Canadian Association of Neuropathologists

ABSTRACTS

September 21-24, 2005
St. John's, Newfoundland
Abstracts of papers and cases presented at the Forty-Fifth Annual Meeting

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The Forty-Fifth Annual Meeting of the Canadian Association of Neuropathologists was held from September 21-24 at the Delta Hotel and Convention Centre in St. John's, Newfoundland. The co-ordinator for local arrangements was Dr. Jane Barron. The scientific sessions were comprised of 24 platform presentations and 14 diagnostic case presentations. The sessions were organized under the following headings: Tumours (three sessions), Neurodegenerative Diseases, Toxic/Metabolic and Miscellaneous Disorders, Pediatric Neuropathology, and Muscle and Nerve.

Special lectures were given by invited guests. **The Royal College of Physicians and Surgeons of Canada Lecture** was given by Dr. Paul Kleihues, Department of Pathology, University Hospital, Zurich. His talk was entitled: "Glioblastoma Multiforme: Epidemiology, Genetics and Prognosis." The newly named **Gordon Mathieson Lecture** was provided by Dr. Roland Auer from The University of Calgary. His lecture was entitled: "Hypoglycemia: Neurochemistry, Electro-encephalography, Neuropathology and…Public Relations."

The meeting included a **Symposium on Nervous System Injury and Repair,** chaired by Dr. Sukriti Nag, President. This included the **Jerzy Olszewski Lecture** presented by Dr. Dale Corbett from Memorial University of Newfoundland. Dr. Corbett's presentation was entitled: "Neuroplasticity, Brain Repair, and Recovery of Function Following Stroke." This was followed by an address by Dr. Karen Mearow, also of Memorial University of Newfoundland, entitled: "Neuronal Survival and Axonal Regeneration in the Peripheral Nervous System-Growth Factors, Sticky Surfaces and Stress Proteins."

Platform Presentations

1. Primary leptomeningeal precursor B cell lymphoma in a ten year old child in the absence of bone marrow involvement.

C. Acharya, J. Barron, C. Pushpanathan, A. Pirzada, L. Bowes, J. Hand, B. Cramer and E. Walsh

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Primary leptomeningeal lymphoma is a rare disease in the pediatric population. We herein report a case of a ten-year-old boy with primary leptomeningeal lymphoma of precursor B cell type. The boy presented initially with recurrent headache and vomiting that progressed to right sided ptosis, drooping of the left side of the mouth, slurred speech, and tingling and numbness of face and hands. MRI with contrast and CT scan revealed enhancement of the 3rd, 7th, and 8th nerves bilaterally. CSF examination disclosed increased white cell count with predominantly mononuclear cells. The mononuclear cells appeared atypical. CSF flow cytometry confirmed the diagnosis of precursor B cell lymphoblastic lymphoma. Bone marrow examination did not reveal any blast cells. No disease was identified in the solid organs or lymph nodes. To our knowledge this is the first case of primary leptomeningeal precursor B-cell lymphoma without any other organ involvement.

2. Intradural spinal tumour of mixed paraganglioma and myxopapillary ependymoma histology

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A 38 year old woman presented with pain in her "tailbone". The pain was worse on the left, and radiated to the hip, posterior thigh, and posterior calf. She also had a single episode of urinary incontinence. Neuroimaging (MRI) demonstrated an intradural tumour at the level of L4. The lesion was resected, and the intra-operative impression was that there were two separate lesions, both arising from the filum terminale. Histologically, the larger lesion was a paraganglioma, and the smaller lesion a myxopapillary ependymoma. The occurrence of simultaneous paraganglioma and myxopapillary ependymoma has been previously reported on one occasion (Caccamo, D.L. et al (1992) *Human Pathology, 23(7)*: 835), and is an interesting occurence as it fuels the discussion surrounding the cell of origin of these lesions. The neuroimaging, gross and histological features of this case will be discussed in the context of the literature, and implications of this case for the proposed pathogenesis of these tumours will be illustrated.

3. The accuracy of frozen section diagnosis at the time of stereotactic brain biopsy

C. Desilva, A. Kirkwood, R. Hammond and J.F. Megyesi

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Background: The goal of this study was to determine the accuracy of frozen sections obtained at the time of stereotactic brain biopsy.

Methods: The charts of 91 patients who underwent stereotactic brain biopsy at the London Health Sciences Centre between 1998 and 2002 were reviewed. The frozen section and final pathology reports were independently analyzed and compared by the first two authors. The final pathology report was deemed to represent the correct diagnosis.

