Canadian Association of Neuropathologists

L'Association Canadienne des Neuropathologistes

ABSTRACTS

October 24th-27th, 2012
Mont-Tremblant, Quebec
Abstracts and unknown cases presented at the 52nd annual meeting

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The Canadian Association of Neuropathologists held their Fifty-Second Annual Meeting at the Fairmont Tremblant hotel in Mont-Tremblant, Quebec, October 24-27, 2012. Outgoing President Dr. David Munoz presided. Drs. Yves Robitaille and Roland Auer handled local arrangements. The banquet was held at the Hotel Quintessence overlooking Lac Tremblant.

The academic program of 26 scientific presentations and 13 unknown case submissions was assembled by CANP Secretary/ Treasurer Dr. Peter Gould into two sessions on Brain Tumours, and one each on Neuropathology and the Internet, Pediatric Neuropathology, and Non-Neoplastic Adult Neuropathology. Session chairs were Drs. Rob Hammond, Sid Croul, Jean Michaud, Jeff Joseph and Roland Auer. Dr. Juan Bilbao presented the Quality Assurance session. Following a successful introduction in 2011, several unknown cases were submitted for scanning and viewing online, as coordinated by Dr. Hammond.

The 2012 Symposium, chaired by Dr. Munoz, explored Neurodegeneration mechanisms: from animal models to the clinic. The Jerzy Olszewski Guest Lecture was delivered by Dr. Michal Schwartz of the Weizmann Institute of Science, Rehovot, Israel, and was entitled "Monocyte-derived macrophages and T cells play indispensable roles in fighting off neurodegeneration." Dr. Pierre Drapeau discussed "Fishing for causes and cures of neurodegeneration" by genetic analysis of zebra fish. Dr. Guy Rouleau reviewed the latest advances in "Molecular Genetics of Amyotrophic Lateral Sclerosis." The Gordon Mathieson Invited Member Lecturer for 2012 was Dr. Stirling Carpenter from Porto, Portugal, who presented his latest findings on "Axonal Dystrophies: the Diversity and 3 Examples."

The Resident Awards Committee (Chair: Dr. Claire Coiré, members Drs. Ana Maria Tsanaclis and Stephan Saikali) named Leslie Hamilton the Mary Tom Award winner for best clinical presentation of the unknown case "Late Infantile Neuronal Ceroid Lipofuscinosis (NCL), with two disease causing mutations in CLN2" (supervisor Dr. Joseph). The Morrison H. Finlayson Award winner for best basic science paper was Colleen Foster (supervisor Dr Dunham) for her talk: "Overexpression of PLK1 predicts poor outcome in pediatric medulloblastoma."

Scientific Papers

1. Teleneuropathology in Canada in 2012

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Teleneuropathology systems for remote intraoperative consultation have been implemented in numerous Canadian centres over the past eight years, starting with Toronto in 2004. Whole slide imaging (WSI) of frozen sections and cytologic preparations with currently available slide scanners can generate a digital image at 200x magnification in a matter of minutes. These images are highly comparable to direct visualisation of the original slide by conventional optical microscopy, and retrospective evaluation of digital diagnosis has shown extremely high concordance.

The digital files generated by WSI can measure several hundred megabytes in size, and were originally accessed over dedicated hospital networks. Nevertheless, continued advances in software and network technology now make it possible to access these files remotely over the internet using a portable or home computer, which frees the neuropathologist from working at a dedicated hospital-based office environment while providing coverage for intraoperative neurosurgical consultations.

The Laval University Integrated Health Care Network (RUIS-Laval) implemented such a system for remote teleneuropathology in December 2011, and over a dozen

intraoperative consultations by teleneuropathology have been successfully performed in the subsequent eight month period.

2. Use of public databases for research in neuropathology

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There is an increasing amount of biomedical data stored in publicly available repositories on the internet. The use of free, easy-to-use online resources has made much of this data amenable to re-purposing and re-interrogation. Such analysis may provide a low-cost tool for hypothesis generation and validation in neuropathology.

3. The CANP National Neuropathology Lecture Series

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Neuropathology is a specialty with rapidly evolving and expanding knowledge demands, and all Canadian Neuropathology residency programs face the challenge of delivering a comprehensive and current curriculum with limited number of faculty. The National Neuropathology Lecture Series aims to supplement the existing curriculum at Canadian post-graduate Neuropathology training programs, address common gaps among all training programs, promote 'sharing' of local subspecialty Neuropathology expertise between training sites, and augment the teaching of non-medical expert CanMEDS roles. It will be launched fall of 2012 and will run as a one year pilot project in the utility of technology and inter-university collaboration in addressing the educational needs of a small specialty. Aspects to the pilot include a post-graduate Needs Assessment Survey, delivery of six lectures based on identified curriculum gaps, and a post-graduate Evaluation Tool at the completion of the year. During the pilot period the National Neuropathology Lectures will be available to all Canadian Neuropathology residency programs, and will also be made available to all members of the Canadian Association of Neuropathologists. At the completion of the pilot a survey will be circulated among members of the Canadian Association of Neuropathologists to assess the need for and utility of the National Neuropathology Lecture Series as a potential Continuing Medical Education Tool.

