

# CANP 2023 Abstracts

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## Abstract #1: Aqueductal stenosis and mesencephalosynapsis in fetal brains, part 1: classification, and morphology.

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### Abstract

Systematic studies of the histology of fetal aqueductal stenosis (AS) are uncommon. Mesencephalosynapsis, (midline fusion of the midbrain colliculi with absence of the dorsal medial septum), is infrequently described in the literature in association with brain malformations. We conducted a 12 year review of our institutional experience with fetal obstructive hydrocephalus and AS using text word searches for aqueductal stenosis, aqueductal atresia, ventriculomegaly, hydrocephalus and rhombencephalosynapsis. We obtained 274 cases. We excluded Chiari malformations, skeletal dysplasias, ex-vacuo ventriculomegaly and cases with unsatisfactory representation of the midbrain. 118 cases of obstructive ventriculomegaly with aqueductal pathology remained. Clinical and histological features of each case were reviewed. The median gestational age was 23 weeks, interquartile range = 21 to 25 weeks. We identified 5 major morphological patterns of AS. **1) Aqueductal atresia** (14 of 118, 11.9%); **2) Severe stenosis** (22 of 118, 18.6%); **3) Mild stenosis** (51 of 118, 43.2%); **4) Borderline stenosis** (10 of 118, 8.5%); **5) Slit-like aqueduct** (13 of 118, 11%). 8 cases had a seemingly patent aqueduct (6.8%), but 7 of these had a clear obstructive lesion (2 had isolated glial webbing of the aqueduct, 5 had other outflow obstructions). Mesencephalosynapsis was seen in 42 of 118 cases (35.6%), more commonly in cases of atresia and severe stenosis. Hemosiderin laden macrophages were present in the aqueduct 39 of 118 cases (33.1%). Atresia and severe AS showed a stronger association with multiple congenital anomalies and other central nervous system malformations when compared with the milder forms of AS.

Disclosures: The authors state that this is original work and is not subjected to any copyrights. The authors have no conflict of interest to disclose.

Learning objectives:

1. Describe the morphologic spectrum of aqueductal stenosis
2. Define mesencephalosynapsis and its association with aqueductal lesions and other CNS malformations.

## Abstract #2: Aqueductal stenosis and mesencephalosynapsis in fetal brains, part 2: associations.

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### Abstract

As part of our review of fetal aqueductal histopathology, we reviewed the brain and autopsy findings accompanying the morphologies of aqueductal stenosis (AS) and mesencephalosynapsis (MeS), the absence of the median dorsal glial septum, in 118 cases of fetal hydrocephalus. We encountered some novel associations. 1. Rhombencephalosynapsis: 21 of 24 (87.5%) cases of rhombencephalosynapsis demonstrated AS with MeS and 6 cases (25%) demonstrated a mass of neurons resembling heterotopic Purkinje cells obstructing the rostral 4th ventricle/caudal aqueduct. 2. Hemifacial Hypoplasia: we encountered 7 cases of hemifacial hypoplasia (HH) with AS and MeS. On review of central nervous system pathology in HH, of the 21 cases of HH in our archives 7 had hydrocephalus, and all 7 had AS and MeS, including two rhombencephalosynapses. AS with MeS seems to be a principal pathology causing hydrocephalus in HH. 3. Tegmental Injury: we identified 3 cases of symmetrical tegmental injury with calcifications and microglial aggregates, in a pattern suggestive of fetal hypoxic ischemic injury. Two cases had AS with atresia, and one a slit like aqueduct, none had MeS. Tegmental injury in a hypoxic ischemic pattern is an infrequent but distinct pattern producing AS and hydrocephalus. Other distinctive pathologies associated with AS are the VACTERL association (2 with MeS, 5 without), holoprosencephaly (n=8) and amniotic rupture sequence (n=3, all with MeS).

Disclosures: The authors state that this is original work and is not subjected to any copyrights. The authors have no conflict of interest to disclose.

Learning objectives:

1. Describe the spectrum of aqueductal stenosis in distinct brain anomalies.
2. Review the presence of the median dorsal glial septum in primary and secondary brain anomalies.

## Abstract #3: A novel association: distal arthrogryposis, KIF21A and fetal neuroaxonal dystrophy

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### **Abstract**

Although fetal neuroaxonal dystrophy is an established etiology for fetal akinesia, the underlying genetics were not known. KIF21A is a kinesin motor protein that plays an important role in microtubule dynamics, including regulation of axonal growth. Recently, Falk et al. (2023) linked bi-allelic loss-of-function variants in KIF21A to severe fetal akinesia with arthrogryposis.