Results: Frozen section identified 84 patients as having tumorous lesions, of which 83 (99%) were confirmed. Frozen section identified seven patients as having non-tumourous lesions, all of which were confirmed (100%). Of the tumourous lesions, frozen section identified 70 cases of glioma, of which 65 (93%) were confirmed, and 14 cases of non-glioma, all of which were confirmed (100%). The accuracy of frozen section for specific diagnostic categories was: inflammatory lesions (100%), meningioma (100%), high-grade glioma (88%), lymphoproliferative disorder (86%), metastases (83%) and low-grade glioma (58%).

Conclusions: Frozen section is excellent at differentiating a tumourous lesion from a non-tumourous lesion. This information may help initiate a patient's treatment planning. Frozen section is fairly good at differentiating glioma from non-glioma. However, a specific diagnosis, and definitive patient treatment, should await the final pathology report.

4. hTERT expression is an independent predictor of outcome in paediatric ependymoma

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Ependymoma is the third most common brain tumour in children with ~50% overall survival (OS). There is uncertainty regarding the histological criteria for grading ependymomas and the lack of firm prognostic indicators impedes consensus as to what constitutes optimum management. In an attempt to identify markers of potential biological and therapeutic significance we tested the hypothesis that hTERT (the catalytic subunit of telomerase) expression is predictive of outcome in paediatric ependymoma. Clinical and hTERT expression data were obtained for 96 primary and recurrent ependymomas presenting between 1986 and 2004. Of the 96 samples, 36 were hTERT(-) and 60 were hTERT(+) with progression-free survival (PFS) of 83±15% and 21±9%, respectively ($p<0.0001$). Of the 56 primary ependymomas, five-year OS was 91.3±12% and 35.1±19% for hTERT(-) and hTERT(+) tumours, respectively ($p<0.0001$). Telomerase activity was confirmed by TRAP assay. TRF measurement revealed lack of alternative lengthening of telomeres and heterogeneous telomere length. On univariate analysis, age at diagnosis ($p=0.006$), higher histologic grade ($p=0.02$), radiation therapy ($p<0.0001$) and hTERT expression ($p<0.0001$) were associated with outcome. On multivariate analysis only radiation therapy (HR 4.2 ±1.8, $p=0.013$) and hTERT expression (HR 12.9 ±2.2, $p=0.001$) were independently predictive of a poor outcome. We present one of the largest studies of paediatric ependymoma and the first to show hTERT expression is predictive of outcome independently of clinical prognostic markers.

5. A distinctive histological correlate of focal clinical presentations with Alzheimer's disease pathology

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A number of patients presenting clinically with asymmetrical focal progressive syndromes, most commonly primary progressive aphasia, show at autopsy Alzheimer's disease pathology. The focal presentation of a widespread, roughly symmetrical process is not understood.

In five patients with primary progressive aphasia and one with a clinical diagnosis of corticobasal degeneration we found at autopsy abundant senile plaques and neurofibrillary tangles in the widespread distribution typical of Alzheimer's disease. In addition, large clusters of Gallyas positive thorny astrocytes were present focally in the cortex and were especially abundant in the subcortical white matter. The astrocytes were stained with a variety of Tau antibodies. Double labeling confirmed co-localization of GFAP and Tau in the same cells. These clusters were not found in six cases of Alzheimer's disease with a typical clinical course. We believe clusters of thorny astrocytes may represent a marker for a subjacent pathological process responsible for the focal manifestations of the disease.

6. Bilateral absence of the dentate gyrus granule cells in an elderly man

A.W. Clark

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Dentate granule cells, a component of the normal hippocampus, have been of interest for several reasons. They are reportedly capable of neurogenesis even in adult brain (Eriksson PS et al. Nature Medicine 1998; 4: 1313-1317) and this production of dentate granule cells may be inhibited by stress (Gould E and Tanapat P, Biol Psychiatry 1999; 46: 1472-1479). I recently found bilateral absence of dentate granule cells from the hippocampus of an 82-year-old man. This was apparently an "incidental finding." I have found no published report of such an anomaly in adult brain. Based on clinical information available in this case, the bilateral absence of dentate granule cells does not grossly interfere with normal function in adult life.

7. Cerebellar atrophy and congenital disorders of glycosylation

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A three-year-old boy suffered from failure to thrive, hypotonia, visual and hearing deficits, and repeated episodes of sepsis. He also had inverted nipples, abnormal fat pads around the buttocks,

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hepatomegaly, adrenal insufficiency, and cerebellar atrophy (CT, MRI). On his final admission he presented with otitis media. The immediate cause of death was severe acute bronchopneumonia.

