Canadian Association of Neuropathologists
L'Association Canadienne des Neuropathologistes
ABSTRACTS

September 15th-17th, 2011
Vancouver, British Columbia
Abstracts and unknown cases presented at the 51st Annual Meeting

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The Canadian Association of Neuropathologists President Dr. David Munoz presided over the Fifty-First Annual Meeting, at the Pinnacle Marriott Hotel in Vancouver, September 15-17, 2011.

Drs. Chris Dunham and Wayne Moore handled local arrangements. A sumptuous Banquet, at spectacular Grouse Mountain, arranged by Deb Dunham, was the highlight of the proceedings. The scientific program of 20 scientific presentations and 10 unknown case submissions was assembled by CANP Secretary/Treasurer Dr. Rob Macaulay into two sessions on Brain Tumours, and one each of Inflammatory Neuropathology, Pediatric Neuropathology and Miscellaneous topics. Session Chairs were Drs. Ian Mackenzie, Clayton Wiley, Sid Croul, Marc Del Bigio and Rob Hammond; for the first time this year several of the unknown cases were submitted for scanning and viewing online only, ably coordinated by Dr. Hammond.

The 2011 Symposium explored Recent Advances in Multiple Sclerosis, and was chaired by Dr. Munoz. The Jerzy Olszewski Guest Lecture was delivered by Dr. Dessa Sadovnick, and was entitled "Genes/Environment and MS: What have we learned from the Canadian Collaborative Initiative?" Dr. Vanda Lennon from the Mayo Clinic then explored "Immunopathology and Pathogenesis of Neuromyelitis Spectrum Disorders". Dr. Moore delivered a fascinating talk entitled "Neuropathologic Correlates of Magnetic Resonance Imaging in Multiple Sclerosis". The Gordon Mathieson Invited Member Lecturer for 2011 was Dr. Sam Ludwin from Queen's University, who provided a timely treatise on "CCVSI - A Perfect Storm", subtitled "Science, Medicine, Economics, Politics and the Role of the Media in Shaping Public Health Action".

The Resident Awards Committee (Chair: Dr. Lothar Resch, members Drs. StephenYip and Julia Keith) named Phedias Diamandis the Mary Tom Award for best clinical presentation of the unknown case 'Gaucher disease' (supervisor Dr. Keith). The Morrison H. Finlayson Award winner for best basic science paper was Murad AlTurkustani (Dr. Hammond) for his talk: 'The role of 3D digital quantitative histopathology coregistration to ultrasound, PET-CT and MRI (Canadian Atherosclerosis Imaging Network)'.

Scientific Papers

1. Next generation sequencing of oligodendroglioma

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The genetic underpinnings of oligodendroglioma (ODG) remain a mystery especially its strong association with co-deletions of chromosomes 1p and 19q which denote superior prognosis and treatment response. Next generation sequencing (NGS) offers extremely powerful basepair resolution interrogation of the cancer genome. We used NGS to examine the exomes, genomes, and transcriptomes of a discovery cohort consisting of 16 pairs of snap frozen 1p/19q co-deleted ODG with matched normal as well as 2 ODG brain tumour initiating cell lines.

The average number of somatic non-synonymous mutations per ODG exome is 20.5 excluding two recurrent ODG which display the hypermutation phenotype consisting of 710 and 2105 somatic mutations. The average rate of somatic mutation per non- hypermutator ODG exome was 2.85 mutations/Mb, lower than that reported for GBM (5- 6 mutations/Mb). Moreover, we identified somatic mutations in *TP53* and MSH6 in these two cases consistent with findings in recurrent glioblastomas. We were able to infer copy number changes and loss of heterozygosity in chromosomes 1p/19q from whole genome data. We also found mutations in *IDH1* and IDH2 in 14/16 and

2/16 ODG exomes, respectively. Lastly, we have also identified over 100 novel and known somatic mutations.

In summary, NGS offers an unprecedented view of the ODG genome which will significantly alter our understanding of this disease.