We present the case of a young infant diagnosed in utero with distal arthrogryposis, who died at 3 weeks of age, that represents an independent discovery of this autosomal recessive KIF21A-related condition. Her course was complicated by respiratory issues, hypotonia, seizures and neurological deterioration. Brain MRI was significant for polymicrogyria, diffuse brain volume loss and mild thinning of optic nerves. Autopsy findings confirmed the bilateral extensive polymicrogyria and reduced brain volume, with probable thinning of the corpus callosum and descending corticospinal tracts. Histologically, axonal spheroids were seen throughout multiple regions of the central and peripheral nervous system. Other findings included cerebellar heterotopia, simplification of the inferior olives and a congenital neurogenic myopathy. Clinical exome sequencing revealed biallelic compound heterozygous variants in KIF21A. Functional yeast studies supported the causality of the described variants.

Our case represents an independent discovery and second report of the autosomal recessive condition related to KIF21A and reveals fetal neuroaxonal dystrophy as the underlying neuropathology, which has not previously been described in the literature. Our findings expand the

spectrum of KIF21A-related disorders, and highlight the importance of a multidisciplinary approach, exome sequencing, and multi-site collaboration in the investigation of rare genetic conditions.

Learning objectives:

1. Describe the biologic roles of KIF21A and their linkage to human disease
2. Discuss the association between KIF21A and fetal arthrogryposis
3. Recognize the neuropathological features of fetal neuroaxonal dystrophy

## Abstract #4: Polymicrogyria through a tensegrity lens

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### **Abstract**

Polymicrogyria is an anomaly of cortical development. It may be pure or associated with other lesions. Polymicrogyria is etiologically diverse and associated with a spectrum of neurological consequences proportional to its extent and associated abnormalities. The literature has mediated a debate on the timing and significance of particular etiologies, inviting a variety of theories to account for its stereotypic architecture.

Congenital cytomegalovirus (CMV) infection is a common cause of polymicrogyria. In a collection of such cases, ranging from 16 to 39 weeks gestational age, several findings were almost invariable: subventricular zone necrosis, subventricular germinal cell infection, radial glial disruption and injuries to the pial-glial border. Subcortical neuronal heterotopias and leptomeningeal heterotopias were also common. Clinical details and pathological findings indicate that the responsible insults occurred before neuronal migration was complete, lasted several weeks and led to a variety of structural perturbations to the developing brain.

These cases add to the evidence that polymicrogyria is not solely post-migrational and that a variety of injuries (and timings) can replicate its relatively stereotyped morphology. A reductionist focus on timing and etiology has distracted from a more fundamental and versatile construct built on the principles of tensegrity, whereby the brain's unique morphology (and disruptions of the same) can be explained on the basis of forces that exist at the tissue, cellular and subcellular levels. The natural experiment of polymicrogyria in congenital CMV infection lends support for tensegrity as a basis for normal and abnormal morphologies while embracing the variables of timing and etiology.

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Learning objectives:

1. To review the pathological features of polymicrogyria, particularly in the setting of congenital CMV encephalitis (CMVE)
2. To consider how the injuries in congenital CMVE can influence the balance of tensegrity within the developing brain

## Abstract #5: Imaging axonal pathology in the retina as a potential non-invasive biomarker for amyotrophic lateral sclerosis

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### Abstract

Imaging biomarkers of axonal pathology in amyotrophic lateral sclerosis (ALS) remain limited. We identified axonal spheroids, a pathological hallmark of ALS, in the post-mortem retina of ALS patients. We aim to establish the imaging of axonal pathology in the retina as a non-invasive ALS biomarker. Following ethics approval, 10 post-mortem ALS and 8 age-matched control eyes were imaged using a clinical eye imaging device (Spectralis, Heidelberg Engineering) combining confocal scanning laser ophthalmoscope and optical coherence tomography (OCT). Confocal microscopy imaging of phosphorylated neurofilament (P-NF) immunostained retinas was performed for histological validation.

Sequential *in vivo* retinal imaging was performed in ALS mice (n=28) and age-matched controls (n=28) with Spectralis. Statistical analysis was performed using Generalized Linear Mixed Modeling (RStudio).

*Ex vivo* human retinal fundus imaging (blue reflectance) detected more hyperreflective puncta in ALS patients compared to controls ( $19.04 \pm 22.5$  vs.  $2.7 \pm 1.6$  /mm<sup>2</sup>,  $p < 0.05$ ). OCT confirmed puncta were localized in the retinal nerve fiber layer (RNFL).

*In vivo* mouse fundus imaging (infrared reflectance) showed significantly more puncta in the retina of ALS mice, compared to controls ( $7.2 \pm 5.2$  vs.  $1.8 \pm 0.9$ ,  $p < 0.05$ ), with a progressive increase over time in ALS mice ( $p < 0.001$ ). Immunofluorescence studies showed the presence of P-NF-positive axonal spheroids in the RNFL in human and mouse ALS retinas.