He had been diagnosed with type Ia congenital disorder of glycosylation (CDG-Ia), an inherited disorder of glycoprotein biosynthesis (phosphomannomutase deficiency) affecting multiple systems. Manifestations are variable and include, in addition to typical findings mentioned above, hydrops fetalis, facial dysmorphism, hypertrophic obstructive cardiomyopathy with pericardial effusions, nephrotic syndrome, and coagulation defects. Neurologic features generally include hypotonia, strabismus, optic atrophy, stroke-like episodes, ataxia, and psychomotor retardation.

Neuropathologic findings in this case are severe olivopontocerebellar degeneration with loss of neurons from cerebellar cortex, pontine nuclei, and inferior olivary nuclei, retinal degeneration with optic nerve atrophy and loss of lateral geniculate nucleus lamination, nonspecific cerebral hemispheric dysmorphism (shortening of the temporal lobes and incomplete formation of temporal gyri), and mild microencephaly (brain weight 1026g, normal 1257 +/- 59g).

This disorder enters the differential diagnosis of an infant with cerebellar atrophy, which also includes cerebellocortical degeneration (Jervis), ADCA II (SCA6), and pontoneocerebellar hypoplasia (Neurology 1986, 36:674-681; Acta Neuropathol 2005, 109:433-442).

8. An experimental trial to investigate the pathogenesis of leptomeningeal brain heterotopia

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The authors reported a case of leptomeningeal brain heterotopia at the 44th Annual Meeting of the CANP (Winnipeg, 2004). In the present study, the pathogenesis was investigated experimentally. Pregnant rats were fed a liquid diet containing 5% (w/v) ethanol. The animals were divided into two groups; Group 1: ethanol exposure between gestational days 2 and 11, Group 2: exposure between gestational days 12 and 21. All pups were sacrificed under anesthesia on the seventh postnatal day and were examined histopathologically. Leptomeningeal brain heterotopia was observed in 0 % (0/36 cases) of the rats in Group 1, and in 8.1 % (3/37) of those in Group 2. Unexpectedly, heterotopic external granular layers were also found in the cerebellum more frequently in Group 2 than in the control. Therefore, it was deduced that ethanol exposure during the mid to late phase of pregnancy could be causative of leptomeningeal brain heterotopia. It has been reported that the formation of the glia limitans-basal lamina complex (GLBLC) is impaired in this model (H. Sakata-Haga, Acta Neuropathol, 2001, 102:36-40). Over-migration through the incomplete GLBLC seemed to be an important part of the pathogenesis of this heterotopia. However, the coexistence of heterotopic external granular layers demonstrated in the present study, which is independent of the GLBLC, suggests additional or alternative mechanisms underlying the migration disorder.

9. A family with multiple childhood deaths due to cerebellar / corticospinal degeneration

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We report a hereditary neurodegenerative disease of infancy. The family is Aboriginal from northern Manitoba. The parents are apparently not related and have no neurodegenerative diseases ascertained. The mother (G11 P10) had four children who had neuromuscular abnormalities including arthrogryposis, seizures, and severe developmental delay. Two had cerebellar atrophy and mild cerebral atrophy documented by imaging. Two male children, who died at eight months and three years one month, underwent complete autopsies. Two children, a male who died at three years six months and a female who died at 22 months, underwent muscle biopsies at three weeks and four months of age respectively. Muscle biopsies obtained at young ages show fiber size variability. At the older ages there is group atrophy and fiber type grouping. Autopsies showed severe atrophy of the inferior cerebellum/vermis, hypomyelination of the white matter fascicles in the striatum, severe atrophy of the corticospinal tracts in the brainstem and spinal cord, and atrophy of the anterior spinal roots. In the spinal cord there was relative sparing of the motor neuron cell bodies and of the posterior columns. Another stillborn male did not appear to be affected and some siblings were affected by fetal alcohol syndrome. This likely represents a novel form of complicated hereditary spastic paraplegia. Investigation to delineate the inheritance is ongoing. (Supported by Manitoba Institute for Child Health)

10. Oculopharyngeal muscular dystrophy: Identification of two new pedigrees

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Oculopharyngeal muscular dystrophy (OPMD) is characterized by progressive ptosis, dysphagia and proximal muscle weakness. The dominant OPMD mutation consists of short $(GCG)_{8-13}$ expansions causing the lengthening of a polyalanine tract located at the N-terminus of the PABPN1 protein in the nucleoplasm.