4. Survey of Canadian muscle antibody availability

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In order to develop muscles standards for the CANP, a survey of available antibodies at most major centres examining muscle (18) was undertaken using an e-mail questionnaire. Antibodies (52) surveyed were determined by those detailed in the Dubowitz & Sewry textbook plus several recent articles on use of muscle immunohistochemistry. All centres had antibodies that are commonly used in anatomic pathology (e.g. CD3, desmin) and most had those commonly used in neurodegenerative diseases (e.g. phosphorylated tau, β-amyloid). Most centres also had access to antibodies against dystrophin, alpha sarcoglycan, and NCAM. The majority of centres also had one or more other sarcoglycans, alpha-2 laminin, and spectrin. Three centres had a majority of the surveyed muscle-specific antibodies; the most complete centre had 33 of the 52 antibodies. None of the centres had a full complement of the antibodies. Only a few centres had antibodies against the following: skeletal muscle actin, α-actinin, calpain-3, caveolin-3, collagen VI, emerin, α- or β-dystroglycan, emerin, lamin A/C, other laminins, any of the MHC-I, complement C5b-9, myosin heavy chains, myotilin, nNOS, perlecan, plectin, telethonin, or titin. Many of these latter antibodies are important for diagnosing specific myopathies.

5. Quantitative whole-slide CD68 expression in Carotid Plaques correlates with [18F]-fluorodeoxyglucose uptake by PET-CT

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Background: The identification of vulnerable carotid plaques is important in the assessment of stroke risk and triaging patients for surgical intervention. Plaque inflammation is a marker of vulnerability. We hypothesized that [18F]-fluorodeoxyglucose (FDG) uptake in carotid plaques as imaged with positron emission tomography (PET) and computed tomography (CT) could identify inflammatory pathology.

Methods: Thirty-one patients (66±10 years, 25 males) scheduled for carotid endarterectomy were prospectively recruited. Patients underwent PET and CT angiography. Maximum FDG uptake (normalized to blood glucose) by the plaques at both the left and right internal carotid arteries was measured, resulting in a glucose Tissue to Blood Ratio (TBR). Excised plaques were fixed, sectioned and immunostained for CD68. CD68 expression was analyzed using computer algorithms on whole-slide digitized images.

Results: Of 31 patients, immunohistology was performed in 22 patients with one patient requiring a second endarterectomy for bilateral disease. Maximum FDG uptake significantly correlated with macrophage infiltration as assessed by CD68 staining (r=0.589, p=0.003). Patients were divided into symptomatic (n=50 plaques, 25 patients) and asymptomatic (n=12 plaques, 6 patients) groups. FDG uptake was greater in the symptomatic group (3.5±1.3 TBR vs. 2.7±0.9 TBR, p=0.04).

Conclusion: Carotid plaque FDG uptake *in vivo* correlates well with the quantitative inflammatory burden within excised plaque at microscopy and may facilitate earlier and more valid triage of high risk patients.

6. Dysembryoplastic neuroepithelial tumours: the SickKids' experience

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Objectives: Dysembryoplastic neuroepithelial tumour (DNT) is a glioneuronal tumour of the CNS. Typically seen in young patients with a long-standing history of refractory seizures, DNT is characterized by its cortical location, multinodular architecture and a glioneuronal cellular composition. It was accepted as a new entity in the 1993 WHO classification as a grade I neoplasm based on early reports of its benign clinical behaviour. The aim of this study was to review the Hospital for Sick Children (SickKids) cohort of DNT patients in terms of their histopathology and clinical outcome.

Methods: The pathology and neurosurgical archives were searched for patients diagnosed with DNT between 1987 and 2012 at SickKids following approval of the study by the Research Ethics Board. Fifty-five tumours from 40 patients were identified and were diagnostically reviewed by two neuropathologists. DNTs were then assessed for morphologic features including: microvascular proliferation, mitoses, necrosis, cellularity, nuclear atypia and MIB1 index. Clinical data, including presentation, surgical management, progression-free and seizure-free survival, were collected.

Results and Conclusion: 35/40 patients were confirmed to have DNT based on pathology review. Other review diagnoses included two patients with oligodendroglioma, one patient with ganglioglioma, 1 patient with focal cortical dysplasia and one patient with mixed low grade tumour. 26/35 DNT patients had no evidence of tumour recurrence. 6/35 patients had recurrent DNT, and 3/35 patients had an alternate primary diagnosis with DNT at recurrence. No specific morphologic features were predictive of tumour recurrence. While mortality from DNT is very rare, this series highlights a 17% recurrence risk in patients with classical DNT, irrespective of extent of surgical resection.

