Canadian Association of Neuropathologists

ABSTRACTS

September 5-8, 2007
Niagara Falls, Ontario
Abstracts of papers and cases presented at the Forty-Seventh Annual Meeting

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The Forty-Seventh Annual Meeting of the Canadian Association of Neuropathologists was held from September 5-8 at the Sheraton Hotel and Convention Centre in Niagara Falls, Ontario. Local arrangements, which included a tour and Banquet at the Peller Estates winery, were coordinated by Drs. Bolek Lach and John Provias; the scientific program was assembled by Dr. Rob Macaulay.

The program comprised 20 platform presentations and 12 diagnostic case presentations. Sessions were organized under the following headings: Tumours (two sessions), Nervous System Damage and Repair, Neuroinflammatory Diseases, Neurodegenerative Diseases, Pediatric Neuropathology, and Neuromuscular and Metabolic Neuropathology. Chairs of sessions were Drs. Cynthia Hawkins, Roland Auer, Rob Hammond, Juan Bilbao, Gerard Jansen and Peter Gould.

Five special lectures were given by invited guests. The Speaker of the Royal College of Physicians and Surgeons of Canada was Dr. Samuel Weiss, Director of the Hotchkiss Brain Institute, University of Calgary; his talk was entitled: "Adult forebrain neural stem cells: From basic biology to brain". The Gordon Mathieson Lecture was provided by Dr. Jacek Kwiecien from McMaster University; his lecture was entitled: "Neuropathology of axonal regeneration in the adult rat CNS."

The meeting included a Symposium on Mitochondria, chaired by Dr. Edward Johnson, CANP President. This included the Jerzy Olszewski Lecture presented by Dr. Hendrik Poinar from McMaster University; Dr. Poinar's fascinating presentation was entitled: "Paleogenomics and the benefit of time travel." This was followed by an address by Dr. Gerald Shadel from Yale University, entitled: "Mitochondrial gene expression: new insights into disease and aging." The meeting ended with a superb lecture by Dr Mark Tarnopolsky from McMaster University, entitled: "Mitochondrial cytopathies in children and adults: Clinical and treatment similarities and differences".

Papers presented by trainees were of very high caliber; the Mary Tom Award for best clinical science paper in neuropathology went to Dr Julia Keith-Rokosh (supervised by Dr Lee-Cyn Ang). The Morrison H. Finlayson Award for best basic sciences and research paper went to Patrick Kim (supervised by Dr Michael Pollanen).

Platform Presentations

1. Telomere maintenance and dysfunction predicts tumour progression in pediatric ependymoma

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We used paediatric ependymoma, a tumour in which multiple resections are performed over time, as a model to examine the role of telomerase in tumour progression and survival. We analyzed 133 ependymomas from 83 paediatric patients for telomere length, dysfunction, hTERT (the enzymatic subunit of telomerase) expression and telomerase activity. We correlated these with markers of proliferation, anaplasia and cytogenetic abnormalities on available tissues. Thirty one patients had multiple resections which enabled us to examine tumour progression and response to therapy. hTERT expression correlated with MIB-1 (Ki67) proliferative index ($p<0.0001$), the mitotic index ($p=0.001$), cell density ($p=0.001$) and tumour grade ($p=0.002$). There was an inverse correlation between hTERT expression and telomere dysfunction as measured by γH2AX expression ($p=0.016$). Although variable telomere length was found, there was no correlation between telomere length and hTERT expression or telomere dysfunction suggesting that hTERT could protect even short telomeres from being detected as DNA double-strand breaks. Radiation and chemotherapy did not affect hTERT or γH2AX expression. Combining γH2AX and hTERT expression could segregate tumours into 3 different survival groups (Log Rank, $p<0.0001$). This study further emphasizes the importance of telomere maintenance as a prognostic and therapeutic target for paediatric ependymoma. Further, we have demonstrated that following tumour progression over time *in vivo* is a novel way of studying tumour biology in humans.