The detection of the typical $(GCG)_6$ repeat expansions established the diagnosis of OPMD in two of our patients. The diagnosis was first suspected on the routine muscle biopsy. This allowed the identification of two new pedigrees in Ontario. One patient was of non-French-European ancestry and had a severe chronic neuromuscular syndrome, progressive ophthalmoplegia and cognitive impairment thought to be a mitochondrial encephalomyopathy. One of this patient's siblings was similarly affected. The other patient was French-Canadian and had the typical oculopharyngeal phenotype diagnosed at age 61 years. In both cases, examination of muscle demonstrated basophilic rimmed vacuoles and characteristic filamentous myonuclear inclusions immunopositive for ubiquitin. Genomic DNA was used to amplify part of exon 1 of the PABPN1 gene that included a $(GCG)_6$ repeat. The GCG repeat was $(GCG)_9$ and normal allele in the French-Canadian patient and $(GCG)_{14}$ and normal allele in the non-French-Canadian. This is the first report of $(GCG)_{14}$ mutation in a patient with OPMD. Our study confirms that: a) a severe phenotype is associated with a longer trinucleotide repeat and b) expansion repeat length of the PABPN1 gene is a reliable test for the diagnosis of OPMD.

11. "Macrophagic myofasciitis" in children. Is this really a disease?

B.Lach and E.J. Cupler

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Objective: To correlate the relevance of histological findings of macrophagic myofasciitis (MMF) from pediatric patients with the clinical presentation.

Methods: Eight muscle biopsies with the diagnosis of MMF were re-examined and the clinical manifestations were reviewed.

Results: Eight children aged seven months to six years underwent quadriceps muscle biopsy for evaluation of mitochondrial disease (3), spinal muscular atrophy (2), myoglobinuria (1), and hypotonia with motor delay (1). All biopsies showed granulomas composed of PAS- and CD68-positive macrophages containing characteristic aluminum hydroxide crystals (two cases). The biopsy established a diagnosis other than MMF in five patients: spinal muscular atrophy (SMA, 2), Duchenne muscular dystrophy (1), phospho-glycerate kinase (PGK) deficiency (1), cytochrome C oxidase (COX) deficiency (1). The remaining three children underwent additional extensive screening for inflammatory or neoplastic disease with negative results. The children had routine vaccinations between two months and one year before the biopsy, with up to 11 injections, including the biopsy sites. There was no correlation between MMF in biopsies and the clinical symptoms. Three children died (SMA and COX deficiency patients) and two were lost to follow up.

Conclusions: We believe, that at least in children, MMF represents a localized histological hallmark of immunization with the aluminum hydroxide adjuvants contained in vaccines, rather than a distinct inflammatory muscle disease.

12. Cyclo-oxygenase 2 expression in type 1 skeletal muscle cells

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In the course of a study on metastatic breast carcinoma with immunological markers for cyco-oxygenase 1 and 2 (COX 1 and COX 2), it was noted that certain skeletal muscle fibers stained with the antibody to COX 2. The pattern of staining was similar to that seen with ATPase staining. To further investigate this finding we studied six normal muscle biopsies from males and females with serial sections stained for ATPase pH 4.6 and pH 10.2 and COX 2 antibodies. We found that the cells which stained for COX 2 were all type 1 cells with no staining whatever of type 2. The observation of COX 2 staining of skeletal muscle has been noted before but the cell types which expressed this enzyme were not determined (COX-2 expression in striated muscle under normal physiological conditions. J Sudbo, A Reith, V A Florenes, J M Nesland. A Ristimaki, M Bryne, Oral Diseases (2003) 9,313-316). The explanation for the expression of COX 2 in normal skeletal muscle is not clear at the present time as few normal tissues express this enzyme.

13. Recurrent brain hemorrhage caused by metastatic angiosarcoma

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Reports of metastatic angiosarcoma causing recurrent intracranial hemorrhage are distinctly uncommon. We report a patient with metastatic angiosarcoma who suffered recurrent cerebral and intraventricular hemorrhage. The 58-year-old woman was admitted to hospital because of prolonged central chest pressure, atrial fibrillation and abnormally elevated plasma troponin. She subsequently developed six separate episodes of cerebral and intraventricular hemorrhage and seizures. She was observed to have recurrent tender petechial bleeding from multiple subcutaneous nodules located in the chest , axillae, and abdomen. CT scan of the thorax demonstrated a 2.0 x 2.6 cm. soft tissue mass in the left atrium and four nodules in the right lung. Cerebral angiography showed no tumor mass or tumor blush. Biopsy of one of the subcutaneous nodules showed histologic findings consistent with metastatic angiosarcoma. The tumor nodule was located in the subcutis. It was composed of anastomosing vascular spaces filled with blood and lined by pleomorphic cells with hyperchromatic, pleomorphic nuclei showing high mitotic index. In the subcutaneous fat, there was hemorrhage with numerous macrophages containing pigment. Immunoperoxidase stains were positive for cytokeratin, vimentin and Factor VIII and negative for S-100, MelaninA, Desmin and EmA. Metastatic angiosarcoma may be a more common cause of intracranial hemorrhage than is generally recognized. Pathologic examination of an appropriate biopsy specimen may be the only means of definitive diagnosis.