7. Composite epithelioid glioneuronal tumor-pleomorphic xanthoastrocytoma shows BRAF V600E mutation in both components

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Epithelioid phenotype is rare in central nervous system tumors but usually identified in high-grade types such as metastases, epithelioid glioblastomas, or malignant rhabdoid tumors. We now report a unique, low-grade composite epithelioid glioneuronal tumor-pleomorphic xanthoastrocytoma (PXA) in an adolescent. Classic PXA areas were abruptly juxtaposed to small, monotonous, discohesive, epithelioid tumor cells with strong neuronal differentiation by immunohistochemistry and electron microscopy and a low MIB-1 labeling index. Unlike previously reported composite PXA-ganglioglioma (GG), there were no neuropil-rich areas or mature ganglion cells. PXA-GGs have been considered "collision tumors" since little intermingling of the two elements has been present. We hypothesized that these two elements might instead derive from a common origin. To test this, we microdissected the separate regions of this biphasic tumor and assessed each for BRAF V600E mutation, a genetic feature seen in 2/3 of pure PXAs. BRAF mutation was found in both tumor areas, indicating common origin for the components rather than a collision tumor. This biphasic glioneuronal-PXA case underscores that epithelioid morphology is not confined to high-grade tumors and illustrates a unique neuronal morphology associated with PXA. It also adds to the growing list of biphasic tumors with BRAF V600E mutation. This microdissection technique was further applied to GGs of spinal cord, including two with multiple tumor components, illustrating its utility in understanding morphologically-different tumor areas.

8. Epithelioid GBMs show a high percentage of BRAF V600E mutation

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Background: BRAF V600E mutation has been identified in up to 2/3 of pleomorphic xanthoastrocytomas (PXA), WHO grade II, as well as varying percentages of pleomorphic xanthoastrocytomas with anaplastic features (PXA-A), gangliogliomas, extra-cerebellar pilocytic astrocytomas, and rarely, giant cell GBMs (GC-GBMs). GC-GBMs and epithelioid GBMs (E-GBMs) can be histologically challenging to distinguish from PXA-A. We undertook this study specifically to address whether these two tumor types were also enriched for the mutation.

Design: We tested our originally-reported cohort of eight E-GBMs and two rhabdoid GBMs (Am J Surg Pathol 2010; 34:341–354) as well as five new E-GBMs (1 pediatric, 4 adult) and nine GC-GBMs (2 pediatric, 7 adult) (n=24) for BRAF V600E mutational status. 21/24 had sufficient material for IDH1 immunostaining, which is usually absent in PXAs, PXA-As, and primary GBMs, but present in many secondary GBMs.

Results: Patients ranged in age from 4-67 years. BRAF V600E mutation was identified in 7/13 of E-GBMs, including three of our original cases; patients with mutation were ages 10-50 years. None of the GC-GBMs or rhabdoid GBMs (n=11) manifested this mutation, including pediatric patients. The sole secondary E-GBM was the single case manifesting positive IDH1 immunoreactivity.

Conclusion: A high percentage of E-GBMs manifest BRAF V600E mutation, paralleling PXAs. All rhabdoid GBMs and GC-GBMs were negative, although larger multi-institutional

cohorts will have to be tested to extend this result. BRAF V600E mutational analyses should be performed on E-GBMs, particularly in all pediatric and young-aged adults, given the potential for BRAF inhibitor therapy in this subset of GBM patients.

9. Pilocytic Astrocytoma in adults

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Pilocytic astrocytoma (PA) is a relatively circumscribed astrocytic tumour, most commonly arising from the cerebellum, but also occurring elsewhere throughout the neuraxis. PA is the most common glioma in children, but relatively rare in adults and extraordinary after the 6th decade of life. Although most PA show benign clinical behavior, a subset recurs and some even undergo malignant transformation. Recent studies have identified a key role for BRAF gene in the development and behavior of pediatric PA. Our aim was to review the histopathologic features, molecular signature and clinical outcome of PA in adults, defined as persons older than 16.

The pathology archives were searched for patients diagnosed with PA at St. Michael's Hospital, Toronto between 2000 and 2012. Twenty one tumours from 19 patients were identified and histopathology was reviewed. Eighteen patients had classical PA (cPA) and one had pilomyxoid astrocytoma. Out of 18 patients with cPA, 12 were males and 6 were females. The age of the patients ranged from 16 to 82 years (yr), with an average of 33 yr and standard deviation of 20.1 yr. Although most patients were under age of 40, 2 patients were 79 and 82 yr at the time of the diagnosis. Two patients had symptoms starting in childhood. Location was: nine cerebellar, four hypothalamic, one thalamic, two cerebral hemispheres, one brain stem and one 4th ventricle tumour. 16/18 patients had biphasic tumours and two patients had tumours with compact dense morphology. The follow-up recorded in the chart ranged from one month to four years, with good outcome in most of the patients. Two patients had tumour recurrence at three yr post-surgery. Long-term follow up is pending. Data on BRAF tandem duplication at chromosome band 7q34 resulting in BRAF/KIAA1549 gene fusion and constitutive activation of BRAF is being completed and will be reported.

10. Multicystic encephalopathy due to HSV-2 detected via PCR in formalin-fixed-paraffin-embedded brain

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Introduction: Multicystic encephalopathy (MCE) results from a global disruption in perinatal brain development and is frequently attributed to hypoxia-ischaemia.