Axonal pathology in ALS is detectable with a widely available clinical eye imaging device. This study suggests imaging of the axonal pathology in the eye is a promising biomarker for assessing ocular phenotype, progression, and treatment response in clinical trials in ALS.

Learning objectives:

1. Understand the axonal pathology in the retina in ALS.
2. Describe the potential use of different non-invasive eye imaging modalities for assessing ocular biomarkers of ALS.
3. Review the advantages and limitations of eye imaging biomarkers and their potential use in combination with other established biomarkers in ALS.

## Abstract #6: Progressive Supranuclear Palsy: a Novel Phenotype of Germline *SQSTM1* (p62) Mutation

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### Abstract

A woman presented at age 61 with anhedonia and emotional lability with an MMSE of 28/30. Two years after presentation, she developed disinhibition — notably inappropriate giggling — as well as a wide-based gait. Five years after initial presentation, there was the development of ocular abnormalities including saccadic intrusions and upgaze limitation. Fine motor movements were slower and less elegant on the left. The patient passed away in a nursing home seven years after presentation.

Family history was notable for a father and paternal grandmother who were prone to giggle and have angry outbursts. Neither carried a formal neurological diagnosis. Antemortem genetic testing in our patient revealed a c.1211T>C(p. Met404Thr) mutation in *SQSTM1*(p62).

At autopsy, there was moderate frontotemporal atrophy. Histological sections showed atrophy and gliosis of the subthalamic nucleus. Grumose degeneration of the dentate nucleus was also present. p62 and phosphorylated-tau(AT8) immunostaining demonstrated globose tangles most prominent in substantia nigra, pontine nuclei, and inferior olive. Neurofibrillary tangles were rare in cortex and basal ganglia where tufted astrocytes and coiled bodies predominated. No abnormal beta-amyloid, TDP-43, or alpha-synuclein staining was present. This was consistent with a pathological diagnosis of progressive supranuclear palsy (PSP).

Mutations of *SQSTM1*(p62) have been associated with FTL/ALS, and inclusion body myositis-like myopathy, and familial Paget disease of bone. Here, we report (to our knowledge) the first case of *SQSTM1* mutation presenting with pathologically-confirmed PSP. The mutation in this case (p.Met404Thr) has been reported to impair ubiquitin binding and has not previously been associated with neurodegenerative disease.

### Learning objectives:

1. Appreciate the genetic landscape of familial neurodegenerative disease

## Abstract #7: A 108 year old brain with near normal cognition

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### Abstract

A 108 year old male veteran lived in a nursing home, and participated in regular cognitive testing. Despite being legally blind and hearing impaired, his last MMSE, 3 years prior to death at age 105 was 25/30. The brain weighed 1365 gr and showed severe bilateral hippocampal atrophy. H&E sections showed complete neuronal loss of CA1 bilaterally, and severe loss of vermal Purkinje cell, but the neuronal populations of the neocortex and entorhinal cortex were mostly preserved. Reactive gliosis was prominent throughout the cingulate cortex, mostly restricted to grey-white junction in the frontal, parietal and temporal cortices, and absent in the occipital cortex. The main protein deposit was TDP-43, present in the frontotemporal neocortex as neuronal cytoplasmic inclusions and thick short process in the superficial layers (type A), and in the hippocampus as a dense network of thin process in CA1. Tau labeled neurofibrillary tangles in the entorhinal cortex and the locus ceruleus, and plaque-like structures in the absence of amyloid in the hippocampus. Beta amyloid plaques were moderately dense in the neocortex, and accompanied by vascular deposits in the occipital cortex only. Alpha-synuclein Lewy bodies were present in the locus ceruleus, but not the substantia nigra. The surprising findings were the extent of hippocampal lesions compatible with near normal function, and the severe cortical astrocytosis out of proportion to abnormal protein deposits or neuronal loss. We propose that astrocytosis may develop in response to neuronal TDP-43, made conspicuous by ageing, and play a neuroprotective role, as postulated in ALS.

Disclosure. The abstract is original work and is not subject to copyright elsewhere in view of a publication in Free Neuropathology. The authors declare no conflicts of interest

Learning objectives:

1. To recognize brain histological changes in the oldest-old
2. To become aware of brain resilience in the oldest-old
3. To explore possible relationships between TDP-43 and astrocytosis

## Abstract #8: Cellular activation patterns of CD10+ fibro-adipogenic progenitors across acquired disease states in human skeletal muscle biopsies.

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### Background

Fibro-adipogenic progenitors (FAP) are resident mesenchymal stem cells of skeletal muscle with defined roles in muscle fiber repair and fibrosis. Experimental studies have shown their involvement in fibrofatty degeneration, denervation atrophy, and their susceptibility for pharmacological intervention. FAP reaction patterns in human muscle biopsies are largely unknown, but have potential to inform translational approaches.