14. Correlation between neuroimaging and neuropathology in pediatric posterior fossa tumors

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Background: The goals of this study were 1) to determine how well the neuroimaging diagnosis correlates with the final pathological diagnosis, and 2) to determine how well the frozen section diagnosis correlates with the final pathological diagnosis in pediatric patients with posterior fossa brain tumors.

Methods: The charts of 26 pediatric patients who underwent surgery for posterior fossa brain tumors at the London Health Sciences Centre were reviewed. The neuroimaging reports (MRI and/or CT), the frozen section pathology reports and the final pathology reports for each patient were independently analyzed and compared. The final pathology report was deemed to represent the correct diagnosis.

Results: In the pediatric population studied there were 14 males and 12 females with an overall mean age of 7.7 years. MRI was used in 25/26 patients (96%). Neuroimaging correlated with final pathology in 11/25 patients (42%). In 8/25 patients (31%) the neuroimaging diagnosis did not correlate with final pathology, while in 7/25 patients (27%) the neuroimaging diagnosis was indeterminate. Sensitivity of neuroimaging was 50% for ependymoma, 33% for medulloblastoma and 50% for low grade glioma. Positive predictive value was 50% for ependymoma, 38%

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for medulloblastoma and 86% for low grade glioma. Frozen section data was available for 22 patients. The frozen section diagnosis correlated with the final pathological diagnosis in 21/22 patients (95%). Sensitivity was 100% for ependymoma, 100% for medulloblastoma and 90% for low grade glioma. Positive predictive value was 100% for all tumor types.

Conclusion: At present, neuroimaging alone cannot be used to reliably diagnose posterior fossa tumors in the pediatric population. However, frozen section pathology correlates very well with final pathology in these tumors.

15. Cdk5 prevents neuronal apoptosis through ERK-mediated upregulation of Bcl-2

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Cyclin-dependent kinase-5 (Cdk5) is required for neuronal survival, but its targets in the apoptotic pathways remain unknown. Here we show that Cdk5 kinase activity prevents neuronal apoptosis through the upregulation of Bcl-2. Treatment of SH-SY5Y cells with retinoid acid (RA) and brain-derived neurotrophic factor (BDNF) generates differentiated neuron-like cells. The DNA damage agent cisplatin triggers apoptosis in the undifferentiated cells through the mitochondrial pathway; however, RA/BDNF treatment results in Bcl-2 upregulation and inhibition of the mitochondrial pathway in the differentiated cells. RA/BDNF treatment activates Cdk5-mediated phosphatidylinositol-3 kinase (PI3K)/Akt and extracellular-signal-regulated kinase (ERK) pathways. Inhibition of Cdk5 inhibits Akt and ERK phosphorylation and Bcl-2 expression, and thus sensitizes the differentiated cells to DNA-damage-induced apoptosis. Inhibition of ERK, but not PI3K, abrogates Cdk5-medidated Bcl-2 upregulation and the protection of the differentiated cells. Finally, targeting of Cdk5 with small interfering RNA in mature human neurons inhibits Bcl-2 expression and increases the sensitivity of the human neurons to DNA damage, further supporting the notion that Cdk5-mediated the Bcl-2 pathway protects human neurons from apoptotic insults.

16. Microarray expression analysis of Schwann cell lesions in NF2

E. Hurwitz, S. Dong, C.L. Nutt, T. Shioda, A.J. Potts, M. MacCollin, E. Yang and A.O. Stemmer-Rachamimov

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Patients with neurofibromatosis 2 (NF2) are affected by multiple schwannomas that, although benign, cause significant morbidity and mortality. In addition to frank schwannomas, NF2 patients often have numerous, small, Schwann cell tumorlets in the cauda equina. Previous studies have demonstrated that inactivation of both NF2 alleles already occurs in the Schwann cell tumorlet stage, suggesting that additional genetic or epigenetic events are necessary for the development of frank schwannomas. In order to identify the mechanisms that promote growth in schwannomas, we compared gene expression of these two Schwann cell lesions (tumorlets and schwannomas) in a single NF2 patient. We employed laser capture microdissection and cDNA microarray analysis, using the Affymterix platform. One hundred and thirty differentially expressed genes were identified (p 0.01, >2 fold) and RT-PCR was used for validation of 5 of these genes. Analysis of the Gene Ontology and KEGG pathway terms associated with the upregulated genes (79 genes) identified many genes with known receptor, growth factor or signaling function. There was over-representation of genes involved in the phosphoinositide 3-kinase/Akt (PI3K/Akt) pathway in schwannomas and overexpression of several receptors that may function as autocrine loops for this pathway. Identification of autocrine loops that promote growth in NF2-associated schwannomas may aid in the development of targeted therapies for NF2 patients.