2. Cytological features of intracranial hemangiopericytoma: A review of seven cases.

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Intracranial hemangiopericytoma (HPC) is a relatively rare tumor accounting for approximately 0.4% of all CNS tumors. Although the histological features of HPC are well known, previous reports on the cytology are few and limited to case reports and small series. We attempt to identify the useful characteristics that might distinguish them from other tumors included in the differential diagnosis. Thirteen cases of intracranial HPC were retrieved from the archive of the Department of Pathology, London Health Sciences Centre between 1985-2007. The diagnosis of HPC was confirmed histologically in these cases, and only seven cases with smear cytology (± touch preparations) performed during intraoperative consultation were available for this study. Cases of meningioma, hemangioblastoma, solitary fibrous tumor (SFT), metastatic carcinoma and melanoma were also included in the study for comparison purposes. All smears showed oval to spindle-shaped cells that are arranged singly and in clusters, with some aggregated around branched capillaries. The nuclei are uniform and oval with finely granular and evenly dispersed chromatin. The nucleoli are visible, but not prominent. Cytology can be a useful tool for intraoperative consultation but before a diagnosis of intracranial HPCs could be made, other tumors with similar cytological features such as meningiomas have to be excluded. Moreover, it is not possible to differentiate SFT and HPC based on cytology alone.

3. Predicting the behavior of gliomas following resection and X- ray therapy

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Although neuropathology has been the "gold standard" for use in comparing patients subjected to various forms of therapy, the implied predictions of the rates of growth and the responses to treatment have been less than might be desired. The classical definition of gliomas as a form of canc er with cells proliferating and invading locally, rho and D, respectively, forms the basis for our bio-mathematical model of glioma behavior. These two factors can be calculated from two sets of MRIs without intervening treatment. For any individual patient we can not only monitor in vivo and in real time but also predict the behavior of contrast-enhancing gliomas of any type or grade, including the degree of radio-sensitivity and the duration of survival following resections of any extent. The effects of chemotherapy can at least be monitored and the results compared with virtual controls matched for size, site, D and rho. For low-grade non-enhancing gliomas, only the velocity of radial expansion can be measured, but with the size the velocity suffices to predict the probable time to the development of contrast-enhancement and the subsequent short duration of survival. The morphological correlates of D, rho and v will probably require more than H&E staining.

4. Observed in vivo regeneration in adult rat spinal cord injury model

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Spinal cord injuries have devastating, permanent effects on individuals because transected central axons do not re-grow in a myelinated environment. We have used a completely dysmyelinated rat model, a Long Evans Shaker (LES) and created a crush in the dorsal column at the T-8 level. The site of injury was then treated with implantation of choroid plexus from a normal adult rat as described previously (Avram R, Kwiecien JM et al. 7th International Neurotrauma Symposium, Adelaide, South Australia, September, 2004.) Fluorescence microscopy of fixed tissues of the spinal cord revealed robust axonal regeneration across the choroid plexus-treated lesion but no such regeneration was detected in lesioned but untreated rats. Fluorescence microscopy is a laborious process with finding of the labeled axons being difficult and hard to interpret. We proceeded with Bio-Fluorescent microscopy of the whole unfixed CNS of experimental rats and observed regenerating axons labeled with cholera toxin subunit B (CTB) trans-ganglionic tracer labeled with AlexaFluor 594m (Invitrogen). The labeled axons were observed rostral to the choroid plexus-treated lesion indicating regeneration across the injury treated with choroid plexus cells. Such evidence of regeneration was not seen in the lesioned but untreated control group of LES rats. We continue to optimize the dorsal column injury in the adult LES rat model to develop better understanding of the cellular mechanisms of axonal regeneration in the CNS.

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5. Neuropathologic characterization of a murine model of non- impact head trauma

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In 1970s, the term 'Shaken Baby Syndrome (SBS)' was first used to describe a triad of brain swelling, subdural hemorrhage (SDH) and retinal hemorrhage (RH) in babies without other evidence of trauma. Traumatic diffuse axonal injury (tDAI) has been proposed as the histological correlate to brain injuries in SBS although retrospective case studies have revealed heterogeneous presentation where most traumatic injuries of the axon were found in the background of hypoxic/ischemic encephalopathy. Past attempts of modelling SBS in animals have failed to reveal the mechanisms of axonal injuries from shaking since the injuries were inflicted by blunt impact or single rotation to the head. In this study, mouse pups of known age and developmental stage were shaken in a controlled manner and the progression of injuries was characterized by histology and immunohistochemistry. While this model may not be a true mechanistic representation of SBS, the molecular pathophysiology in response to non-impact injuries in animals could complement the inherent shortfall of retrospective case studies where confounding variables cannot easily be avoided.