2. Leptomeningeal dissemination of gliomas

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Introduction: Unusual neuroectodermal tumours have been reported with diffuse leptomeningeal involvement in the absence of intraparenchymal lesions. Controversy has arisen regarding the nature of these lesions and whether they represent a new entity. A number of these cases with similar clinical, radiologic, and pathologic features have been named primary disseminated leptomeningeal oligodendroglioma. Molecular testing for 1p 19q deletion has shown co-deletion in some cases and only 1p deletion in others.

Case report: An eight year-old boy with a complex neurologic history developed seizures and progressive ataxia. Imaging revealed diffuse meningeal enhancement and focal lesions including a small left frontal meningeal enhancing nodule and a larger mass at the right cerebellopontine angle. The small nodule was resected and was found to be an intermediate grade glioneuronal tumour with desmoplasia and meningothelial reaction. Fluorescence *in situ* hybridization (FISH) showed isolated deletion of 1p without deletion of 19q. Recent imaging suggests progression of the neoplasm throughout the leptomeninges.

Conclusions: The case described has pathologic and genetic features resembling previously reported diffuse leptomeningeal gliomas. The behaviour of these tumours remains unclear. We consider whether to classify them as a new entity.

3. Angioleiomyomas of the dura: rare entities that lack KRIT1 mutations

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Angioleiomyomas (ALMs) also known as vascular leiomyomas or angiomyomas, are cutaneous and soft tissue lesions usually seen in lower extremity of middle-aged women. Lesions are nodular, mulberry-like, and composed of thick-walled vessels, with abundant muscularis; arterial component is absent. Intracranial examples are exceedingly rare, with less than 10 cases reported to date, usually dural in location. We now report two young males with dural ALMs, one intrafentorial and located near the incisura and the second falcine, posterior to the splenium. Both patients came from the same medium-size community in southern Colorado with a known high incidence of a Hispanic population at risk for familial cavernous cerebral hemangiomas (CCM). Both presented with greater than eight year histories of headaches; preoperative and intraoperative diagnoses were CCM and vascular meningioma, respectively. Histologically both had discrete lesions composed of large cavernous channels lined by CD34+ endothelium and surrounded by thick mature SMA+ muscle that was orderly near the lumen and more disorderly peripherally. We posited that there might be a relationship between this lesion and CCMs and undertook PCR-based mutational analysis for the single, common mutation seen in this population, ie., c.1363C>T *KRIT1*. Testing proved negative despite the fact that one patient was of strong Hispanic heritage. We conclude that angioleiomyomas are easily mistaken in the dura for CCMs, or other lesions, but are not of similar pathogenesis.

4. Regulatory T cells in CNS inflammation

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Regulatory T cells (Tregs) are thymus-derived CD4+ CD25+T lymphocytes that play an important role in maintenance of self-tolerance and suppression of autoimmunity. Tregs recognize both self and foreign antigens and operate at sites of inflammation by suppressing the function of effector T cells, thus modulating the intensity and quality of immune responses. Their identification is based on the expression of activation markers and the forkhead transcription factor P3 (Foxp3). The contribution of Tregs to CNS inflammatory diseases has not been previously addressed. We investigated the presence and distribution of Tregs in cases of multiple sclerosis (MS), primary CNS angiitis, sarcoidosis, bacterial, viral and parasitic infections, acute infarction and normal brain. Formalin fixed, paraffin embedded sections of surgical and autopsy material were stained with the indirect immunoperoxidase technique using monoclonal anti-Foxp3 and CD4 antibodies. CD4+Foxp3+Tregs were present within the perivascular chronic inflammatory infiltrates in primary CNS angiitis and active MS lesions, but not in chronic inactive MS plaques. In sarcoidosis, tuberculosis, viral infections and abscesses, frequent Tregs were identified in perivascular location and scattered in the inflamed tissue. A smaller number were present in parasitic and fungal infections and in leptomeningeal exudates in bacterial meningitis. Tregs were absent in the normal brain and acute ischemic lesions. The present study shows participation of Tregs in autoimmune and infectious diseases suggesting a complex immune regulatory role in CNS inflammation.