### Method

32 muscle biopsies from the archives of Vancouver General Hospital were selected from 8 groups (normal, dermatomyositis, IBM, anti-synthetase syndrome, IMNM, denervation, type 2 atrophy, rhabdomyolysis). FAP reaction patterns were analysed on routine CD10 immunohistochemical staining and compared between groups. Double staining with MxA was performed on a subset. Groups were compared histologically and by semi-quantitative scoring.

### Results

Activated endomysial CD10+ FAPs showed thickening and expansion of their normally delicate cell processes surrounding muscle fibers, and endomysial cell clusters evidencing proliferation. Comparison across groups confirms FAP activation in association with fiber degeneration/regeneration, foci of inflammation, and denervation, in keeping with experimental results. Unexpectedly, dermatomyositis and anti-synthetase biopsies show diffuse activation. FAP activation in dermatomyositis coincided with sarcoplasmic MxA expression.

### Conclusion

Assessment of CD10+ FAP activation is routinely possible using CD10 immunohistochemistry and demonstrates cellular FAP reaction patterns often in keeping with preclinical results.

Prominent expansion of FAP processes surrounding myofibers suggests enhanced interaction between myofiber/basement membranes and FAPs during activation. The presence of diffuse FAP activation in dermatomyositis and anti-synthetase biopsies raises the possibility of FAP activation as part of the autoimmune process. Future diagnostic applications, clinical significance and therapeutic potential remain open questions.

Learning objectives:

1. Describe the histological appearance and pathological reaction patterns of fibro adipogenic progenitors upon CD10 immunohistochemical staining.
2. List patterns of fibro adipogenic progenitor activation for several myopathological conditions.

## Abstract #9: Assessment challenges and headaches in the implementation of Competence By Design (CBD): The experience in a Diagnostic and Molecular Pathology residency program

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**Background/Objectives:** The recent implementation of Competence by Design (CBD) in Neuropathology residency creates changes in both education philosophy and practical administration. This study analyzes perceptions of specific assessment criteria in CBD at one Diagnostic and Molecular Pathology (formerly Anatomical Pathology) residency program, and the lessons learned.

**Methodology:** We focused on assessment interpretation of Transition to Discipline (TTD) Entrustable Professional Activities (EPAs), which overlap with those in Neuropathology – basic specimen handling, basic microscopy, and summarizing clinical information for clinicopathologic correlation. Eight pathology faculty were interviewed. They were first shown the EPA titles only (“gestalt” impression), then the full descriptions, and expressed their perceived expectations of the EPAs during each phase. Interviews were recorded, transcribed, and subjected to thematic analysis.

**Results:** The gestalt impression of specimen handling and microscopy EPAs varied widely in the expected level of performance at a “basic” stage. While the descriptions clarified expectations, participants disagreed on whether they were valid and complete, due to contrasts with their own training experience, daily work, and subspecialty niche. It was also felt that all EPA descriptions contained internal inconsistencies that were challenging to interpret. Consequently, faculty described varying approaches to resident assessment despite identical criteria.

**Conclusions:** Our findings demonstrate significant subjectivity in the interpretation of CBD EPAs, even with detailed assessment criteria. This is due to both inadequate clarity of descriptions as well as faculty attitudes and biases. Therefore, further refinement of EPA

descriptions may be necessary, along with education of faculty on the underlying purpose of each assessment item.

Disclosures: The authors have no conflicts of interest. This abstract is original work and is not subject to copyright elsewhere in view of a publication in Free Neuropathology.

#### Learning Objectives

1. List potential challenges with respect to assessment in Competency by Design (CBD) in Neuropathology residency
2. Describe the reasons for such challenges
3. Propose possible solutions to such challenges which are applicable to individual residency programs

## Abstract #10: Isolated small vessel inflammation in temporal artery biopsies: small red flags

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Temporal arteritis (TA) is the most common vasculitis over age 50. Untreated, many patients will suffer blindness or stroke. Gold standard diagnosis is achieved by temporal artery biopsy. The aim of this research is to investigate the relevance of small vessel inflammation in such biopsies. Our dataset is comprised of 72 temporal artery biopsies subjected to a uniform re-examination paired with clinical data including demographics, history, physical examination, and laboratory findings. Documented pathology variables include the presence or absence of TA, angiitis of vasa vasorum (AVV), and inflammation of small peri-adventitial vessels consistent with small vessel vasculitis (SVV). Clinical and pathological variables were subjected to multivariate analysis. In brief, 25% of cases were identified as TA, 21% as isolated AVV, 7% as isolated SVV, and 5% as mixed AVV/SVV, while 42% showed no inflammation. All cases of TA were accompanied by small vessel inflammation: 94.4% exhibiting AVV with or without SVV, and 5.6% exhibiting SVV, demonstrating a strong association between TA and small vessel inflammation. Of the 24 cases with isolated AVV/SVV, 25% progressed to a clinical diagnosis of TA within one year whereas only 10% of cases with no identifiable inflammation showed such progression. Furthermore, isolated AVV/SVV was identified in 25% of patients with a high clinical probability for TA, 60% of whom acquired a diagnosis of TA on clinical grounds within one year of follow up. Our findings suggest that isolated AVV/SVV identifies a subgroup of patients with a higher risk of harboring or developing TA.