6. Relevance of neuropathological investigations in ADEM

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Acute Disseminated Encephalomyelitis (ADEM) is characterized by obtundation, focal neurological deficits, seizures and severe brain edema, after a ten days to three weeks long latency period preceded by unremarkable upper respiratory tract viral infection. Neuroradiological investigations aim to highlight the leukoencephalopathy associated with ADEM in order to plan efficient therapeutic strategies. Although about 60% of patients survive without sequelae, some either die or survive with major neurological complications. We report two pediatric cases in whom brain biopsies became indicated to ascertain the diagnosis. In one biopsied subject and one non-biopsied child who survived several years with major cognitive decline, results of complete autopsies were available; patient ages were between 9 and 14 years. Both brain biopsies revealed extensive demyelination and axonal loss associated with perivascular lymphocytic cuffs, macrophages and widespread gliosis. Biopsy results were helpful to re-aim therapy towards immunosuppression. In the third case, cognitive deficits were associated with large confluent areas of demyelination which also involved optic nerves and spinal cord. In all cases, axonal loss was quite extensive, reaching levels of multisegmental depletion, particularly at spinal cervical levels. In conclusion, brain biopsies may be useful to properly focus therapy in the early phases of ADEM in order to decrease edema and mitigate the inflammatory response, However, in retrospect, it appeared strongly indicated to decrease as early as possible the rate and extent of acute demyelination, in order to prevent the intracerebral accumulation of potentially axonopathic by-products of myelin.

7. Alpha-synuclein immunoreactivity in multiple sclerosis

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Multiple sclerosis (MS) is associated with neurodegenerative features that lead to widespread brain atrophy. The cause of neurodegeneration in MS is thought to be due to inflammatory insults of the CNS but extensive oligodendrocyte apoptosis preceding infiltrating lymphocytes or myelin phagocytes have been noted. We have tested the hypothesis that MS shares the pathogenesis of neuronal cell death with classical neurodegenerative diseases. We examined immunoreactivity for α-synuclein in autopsy tissues from 9 patients with MS (age 46.2 ± 14.0 years; 2 with acute active lesions and 3 with chronic active lesions) and 6 control subjects with no CNS pathology (age 47.3 ± 8.6 years). α-Synuclein immunoreactivity was found in the cytoplasm of neurons, axons, activated microglia and other cells of unknown origin within and surrounding active MS lesions; both acute and chronic active lesions presented with α-synuclein immunoreactivity while this was rare in inactive lesions. This α-synuclein immunoreactivity was preferentially expressed in lesions of the brainstem. Confocal analysis of double-immunofluorescence labeling confirms co-localization of α-synuclein with the neuronal marker, neurofilament protein, and with the microglial marker, Iba1, in MS lesions. These results support the hypothesis that neuronal cell death in a proportion of lesions in MS shares some common features with other neurodegenerative diseases, and suggest that α-synuclein regulated by inflammatory signals is involved in the pathogenesis of MS.

8. Blastomycosis involving the central nervous system: the Manitoba experience

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Introduction: Blastomyces dermatitidis is a dimorphic fungus endemic to northwestern Ontario. Blastomycosis commonly involves the lungs with dissemination reported in up to two thirds of patients. The wide range of clinical presentations and radiologic features and the diverse pathology of blastomycosis involving the central nervous system (CNS) prompted a review of cases diagnosed at Winnipeg, Manitoba. The largest series of CNS blastomycosis reported to date is 5 patients (Ward et al 1995).

Material and methods: Review of 15 cases, including two autopsies, of CNS blastomycosis diagnosed at Winnipeg, Manitoba, 1994-2006.

Inclusion criteria: Blastomycosis diagnosed by recovering B. dermatitidis in culture or by histologic morphology.

Results: 7/15 cases in this series were under 18 years of age. Antecedent or concurrent pulmonary blastomycosis was not reported in 7/15 cases. Focal lesions within CNS parenchyma occurred in 8/15 cases. Only 2/15 cases had leptomeningeal disease without focal parenchymal lesions. The skull or scalp was involved in 4/15 cases. Cerebrospinal fluid analysis (5 cases) did not yield B. dermatitidis. Neurosurgical intervention was critical in the diagnosis of 11/15 cases.