5. Exacerbation of experimental allergic encephalomyelitis in chitinase 3-like protein 1 knockout mice

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Experimental allergic encephalomyelitis (EAE) is an animal model of multiple sclerosis mediated by autoimmunity to central nervous system (CNS) myelin. Previously it was shown that reactive astrocytes play a critical role in limiting immune infiltration. Using wild type and knockout mice, we demonstrate the importance of chitinase 3-like protein 1 (gp39) in modulating the severity of EAE clinical symptoms and neuroinflammation. EAE in gp39 knockout mice showed more severe and persistent

clinical disease then wild type controls. Immune infiltrates in knockout mice developed more quickly, became more extensive and persisted longer than that observed in wild type mice. These findings support the role of astrocyte chitinase 3-like protein 1 expression in limiting immune infiltration into the CNS and offer a new target to modulate neuroinflammation.

6. Autopsy findings from a fatal case of Murray Valley encephalitis (MVE) in a returning traveller.

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Murray Valley Encephalitis Virus (MVEV) is a mosquito-borne flavivirus closely related to Japanese Encephalitis Virus (JEV). MVEV is endemic to Australia, where enzootic transmission is maintained in a cycle predominantly involving mosquitos *(Cx. annulirostris)* and migratory water-birds. We report autopsy findings from a fatal case of MVE in a 19-year-old-female who recently returned from travel in the Northern Territory of Australia. She presented with a two day history of fatigue, rigors, chills and confusion. CSF analysis demonstrated a lymphocytic pleocytosis and was negative for common viruses known to cause encephalitis. Magnetic resonance (MR) imaging revealed restricted diffusion in the splenium of the corpus callosum, and vasogenic edema (increased T2 signal on FLAIR) in both posterior thalami. Reverse-transcriptase PCR on CSF, using primers targeting the NS5 gene of the flavivirus genus (Ayers et al, J Virol Met 2006;135:235-9), produced a 770 bp sequence with a 98% identity to MVEV (NCBI nucleotide database - AF161266.1). Despite interventions, the patient died 10 days after onset of illness. The general autopsy revealed edematous lungs. The brain was diffusely swollen and weighed 1527 grams. Microscopy revealed a widespread meningo-encephalitis, with necrosis in the thalamus; and particularly severe damage and loss involving lower motor neurons. This is the first recognized case of MVE in Canada.

7. Clinical and pathological comparison of infectious and non-infectious intracranial caseating granulomas

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In a subset of patients with intracranial caseating granulomas no infectious agent can be found by culture, histological staining or Amplified Mycobacterium Tuberculosis Direct (AMTD) test to detect M. tuberculosis rRNA. We have previously named and characterized such cases as intracranial caseating granulomas with no identifiable infectious pathology (ICGNs). In the current study we retrieved all biopsy-proven intracranial caseating granulomas since 2000 at our hospital, obtaining ten patients with ICGNs and seven patients in whom an infectious agent was identified from the biopsy (ICGI), including four Mycobacterium tuberculosis, one Mycobacterium Avium Complex, and two fungi. We then compared clinical, laboratory, histological, and imaging features, with special attention to response to therapy. There was no statistically significant difference in age, or clinical presentation (seizures followed by confusion and headache not accompanied by fever, chills, headache or neck-stiffness), but risk factors for infection were present in all ICGI patients and only 1 ICGN subject. Laboratory data in blood (including ACE, ESR, ANA and ANCA) and CSF were not helpful. ICGNs showed a homogeneous enhancing pattern on MRI, contrasting with a ring pattern in ICGI. Histologically, areas of necrosis greater than 1 mm were restricted to ICGI. ICGI responded to antimicrobial therapy; ICGN did not, but did respond to immunomodulatory treatment. Thus, the distinction between ICGN and ICGI, based on tissue investigation only, is clinical relevant.