Disclosure: It is original work and is not subject to copyright elsewhere in view of a publication in Free Neuropathology. The authors have no conflicts of interest to declare.

Learning objectives:

1. Gaining insight into the various subtleties of pathologic features observed in temporal artery biopsies.
2. Understanding the possible clinical and prognostic significance of small vessel inflammation identified in temporal artery biopsies.

## Abstract #11: The International Spinal Cord Injury Biobank: Neuropathological contributions to global translational research in traumatic spinal cord injury

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Much of the scientific research dedicated to traumatic spinal cord injury (tSCI) has focused on animal models of tSCI. Our understanding of human tSCI is hampered in part by lack of biospecimens from patients. This gap in knowledge represents an important void in tSCI translational research, as biological differences between animal models and the human condition need to be considered in the development of therapeutic approaches. Herein we introduce the International Spinal Cord Injury Biobank (ISCIB; [www.sci-biobank.org](http://www.sci-biobank.org)), a Vancouver-based, multi-user biorepository with global range and the mission of accelerating therapeutic development in SCI, including tSCI, through improved biological understanding of human SCI. Certified by the Canadian Tissue Repository Network, ISCIB will be introduced to the community of Canadian neuropathologists as a possible resource for research or post-mortem spinal cord donation. We describe the translational research gap that ISCIB is helping to fill; its structure, governance, and certification; how data and samples are accrued, processed and stored; the process through which samples and data are shared with global researchers; and finally, an example of novel clinicopathological insights we are gathering in human tSCI. By expanding awareness of the existence of ISCIB within the community of Canadian neuropathologists, we hope to further the mission of this pioneering world-class SCI biorepository.

Learning objectives:

1. Understand the need for human biospecimens in translational traumatic SCI research.

2. To introduce the International Spinal Cord Injury Biobank, a Canadian resource with global impact

## Abstract #12: Title: Death and the MAiD at the Calgary Brain Bank

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### Abstract:

**Objective:** Determine tissue quality parameters in Medical Assistance in Dying (MAiD) brain donations

**Background:** In Canada, Medical Assistance in Dying (MAiD) was decriminalized in 2015 and was legalized in Canada and Alberta in June 2016.

**Methodology:** Review 18 brain donations from MAiD patients to the CBB and compare them to non-MAiD donations. Four quality parameters were compared to non-MAiD patients in the CBB: post-mortem interval (PMI), neuronal acidophilia (surrogate marker for hypoxia-ischemia), type 2 astrocytes in the globus pallidus externus (surrogate marker for systemic metabolic derangements), and cerebellar internal granular neuron autolysis (reflection of patient's pre-mortem medical state, including systemic acidosis).

### Results:

1. Two procedural changes have brought the PMI from an average of 44 hours to 6 hours in MAiD patients. MAiD patients have a significantly shorter PMI than non-MAiD patients.
2. Unlike many brain bank patients, who die from non-neurological terminal diseases, most MAiD patients die without significant systemic diseases; they die without undergoing prolonged dying.
3. MAiD patient brains have no or only early acidophilia in sensitive sites.
4. MAiD patient brains have no type 2 astrocytes.
5. MAiD patient cerebellums lack internal granular neuron autolysis.

**Conclusions:** MAiD patients represent an important source of autopsy tissue, which circumvents degradation of brain tissue during the dying process that affects many brain banks.

### Learning Objectives:

1. Learn important quality parameters in brain bank tissue
2. Understand that MAiD patients represent an important source of autopsy brain tissue

## Abstract #13: Blunt truths: Innovations in identifying neck injuries from infant head trauma.

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Radiologic and pathological evidence, supported by case practice, reveal that blunt head trauma in infants often concurrently injure neck structures. Initial studies suggested that shearing forces might compromise cervical nerves, particularly at the dorsal root ganglia. Subsequent publications, however, shed light on possible harm to other vulnerable anatomical structures, such as hemorrhaging or swelling in the nuchal ligament, interspinous ligaments, and the junction between the anterior arch of C1 and the odontoid process. Conventional in situ spine examinations, with or without spinal cord removal, fail to detect these injuries. An enhanced ex situ cervical spine evaluation method, evolved from prior techniques, offers a comprehensive macro- and microscopic exploration of the infant's internal neck anatomy. This advanced approach provides a deeper insight into potential injuries throughout the cervical soft tissues, chondro-osseous structures, and neuroanatomy. Adopting this method elevates the reliability of conclusions in the complex landscape of infant head and neck trauma research. Disclosure: This abstract represents original work by the author, is not subject to copyright elsewhere, and is intended for publication in Free Neuropathology.