Methods: We report the case of a female with MCE who was born healthy at 35+5 weeks and presented at two months with a five day history of lethargy and hypothermia.

Results: CT scan showed multicystic encephalomalacia and calcifications. CSF analysis revealed lymphocytic pleocytosis, but PCR testing for HSV-1&2, enterovirus, and CMV was negative. Normal CSF interferon-alpha levels argued against Aicardi-Goutières syndrome. Low CSF monoaminergic neurotransmitter metabolites suggested dihydropterin-reductase-deficiency, but enzymatic tests were normal. The patient died two weeks after presentation. At autopsy, MCE was confirmed. Microscopy included bilateral gliosis with multinucleated giant cells and calcifications. Pathologic examination of the eyes demonstrated bilateral healing necrotizing retinitis, suggestive of a viral etiology, but retina and brain were free of viral inclusions and immunohistochemistry for HSV-2 and CMV was negative. However, microbiological testing using PCR revealed HSV-2 DNA in four cerebral paraffin blocks. Subsequent repeat testing of the initial CSF sample using a different PCR assay detected minimal HSV-2 DNA levels.

Conclusions: Infectious etiologies should be entertained in the differential diagnosis of MCE. Multinucleated giant cells may serve as a clue to the presence of an infectious agent in immunohistochemically negative cases and prompt PCR based analysis.

11. Unusual autopsy findings in a fatal case of chromosome 6q deletion syndrome

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Deletions of the long arm of chromosome 6 (6q) have been associated with mental retardation, dysmorphic faces, hydrocephalus, feeding difficulties, and seizures. Brain imaging studies have described colpocephaly, ventriculomegaly, complete or partial agenesis of the corpus callosum, polymicrogyria, and a small cerebellum. In spite of these complications and refractory epilepsy, the majority of patients survive. We present the necropsy findings of a ten year-old girl with congenital hydrocephalus who was diagnosed in the first week of life with chromosome 6q deletion. She had developmental delay, refractory seizures, dysmorphic features, and a previously removed retroauricular vascular malformation. In addition, she also experienced repeated choking and aspiration, with upper respiratory tract infections. She unexpectedly died at home. The general autopsy revealed pneumonia. Brain findings included the previously described hydrocephalus, colpocephaly, partial agenesis of the corpus callosum, polymicrogyria, and a small cerebellum. Additional brain findings included abnormal proliferation and distribution of vessels in the dura and meninges, left schizencephaly, immature hippocampi, and changes suggestive of Chiari type II malformation. These lesions had not been previously described in chromosome 6q deletion syndrome patients.

12. Neuropathological phenotypic spectrum associated with mutations in the β-tubulin gene TUBB2B

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In 2007, a spectrum of lissencephalies associated with TUBA1A mutations was identified. In view of the essential role of the tubulin superfamily during CNS development, a screening of several other candidate tubulin genes was performed in subjects presenting with different cortical dysgeneses. Heterozygous missense mutations in TUB2B were found in subjects with mental retardation, epilepsy and quite identical imaging features. In all mutated cases, MRI showed a complex brain dysgenesis associating bilateral, asymmetrical cortical anomalies suggesting a polymicrogyria, anomalies of basal ganglia, corpus callosum, brain stem and cerebellum. A neuropathological study of two fetuses mutated for TUBB2B allowed us to describe the neuropathological features associated with these mutations. In one case, histological analysis confirmed the bilateral, asymmetrical polymicrogyria with a focal overmigration of neurons into the meninges through a defect of glia limitans, close to that observed in GPR56 mutations, associated with neuronal heterotopias, callosal, hippocampal and cerebellar anomalies. In a second case, a microcephaly with severe ventriculomegaly and cerebellar hypoplasia was observed and histological examination showed a diffuse overmigration of cells into meninges throughout the surface of both hemispheres, as well as around the brain stem and cerebellum resembling "cobblestone" lissencephaly. TUBB2B mutations are responsible for a wide spectrum of neuropathological phenotypes overlapping with other lissencephalies and cortical dysgeneses with distinct molecular basis.

13. Synaptogenesis in the fetal and neonatal cerebellar system

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Precise temporal and spatial sequences of synaptogenesis occur in the cerebellar system, as demonstrated by synaptophysin immunoreactivity. Synaptophysin was studied prospectively at autopsy in 172 fetuses and neonates, in nuclei of the Guillain-Mollaret triangle, pontine nuclei and cerebellar cortex. Synaptophysin demonstrates not only progressive increase in synaptic vesicles, but also development of shape of the inferior olivary and cerebellar nuclei. Reactivity is intense before mature shapes are achieved. The dorsal blade forms earlier than the ventral; reactivity is initially peripheral. Accessory cerebellar nuclei are reactive earlier than the dentate. The pontine nuclei exhibit a patchiness reminiscent of the fetal corpus striatum, becoming uniformly intense at 34 weeks (wk). In the cerebellar cortex, morphogenesis and synaptophysin reactivity mature earlier in the vermis than the hemispheres, beginning around Purkinje cells. Initiation of synaptophysin reactivity is at 13wk inferior olive, 16wk dentate, 12wk red nucleus, 15wk pontine nuclei and vermis and 16-17wk cerebellar hemispheres. In conclusion, development of both form and reactivity follows caudorostral and dorsoventral gradients in the longitudinal and vertical axes of the brainstem, and a mediolateral gradient in the cortex. This study of normal fetal neuroanatomy provides a basis for interpreting aberrations in timing and sequence of synaptogenesis in cerebellar system malformations, genetic and metabolic disorders, and acquired fetal insults.