8. The physician as global health advocate

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The Royal College of Physicians and Surgeons of Canada has designated Health Advocate as one of the seven CanMEDS Roles (competencies) for all specialists. As with the other Roles so designated, the meaning of "Health Advocate" will grow by example. The purpose of this presentation is to summarize my own approach to global health advocacy (global citizenship). Included in the presentation will be a synopsis of the conceptual framework for that approach, from the book The ABCs of Human Survival: A Paradigm for Global Citizenship (Athabasca University Press 2010); and background and update on the Calgary Centre for Global Community (www.calgarycgc.org) as a new type of civil society organization, designed to enhance and encourage such work not only among physicians, but among all who are concerned about conditions that affect human well-being ("determinants of health"). I will emphasize the importance of global health advocacy for human health and well-being worldwide; as well as the opportunities for personal growth and self-actualization to be found in developing this capacity.

9. Institutional review of epilepsy resection specimens with focal cortical dysplasia

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The term focal cortical dysplasia (FCD) was first used by Taylor, et al (1971). In 2004, Palmini et al proposed a histologic classification system for FCD that has been generally accepted by neuropathologists. With advanced neuroimaging studies, subtle cortical change can be identified and the need for objective and reproducible criteria for classify FCD based on electro-clinical, neuroimaging and pathological features is warranted. The recent International League Against Epilepsy (ILAE) Classification for FCD attempts to incorporate the clinical, radiological and pathological criteria has been published (Blumcke et al 2011).

The aim of this study is to review the histopathology and classification of the FCD cases from the corticectomy/lobectomy specimens of epilepsy patients at the LHSC. Fifty-eight cases were retrieved from the pathology archive from 1989 to 2007. The term "cortical dysplasia" was used as key words in search retrieval. The cases were reviewed and the histological subtypes

for FCD were assigned using the Palmini classification and then reassigned using the ILAE classification. All cases were confirmed as FCD with type 2B using the Palmini classification being most common (22 cases, 37.9%). There were 17 cases (29%) with other pathological findings, including six hippocampal sclerosis (dual pathology), six low-grade neuroepithelial tumours, two polymicrogyria, two hamartomatous lesions and one destructive lesion.

Conclusion: Approximately in 1/4 of the FCD cases have a second lesion. The application of the ILAE Classification has resulted in substantial changes in the categorization of our FCD cases.

10. Infant brain tumors: a neuropathologic reappraisal

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Purpose: Current management strategies have yet to fully define the factors that impact the long term functional outcome for infants with brain tumors.

Methods: To address this issue, the clinicopathologic features of all infant brain tumors occurring between 1982- 2005 at British Columbia's Children's Hospital (BCCH) were re-examined. This report focuses on the neuropathologic review that was conducted.

Results: 35 cases were re- examined. Review diagnoses included: seven astrocytomas (six low grade astrocytomas, including two pilocytic and one pilomyxoid astrocytoma, PMA, as well as one glioblastoma), six atypical teratoid rhabdoid tumors (ATRT), five choroid plexus papillomas, four ependymomas (three anaplastic), four teratomas (three immature), two supratentorial primitive neuroectodermal tumors (sPNET), two gangliogliomas, two desmoplastic tumors of infancy (DTI) and one each of "medulloblastoma with extensive nodularity" (MBEN) and adamantinomatous craniopharyngioma. Nonspecific diagnoses were rendered in four cases (three "low grade astrocytoma" and one "malignancy NOS"). In comparison with the literature and upon review, our cohort contained significantly higher frequencies of ATRT and teratoma, yet relatively few medulloblastomas. Review led to a change in diagnosis in eight cases (23%), of which ATRT was the most common revision (N=5). Tumor grading was altered in six cases (17%), amongst which was only one major modification (sPNET→→DTI).

Conclusions: Our results suggest that ATRT may be the most common infant brain malignancy. Neuropathologic review infrequently led to major changes in diagnosis and/or grade, but minor changes were not uncommon and are considered to most likely reflect upon the evolution of tumor classification and grading schemes.

11. Anencephaly: a modern microscopic and genetic survey

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Purpose: The histologic and genetic features of human anencephaly have been poorly characterized by modern laboratory techniques. Our objective was to provide a detailed microscopic and genomic survey of a large series of anencephalics.