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Learning Objectives:

1. Understand the Connection between Blunt Head Trauma and Neck Injuries in Infants

2. Evaluate Traditional and Advanced Spine Examination Techniques
3. Comprehend the Limitations of Conventional Examination Methods

## Abstract #14: Eyes or lies? Navigating ocular pathology controversies in infant head trauma.

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For years, the medical community has believed that specific ocular pathologies, including retinal hemorrhages, retinoschisis, macular folds, peripapillary intrascleral hemorrhages, and perioptic nerve sheath hemorrhages, are markers of inflicted pediatric injury with medicolegal significance. The mechanism of injury responsible for these findings was believed to be shaking, impact, or a combination thereof, each with serious legal implications. Despite growing skepticism over the last four decades, a pervasive opinion exists that shaking and/or impact trauma exert "shearing" forces to the eye structures. This proposition, particularly in relation to retinal abnormalities, hinges on the unvalidated "vitreo-retinal traction" (VRT) theory. If VRT provides the true pathophysiological basis for intra-ocular hemorrhages, then this finding implies intense force application to an infant's head. However, extensive reviews of literature and case experience suggest that these pathologies are not exclusively linked to head trauma, particularly deliberate injury. Notably, the foundational research often cited to establish the specificity of ocular pathology in child abuse has undergone considerable scrutiny, with critiques targeting its circular logic and other biases. Thus, a comprehensive and cautious evaluation is needed for the diagnostic value of ocular pathology in child abuse cases.

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Learning Objectives:

1. Understand the spectrum of ocular pathologies linked to pediatric head trauma
2. Review the underlying theories of ocular pathology frequently documented in infant head trauma cases

## Abstract #15: Pathology of the vertebral artery in medicolegal autopsies

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**Objective:** Describe the clinicopathologic features of the vertebral artery (VA) in medicolegal autopsies. **Methodology:** Cases with fatal or significant VA pathology from 1996 to 2011 in the Provincial Forensic Pathology Unit, Toronto, were studied. Reports and histologic slides were reviewed. VA examination by segment and pathological findings were analyzed. **Results:** Twenty-six cases were included, 2.7 male to female ratio, 15 to 76 years. Fourteen cases (14/26, 54%) were trauma related, 11 cases (11/26, 42%) were non-traumatic, and 1 overlap (1/26, 4%). The 14 traumatic cases had mild to moderate external injuries. Thirteen of the 14 trauma cases (93%) had a basal subarachnoid hemorrhage (SAH) and showed transmural tears in the intracranial (V4) segment. The other trauma case had dissection between V1 and V2, associated with cerebellar, brainstem, and upper spinal cord (CBSUSC) infarctions. COL3A1 mutations and segmental mediolytic arteriopathy (SMA) were found among the cases. The eleven (42%) non-traumatic cases included basal SAH, CBSUSC and thalamic infarctions. VA thrombosis, atherosclerosis, dissection, fibromuscular dysplasia (FMD), SMA and COL3A1 mutations were present among cases. The overlap case presented upper posterior neck trauma and basal SAH due to a V3 dissection. In this case, there was also FMD, SMA, multifocal intramural hemorrhages and dissections involving craniocervical and visceral arteries and a COL3A1 mutation was found. **Conclusion:** Traumatic rupture of V4 resulted frequently in SAH. Non-traumatic pathology predominately occurs in extracranial VA. We recommend that postmortem examination of these cases includes examination of the entire vertebral artery.

Learning objectives:

1. Understand segmental vulnerability of the vertebral artery to injury and disease under a forensic perspective.
2. Analyze the role of peripheral arteries examination and COL3A1 mutations testing in fatal vertebral artery pathological.
3. Provide recommendations regarding the examination of vertebral arteries on forensic autopsies of fatal vertebral artery pathology cases.

