Canadian Association of Neuropathologists

ABSTRACTS

September 17th - 20th, 2008
Edmonton, Alberta
Abstracts of papers and cases presented at the Forty-Eighth Annual Meeting

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The Canadian Association of Neuropathologists held its Forty-Eighth Annual Meeting at the Fairmont Hotel Macdonald in Edmonton, Alberta, September 17-20, 2008. Local arrangements were coordinated by Dr. Lothar Resch and by CANP President Dr. Edward Johnson; highlights were the banquet at il Portico restaurant and a tour of Fort Edmonton Park. The scientific program was assembled by Dr Rob Macaulay.

The program comprised 17 scientific presentations and 12 unknown case submissions, organized into Sessions of Tumours (2), Neuromuscular, Pediatric Neuropathology, Neurovascular and Inflammatory, and Neurodegenerative Disease..Session Chairs included Drs. Juan Bilbao, John Maguire, Bolek Lach, Yves Robitaille, Alex Easton and David Munoz.

Attendees were treated to four excellent invited lectures: Dr Peter Burger, from Johns Hopkins in Baltimore, MD, was the Speaker of the Royal College of Physicians and Surgeons of Canada; he gave a fascinating talk entitled "Revising WHO classification of CNS tumours: The science, the criteria and the diplomacy".

Three invited lectures comprised a Symposium on Epilepsy, chaired by Dr. Johnson. Dr. Bill Colmers, from the Department of Pharmacology, University of Alberta, delivered the Jerzy Olszewski Guest Lecture; he provided insight into pathophysiology in his talk "Neuropeptide Y, Hippocampal Function and Epilepsy". Dr. Don Gross, Division of Neurology, U of A, provided an interesting clinical-radiological perspective in his talk "Studying the extent of extratemporal abnormalities in temporal lobe epilepsy with magnetic resonance imaging". The Gordon Mathieson Invited Member Lecturer was Dr. Harry Vinters, David Geffan School of Medicine at UCLA; he waxed eloquent on "Neuropathologic studies of epileptogenic tissue: How the tissue speaks to neuropathologists and other neuroscientists".

Several high quality papers were delivered by trainees, including neuropathology residents and fellows as well as basic neuroscience graduate students. The Resident Awards Committee, chaired by Dr. Ian Mackenzie, presented the Mary Tom Award to Dr. Jian-Qiang Lu for best clinical presentation, and the Morrison H. Finlayson Award to Krystyna Cowan for the best best basic science paper.

Scientific Papers

1. Retrospective review of oligodendroglioma, WHO grade II: outcome and determination of prognostic markers

M-C. Guiot, B. Dion, H. El-Hateer, D. Roberge, P. Kavan, L. Souhami

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We reviewed a group of 69 supratentorial oligodendrogliomas, WHO grade II, diagnosed at the MNH between 1991 and 2006. Clinical presentation, age, performance status, imaging (tumor location, size, and presence of enhancement on the pre-operative MRI/CT), surgical treatment, adjuvant treatment (radiotherapy or chemotherapy) were recorded. A review of the pathology was conducted; the presence of mitoses, Ki-67 index and focal anaplastic transformation as endothelial proliferation were noted. In addition determination of 1p and 19q loss and the MGMT promoter methylation status was performed.

The median follow up was 73.6 months. 63% of the patients had recurrent disease after a median of 59.8 months. The 5, 10 & 15 year overall survival rates were respectively 83, 59 & 29 %. On univariate analysis, seizure at presentation, tumor size, resectability, tumor enhancement and LOH 1p and 19q significantly influenced survival. Gross total resection and tumor size < 6cm showed a trend for progression free survival; but only LOH 1p and 19q reached significance (p= 0.007).

2. Are paediatric pleomorphic xanthoastrocytomas low grade astrocytomas? The Sick Kids experience

L.N. Hazrati, A. Brown, E. Lee, E. Monsalves, U. Tabori, C.E. Hawkins

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Pleomorphic xanthoastrocytoma (PXA) is a rare primary brain tumour of children and young adults that is classified as a WHO grade II low grade astrocytoma (LGA), but recent publications

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suggest that with time PXAs may progress to a malignant subtype with a similar prognosis to anaplastic astrocytoma and glioblastoma. We reviewed the clinical experience at our institution and, as malignant progression of LGA is rare in children, we sought to uncover the genetic changes that underlie this transformation.