Methods: 30 consecutive archived cases of ~midgestational anencephaly were chosen for microscopic analyses (including a battery of immunohistochemistry) of the "area cerebrovasculosa" (AC). A subset of ten cases (nine with normal karyotypes; one with a 3 Mb 5p deletion) were investigated via Affymetrix 6.0 SNP microarray for instances of copy neutral LOH (CNLOH) and non-polymorphic copy number variations (NPCNVs).

Results: H&E stained sections revealed a consistent laminar architecture to the AC across cases, generally typified by: 1) A superficial and nodular "primitive neural tissue" (PNT) layer; and, 2) a deeply situated vascular layer populated by thin walled, dilated, closely packed and congested blood vessels. A 3rd phagocytic layer was occasionally seen adjacent to the PNT layer. Multinucleated giant cells (MNGC) were often aggregated at the atrophic skin-AC boundary. The most sensitive and specific immunostains for the PNT included MAP2, synaptophysin and GFAP, with the latter often highlighting the periphery of these nodules. SNP microarray analyses did not reveal any CNLOH. NPCNVs were few and usually limited to isolated cases. However, a recurrent NPCNV, ~7-37 Kb in size and encompassing *KIAA1217*, was identified on 10p12.1 in three cases.

Conclusions: While the laminar histoarchitecture of the AC in anencephaly was remarkably consistent across cases, SNP microarray analyses failed to reveal a characteristic form of CNLOH or NPCNV.

12. Endothelial ultrastructural alterations in intramuscular capillaries in infantile mitochonria cytopathies

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Background: Electron microscopy (EM) is a reliable method for diagnosing mitochondrial diseases in striated muscle biopsy in infancy. Ultrastructural alterations in mitochondria of myofibres are well documented, but there are few studies of endothelial involvement in intramuscular capillaries.

Materials and Methods: Quadriceps femoris biopsies of five infants and toddlers, ages neonate to 3.5 years, were performed

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because of clinical and laboratory data consistent with mitochondrial disease. Pathological studies included histochemistry, EM, respiratory chain enzymatic assay and mtDNA sequencing and deletion/duplication analysis.

Results: EM demonstrated frequent and more severe alterations of mitochondria in capillary endothelium than in myofibres. Changes included stacked cristae, osmiophilic spheroids and paracrystallin structures that often were large and spheroid in form with stress fractures or were smaller and elongated. Mitochondria often were surrounded by closely adherent membranes of granular endoplasmic reticulum. Long narrow and looped endothelial villi extended into the lumen; thick villi containing abnormal mitochondria also occurred.

Conclusions: We conclude that mitochondrial cytopathies in early life exhibit more severe ultrastructural alterations in the endothelium than in myofibres in muscle biopsies and that paracrystallin body structure differs. The distribution may explain the frequent lack of prominent histochemical and biochemical abnormalities in muscle biopsies of young patients. Endothelial involvement in brain may contribute to neuronal death by both impairment of molecular and nutrient transport and ischaemia.

13. Microlissencephaly with cerebellar hypoplasia and dysplastic glia

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We report a case of fetal microlissencephaly with cerebellar hypoplasia. The fetus was stillborn at 35 weeks gestational age to a 41 year-old mother with a history of three spontaneous abortions. Systemic findings included arthrogryposis. The brain demonstrated micrencephaly, agyria and ventriculomegaly with agenesis of the corpus callosum and anterior commissure. The cornu ammonis was rudimentary and the remainder of the cerebral cortex simplified to an undulating layer of granular and pyramidal neurons. The cerebellum was hypoplastic without foliation or deep nuclei. Disorganised Purkinje and granular cell layers were identified. The striatum and globus pallidus were absent. Thalamic and mesencephalic architecture was disorted by perivascular proliferations of large, GFAP and Nestin (+) cells with abundant cytoplasm, fibrillary processes and large, occasionally multiple nuclei. These were also present in the caudal brainstem and spinal cord. There was an almost complete absence of central myelination, although occasional cells with glial morphology did stain for myelin basic protein. Along cranial and spinal nerve roots however, there was extensive schwannosis. Retinal layering was normal, but ganglion cell layer glia were hypertrophic. This morphology shares features of microlissencephaly with cerebellar hyopoplasia and cleft palate, but the glial pathology, so far as we are aware, has not been described.