14. Retrospective autopsy review of encephalitis in Manitoba

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All cases of viral and presumed viral meningoencephalitis in Manitoba autopsy cases (1997-2012) were reviewed to determine if it contributed to the cause of death. Approval was obtained under the University of Manitoba Research Ethics Board (H2011:051). Seventy-five cases with lymphocytic inflammation and microglial activation in brain were identified in 14 years (approximately 400 brain examinations per year). The patient age ranged from stillborn fetus (three cases) to 81 years (average 34 years). In almost half (43%) of the cases the encephalitis was an incidental finding, not associated with the cause of death. In six cases viral encephalitis was the clinical diagnosis and was confirmed to be the cause of death. In nine cases vague neurological or viral infection symptoms preceded death and significant inflammation was found in the brain without other obvious cause of death. Serologically or immunohistochemically diagnosed entities such as Herpes simplex virus (HSV) (four cases), Herpes zoster (two cases), cytomegalovirus (CMV) (one case), West Nile virus (two cases), and polyoma virus (progressive multifocal leukoencephalopathy) (seven cases) were the minority. In the remainder a viral cause is only suspect. Seasonal variation was identified with peaks in May and in July-October suggesting that specific viruses (e.g. arboviruses or enteroviruses) are more likely to cause encephalitis at certain times of the year. This information might be useful for directing targeted identification of the viral infection.

15. Primary brain abscess caused by Legionella micdadei

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Brain abscesses that fail to yield a pathogen using conventional staining techniques and culture media pose significant challenges in diagnosis and clinical treatment. At times, unusual micro-organisms requiring special approaches in identification are involved as illustrated in this case report. A 59-year-old man, completing a course of chemotherapy for Waldenstrom macroglobulinemia, was admitted to hospital with a five day history of frequent falls, progressive somnolence, and fever. CT and MRI scans disclosed a 6.4 x 5 x 5 cm necrotic

mass with peripheral gadolinium enhancement in the right frontal lobe, prompting neurosurgical resection of a brain abscess. Notwithstanding broad spectrum antibiotic coverage, his condition deteriorated and he died two days later. Autopsy confirmed the presence of a subacute brain abscess accompanied by massive edema with associated axial herniation. No pneumonia or other site of infection was found in the other organs. Conventional stains and cultures for micro-organisms initially failed to identify a pathogen in the surgical specimen and aspirate. However, 16SrRNA PCR analysis of this aspirate, and that taken at autopsy, was positive for Legionella micdadei, subsequently confirmed by isolation on appropriate culture media. In conclusion, this report demonstrates the crucial role of molecular techniques in diagnosis of culture negative abscesses and documents the rare occurrence of CNS infection by a Legionella species without concurrent pneumonia.

16. Heterogeneity of adult-onset leukodystrophy: report and review of three neuropathological phenotypes

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Adult-onset leukodystrophy are chronic progressive white matter disorders with diverse clinical features and pathological substrates. We present three recent cases of leukodystrophy with differing neuropathological phenotypes.

The first pattern is the prototypical hereditary diffuse leukoencephalopathy/leukodystrophy with spheroids (HDLS). Such cases contain abundant axonal spheroids in white matter, with a tendency to spare cerebellum and brain stem. A CSF1R mutation has been recently described in cases of HDLS. A second pattern is of lesser axonal spheroid formation but more diffuse involvement (cerebrum, cerebellum and brain stem). A third pattern, a well-defined clinical entity (autosomal dominant leukodystrophy) with a mutation in LMNB1, is characterized by marked white matter vacuolation involving cerebrum, cerebellum and brain stem.

The three cases presented an opportunity to examine differing phenotypes of adult-onset leukodystrophy and consider their clinical-pathological-genetic correlations. The literature on this topic is also reviewed.

17. Hereditary motor and sensory neuropathy associated with agenesis of the corpus callosum (HMSN/ACC) is a white matter disease associated with hypoplasia of long midline crossing projections as well as axonal swelling

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Hereditary Motor and Sensory Neuropathy with Agenesis of the Corpus Callosum (HMSN/ACC) is an autosomal recessive disease due to a mutation in a gene that encodes a potassium/chloride cotransporter termed KCC3, resulting in a syndrome including areflexia from birth, early onset polyneuropathy, hypotonia with abnormal facial features, psychosis and muscle wasting, with a wheelchair existence by the second decade of life. The central nervous system (CNS) involvement is more noticeable in the second and the third decades of life.