A search of the Sick Kids database for patients with PXA diagnosed between 1985 and 2007 identified seven patients (six females and one male, age range six to ten years at initial presentation). All patients, except one who had had a recent resection, had recurrences and two had succumbed to their disease. DNA was extracted from snap-frozen surgical samples and hybridized onto 500K single nucleotide polymorphism (SNP) mapping gene arrays (Affymetrix). Areas of copy number variation (CNV) and loss of heterozygosity (LOH) were identified.

Unlike other paediatric LGAs, PXAs contained abundant LOH at first presentation, many of which were within fragile sites. Recurrence involved the acquisition of CNVs, disrupting pathways involving tumour invasion, angiogenesis and cell growth. Our experience supports the concept that PXAs are not typical paediatric LGAs but rather have a high likelihood of recurrence.

3. Telomerase inhibition as a novel therapy for paediatric ependymoma

C.E. Hawkins, U. Tabori, J. Ma, V. Wong

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Ependymomas are the third most common paediatric brain tumour with an overall survival of ~30-50%. There is a lack of firm prognostic indicators impeding consensus as to what constitutes optimum management. Recently, we showed that telomerase (hTERT) expression is a predictor of poor outcome in paediatric ependymoma. Thus we hypothesized that ependymomas with functional telomerase may behave more aggressively and that these patients may benefit from anti-telomerase therapy. To begin to address these questions we investigated the effect of telomerase inhibition on primary ependymoma cells (EC). We then compared the *in vitro* data to findings in ependymoma tissue samples.

Ependymoma cells were characterized for GFAP and hTERT expression, initial telomere length and telomerase activity. After 72-hours of telomerase inhibition (MST-312, 1μM) ECs showed a significant decrease in cell number ($p<0.001$), accompanied by increased γH2AX expression ($p<0.01$) and decreased MIB-1 ($p<0.01$). Half showed an increase in cleaved-caspase-3. Mirroring this, hTERT-negative ependymoma tissues showed lower MIB-1 and more γH2AX expression. The EC growth-arrest following telomerase inhibition occurred within 72-hours suggesting independence from telomere length effects. Similarly, in tissue samples there was no correlation between telomere length and γH2AX expression in hTERT-negative tumours. These data suggest telomerase inhibition may be an effective therapy in paediatric ependymoma, potentially inducing tumour growth arrest in the short-term, independent of telomere shortening.

4. Connexin 43 immunohistochemistry in glioblastoma

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Intercellular gap junctions are made up of connexin molecules, which are restricted to specific cell types and can thus be used to investigate tumour cell lineage. Connexin 43 (Cx43) is the primary astrocyte connexin in the central nervous system while Cx32 is found in oligodendroglia. The status of Cx43 in glioblastoma is unclear.

Immunohistochemistry for Cx43 on frozen sections revealed widespread staining of tumour cells without obvious restriction to the cell surface. In order to better understand the role of Cx43 in glioblastoma we have evaluated Cx43 expression, localization and functionality in glioblastoma cell lines, biopsies and primary cell cultures.

In three glioblastoma cell lines, Cx43 was the major connexin subtype, and accumulated mainly in a perinuclear location. Nevertheless, gap junction permeability was preserved and a strong bystander effect was seen after viral transfection. Cx43 expression was observed in 77% (57/74) of glioblastoma biopsies and seven of eight primary cell cultures derived from surgical resection. Four of seven cultures showed cytoplasmic localization of Cx43 with preservation of gap junction permeability.

These results indicate that Cx43 is a useful immuno-histochemical marker for glioblastoma.

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5. Effects on post-therapy survival of CD56 and INI1 deficit in atypical teratoid/rhabdoid tumor and medulloblastoma

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Biological markers are useful to differentiate between malignant pediatric central nervous tumors and may help to predict prognosis and long term outcome of these patients. The aim of our study was to analyze the immunohistochemical expression of CD56 and INI1 in atypical teratoid/rhabdoid tumors (AT/RT) and medulloblastomas, in order to determine the impact on grade and survival time. Using the indirect immunoperoxydase method, we studied 17 patients, of whom 3 were immunophenotyped as AT/RTs and 14 as medulloblastomas. Mean age was 92.3 months (range 3 to 207) and differed in both entities without statistical significance (14.4 vs 109.0, $p=0.089$). The markers were: synaptophysin, neurofilament, GFAP, S-100, vimentin, smooth muscle actin, desmin, CD56, cytokeratin, EMA, MIB-1 and INI1. Cytogenetic FISH techniques were applied on frozen specimens of AT/RT tumors. Kaplan-Meier curves were done in order to display survival time depending on expression of CD56 as well as INI1. The three patients afflicted by AT/RT survived an average 3.9 months and displayed extensive tumor recurrence even during chemotherapy. CD56 deficit was detected in patients with lower survival time (CD56-loss 2.9 months vs CD56-immunopositive 6.0 months). In the medulloblastoma cohort, all patients responded very well to chemotherapy and survived during the follow up