Conclusions: Our findings refute many common assumptions regarding CNS blastomycosis. Blastomycosis should be considered in the differential of CNS disease in Canada, particularly in persons who have visited or reside in areas endemic for B. dermatitidis. Early biopsy is essential to prevent delays in diagnosis and treatment.

9. Semi-quantitative characterization of inflammatory cells in gangliogliomas

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Gangliogliomas are rare, low grade glioneuronal tumors. They most often arise in the temporal lobe and account for approximately 20% of cases of intractable temporal lobe epilepsy. Inflammatory infiltrates are typical of gangliogliomas, yet little is understood about the nature of the inflammation including the role it may play in clinical manifestations of this tumor. Our objective was to take an initial step towards the characterization of this inflammation.

Representative sections of gangliogliomas (n=14), dysembryoplastic neuroepithelial tumours (n=6), pilocytic astrocytomas (n=6), oligodendrogliomas (n=6), glioblastomas (n=7) and "normal" temporal neocortex from epileptic patients (n=7) were immunohistochemically stained for: lymphocytes (CD45-LCA), T-lymphocytes (CD45-Ro-UCHL-1), B-lymphocytes (CD20) and microglia (HLA-DR). Sections were evaluated semi-quantitatively for density and distribution of stained cells.

The dominant inflammatory cells in these tumors were microglia and T-lymphocytes; B-lymphocytes were sparse with rare exceptions. While all five tumors had more inflammation than control, pilocytic astrocytomas and gangliogliomas were most inflamed and dysembryoplastic neuroepithelial tumours were least inflamed. Gangliogliomas had significantly increased microglial, T-lymphocytic and B-lymphocytic infiltrates compared to control ($p<0.05$).

Characterization of inflammation in gangliogliomas and other brain tumours may spur investigations into why this occurs and what role it plays in clinical behaviour, with possible implications for anti-inflammatory therapies.

10. Multifocal periventricular dysembryoplastic neuroepithelial tumor (DNT) associated with hemorrhage and obstructive hydrocephalus in an 82 year old man

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Dysembryoplastic neuroepithelial tumors (DNT) usually present as focal cortical lesions associated with epilepsy in young patients. Unusual features of DNT include multifocality and subcortical locations (Leung SY, et al 1994, Whittle IR, et al 1999, Fujimoto K et al. 2000, etc.), presentation with acute hemorrhage (Thom M et al. 1999), and advanced age of the patient at diagnosis (Gottschalk J et al. 1993). We recently identified at autopsy a previously undiagnosed multifocal DNT in an 82 year old man with no history of seizures, who presented with hemorrhage and obstructive hyrdocephalus. Imaging revealed a hemorrhagic mass in the posterior third ventricle and marked obstructive hydrocephalus. Despite treatment, the patient died about two weeks after a recurrence of symptoms. Postmortem neuropathologic examination confirmed a roughly spherical hemorrhagic mass in the posterior third ventricle, immediately anterior to the pineal; and hydrocephalus affecting the anterior third ventricle, and the frontal and temporal horns of the lateral ventricles. Microscopic examination revealed multiple microfoci with the histologic features of DNT, scattered along the walls of the third ventricle from anterior to posterior, with one such focus immediately adjacent to the hemorrhage. The features in this case emphasize the broad clinical and pathologic spectrum of DNT.

11. Cerebellar liponeurocytoma: A case report and review of the literature

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Cerebellar liponeurocytoma is a rare and relatively newly described lesion found generally within adults. This lesion is benign, affecting both genders equally and more commonly presenting within the cerebellum, although there have been reports of its occurrence in supratentorial regions. We present a case of a 40-year-old female with a one year history of headaches. CT and MR imaging illustrated an ill-defined, poorly enhancing lesion in the right cerebellum, causing moderate compression of the brain stem. A suboccipital craniotomy for tumor resection was performed with a neuropathological diagnosis of liponeurocytoma. Microscopic examination of the pathology revealed a cellular neoplasm composed of small cells with light eosinophilic cytoplasm, oval to round nuclei, focally admixed with lipomatous cells. We also present a compilation of all previously reported cases from the literature (42), the largest to date, and strengthen our understanding of the epidemiology of this disease.