14. Hemimegalencephaly as a fetal microtubular disorder with phosphorylated tau

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Introduction: Microtubules are essential subcellular structures in CNS development that determine neural cell growth, polarity, lineage, differentiation and migration. Disturbance of microtubular function during embryogenesis can produce hamartomatous malformation, well documented in tuberous sclerosis (TS) that involves abnormal increased signaling in the mTOR cascade. Tau is a microtubule-associated (MAP) protein, the abnormal phosphorylated form of which is upregulated in several adult neurodegenerative diseases. Because hemimegalencephaly (HME) is another hamartomatous malformation, we hypothesized that a disorder of microtubular formation or function may underlie the pathogenetic mechanism.

Methods: We examined surgical resections for epilepsy of three infants with HME; one died in the post-operative period and brain autopsy was performed promptly. Multiple immunocytochemical markers were applied including a phosphorylated tau protein used in the diagnosis of adult dementias. The mTOR pathway also was studied.

Results: Over-expression of phosphorylated tau was demonstrated in all cases within the malformation; α-synuclein, ubiquitin and TDP43 were negative. In the infant who died, the contralateral "normal" hemisphere showed tau expression only in widely scattered dysmorphic neurons and strong cortical expression limited to the cingulate gyrus, both in a small surgical biopsy at age three weeks during corpus callosotomy and re-confirmed post- mortem. The cerebellum and brainstem did not exhibit tau reactivity. MAP-2 was normally expressed in neurons including those within the malformation. A phosphorylated isoform of S6 protein, a marker of activated mTOR signaling, was strongly immunolabelled in dysmorphic cells within the malformation.

Conclusions: HME and TS may share a similar pathogenesis with disrupted microtubular assembly and mTOR pathway during early cellular differentiation and growth in the CNS, resulting in hamartomatous malformation. At least a subset of HME cases are also associated with up-regulation of abnormal phosphorylated tau protein as a "fetal tauopathy".

15. Cardiomyopathy of Friedreich's ataxia: insights gained from X-ray fluorescence of metals

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Cardiomyopathy is the most common cause of death in patients with Friedreich's ataxia (FRDA). Lamarche et al (1980) discovered minute iron-containing granules in cardiomyocytes

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in FRDA, and this observation grew in importance after the underlying mutation and deficiency of frataxin were identified (Campuzano et al 1996). Frataxin is firmly linked to iron homeostasis of all cells, but not all organs are equally vulnerable. Total iron and ferritin levels in the heart remain normal but a new non-destructive physical technique, X-ray fluorescence (XRF) of polyethyleneglycol (PEG)-embedded tissues showed a significant regional iron excess in left ventricular wall (LVW), interventricular septum (IVS), sinoatrial node (SAN), and atrioventricular node (AVN) of six patients with FRDA. Respective mean iron levels in LVW, IVS, SAN, and AVN were, in µg/ml PEG, 211, 189, 106, and 105. Mean concentrations in six matching normal samples were 110, 96, 52, and 61 µg/ml. Heart tissue also showed strong XRF of zinc, but levels in FRDA did not differ from controls. Copper levels were below detection limits while calcium concentrations were variable. Tissues were recovered from the water-soluble PEG matrix and embedded in paraffin for histochemical iron stains and immunocytochemistry of ferritin and ferroportin. In sections of regions with high iron XRF, iron and ferritin reaction products showed co-localization in cardiomyocytes. In contrast, ferroportin reaction product was more diffuse but disappeared from fibers with severe iron overload. The proposed sequence of individual fiber necrosis in FRDA is: iron excess→ferroportin biosynthesis→ferritin accumulation→oxidative damage.

16. Two unusual causes of vertebral artery rupture with subarachnoid hemorrhage

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We describe two uncommon causes of fatal subarachnoid hemorrhage as a consequence of vertebral artery rupture.

