = 0.97) or tumor size (r = 0.40, p = 0.16). These findings support a clonal evolution model and highlight the importance of molecular surveillance in long-standing craniopharyngiomas.

Abstract 18

Free Neuropathol 6:23:23

Meeting Abstract

Methylation classification in meningioma prognostication: strengths and caveats

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DNA methylation patterns have emerged as a useful signature for classifying brain tumours. These patterns tend to be consistent within tumour entities and even within subtypes, and have proved to be a helpful tool in resolving diagnostically challenging cases. However, methylation classification is not always reliable. In particular, in light of the recent cIMPACT-NOW guidelines for meningioma prognostication, inconsistencies have appeared between the prognostic subtypes defined by methylation profiling and the grading recommended on the basis of copy number profiles. To explore this, we reviewed methylation results from cases at SickKids Hospital, focusing on areas of concordance and discordance. From 841 total methylation cases, 46 were meningiomas. Within this group 13 % showed discordant prognostication between methylation subtyping and the copy number-based stratification described in cIMPACT-NOW update 8. We present several illustrative cases to highlight when methylation was useful, when it led to conflicting results, and the factors contributing to the discordance. Previous studies have suggested a multi-factorial approach to meningioma grading and prognostication underscored by our results. How to approach grading in the setting of discordant findings will require further study with well annotated clinical outcome data. While methylation can be a powerful diagnostic adjunct, these results caution against overreliance on this method alone for meningioma classification and prognostication.

Abstract 19

Free Neuropathol 6:23:24

Meeting Abstract

Liquid biopsy for CNS tumours

Yoshiko Nakano[1], Robert Siddaway[2], Liana Nobre[3], Ian Burns[4], Mansuba Rana[2], Richard Yuditskiy[2], Cyril Li[2], Julie Bennett[1], Anthony Liu[1], Uri Tabori[1], Cynthia Hawkins[2]

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Liquid biopsy (LB) is an emerging diagnostic tool for detecting tumor-specific alterations in body fluids that has many potential advantages including: identifying tumors with higher sensitivity and specificity than imaging; replacing invasive surgical biopsy; and monitoring tumor evolution by serial assessments. We investigated the feasibility and utility of cerebrospinal fluid (CSF)-based LB for patients with CNS tumors. 475 CSF samples were collected from patients with known or putative CNS tumors. To detect circulating tumor DNA (ctDNA), cell-free DNA was extracted and panel sequencing and/or low-pass whole genome sequencing were performed. At diagnosis/baseline assessment, ctDNA was detected in 78 % of high-grade gliomas, 44 % of low-grade gliomas, 55 % of medulloblastomas and 93 % of germ cell tumor cases. In patients with non-biopsied CNS lesions, ctDNA was diagnostic in 14 patients including for glioma, neuroblastoma and leukemia. Furthermore, in seven recurrent medulloblastoma cases where primary tumor copy number profiles were available, new copy number variants suggestive of tumor evolution/new subclones were seen. In patients for whom serial sampling was performed during and/or after completion of therapy, ctDNA clearance was observed in response to therapy. However, persistent ctDNA was observed in some patients despite imaging showing no residual tumor, highlighting the potential utility of ctDNA as a molecular-based measurable residual disease assessment for better risk stratification. These findings pave the way for the clinical use of LB in CNS tumors and provide proof of concept for future incorporation of LB into clinical trials.

Abstract 20

Free Neuropathol 6:23:25

Meeting Abstract

Pituitary inflammatory lesions including lymphocytic hypophysitis: a 30-year single centre experience

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In Manitoba (population 1.4 million) all neurosurgical procedures and all autopsy neuropathology examinations are done at one center. In a retrospective review (1996–2025) I searched for cases with pituitary inflammation. Among 678 surgical pituitary biopsies we encountered: 15 idiopathic lymphocytic hypophysitis; 18 PitNET with inflammation; 34 PitNET + apoplexy with inflammation; 13 inflammation associated with Rathke cleft cyst; 3 bacterial infection. Among 4768 pituitaries from autopsies we encountered: 16 idiopathic lymphocytic hypophysitis; 1 PitNET + apoplexy; 2 pituitary apoplexy without obvious cause; 3 inflammation associated with Rathke cleft cyst; 19 pituitary inflammation and associated disseminated infection (2 Herpes simplex; 5 suspected viral; 5 Mycobacterial; 7 other bacterial sepsis / meningitis). In some autopsy cases lymphocytic hypophysitis was incidental, 1 had chronic demyelinating disease, 4 had prominent inflammation in the thyroid, and in 1 case it was considered to be a major contributor to death. Four decedents had pre-mortem clinical endocrine syndrome (38-year female hypothyroidism; 49-year female hyperprolactinemia; 44-year male Addison disease and hypothyroidism; 49-year female diabetes mellitus). Conclusive proof of autoimmune lymphocytic hypophysitis is elusive. PitNET, apoplexy, and cyst-associated inflammation are common and of uncertain significance. In all specimens, complete history and imaging correlates are necessary. Although rarely a contributor to death, examination of the pituitary gland is an important part of the autopsy in individuals who die unexpectedly, particularly if they have a history of endocrine disease or recent neurological symptoms.