We here describe a series of eight patients with autopsy findings. HMSN/ACC features a small soma, with body weights into the 30 kg range. Both central and peripheral nervous systems are affected. In the telencephalon, agenesis of the corpus callosum and central axonopathy with profound corticospinal tract hypoplasia results in a disconnection axonopathy explains central motor and psychotic features. The central neuro-degenerative aspect of this disorder was found to be widely disseminated. Neoplastic-like overgrowths of bare axons, termed axonomas, are an end stage of the axonopathy. The pathogenesis involves a progression from a genetic abnormality of a potassium channel, leading to early subtle axonal dilatation, beading and irregularity, followed by progressive axonal pathology ending in functional interruption, and occasional axonomas attempting regeneration.

We conclude that HMSN/ACC is a remarkably protean disease comprising a CNS & PNS channelopathy resulting in primarily axonal abnormalities in CNS and PNS, leading to widespread structural axonal degeneration with clinical features ranging from psychiatric to motor manifestations.

18. Head injury old and new

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Introduction: Head injury was vividly described nearly three thousand years ago by Homer in the Iliad. The head injuries suffered by Homeric warriors were mainly acute and fatal. Modern descriptions of the pathology of acute traumatic brain injury explain these injuries. More recent studies also explain the effects of chronic head injury. This phenomenon of chronic traumatic encephalopathy was not described by Homer, but was probably well known in ancient Greece.

Aim and Methods: Reviews are undertaken of a) previous analyses of traumatic injuries in Homeric epic (the Iliad) including catalogues of wounds by body part involved, weapon used, method of striking, and outcome, and b) depictions of head injury in ancient Greece outside epic storytelling, and c) recent studies of the pathology of chronic traumatic encephalopathy. Homeric wounds are re-catalogued. These reviews are combined in order to understand old and new concepts of both acute and chronic head injury.

Conclusions: Head injury in ancient Greek epic, in addition to describing death, reveals concepts of neurologic function beyond the sphere of epic heroes. A review of wounds in ancient Greek epic and of depictions of head injury in early Greek art reveals concepts of acute and chronic brain injury that are ancient and enduring. These are discussed.

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19. Variant Alzheimer disease with spastic paraparesis and supranuclear gaze palsy with a missense mutation in exon 8 of the PSEN1 gene

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Introduction: Variant Alzheimer's disease (VarAD) is characterised by spastic paraparesis, dementia and "cotton wool plaques" (CWPs). It has been associated with different mutations in the PSEN1 gene. The clinical diagnosis of VarAD may be difficult in subjects presenting with paraparesis as the initial symptom.

Results: A 66-year-old man presented with a 19 year history of spastic paraparesis. Clinical diagnoses included postpolio syndrome, primary progressive multiple sclerosis and hereditary spastic paraparesis (HSP). Late in his course he developed dementia, dysphagia, dysarthria and the unusual symptoms of a supranuclear gaze palsy. He died after a 20 year course. At autopsy, microscopic examination revealed AD type changes with widespread CWPs. Sequencing of the PSEN1 gene revealed a pathological mutation (E280G). In addition, we sequenced the ZFYVE26 spastic paraparesis gene mapped ~5 Mb from PSEN1, as a potential genetic modifier responsible for the variant phenotype. Analysis of ZFYVE26 in our patients revealed two missense variations with unknown pathological significance (rs3742883 and rs17192170).

Conclusion: Understanding the phenotypic heterogeneity seen in association with PSEN1 mutations may illuminate important biological mechanisms that give rise to the variable phenotype and help in designing novel Aβ-targeting therapies. Our analysis of the ZFYVE26 gene did not reveal truncating mutations (the type of mutations reported to cause spastic paraplegia in HSP15-linked families).

20. Clinical, pathological and genetic aspects of C9ORF72 mutations

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Frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) are closely related clinical syndromes with overlapping molecular pathogenesis. Several families have been reported with autosomal dominant inheritance of FTD, ALS or both; showing genetic linkage to a region on chromosome 9p21. Recently, the FTD/ALS gene defect on 9p was identified as a massively expanded GGGGCC repeat in a non-coding region of the C9ORF72 gene. Subsequent studies from many centers have shown the C9ORF72 mutation to be the most common genetic cause of familial and sporadic forms of both FTD and ALS. The associated phenotype is heterogeneous with wide variation in age of onset and survival. FTD is most often the behavioral variant and the motor features are usually classical ALS but with more frequent bulbar onset. The neuropathology is characterized by TDP-43-immunoreactive inclusions in the cerebral cortex (FTLD-TDP), motor neurons (ALS-TDP) and many other neuroanatomical regions. Ubiquitin-positive, TDP-43-negative inclusions in the cerebellum and hippocampus are a consistent and unique feature. The hexanucleotide repeat is located between two alternately spliced first exons and abnormal expansion results in loss of one alternatively spliced C9ORF72 transcript and the formation of nuclear RNA foci. In summary, the C9ORF72 mutation is a major cause of both FTD and ALS; further evidence that FTD and ALS represent a clinico-pathological spectrum of disease.

21. Comparison between manual and automated assessment of 1p-19q status in gliomas by FISH assay on paraffin embedded tissue: a need for standardization

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The study of 1p-19q status in glial tumours with an oligodendroglial component is a common practice in many neuropathology laboratories. Several methods for 1p19q testing are available, of which fluorescence in situ hybridization (FISH) is most commonly used.