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period (mean = 26.4, range 3 to 67 months). In one patient with a markedly decreased CD56 expression, medulloblastoma recurrence was documented. INI1 immunocytochemistry was consistently characterized by a striking specific decrease of its nuclear expression in AT-RT tumors, compared to medulloblastomas in which INI1 nuclear expression was generally high. Cytogenetic results in AT/RTs showed monosomy 22 in one patient and hypotetraploidy in another.

6. Ballooned neurons in the nuclei basis pontis following loss of frontopontine afferents

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Anterograde trans-synaptic degeneration (ATSD) occurs in certain nuclei such as the lateral geniculate body, the inferior olive, and the nuclei basis pontis after loss of their afferents. While hypertrophy is sometimes an intermediate part of the process in the olive, only atrophy and extinction of neurons is thought to characterize ATSD elsewhere. We here report four cases of ATSD in the nuclei basis pontis, in which ballooned neurons were part of the process. These include two cases of frontotemporal degenerations with severe depletion of the frontopontine afferents; and two cases in which the frontopontine afferents had undergone Wallerian degeneration unilaterally because of an infarct years previously. In each of the four cases ballooned neurons were found in the nuclei basis pontis, bilaterally in the two cases of frontotemporal degeneration and unilaterally in the two cases with old infarcts, ipsilateral to the side of the infarct. Lippa et al (Human Pathology 1990; 21: 1076-1079) reported a similar finding in one case of frontotemporal degeneration, suggesting it was unlikely to be an anterograde trans-synaptic effect. We have drawn a different conclusion not only because of the unilateral distribution in the cases of old infarction but also because of degeneration in the relevant frontopontine tracts of these cases.

7. Crooke cell adenoma (CCA): a case report

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Crooke cells are corticotrophs which accumulate perinuclear cytokeratin filaments in the setting of glucocorticoid excess, giving the cytoplasm a distinct hyalinized appearance. PAS and ACTH positivity is seen in subplasmalemmal area. Such a change is usually seen in non-neoplastic corticotrophs but rarely in neoplastic cells of ACTH-producing adenoma. When greater than 50% of tumor cells show above described changes, the adenoma is called CCA. CCA accounts for 0.4% of pituitary adenomas and 3.5 % of corticotroph adenomas. 65% are Cushingoid, 81% are macroadenomas, often invasive. Crooke cell adenoma is aggressive and has unfavorable prognosis with recurrence rate of 60%. Mean time for recurrence is 3.6 years. Five percent showed malignant transformation in the large series reported by David George in 2003. Other than this series, CCA are documented as case reports of one or two cases. We add another case of CCA in a 77 year-old female who presented with progressive visual loss, in particular loss of peripheral vision. Ophthalmological examination revealed bitemporal hemianopsia. Endocrinological work up revealed ACTH level to be 116 ng/dL (N 5-27 ng/dL) and p.m. cortisol was elevated to 26 ng/dL (N 3-17 ng/dL) but without Cushingoid features. The patient underwent transnasal transsphenoidal resection of the tumor. A year later patient presented again with headaches and neuroradiological work up revealed a 2.5 cm recurrent suprasellar mass.

8. Alpha-B-Crystallin as a tissue marker of epileptic foci

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Introduction: A neuropathological tissue marker to demarcate the extent of epileptic foci in surgical resections would be useful for patient management and prognosis. Heat shock chaperone proteins are upregulated by various "stresses" and epileptic activity could be another of these stresses; α-B-crystallin is a small heat shock protein related to HSP-27.

Materials and Methods: We prospectively examined 41 resected brain tissues of epileptic patients, 4 months to 23 years of age, from July 2005 to June 2008. Immunoreactivity of α-B-crystallin supplemented neuronal, glial and inflammatory cell markers. Cerebral tissues taken at autopsy from two epileptic children and from 20 normal human fetuses of 10 to 41 weeks gestation and two neonates with cerebral infarcts were similarly studied. EM was performed in all surgical cases.