12. Progressive supranuclear palsy: clinicopathologic correlation between dementia, tau burden and co-existing neurodegenerative phenomena

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Progressive supranuclear palsy (PSP) is a tauopathy which presents with symptoms of Parkinsonism, axial rigidity and limited vertical eye movements. Dementia can be a part of the clinical presentation, and there is no consensus regarding the pathogenesis of dementia in this condition. The goal of this research was to determine whether there is a significant difference in the burden of tau pathology in selected anatomical areas in PSP patients whose presenting or predominant symptomatology was a movement disorder versus those with dementia. The co-existence of other neurodegenerative phenomena (such as Alzheimer's, Lewy Bodies, argyrophilic grains and corticobasal degeneration) was also explored. A retrospective review of all post mortem cases of PSP at London Health Sciences Centre between 1991 and present (N = 28) was undertaken. Sections from selected anatomical areas (including frontal, temporal and cingulate corticies, amygdala, caudate head, putamen, globus pallidus, subthalamic nucleus, substantia nigra, basis pontis, medullary olive, and dentate nucleus) were examined at 10X magnification, and the maximum number of tau immunopositive inclusions (total, neurofibrillary tangles, tufted astrocytes, thorny astrocytes and coiled bodies) per 10X field were counted. The number of tau inclusions in each anatomical area was compared between the two groups using t-tests, and the difference in co-existing neurodegenerative phenomena between the two groups noted. Results indicate that there is a statistically significant difference ($p<0.05$) in the burden of tau pathology between the two groups in several anatomical areas, including the caudate, putamen, cortex and amygdala. In addition, there is frequent over-lap between PSP and other neurodegenerative conditions. The significance of these findings with respect to symptomatology will be discussed in light of the previous literature.

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13. Superficial siderosis of the central nervous system: An update on pathogenesis

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Superficial siderosis of the central nervous system (CNS) is caused by recurrent low-volume subarachnoid bleeding though in many cases imaging or autopsy do not establish the source of hemorrhage. The disease is now often discovered serendipitously because patients undergo magnetic resonance imaging for progressive ataxia. This report is based on experience with 39 patients with superficial siderosis (9 autopsies). In twelve (1 autopsy), a bleeding source could not be found. The most common established lesions were brain and spinal tumors, and CNS trauma. An unusual cause was a herniated thoracic disc. All affected regions showed abundant hemosiderin and more diffuse iron infiltration. Neuronal loss was most extensive in the cerebellar cortex, irrespective of the site of bleeding. Immunocytochemistry revealed ferritin in hypertrophic microglia and spheroids. In brain stem, spinal cord, and eighth cranial nerves, ferritin in spheroids co-localized with an axonal marker. Siderotic brain tissue contained a 2- to14-fold excess of total iron and a 15- to 35-fold excess of holoferritin. Western blots showed an increase of light-ferritin subunits. X-ray fluorescence of polyethyleneglycol-embedded siderotic spinal cord confirmed iron excess but also detected increased zinc. It is likely that tissue injury in superficial siderosis includes an iron-catalyzed axonopathy. (Supported by the Department of Veterans Affairs and Neurochemical Research, Inc.).

14. Amyloid-beta associated vasculitis: a case report with radio-pathologic correlation

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We report a case of cerebral amyloid angiopathy associated with necrotizing vasculitis. This 85 year-old woman presented with a three week history of cognitive decline and psychomotor slowing. Previous history included atrial fibrillation and mild cognitive impairement. On clinical examination there was left hemiparesis and hypoesthesia, left hemianopsia and ideomotor apraxia. Investigation revealed ESR slightly elevated and elevation of protein in the CSF. On MRI, there was extensive bilateral T2/FLAIR hyperintensity of the white matter of the frontal, temporal and parietal lobes mainly in the right side. The patient deteriorated in the following two weeks and by this time a head CT showed multifocal intralobar hemorrhages. The patient died after ten days. Pathological examination of the brain showed six sites of recent hemorrhage and small petechial older areas in the cortex. Microscopical examination disclosed a few vessels with fibrinoid necrosis and mild inflammation; images of microthrombosis and recanalization were also seen in some vessels. Deposition of amyloid was identified in small vessels; lymphocytes were mainly CD8+. This case highlights the importance of early recognition of cerebral amyloid angiopathy that may present initially with symptoms and signs suggesting ischemic disease before the occurrence of multiple intracranial hemorrhages. Successful treatment with corticosteroids and cyclophosphamide has been reported.