17. Intractable epilepsy and neurofibromatosis vasculopathy

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Seizures in neurofibromatosis type I are relatively uncommon. We describe a child known to have NF1 who presented early in life with some infantile spasms and developed rapidly a severe unilateral right hemispheric atrophy. This girl was born with a right buphtalmy with glaucoma for which she underwent an enucleation at 3 months. At 15 days of age, she started having seizures that became refractory to anticonvulsant drugs. In the following months, multiple MRIs confirmed a progressive right hemispheric atrophy with subsequent evidence of a decreased flow in the right internal carotid and right cerebral vessels. The child underwent a right peri-insular hemispherotomy at the age of 18 months. The surgical material obtained revealed striking cerebral atrophy of the cerebral cortex with significant vascular changes. Occasional vessels showed dysplastic changes of their wall. Vascular pathology is an underestimated and poorly recognized complication of NF. It frequently involves the renal artery, leading to aneurysm, rupture and hemorrhage or to vessel occlusion resulting in stroke, visceral infarcts and arteriovenous fistulas. Little is known on the pathogenesis of this vasculopathy. According to the literature, it may be due to an inadequate repair process secondary to a deficiency of neurofibromin function giving rise to an excessive proliferation of fibroblasts and smooth-muscle cells in various organs. The vascular lesions may occur early in life, are congenital or develop very rapidly.

18. Ionic contrast media and the CNS; case report

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Contrast media is a substance routinely used in radiology and adverse effects of variable severity are, unfortunately, rather frequent. Direct administration of ionic contrast media into the CSF has well documented adverse side effects making them unsuitable for such applications.

We report the case of a 71-year-old woman who underwent a myelography with inadvertent administration of Conray (lothalamate meglumine) for investigation of a lumbar discopathy.

She initially complained of lower leg pain followed by spasticity of the upper extremities. Her neurological condition deteriorated, rapidly becoming unconcious, followed by cardiac arrest. The histological changes as well as a review of the literature are presented.

19. Neuropathology of vacuolar leukoencephalopathy after inhalation of heroin: study of three cases with variable length of survival

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Inhalation of heated heroin vapour (heroin pyrolysate) or "chasing the dragon" is associated with a progressive leukoencephalopathy in a subset of users. Here we report the stereotypic clinical, neuroradiologic and neuropathologic features of this entity in three patients. These patients were followed clinically and had serial imaging performed. All patients presented with varying degrees of bradykinesia, dysarthria, cerebellar dysfunction, lethargy and confusion. MR scans demonstrated extensive hyperintense T2 and FLAIR signal changes in the hemispheric white matter. The signal abnormalities also involved the cerebellar hemispheres and cerebral swelling was noted in all cases. Post-mortem neuropathological examination revealed diffuse, severe, vacuolar leukoencephalopathy involving the cerebral hemispheres, particularly posteriorly and cerebellar deep white matter. There was uniform sparing of the U- fibers. Axonal damage was also evident in the form of fragmentation and focal axonal spheroid formation in association with myelin vacuolation. Surprisingly, there was only a muted inflammatory response and mild gliosis. However, the degree of inflammation, astrogliosis and presence of myelin pallor appeared to increase with length of survival post-exposure. These three cases of heroin-induced leukoencephalopathy underscore the unique features of this disorder which has diagnostic, radiological, and neuropathological findings.