Results: In all epileptic resections, α-B-crystallin was overexpressed in both astrocytes and oligodendrocytes of the subcortical white matter, in some satellite cells adherent to neurons in grey matter, and occasionally in neurons of the neocortex, hippocampus and amygdala. Reactivity was most intense at or near to the epileptic focus, with a diminishing gradient of intensity and lack of expression 2.5-4 cm away in 10/41 cases and was diffuse without a gradient in the others. The presence or absence of structural lesions, including focal cortical dysgeneses, did not correlate. Balloon cells in Taylor-type cortical dysgenesis and in tuberous sclerosis were intensely reactive. No correlation was found with microglial activation, inflammation or gliosis. Ultrastructural changes were not demonstrated in reactive cells of all types. Expression was not found in normal fetal brains at any age, but was seen in ischaemic tissue adjacent to infarcts.

Conclusions: The small heat-shock protein α-B-crystallin is a reliable metabolic tissue marker demarcating epileptic foci as a reactive, probably neuronal-protective, protein, regardless of the presence or absence of structural lesions. We recommend that this marker be included in the neuropathological examination of surgically resected brain tissue of epileptic patients.

9. Fetal neuroaxonal dystrophy: A report of four midgestational cases

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We report four fetal cases of central neuroaxonal dystrophy, ranging in gestational age from 18 to 26 weeks. None are related, and no relevant parental history is present in any. All four had

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features of fetal hypokinesia. The eldest was associated with a strikingly abnormal facies, with redundant facial skin and skeletal features suggesting osteopetrosis. Two demonstrated axonal spheroids in the peripheral nervous system. In the central nervous system, all displayed agenesis of the corpus callosum, as well as agenesis or severe hypoplasia of corticofugal long tracts. The cerebellum in all four was hypoplastic, and two demonstrated Blake's pouch cysts. In two the spinal cord was notably atrophic, and these two had severe motor neuron involvement. Axonal spheroids were distributed widely in the central nervous system in all cases, occasionally showing aggregation near blood vessels, and sometimes reaching in excess of 100 microns in diameter. With the exception of dentate-olivary simplification, which was present in 2 cases, the nuclear organization of deep and brainstem structures was undisturbed. One case showed definite features of cerebral cortical neuronal disarray. We propose that axonal growth disturbance results in axonal spheroids and agenesis of long tracts.

10. Diffuse inflammation in normal-appearing human brains after allogeneic hematopoietic cell transplantation

J-Q. Lu[1], J.T. Joseph[1], A.M. Stevens[2], J. Storek[1], L. Metz[1], A.W. Clark[1], E.S. Johnson[3], V.W. Yong[1]

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Allogeneic hematopoietic stem cell transplantation (allo-HCT) is the treatment of choice for many hematological disorders, and being considered as a potential therapy for refractory multiple sclerosis (MS). However, this treatment results in frequent complications. Its failure to halt MS disease activity has repeatedly been encountered. We examined three brain regions of postmortem tissues from five neuropathologically-normal patients with allo-HCT (post-allo-HCT: 1.0~29.0 months; median, 10.0 months) and 5 age-matched neuropathologically-normal subjects. The numbers of T-lymphocytes were counted; frequency of CD68+ microglia/macrophages was scored 0-3, by summing 10 consecutive 200x microscopic fields. The results are summarized in the table below.

	CD3+ T-cells		CD8+ T-cells		CD68+ microglia/macrophages	
Group	Parenchyma	Perivascular	Parenchyma	Perivascular	Parenchyma	Perivascular
Allo-HCT	35 (3–72)***	35 (2–96)**	11 (1–93)***	18 (2–90) ^{NS}	19 (11–21)**	11 (5–18)*
Control	4 (0 – 14)	18 (4 – 27)	3 (0 – 16)	16 (2 – 38)	11 (10 – 19)	5 (3 – 14)

Values: median; NS, not significant; *, P <0.05; **, P <0.01; ***, P <0.001 by Mann-Whitney U-test, vs. the control

This study suggests that allo-HCT and its complications are associated with diffuse infiltration of T-lymphocytes and potential activation of microglia/macrophages. These immune changes may provide a favorable microenvironment for CNS inflammatory and/or autoimmune diseases including MS.