15. CNS TDP-43 proteinopathy in clinically definite amyotrophic lateral sclerosis

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TDP-43, a widely distributed nuclear protein with functions in transcription regulation and exon skipping, was recently identified as the major disease protein in the inclusions in FTLD-U in both sporadic and hereditary cases, and in ALS. We undertook immunohistochemical analysis for TDP-43 (TARDBP, ProteinTech Group, Inc) in a series of eleven cases (Sunnybrook Hospital's archive) of clinically definite amyotrophic lateral sclerosis. Areas included: spinal cord (built-in control), brainstem, cerebellum, frontal lobe, sensory-motor cortex, temporal lobe, parietal lobe, basal ganglia-forebrain, cingulum, thalamus and hippocampus. The clinical diagnosis of ALS was confirmed using conventional stains and ubiquitin immunostaining. In the spinal cord and brain stem TDP-43 positive inclusions conformed to the well-known spectrum of skeins, solid cytoplasmic neuronal and neuropil threads. In all cases similar inclusions were detected in brain regions besides motor nuclei, including threads and neuronal inclusions in the cerebral cortex, and skeins in the substantia nigra. The inclusions were far less common than in FTLD-U. Inclusions in the dentate fascia were rare, and often absent. Rare inclusions in oligodendrocytes were noted. These results expand the range of CNS changes in ALS and indicate that traces of FTLD-U pathology are detectable in all cases of clinically definite ALS. TDP-43 is found to have a greater sensitivity, especially for threads, and a much greater specificity than ubiquitin.

16. A cause of congenital aqueductal stenosis: embryonic downregulation of a dorsalizing gene

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Congenital aqueductal stenosis is a common cause of fetal and neonatal hydrocephalus. It may be detected in utero by ultrasound. It may be isolated or associated with other malformations of the brain in genetic disorders. We used immunocytochemical markers, including vimentin, to study six human fetuses at midgestation with aqueductal stenosis. None had acquired causes, such as congenital infections or intraventricular haemorrhage. We noted in all that the stenotic aqueduct was associated with absence of the dorsal median septum of the midbrain, loss of the sagittal intercollicular sulcus and noncleavage of the superior or both pairs of colliculi. In some cases, the oculomotor nuclei were fused, but the red nuclei, substantia nigra and cerebral peduncles were well formed. Other frequent but variable anomalies included agenesis of the corpus callosum, hypoplasia of the hippocampi and/or of the cerebellar vermis. These findings suggest downregulation of genetic expression in the dorsoventral gradient of the vertical axis of the neural tube (J Child Neurol, 2000, 15:675-687; Am J Med Genet, 2004, 126A:386-392). Candidate genes include those of the BMP, PAX and EMX families. We propose that this pathogenesis

may be frequent in fetal aqueductal stenosis with hydrocephalus, and can be confirmed neuropathologically by midgestation. Vimentin immunoreactivity well demonstrates the median septa of the fetal mesencephalon and is resistant to postmortem autolysis.

17. Vacuolar leukoencephalopathy in siblings

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A white matter disease in two pairs of Mennonite siblings is reported. All presented at birth with hypotonia, severe retardation, and seizures. A brother and sister died at ~3 years each. In the other family one boy died at 11 years and his brother remains alive at 19 years. MR imaging of the brothers revealed mildly enlarged ventricles and abnormal white matter signal. At autopsy, the girl's brain was small; the other two were normal weight. All three had essentially normal myelin staining intensity with large vacuoles in a similar distribution. Most severely affected were the optic nerves/tracts, deep white matter, thalamic bundles, and superior cerebellar peduncle. The internal capsule and cerebellar white matter were moderately affected. Electron microscopy showed myelin splitting at the intraperiod line. Frozen white matter from the 3-year and 11-year boys was analyzed by Western blotting. Compared to controls, the older boy had slight reduction in CNPase and myelin basic protein. Proteolipid protein was slightly more abundant in both. Connexin 47 was detected at an abnormally small size in the 11 year old, but sequencing showed only a silent polymorphism (594C>T). Although the families are not linked to 3 generations, this appears to be a similar disorder. It differs from aspartoacylase deficiency, proteolipid protein mutation, and EIF2B mutation. The precise nature is unclear. Linkage analysis will be performed to identify candidate gene mutation(s). The abnormality is presumably involved in oligodendroglial metabolism or myelin function.