First case: A 47 year-old man suffered severe anoxic ischemic encephalopathy after cardiac arrest with prolonged resuscitation. Head CT scan demonstrated subarachnoid and intraventricular hemorrhage and thorax CT scan demonstrated type B aortic dissection extending up to the aberrant right subclavian artery. The autopsy examination confirmed the dissection in the aorta, and showed occlusion of the right vertebral artery by the dissection. The left vertebral artery contained the rupture site and the arterial wall changes were consistent with segmental arterial mediolysis.

Second case: A 52 year-old man suffered a fall complicated by decreased level of consciousness and severe headache. Head CT scan with angiogram showed extensive subarachnoid hemorrhage with intraventricular extension, a possible dissecting aneurysm of the distal right intracranial vertebral artery, and fusiform dilatation of the right A2 segment of anterior cerebral artery. The autopsy examination demonstrated rupture of the right vertebral artery with changes of fusiform aneurysm.

These two cases demonstrated unusual types of vasculopathy, which result in fatal intracranial hemorrhage. The awareness of these entities is important as it guides the investigations at autopsy and subsequent neuropathological examination.

17. The role of 3D digital quantitative histopathology co-registration to ultrasound, PET-CT and MRI (Canadian Atherosclerosis Imaging Network)

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Stroke remains the third most common cause of death in Canada, compounded by high morbidity amongst survivors. Carotid atheromatous disease accounts for the majority of embolic strokes. Identifying high risk individuals involves a number of imaging modalities that would benefit from greater precision in the identification of histopathological changes.

Digital imaging continues to evolve in speed and resolution. Whole-slide scanning now facilitates high resolution capture of histopathology for manual and algorithm-based image analysis. Coupled with special stains and immunohistochemistry, semi-automated analysis of individual components on whole slides has become readily available.

We have studied semi-serial sections from carotid endarterectomies to resolve Ultrasound, PET-CT and MRI signal characteristics at the microscopic level. Atheromatous components have been quantified manually and with semi-automated digital algorithms. The resulting annotated images permit co-registration with various imaging modalities in the identification of tissue components such as calcification, inflammation and necrotic lipid core.

It is hoped that this technology will permit imaging modalities to better identify unstable plaque components, optimizing patient triage into medical and surgical treatments as well as providing greater insight into atheroma progression or regression over time.

18. Midbrain infarct with 27 year survival associated with local neurofibrillary tangle formation and bilateral anterograde olivary atrophy.

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Anterograde effects on the inferior olivary nuclei can occur following damage to axons projecting from the cerebellar dentate nuclei. Over months to years, the changes in the olivary nuclei evolve through several stages, of which hypertrophy and pseudohypertrophy are well documented. A very late stage of olivary atrophy is postulated, but there has been little or no documentation of cases with sufficiently long survival to assess this adequately. We here report the case of a 67 year-old man who died 27 years after a left mesencephalic infarct. Postmortem examination confirmed an old left paramedian midbrain infarct and bilateral atrophy of the inferior olives. Additionally, there was florid neurofibrillary tangle formation largely restricted to the vicinity of the rostral end of the old midbrain infarct. Reports of neurofibrillary tangle formation as a late effect of infarction

are rare. The post-mortem findings in this case support previous suggestions: 1) that olivary atrophy may be a very late stage, subsequent to olivary hypertrophy and pseudohypertrophy, of anterograde trans-synaptic changes after damage to dentatofugal fibres (Goto and Kaneko, Acta Neuropathol 1981; 54: 275-282); and 2) that infarction can predispose to neurofibrillary tangle formation (Kato et al. Ann Neurol 1988; 23: 620-623).

19. Immune myopathy secondary to HMGCR antibodies : clues and pitfalls

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This 70 year-old man with type II diabetes mellitus sustained several episodes of hyperCKemia up to 3000U\L without myalgias or muscle weakness since 2009. An exhaustive laboratory investigation revealed no other significant changes. There were no ANA serum antibodies. Statins (Lipitor) were then stopped. Serum HMGCR titers were then reported as positive. A partial response to prednisone resulted in a fall of CPK levels to 1000U\L. A muscle biopsy revealed a very mild peri and endomysial lympho-monocytic response, mostly CD4 + T lymphocytes with CD68 + macrophages. Necrotic fibers were few. Regenerating fibers were more abundant. MAC complex antibodies revealed extensive membranous deposits which predominated in peritendinous attachments of muscle fibers, around necrotic fibers, as well as a moderately extensive deposition within the walls of endomysial capillaries. HMGCR myopathy is a rare form of immune myopathy, which involves antibodies raised against the main synthesizing enzyme of cholesterol, often after many years of statin therapy. Response to steroids is often incomplete and may require a more aggressive approach.