Although manual and automated methods are commonly used together in FISH testing, there is very little comparative data in the literature between these two methods. To address this, we compared manual and automated assessment of 1p-19q status on a local retrospective series of 53 consecutive oligodendroglial tumours including 11 O II, 19 O III, 13 OAII, 7 OA III and 3 GBMO.

For each chromosome probe mix, hybridization signals of control and test probes were visually counted on 200 nuclei and classified into three groups (deleted, normal and imbalanced pattern) according to the ratio of red test signal to green control signal. For chromosome arm 1p, the concordance between the two methods was 87%. Similar concordance was observed for 19q with a concordance of 89%.

Automatic analysis also allowed a nuclear morphometric study which demonstrated the absence of statistically significant differences in nuclear size between histologic grade or chromosomal status of the tumour.

22. Synovial sarcoma of the nervous system: a clinicopathologic review of 10 cases and comparison to malignant peripheral nerve sheath tumour

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Synovial sarcoma of the nervous system is rare and pathologists may mistake monophasic variants for malignant peripheral nerve sheath tumours (MPNST). In attempt to better describe the clinicopathologic features of synovial sarcoma of the nervous system, the pathology archives from three academic hospitals in Ontario were searched for a diagnosis of 'synovial sarcoma' over the past ten years.

Twelve tumours from ten patients having a diagnosis of 'synovial sarcoma' where the lesion affected the nervous system underwent central pathology review including immuno-histochemistry for cytokeratins, EMA, S100, SOX10, CD34, bcl2, CD99, and Ki67. Molecular studies on these 10 patients for t(X,18) SYT-SSX1 or SYT-SSX2 translocation via PCR confirmed the diagnosis of synovial sarcoma in seven patients, and review of the three cases lacking this translocation by a soft tissue pathologist suggested alternative diagnoses. The central pathology review and immunohistochemical panel was also applied to a series of MPNST.

The results indicate that synovial sarcomas affecting the nervous system were most commonly primary tumours of brachial plexus or spinal nerve roots with an aggressive clinical course. The histology was either a monophasic spindle cell tumour with frequent myxoid change and hemangio-pericytomatous vasculature, or a biphasic tumour with predominantly glandular morphology, and all synovial sarcomas expressed at least one of lmwCK, panCK or EMA, often in a 'rare positive cells' pattern. The utility of molecular testing and immunohistochemistry, including SOX10, in distinguishing these tumours from MPNST will be discussed.

23. Atypical teratoid rhabdoid tumor of sellar region

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Atypical teratoid/rhabdoid tumor (AT/RT) of the central nervous system is a rare, aggressive neoplasm found in infants and children. However, it is extremely rare in adulthood, where it has been reported in the cerebral hemispheres, cerebellum and spinal cord. In the English literature, only three cases of AT/RT have been reported in the sellar region in an adult. Here we are report a case of a sellar region AT/RT in a 56-year-old previously-healthy female, who presented with recurrent cavernous sinus syndrome requiring two surgical resections over a six-week period. The histopathology showed the tumor was comprised of cells with a morphology that resembled cells of adenohypophyseal origin but had faint "rhabdoid" inclusions. Immunohistochemically the tumor was positive for AE1/AE3 and vimentin. It was focally positive for EMA, synaptophysin and chromogranin. It was negative for pituitary hormones. INI-1 was absent within tumor cells but positive in the small fragments of adenohypophysis included in the second resection. Her metastatic workup showed mild mediastinal lympha-denopathy of uncertain significance. After the second resection the tumor continued to rapidly expand. She is currently receiving radiation for treatment of residual tumor. However, given the aggressive nature of this tumor, her overall prognosis remains poor.

24. Overexpression of PLK1 predicts poor outcome in pediatric medulloblastoma

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Introduction: Recent in vitro work has identified polo-like kinase 1 (PLK1), a molecule critical to normal mitotic division, as a potential therapeutic target in pediatric medulloblastoma. However, published data on large clinical cohorts is limited.

Methods: We performed a retrospective clinicopathologic analysis of 81 medulloblastomas treated at C&W from 1986-2011 (REB # H11-03397). As part of our study, we constructed a tissue microarray (TMA) that included 76 patients. Each tumor resection (including recurrences) was represented in the TMA via triplicate 1 mm FFPE cores. PLK1 immunohistochemistry (IHC) was scored in a blinded fashion. Semiquantitative scores were issued according to a 4-point scale (0→3, with "0" corresponding to no staining and "3" being strongly positive). Data was subsequently binarized into "high" (2 & 3) and "low" (0 & 1) expressing cases. Kaplan-Meier survival analysis was conducted using SPSS version 20 (IBM).

Results: It was possible to assess PLK1 IHC activity in 67 cases. "High" PLK1 expression (31/67) was significantly associated with worse 5-year overall and event free survivals (P< .002 and .005; Breslow/Generalized Wilcoxon) as compared to "low" expression.