18. Percutaneous muscle biopsies: review of 900 consecutive cases at London Health Sciences Centre

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This study reviewed 900 consecutive percutaneous muscle biopsies performed at LHSC to evaluate the efficacy, tolerability, and diagnostic utility of this procedure and to identify its limitations and advantages in comparison with open biopsies. All biopsies were performed between 1993 and 2007. Skeletal muscle samples were obtainable from the vast majority of patients (98%) with vastus lateralis or deltoid muscles biopsied in more than 90% of cases. Patients with morbid obesity, anasarca or cachexia accounted for the majority of cases with inadequate samples. There were no perceived limitations to histological or ultrastructural details or to the diagnostic range achieved although repeat biopsies were occasionally helpful in identifying patchy entities. Multiple biopsies were in some instances retrieved for larger volume biochemical studies, but in general, open biopsies were optimal for this and are essential in cases where nerve and muscle are required.

An outpatient survey concluded that percutaneous biopsies were arranged with short wait times and were very well tolerated with most patients reporting minimal discomfort from the procedure.

In summary, percutaneous muscle biopsies require fewer resources than open biopsies and yield excellent diagnostic material. They can be readily performed at the bedside (including intensive care) or outpatient clinic, with minimal risk and discomfort.

19. Neuropathological description of an autopsy case of 3-hydroxyisobutyric aciduria

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Signature pathology of disorders of amino acid metabolism is spongy myelinopathy. Dysmyelination is often described but infrequently demyelination with products of myelin degeneration is reported. Teratogenicity of disorders of amino acid metabolism is well documented. 3-hydroxyisobutyric aciduria is a rare organic aciduria (14 cases in literature). Clinical findings, dysmorphic features and central nervous system malformations are documented in these cases. With only two autopsies (J Pediatr. 1992;121:86-9) out of four deaths that occurred in 14 reported cases, description of neuropathological findings is scant and photographically undocumented. A case of 4-year-old boy with 3-hydroxyisobutyric aciduria is presented, who came with tachypnea, fever, growth and developmental retardation. He had multiple admissions to the hospital with tachypnea and metabolic acidosis. He was diagnosed as having cerebral palsy at the age of six months and his dysmorphic features lead to the diagnosis of Cornelia de Lange syndrome. He died of severe respiratory distress. Neuropathological examination revealed microencephaly, partial agenesis of corpus callosum, bilateral pachygyric bands of aberrant cortex separating left and right abnormally positioned basal ganglia and thalami, extensive white matter discoloration with focal cavitory areas sparing U fibers. Microscopically extensive myelin pallor with or without myelin degradation products with focal cystic areas and focal lacunar areas in white matter and basal ganglia were seen.

20. Systemic Microangiopathy in Leber's Hereditary Optic Neuropathy with #13708 and #3394 Mitochondrial DNA Point Mutations.

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Leber's hereditary optic neuropathy (LHON) is a maternally inherited mitochondrial disease characterized by loss of vision, affecting predominantly men. Ophthalmologic examination shows abnormalities of the retinal vessels before development of blindness. To evaluate the hypothesis of a systemic vascular pathogenesis of LHON, we carried-out ultrastructural and morphometric assessment of muscle capillaries in seven families with LHON: affected males (7) and females (1), and female carriers (3). Biopsies from other mitochondrial myopathies (5) and

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malignant hyperthermia suspects (5) were used as controls. All patients and carriers had mtDNA mutations at the nucleotide positions 13708 and 3394, and showed mitochondrial abnormalities in many cell types. However, only the blind patients showed frequent necrosis of pericytes as well as marked thickening and reduplication of basal lamina. They also revealed a statistically significant increase in the total capillary area, the area of the extracellular matrix of capillary walls, and area occupied by pericytes. Microangiopathy was not seen in the carriers or controls.