## Abstract #16: Study of gamma-aminobutyric acid and glutamate signaling pathways in glioblastoma

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Glioblastomas (GBM) represent the majority of malignant primary brain tumors, and cannot be cured. The identification of their survival- and proliferation-associated mechanisms may help introduce new therapeutic targets. Several lines of evidence suggest that neurotransmitters gamma-aminobutyric acid (GABA) and glutamate are involved in gliomagenesis. Their signaling pathways within the tumor microenvironment (TME) remain nonetheless poorly defined. We hypothesize that the modulation of GABA and glutamate genes may control tumoral aggressivity. We (1) identify vulnerable biomarker genes for GBM (stage IV glioma), and (2) assess their validity in *in vitro* and clinical studies. A GABA-treated U87 GBM cell line was bulk RNA sequenced, and single-cell RNA-seq data of 9 resected new-diagnostic, and 5 recurrent IDH-wildtype GBM allowed for differential and enrichment analysis. Data suggested that GABA regulates cancer-associated pathways, such as survival, and metabolism. Using a novel algorithmic cell type identification approach, GBM cells, along with neuroimmune pro- and anti-inflammatory populations were identified. Potential GABA, glutamate, and calcium neurotransmitter-associated biomarkers previously identified in the laboratory were found to be differentially expressed between cell-group clusters. Further enrichment aims to identify cell types, and genes associated with protumoral activity. A cohort comprising 50 resected GBM samples was utilized to associate those new genes, as well as previous markers *C5AR1*, *VGAT*, *GAD-1*, and *GABA-B* to histologic characteristics including necrosis, angiogenesis, and infiltration. Immunohistochemical alignment between our, and clinical markers (ex. MIB1 for proliferation) was performed. GABA was significantly overexpressed in MIB1-rich zones. This study introduces GABA- and glutamate-associated biomarkers as potential GBM therapeutic vulnerabilities.

Disclosure statement: this is original work and is not subject to copyright elsewhere in view of a publication in Free Neuropathology. No conflicts of interest have been declared by the authors involved in this work. The research and conclusions presented are based solely on objective analysis and interpretation of the data.

Learning objectives:

1. Discuss the role of neurotransmission molecules regarding glioblastoma development and survival.
2. Recognize informatic tools utilized for both cellular identification in single-cell RNAseq experiments and digital slide analysis, which may improve the speed and quality of their research pipeline.

## Abstract #17: Using molecular and immunohistochemical features to predict outcomes in grade 3 meningiomas

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**Objective:** The WHO 2021 classification introduces molecular alterations in meningiomas that are associated with increased risk of recurrence and/or shortened overall survival (OS). These include *TERT* promoter (*TERTp*) mutations, *CDKN2A/B* homozygous deletion, H3 K27me3 loss, and BAP1 loss. With precise prognostic implications pending further characterization, we explored these molecular alterations and associated clinical outcomes in a single-center cohort of grade 3 meningiomas. Furthermore, we examined whether MTAP and p16 immunohistochemistry can predict *CDKN2A/B* status.

**Methods:** Clinical and histopathological information were obtained from the electronic medical records of grade 3 meningiomas resected at a tertiary center between 2007-2020. Molecular testing for *TERTp* mutations and *CDKN2A/B* status, methylation profiling, and immunohistochemistry for H3 K27me3, BAP1, p16, and MTAP were performed. Predictors of survival were identified by Cox regression. MTAP and p16 expression were assessed and correlated with *CDKN2A/B* status.

**Results:** Out of 15 cases included in the study, 8/15 were classified as anaplastic, 6/15 as rhabdoid and 1/15 as papillary. One rhabdoid tumour exhibited BAP1 loss, four tumours harboured *TERTp* mutations and three demonstrated *CDKN2A/B* homozygous deletion. *TERTp* mutations and *CDKN2A* status were associated with significant reductions in OS, which was independent of Simpson resection grade. Meningiomas with *CDKN2A/B* homozygous deletion showed consistent loss of p16 and MTAP immunoreactivity.

**Conclusion:** *TERT* mutations and *CDKN2A/B* homozygous deletion are significantly associated with reduced OS independent of resection extent. Our findings support using these molecular markers for prognostication in meningiomas. Additionally, this small series demonstrates that p16 and MTAP immunohistochemistry can predict *CDKN2A/B* status.

Learning Objectives:

1. Discuss molecular alterations that impact survival in grade 3 meningiomas.
2. Illustrate immunohistochemical stains that may be used as potential surrogate markers for predicting molecular alterations in grade 3 meningiomas.

## Abstract #18: Pediatric-type gliomas in adults: pathologic and molecular features

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The 2021 WHO classification of CNS tumours recognizes adult- and pediatric-type gliomas, which have important clinical and biological differences. While pediatric-type gliomas occur most commonly in children, their frequency and pathologic and molecular features in the general adult population have not been well studied.

We prospectively characterized a single-institution cohort of 498 consecutive gliomas (diffuse gliomas, circumscribed gliomas, and glioneuronal tumours) using immunohistochemistry, Sanger sequencing, panel-based NGS, FISH, SNP array, and/or DNA methylation profiling. Of 490 cases that could be evaluated (median age 58, range 18-91), pediatric-type alterations were identified in 61 (12%, median age 34, range 18-73). Excluding patients >55yo with glioblastoma (for whom no molecular testing was performed; n=227, 46%), pediatric-type alterations comprised 23% of the remaining cohort (61/263), compared to 45% for IDH mutations, and 32% for adult-type GBM. The frequency of pediatric-type alterations exceeded that of non-canonical IDH mutations in histologic GBMs ≤55yo (8% vs 3%, n=96), and exceeded both non-canonical IDH mutations and adult-type GBM in tumours with diffuse lower-grade histology (20% vs 8% and 17%, respectively, n=138). *H3-3A*, *BRAF*, *NF1*, and mismatch repair were the most commonly altered genes in pediatric-type diffuse high-grade gliomas, while *BRAF*, *FGFR1*, and *FGFR2* alterations prevailed in diffuse low-grade gliomas, circumscribed gliomas, and glioneuronal tumours.