11. Persistent inflammation and demyelination in patients with multiple sclerosis after allogeneic hematopoietic cell transplantation

J-Q. Lu[1], J.T. Joseph[1,2], A.M. Stevens[3], J. Storek[4], L. Metz[2], A.W. Clark[1,2], E.S. Johnson[5], V.W. Yong[2]

Departments of [1]Pathology and Laboratory Medicine, [2]Clinical Neurosciences, and [4]Internal Medicine, University of Calgary, Calgary, Alberta; [3]Department of Pediatrics, University of Washington, Seattle, WA, USA; [5]Department of Laboratory Medicine and Pathology, University of Alberta, Edmonton, Alberta

Allogeneic hematopoietic stem cell transplantation (allo-HCT) has been used in trials to treat multiple sclerosis (MS) refractory to conventional treatment. Its efficacy has repeatedly been challenged by clinical and radiological observations. We performed postmortem histopathological examinations on four patients with hematologic malignancies and concomitant MS who received allo-HCT (post-allo-HCT: 2.5 ~ 9.0 months; median, 4.5 months). All the patients showed active and/or chronic active lesions. These lesions had significantly higher numbers of CD3+ T-lymphocytes and CD8+ cytotoxic T-lymphocytes, as well as significantly higher scores of CD68+ microglia/macrophages than chronic inactive lesions or normal-appearing white matter ($P < 0.01$ by Mann-Whitney U-test). Ongoing demyelination was confirmed by colocalization of myelin basic protein with CD68+ macrophages. FISH analysis in the female patient with active lesions revealed that CD45+ cells with X-chromosomes (of the recipient) outnumbered those with Y-chromosomes from the male donor. This study suggests that allo-HCT fails to halt MS inflammatory and demyelinating activity. Our interpretations for this failure include insufficient penetration of allo-HCT into the brain, and a generalized inflammatory activation in the brain after allo-HCT [see our accompanying abstract].

12. Neutrophils do not induce disruption of the inflamed blood-brain barrier

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The blood-brain barrier (BBB) is a permeability barrier formed by the endothelial cells that line cerebral microvessels. During inflammation, large scale disruption of the BBB can occur, resulting in vasogenic cerebral edema. Neutrophils are participants in the acute inflammatory responses of many CNS diseases including meningitis, head injury and stroke. It has been proposed that they are causal factors in brain injury and vasogenic edema. Therefore we carried out in vivo studies to explore the role of neutrophils in BBB disruption. Untreated neutrophils injected into the striatum of anesthetized juvenile Wistar rats induced significantly lower permeability in their vicinity than activated neutrophils or saline. Neutrophils activated with tumor necrosis factor (TNF, 100U/ml) and leukotriene B_4 (10^{-7}mol/l) did not increase permeability over the saline control, while arachidonic acid (10^{-3}mol/l) induced a significant increase. To explore the effects of endogenous neutrophils in stroke, we have generated a focal infarct by injecting endothelin-1 (400pg in 1µl) into the striatum of anesthetized adult Wistar rats. This treatment induces a significant increase in permeability 48-72h after injection. Ongoing studies are underway to increase neutrophil infiltration

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by co-administration of the neutrophil chemokine CXCL1 (0.5µg). Thus far, our data suggests that in an inflammatory context, neutrophils do not further disrupt the BBB or result in vasogenic cerebral edema.

13. Effects of Neutrophils on an In vitro Model of the Blood-Brain Barrier

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This study examines the role of neutrophils in blood-brain barrier (BBB) breakdown. The BBB is formed by endothelial cells lining brain blood vessels. In health, it prevents water soluble substances from entering the brain, but in disease such as stroke, it breaks down, allowing proteins to enter the brain and cause brain swelling (edema). The role of neutrophils in stroke has not been fully elucidated, and some investigators believe neutrophils may make edema better, or have no deleterious effects. An *in vitro* model of the BBB was used to demonstrate changes to permeability in relation to the direct application of neutrophils. Using a human brain endothelial cell line (hCMEC/D3), cells were grown to confluence on Transwell inserts. Application of untreated neutrophils to resting endothelium significantly decreased permeability compared to baseline. Neutrophils were then primed and activated which returned permeability to baseline, an effect that was blocked by co-application of superoxide dismutase and catalase to scavenge reactive oxygen species. An *in vitro* ischemia/reperfusion model employing oxygen-glucose deprivation (OGD) for 1 and 12 hours was used to examine the effects of neutrophils on activated endothelium. Permeability after OGD increased significantly with respect to baseline. However, neutrophils (resting and activated) produced no significant changes in permeability compared to OGD alone.