Conclusion: Mitochondrial morphological abnormalities in many cell types are similar in the LHON patients as well as carriers; however, only the blind individuals show microangiopathy in the muscle biopsies. One may postulate that development of blindness in LHON is related to occurrence of similar changes in the retina and the cumulative effect of ischaemia with abnormal oxidative phosphorylation.

Titles of Diagnostic Case Presentations

1. Angiomatoid fibrous histiocytoma (AFH)

C. Dunham,[1] J. Hussong,[2] M. Seiff,[3] J. Pfeifer[4] and A. Perry[1]

[1]Division of Neuropathology, Washington University School of Medicine, St. Louis, MO, USA; [2]Department of Pathology, Sunrise Hospital & Medical Center, Las Vegas, NV, USA; [3]Western Regional Center for Brain and Spine Surgery, Las Vegas, NV, USA; [4]Division of Anatomic and Molecular Pathology, Washington University School of Medicine, St. Louis, MO, USA.

2. Primary anaplastic large cell lymphoma of the brain

C. I. Coiré,[1] A. G. Ninos[1] and E. Marmor[2]

Departments of [1]Pathology and [2]Neurosurgery, Trillium Health Centre, Mississauga, Ontario, Canada.

3. Lymphomatoid granulomatosis with Epstein-Barr virus positivity in atypical cells by in-situ hybridization and clonality for both B and T cells by gene re-arrangement studies

J.M. Bilbao, Z. Ghorab, G. Yang and B.Young

Department of Pathology, Sunnybrook Hospital, University of Toronto, Toronto, Ontario.

4. Intraneural nodular fasciitis

J. Lu,[1] A. Fallah,[2] J. Grochmal,[2] L. Ddfrancesco,[1] M. Khalil,[1] R. Midha,[2] and A.W. Clark[1,2]

Departments of [1]Pathology and Lab Medicine, and [2]Clinical Neurosciences, University of Calgary, Calgary, Alberta.

5. Neuromyelitis optica (Devic's disease) with extensive involvement of brain

B. Lach and D. Jichici

Department of Pathology & Molecular Medicine, Hamilton Health Sciences, Hamilton General Site, McMaster University, Hamilton, Ontario.

6. Meningoencephalitis with preferentially severe involvement of the diencephalon, brainstem (especially the substantia nigra) and cerebellum; pattern very suggestive of an arbovirus encephalitis. Immuno-histochemical staining for West Nile virus, and generic Flavivirus and Powassan encephalitis virus RT-PCR analyses and West Nile virus ELISA were all negative

J.P. Rossiter

Department of Pathology and Molecular Medicine, Queen's University and Kingston General Hospital, Kingston, Ontario

7. Benign glioneuronal tumour

K. Dakin-Hache,[1] D.B. Clarke[2] and A.S. Easton[1,2]

Departments of [1]Pathology, and [2]Neurosurgery, Dalhousie University, Halifax, Nova Scotia

8. Anaplastic ganglioglioma (WHO Grade IV)

S. Aabu-Abed,[1] R.L. MacDonald,[2] D. G. Munoz[1]

[1]Department of Laboratory Medicine and Pathology, and [2]Division of Neurosurgery, University of Toronto, Toronto, Ontario

9. Cerebral hemispheric asymmetry with a) smaller left than right hemisphere, and b) left temporal atrophy and gliosis with abundant corpora amylacea

S. Krawitz

Department of Pathology, University of Manitoba, Winnipeg, Manitoba

10. Cerebroretinal microangiopathy with calcifications and cysts

L.-N. Hazrati and W.C. Halliday

Department of Paediatric Laboratory Medicine, Division of Pathology, University of Toronto, Toronto, Ontario, Canada

11. Seizures with cytoplasmic astrocytic inclusions

L.-N. Hazrati,[1] S. Weiss,[2] J. Rutka[3] and C. E. Hawkins[1]

[1]Hospital for Sick Children, Department of Paediatric Laboratory Medicine, Division of Pathology, Departments of [2]Neurology, and [3]Neurosurgery, University of Toronto, Toronto, Canada

12. Myonecrosis in a non-compliant type I diabetic patient

Y. Robitaille

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