In our cohort of adult patients, pediatric-type alterations are relatively common, especially in younger adults and lower-grade tumours. Pediatric-type alterations should be routinely included in the diagnostic evaluation and molecular testing of gliomas in adults.

### Disclosures

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No conflicts of interest for all authors

#### Learning Objectives

1. Understand the prevalence of pediatric-type alterations in gliomas in adults
2. Appreciate the molecular and pathologic features of pediatric-type gliomas in adults
3. Integrate pediatric-type alterations into the diagnostic workup of gliomas in adults

## Abstract #19: Extra-pineal papillary tumor of the pineal region (PTPR) masquerading as a subependymal giant cell tumor (SEGA)

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Papillary tumor of the pineal region (PTPR) is a rare neuro-epithelial tumor arising in the pineal region characterized typically by papillary and solid architecture with epithelial-like cells and reactivity for cytokeratins, while subependymal giant cell tumor (SEGA) is a periventricular tumor composed of large ganglion-like astrocytes. Here we describe the case of 75-year-old man with a slowly enlarging superior cerebral aqueduct mass first discovered and followed over six years prior to biopsy. Given its increasing size a small biopsy was performed which was characterized by large pleomorphic ganglion-like giant cells with abundant cytoplasm and prominent nucleoli. Immunohistochemistry showed that tumor cells were strongly positive for S100, but negative for GFAP. Despite the patient not carrying a diagnosis of tuberous sclerosis, given the ventricular location, histologic appearance, and immunohistochemical results a diagnosis of a low grade tumor consistent with subependymal giant cell astrocytoma (SEGA) was issued, with outside expert consultation in agreement with this interpretation.

Subsequently, despite surgery the mass continued to slowly grow over the next few years and the decision was made to perform next generation and methylation sequencing 4 years following the initial biopsy. Next generation sequencing returned only the presence of an NF2 mutation, while methylation sequencing was a match for papillary tumor of the pineal region. Subsequent immunohistochemistry for Keratin AE1/3 was strongly positive on the original biopsy, consistent with this new diagnosis. This case demonstrates the utility of methylation sequencing, particularly when biologic behavior and sequencing results do not correlate with histologic diagnosis.

Learning objectives:

1. Identify the diagnostic features of papillary tumor of the pineal region.
2. Identify the diagnostic features of subependymal giant cell astrocytoma.
3. Explain the utility of methylation sequencing in resolving diagnostic discrepancies between histologic and genomic findings.

## Abstract #20: Ethical considerations in the use of DNA methylation profiling for tumor diagnostics

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DNA methylation profiling has become essential for CNS tumor classification. Unlike traditional molecular testing, methylation profiling does not interrogate specific genetic alterations. Rather, it evaluates a genome-wide methylation profile, typically in conjunction with a machine-learning classifier that assigns a diagnostic category. Patients benefit from an unprecedented ability to accurately diagnose and classify tumors, but there is little formal evaluation of the unique ethical considerations raised by this modality. Our objective is to apply principles of medical ethics to the use of methylation profiling, with a focus on three principles: (1) Informed consent: The diagnostic paradigm of methylation is complex for patients and clinicians to understand and risks confusion regarding the diagnostic significance of a methylation profile. Patients may be unaware of what data is stored and how it will be stored, transferred, and re-analyzed for clinical and research purposes. (2) Harm to patients: Methylation profiling generates epigenetic data that exists indefinitely and can be analyzed in a dynamic fashion. As new classifiers are implemented, a previously unclassifiable tumor may become classifiable without re-sequencing or a clinically significant change in methylation class may occur. (3) Justice and resource utilization: The extensive granularity of diagnostic categories defined by methylation profiling creates a risk of over-testing that may not generate clinically actionable results. The use of machine learning carries specific considerations of justice, including inherent biases in the populations used for classifier generation. Neuropathologists should keep these ethical considerations in mind when implementing methylation as a clinical test or in clinical practice.

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The authors have no conflicts of interest to declare.

Learning objectives:

1. Apply traditional principles of biomedical ethics to the implementation and application of DNA methylation profiling for tumor diagnostics.

2. Distinguish the ethical considerations raised by DNA methylation profiling from those in traditional germline and neoplastic molecular testing.
3. Develop basic procedures for appropriate implementation, utilization, and reporting of DNA methylation testing in light of the ethical considerations of testing.