Conclusion: A substantial number of medulloblastomas demonstrate "high" PLK1 IHC expression and incur a significantly worse outcome. These initial analyses further support a potential management strategy involving chemo-therapeutic manipulation of PLK1 in a subset of pediatric medulloblastoma.

25. Intrasellar cavernous hemangioma presenting as pituitary adenoma

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Intrasellar cavernous hemangioma in the sellar region is a rare lesion with only a handful of cases being reported in the English literature. Its clinical manifestations and imaging characteristics can often mimic a pituitary adenoma. We report two cases of recurrent sellar tumours, both of which were clinically suspected of being pituitary adenomas but histologically confirmed as cavernous hemangiomas. The first

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case is of a 67-year-old female who underwent resection of her initial tumour in 1984. Follow-up examination in June 2011 was notable only for bitemporal hemianopsia. Subsequent imaging revealed significant growth in the size of the tumour involving the right cavernous sinus and encasing right internal carotid artery. The patient then underwent transphenoidal endoscopic resection of the tumour. At the time of the surgery, the tumour was noted to be quite vascular. Residual tumour was left behind.

The second case is of a 48-year-old female who underwent emergency resection of a pituitary mass following an apoplectic event in 2008. On follow-up in May 2012, the patient reported recurrence of galactorrhea and MRI had demonstrated regrowth of her tumour. She subsequently underwent subtotal resection of the tumour. At the time of surgery, brisk bleeding was noted in the operative area. The above two cases demonstrate that cavernous hemangiomas in the sellar region can clinically and radiologically mimic pituitary adenoma, and should be considered in the differential diagnosis of hemorrhagic sellar mass.

26. Differential gene expression in recurrent grade I meningiomas

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Several series have reported the recurrence rates for Grade I meningiomas to vary from between 10 and 33%. We sought to determine if the grade I meningiomas that recur have significantly different gene expression profiles as compared to their non-recurring counterparts. We examined a publicly available dataset (GSE16153) containing gene expression from 252 tumors. From this superset we analyzed 140 cases of grade I meningiomas, 21 of which recurred. Both class neighbors analysis and a 'leave one out' logistic regression model identified a similar list of 100 genes that were differentially expressed in recurring and non-recurring grade I meningiomas. Using the top 200 genes identified by the leave-one-out logistic regression model combined with K-nearest neighbour analysis we were able to correctly classify 136/140 (96.5%) of cases accurately.

Titles of Diagnostic Case Presentations

1. Papillary tumour of the pineal region

Alaa Alkhotani, Juan M. Bilbao, Todd G. Mainprize

Sunnybrook Health Sciences Center, University of Toronto, Toronto, Ontario, Canada

2. Primary melacytoma, sclerozing, of leptomeninges, associated with NF 1

Y. Robitaille, R. Auer

CHU Ste-Justine, University of Montreal, Montreal, Quebec, Canada

3. Lhermitte-Duclos disease

D. G. Munoz[1], M. Hossain[2]

[1]Department of Laboratory Medicine, St. Michael's Hospital, University of Toronto, Toronto, Ontario; [2]Department of Laboratory Medicine, St. John Regional Hospital, St. John, New Brunswick, Canada

4. Lymphomatosis cerebri

Claire I. Coiré

Trillium Health Centre, Mississauga, Ontario, Canada

5. Glioblastoma, giant cell

N. Basahel, L. Macdonald, D. G. Munoz

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

6. Polyglucosan body disease (glycogenosis type 4)

F. AlSufiani, M. Shkrum, D. Ramsay

London Health Sciences Centre, London, Ontario, Canada

7. Late infantile neuronal ceroid lipofuscinosis (NCL), with two disease causing mutations in CLN2

L. Hamilton, J. Joseph

University of Calgary, Calgary, Alberta, Canada

8. Poorly differentiated sarcoma, NOS, with:
a) IHC suggestive of "desmoplastic small round cell tumor"
b) Break apart FISH evidence of a translocation event involving EWS but not WT1

C. Dunham, A. Singhal, J. Hukin, G. Hendson

Children's and Women's Health Centre of British Columbia, Vancouver, British Columbia, Canada

9. Primary Rhabdomyosarcoma, embryonal subtype with diffuse anaplasia

L. Hamilton, J. Chan

University of Calgary, Calgary, Alberta, Canada

10. Action myoclonus- renal failure syndrome

J. Ferreira

Hôpital Maisonneuve-Rosemont, University of Montreal, Montreal, Quebec, Canada

11. Rhombencephalic PML with JC virus granular neuronopathy

A.F. Gao, J. Bilbao, R. Baskind, J. Keith

Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada

12. Ganglioneurocytoma, WHO grade 2

N. Sinha[1], J. Wooff[2], J.J.S. Shankar[3], P. Gorman[4], R.J. Macaulay[1]

Queen Elizabeth II Health Sciences Centre and Dalhousie University, Halifax, Nova Scotia; Moncton Hospital, Moncton, New Brunswick, Canada

13. Plasma cell myeloma with small lymphocytic morphology, confirmed CCND-1 - IgH t(11;14) translocation and massive amyloid deposition

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