20. Small vessel vasculopathy of unknown origin with tumefactive like lesions

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We report two men with subacute onset of personality and cognitive symptoms and multifocal white matter lesions on neuroimaging. Brain biopsy in both showed identical histological features: ovoid, mixed ischemic-demyelinating lesions, without intravascular thrombi, petechial hemorrhages, perivenular demyelination, or vasculitis. The findings were not typical of ADEM, collagen vascular disease or autoimmune disorders. Patient 1, a 54-year-old man presented with one month of easy irritability and word finding deficits; diffuse bilateral cerebral leukoencephalopathy was associated with more tumor-like contrast-enhancing lesions in pons and bilateral cerebellar dentate nuclei. He had several seizures after discharge, and sought a second opinion at a second institution where eyelid biopsy, *NOTCH3* testing, and further workup were negative. He was treated with IV steroids, with minimal residual deficits. Patient 2, a 36-year-old man had two seizures prompting an ED visit. Retrospectively he was thought to be irritable with memory loss and lack of concentration. Magnetic resonance imaging demonstrated numerous contrast-enhancing lesions throughout cerebrum, the largest of which was a large, tumefactive, left frontal lobe lesion without mass effect. He received anticonvulsants, several days of oral steroids, stabilized, and returned to work with minimal deficits. Extensive work-ups in both patients for infectious agents, collagen vascular disorders, neurosarcoidosis, toxins, and multiple sclerosis; were negative except for elevated CSF protein levels. To date, neither has had a recurrence. This monophasic condition is of unknown etiology and characterized by extensive destruction with both demyelinating and ischemic components. Possibilities of an extremely destructive demyelinating process and/or an autoimmune condition with vascular injury should be considered.

Titles Of Diagnostic Case Presentations

1. Rosetting glioneuronal tumour of the fourth ventricle

A. Alkhotan, D.G. Munoz

St. Michael's Hospital, University of Toronto, Ontario, Canada

2. Mature glial tissue

J. Karamchandani

St. Michael's Hospital & Stanford University Medical Center

3. Gliofibroma, high grade

Z. al-Hajri, M.R. Del Bigio

Department of Pathology, University of Manitoba, Winnipeg, Manitoba, Canada

4. Rasmussen's encephalitis

A. Alkhotani, S.E. Croul

Toronto General Hospital, University Health Network, University of Toronto, Ontario, Canada

5. Metastasis of papillary thyroid carcinoma into a primary mesenchymal tumour versus metastatic papillary thyroid carcinoma with sarcomatoid differentiation

S. Das, L.C. Ang, D. Ramsay, P. Ra

Division of Neuropathology, London Health Sciences Centre, University of Western Ontario, London; Hotel-Dieu Grace Hospital Windsor, Ontario, Canada

6. Desmoplastic tumour of infancy

Y. Robitaille Y, L. Crevier

CHU Ste-Justine, Department of Pathology, Universite de Montreal, Quebec, Canada

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7. Gaucher disease

P. Diamandis[1], D. Amato[2], J. Finklestein[3], B. Young[1], J. Keith[1]

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8. Ependymoblastomatous exencephaly

C. Dunham, C. Fauth

Department of Pathology and Laboratory Medicine, Division of Anatomic Pathology, British Columbia's Children's Hospital (BCCH), Vancouver, British Columbia, Canada

9. Cerebral vasculitis associated with ulcerative colitis

A.S. Easton

Dalhousie University, Halifax, Nova Scotia, Canada

10. White matter tauopathy with globular glial inclusions (WMT-GGI)

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