20. Functional cortical re-organization accompanies axonal injury in multiple sclerosis

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Axonal injury occurs even in the earliest stages of multiple sclerosis. This injury can be assessed by pathological studies, as well as by lesion load on conventional MRI and by magnetic resonance spectroscopic imaging (MRSI). Some of the acute axonal injury in MS is reversible. Functional MRI (fMRI) has shown abnormally large activations of motor pathways in contralateral and ipsilateral hemispheres in patients with recovery after stroke. We wished to test whether cortical adaptive responses contribute to maintenance of normal motor function in patients with early MS. We first followed a single patient with a large acute left hemispheric lesion causing right hemiparesis. MRSI demonstrated axonal injury in the corticospinal tract of the patient as compared to controls that partially recovered over time. Initially there was greater fMRI ipsilateral motor cortex (IMC) activation for the impaired hand movement which normalized with both axonal and clinical recovery. We then performed MRSI and fMRI on NINE MS patients with unimpaired hand function as well as ten normal controls. Patients with greater lesion load and axonal injury had increased IMC activation suggesting that cortical adaptive responses have an important role in compensating for axonal injury in MS patients without clinical deficits. Finally, we grouped 14 MS patients according to level of disability and level of brain injury and had them perform active and passive fMRI tasks. Changing patterns of activation occur both with injury and with disability in distinct ways and are found even with passive tasks, reflecting true re-organization and not increased effort.

21. Dysmorphic neurons in the hilum/end folium: Occurrence in routine hippocampectomies for intractable epilepsy

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Background: "Dysmorphic" hilar/end folium neurons of undetermined etiology have been rarely described in epileptics (Thom et al, 1999; Blumcke et al, 1999). These descriptions and a recent similar surgical case led us to review our experience with hippocampectomies searching for dysmorphic hilar neurons.

Methods: NFP, Tau and Bielschowsky stains were conducted on blocks containing sufficient hilar tissue. Dysmorphic neurons were defined as Tau negative and intensely NFP positive enlarged forms, +/- Bielschowsky positivity. The experimental group included patients with a history of "seizures" +/- mesial temporal sclerosis.

Results: Although varied, all experimental cases displayed dysmorphic hilar neurons, some with a tendency to aggregate near the dentate granule layer. Findings in sclerotic and non-sclerotic epileptics were similar. Dysmorphic changes were not seen with controls. Tau was universally negative. Exempting dysmorphic hilar neurons, no case demonstrated abnormalities that could invoke a dysplastic process. Some cases exhibited the classic histologic features of mesial temporal sclerosis.

Conclusions: These findings corroborate the previous literature. However, as opposed to Blumcke et al (1999), differences in dysmorphic hilar neuron staining were not seen in subgroups of epileptics. A tendency for these neurons to aggregate near the dentate granule layer, and lack of concomitant dysplastic changes, suggest a reactive pathogenesis. Although surgical controls are limited, dysmorphic changes were not seen in our cases nor in those reported by Blumcke et al. It should be recognized that dysmorphic neurons, similar to those seen in focal cortical dysplasia, can be identified in the hilum of surgical hippocampectomies from epileptics and do not necessarily represent a dysplastic process.

22. The presentation of patients with high grade glioma: regional differences within Canada

C. Desilva, P.K. Ganguly, D. Gorassini, R Hammond and J.F. Megyesi

Division of Neurosurgery, Department of Pathology and Department of Psychology, University of Western Ontario, London, Ontario and H Bliss Murphy Cancer Centre, St. John's, Newfoundland.

Background: The goal of this study was to determine if there is a difference in how patients with high grade glioma (HGG) present

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within two regions of Canada: south-western Ontario (SWO) and Newfoundland (NFLD).

Methods: The charts of 137 patients who underwent treatment for HGG in SWO and NFLD between 1998 and 2002 were identified. There were 73 patients treated at the London Health Sciences Centre (SWO) and 64 at the H. Bliss Murphy Cancer Centre (NFLD). The charts were reviewed with respect to patient demographics and presenting symptoms.

Results: The patients from SWO consisted of 46 males and 27 females with a mean age of 63.1 years at the time of presentation. The patients from NFLD consisted of 43 males and 21 females with a mean age of 59.3 years. There was no significant difference in the mean age but there were significantly more patients under the age of 60 in NFLD ($p<0.02$). Chi-square analysis revealed that SWO and NFLD patients presented differently ($p<0.03$). Patients from SWO presented more often with focal neurological deficit while patients from NFLD presented more often with seizures and symptoms of raised intra-cranial pressure.

Conclusions: There appear to be regional differences within Canada in how patients with HGG present.

23. Methylation of MGMT promoter gene in oligodendrogliomas

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The combined loss of alleles on the chromosome arms 1p and 19q has been associated with a better response to chemotherapy and a good prognosis in oligodendrogliomas. The molecular mechanisms behind this association are not yet determined. The treatment of these tumors often includes alkalyting agents such as Temozolomide. A number of studies have shown that the DNA repair enzyme MGMT (O6-methylguanine-DNA methyltransferase) plays an important role in the resistance of tumor cells to alkylating agents. The silencing of the MGMT gene by promoter methylation has also been associated with an overall longer survival in high-grade gliomas. In this study, we report the analysis of 95 oligodendrogliomas for MGMT promoter methylation and LOH on 1p and 19q. We study the relationship between the two molecular alterations. The analysis of a subset of the database shows that methylation of MGMT promoter gene is more frequent in tumors with LOH on 1p and 19q.