Abstract 21

Free Neuropathol 6:23:26

Meeting Abstract

Additional presence of *LZTR1* mutation in a VGLL-fused central nervous system schwannoma with neuroblastoma-like cell dense areas

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Vestigial-like family (VGLL) altered CNS schwannoma (VGLLACS) is a new tumor entity, recognizable by DNA methylation approaches. The critical alteration is a fusion, involving either VGLL1 or VGLL3. The fusion partner can be EWSR1, CHD7, and rarely SS18. A recent series of 20 VGLLACS did not identify additional recurrent mutations. To add to the span of the condition, we report a previously healthy 29-year-old man who presented with a clonic seizure. Head MRI showed an avidly enhancing well-demarcated intra-axial nodule in the left superior frontal gyrus extending to cortex. At surgery the intra-axial firm mass, well-demarcated from the brain, was completely resected. Histologically, most of the tumor consisted of spindle cells arranged in streams organized in rhythmic palisades in a collagenous background. In addition, there was a peripheral nodule made up of densely packed neuroblastoma-like cells. Both areas showed GFAP expression, and reticulin single cell wrapping. At the periphery the tumor was interspersed with synaptophysin-rich neuropil, and Rosenthal fibers were present within the tumor. A methylation profile analysis carried out at the National Cancer Institute matched to CNS Schwannoma VGLL-fused. TruSight PanCancer next generation sequencing (NGS) revealed a *EWSR1::VGLL1* fusion, specifically EWSR1 NM_013986 (exon 9, 331 AA) to VGLL1 NM_016267 (5' UTR , exon 2). A tier II mutation in LZTR1 (p.Trp265*NM_006767.4:c.794G>A) was identified by hybridization-capture NGS assay. Our case represents another rare case of VGLLACS with neuroblastoma-like areas in association with an additional mutation in LZTR1, a gene mutated in both schwannosis and glioblastoma.

Abstract 22

Free Neuropathol 6:23:27

Meeting Abstract

Histopathological and clinical features can discriminate immune from non-immune statin-induced myotoxicity

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Anti-HMGCR immune-mediated necrotizing myopathy (IMNM) is a subacute to chronic progressive auto-immune myositis diagnosed on clinical phenotype, serology and muscle biopsy, and non-immune toxic rhabdomyolysis (TR) is an acute potentially lethal condition usually diagnosed on clinical phenotype alone. However, muscle biopsies are sometimes still performed in TR patients on statins to rapidly rule out IMNM, particularly when there is no quick access to serology results. Our objective was to describe histopathological and clinical features of TR patients and compare them with a group of IMNM controls. Out of 924 muscle biopsies received between 2019 and 2024 at our referral center, 36 biopsies from statin-exposed TR patients and 29 anti-HMGCR IMNM controls were identified. Histopathologic analysis revealed overlapping morphology in 85 % of cases. Discriminating features highly suggestive of TR included predominance of pale acute necrotic fibers ($p < 0.001$), groups of 4+ adjacent necrotic fibers ($p < 0.01$), regenerative basophilic cuffs ($p < 0.001$), and lack of $LC3^+$ granular staining in non-necrotic fibers ($p < 0.001$). Review of clinical data revealed acute creatinine elevation in 94 % of TR patients and none of IMNM controls ($p < 0.001$). Peak creatine kinase levels (CKs) > 25,000 IU/L were seen in 44 % of TR and none of IMNM ($p < 0.0001$). CKs normalized on average in 12 days (range 8–21) in TR and in >30 days in all IMNM cases. Although pathology can be discriminating, TR should be confirmed by following CKs closely over a few days without immunosuppression and muscle biopsy only performed to confirm IMNM in patients with persistently elevated CKs.

Abstract 23

Free Neuropathol 6:23:28

Meeting Abstract

Muscle biopsy findings in an infant with arthrogryposis associated with a *THOC2* variant: a case report

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This case report provides the second reported description of muscle biopsy findings in an infant with arthrogryposis associated with a *THOC2* variant. *THOC2*-related neurodevelopmental disorder is caused by deleterious variants in *THOC2*; this gene encodes a component of the TREX (TRanscription-EXport) complex, which plays a critical role in mRNA processing and export. *THOC2*-related disorder is characterized by intellectual disability, often associated with seizure disorders, infantile hypotonia, tremors, gait disturbance and growth impairment. More recently, *THOC2* variants have been linked to X-linked recessive fetal arthrogryposis multiplex congenita (Cureus 2021; 13(11):e19682; NMD 2023;33(12):978-982). We present a case of an infant who died shortly after birth at 33 weeks gestational age (GA). A fetal ultrasound at 30 weeks GA was significant for arthrogryposis, hydrops and massive polyhydramnios. Genetics consultation and amniocentesis was pursued prior to delivery, and initial genetic testing showed a normal karyotype and rapid aneuploidy detection (RAD). A limited postmortem examination was performed. Biopsy of the quadriceps muscle was significant for moderate variation in myofiber size, and cytoplasmic bodies within several myofibers. Trio whole exome sequencing detected a hemizygous, likely pathogenic variant in *THOC2,*c.2482-1_2482del . The results of muscle biopsy are identical to those described in a previously reported fetus with arthrogryposis and a *THOC2* variant (NMD 2023;33(12):978-982), further validating this neuromuscular phenotype. This case report highlights the critical role that the correlation of whole exome sequencing and postmortem examinations play in expanding our clinical knowledge of rare genetic diseases and their phenotypes.