24. Genomic alternations in triploid human malignant glioma cells associate with the inhibition of DR5, caspase-8, Bid and Smac expression and TRAIL resistance

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Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is currently under development as a cancer therapeutic agent, particularly in combination with conventional chemotherapy. Here, however, we identified two human malignant glioma cell lines that are resistant to the TRAIL and chemotherapy treatment. To explore genomic imbalances in the resistant cells, we applied molecular cytogenetic technologies to the systematic analysis of the genomic alterations in the chromosomal regions that harbor apoptotic genes of the TRAIL pathways. Through comparative genomic hybridization (CGH), we detected loss of the chromosomal regions that contain the following genes: 8p12-p23 (DR4, DR5), 2q33-34 (caspase 8), 11q13.3 (FADD), 22q11.2 (Bid), and 12q24.1-q24.3 (Smac/DIABLO) in TRAIL resistant cell lines. G-banding/spectral karyotyping (SKY) was then conducted and identified numerical and structural aberrations involving these chromosomal regions. In addition, a combination of G-banding/SKY and fluorescence in situ hybridization (FISH) with chromosome region specific probes further defined the loss, or gain of gene copy of the TRAIL apoptotic gene loci. This study revealed the simultaneous loss of one copy of the key TRAIL genes, DR4/DR5, caspase-8, Bid, and Smac, in the two near triploid cell lines that were resistant to the TRAIL and chemotherapy treatment. This correlated well with the inhibition of protein expression of these genes in the cell lines. The findings not only shed some light on the genomic mechanisms of glioma cell resistance to TRAIL, but also identify genetic markers that could be used to predict the responsiveness of gliomas to TRAIL therapy in clinical trials.

Titles of Diagnostic Case Presentations

1. Intravascular large B-cell lymphoma with associated multifocal cerebral infarcts

J.P. Rossiter

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

2. Limbic encephalitis

H. Reddy and R. Hammond

Department of Neuropathology, University of Western Ontario.

3. 1. Neuronal intranuclear inclusion body disease and 2. Hippocampal sclerosis

Mackenzie, D. Foti and J. Woulfe

Department of Pathology and Division of Neurology, University of British Columbia and Department of Pathology, University of Ottawa.

4. Variant Alzheimer Disease with Spastic Paraparesis: A presenilin-1 Exon 8 P264L Mutation

J.A. Pettersen,[2] B. Curry,[1] P.H. St. George-Hyslop,[3] D.G. Patry[2]

Department of Pathology & Laboratory Medicine[1] and Department of Clinical Neurosciences,[2] University of Calgary, Calgary, Alberta, Canada; and The Centre for Research in Neurodegenerative Diseases,[3] University of Toronto, Toronto, Ontario, Canada)

5. Subtype of lissencephaly with cerebellar hypoplasia

C. Hawkins and S. Viero

Department of Paediatric Laboratory Medicine, Sick Kids, Toronto.

6. Dentato-olivary dysplasia with intractable seizures in infancy

L.-N. Hazrati and W. Halliday

Department of Laboratory Medicine and Pathology, University of Toronto and Hospital for Sick Children.

7. Neuropathological changes in L-2-Hydroxyglutaric aciduria

K. Meagher-Villemure, M. Bollman, E. Roulet and L. Bonafe

Department of Pathology, Legal Medecine, Pediatry)

8. Granulomatous Peripheral T-Cell Lymphoma

L. Naz-Hazrati, D. Bailey, S. Kamel-Reid, V. Bril[1] and S. Nag

Departments of Pathology and Neurology,[1] University Health Network and University of Toronto.

9. Extopic ependymoma

D.G. Munoz and M. Cusimano

Departments of Laboratory Medicine and Pathobiology and Surgery, St. Michael's Hospital.

10. Medullomyoblastoma, predominantly large cell type, with divergent epithelial differentiation

B. Lach

Department of Pathology, Hamilton Health Sciences Centre and McMaster University, Hamilton, Ontario.

11. Cerebral blastomycoma

C. I. Coiré,[1] A. Sarabia[1] and S. Mohan[2]

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12. Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)

A.S. Easton

Department of Pathology, Capital Health and Dalhousie University, Halifax.

13. Extraventricular glioneuronal tumor with neurocytic features

C. Dunham,[1] A.W. Clark,[1] B. Curry[1] and G. Sutherland[2]

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14. Anaplastic ependymoma

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