14. Effects of tumor necrosis factor (TNF) family members and resveratrol on an in vitro model of cerebral angiogenesis

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The inflammatory effects of tumor necrosis factor (TNF) family members, TRAIL (TNF-Related Apotosis Inducing Ligand) and FasL (Fas Ligand) are increasingly well characterized, however, their role in regulating cerebral angiogenesis are not as well understood. Resveratrol, one of the phytochemicals found in the skin of grapes and thus a constituent of red wine, has been increasingly recognized for its anti-inflammatory and anti-angiogenesis effects. The impact of the TRAIL and FasL on cerebral angiogenesis was modeled *in vitro* with the human brain endothelial cell line hCMEC/D3. Three critical steps of angiogenesis, including cell proliferation, migration, and tube formation, were investigated. By flow cytometry, surface expression of the FasL receptor Fas and the TRAIL receptor R2, was demonstrated. Endothelial proliferation was measured by DNA synthesis (BrdU ELISA) and mitochondrial activity (MTT assay) on hCMEC/D3 cells treated with different ligands. TRAIL induced a dose-dependent reduction in proliferation while FasL marginally increased proliferation. Endothelial migration and tube formation were assessed by two image-based assays, a scratch wound healing assay and an *in vitro* Matrigel matrix assay. Preliminary results show that TRAIL inhibited endothelial migration and reduced tube number and density on a Matrigel matrix. We present evidence that cerebral angiogenesis is inhibited by TRAIL and may be stimulated by FasL. We are currently investigating the role of resveratrol in these processes.

15. Granulovacuolar degeneration in Alzheimer's disease and other neurodegenerative diseases

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Granulovacuolar degeneration (GVD) is strongly linked to Alzheimer's disease (AD) but has also been observed with ageing. Similarly, GVD has been noted in other neurodegenerative diseases which often occur with increasing age. In this study we investigate the frequency of GVD in neurodegenerative diseases and attempt to determine whether GVD is disease-related or age-related. A retrospective review of post-mortem cases of neurodegenerative diseases [including AD (n=57), AD/LBD (n=9), AGD (n=2), CBD (n=5), FTLD-U (n=4), LBD (n=10), MSA (n=5), Parkinson's disease (n=5), Pick's disease (n=2), PSP (n=5) and normal ageing controls (n=70)] at University Hospital between 1993 and 2005 (n=174) was undertaken. One section of the hippocampus at the level of the lateral geniculate nucleus was examined from each case with hematoxylin-eosin and Bielschowsky stains at 250x magnification. The %GVD (number of neurons with GVD/total number of neurons) for the CA1 – CA4 regions was counted for each case. The %GVD in regions CA1 – CA4 in the neurodegenerative disease and control cases was compared using one-way ANOVA. Preliminary results indicate that AD and AD/LBD have a statistically significant effect ($p<0.05$) on %GVD in CA1 as compared to normal ageing controls. Since the %GVD of the other neurodegenerative diseases did not differ significantly from control, we conclude that the %GVD in these diseases is likely age-related.

16. Association of atypical (TDP-43 negative) FTLD-U (a FTLD-U) with alpha-synucleopathy of idiopathic Parkinson disease (IDP) distribution

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FTLD-U is a recently described sporadic entity characterized by FTLD with neuronal cytoplasmic ubiquitinated, but TDP-43 negative inclusions (NCI), accompanied by filamentous neuronal intranuclear inclusions (NII). The cases reported did not have parkinsonism or alpha-synuclein (AS) pathology, although neuronal loss in the substantia nigra was consistently found. We expand aFTLD-U's clinical and pathological spectrum.

A man presented at age 59 with slurred speech, progressing to being unintelligible in 18 months, accompanied by fasciculations and slow tongue movements, and pseudobulbar affect. Within months he developed asymmetric-onset parkinsonism and a frontal type dementia. Death at age 62 was

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preceded by bilateral limb weakness. At autopsy the brain showed frontotemporal atrophy, marked hippocampal sclerosis, and a latero-medial gradient of atrophy in the putamen. Numerous NCI and filamentous NII, all TDP-43 negative, were present in dentate gyrus, hippocampus, frontotemporal neocortex, amygdala, neostriatum, and brainstem. Neuronal loss in substantia nigra was accompanied by AS immunoreactive Lewy bodies and neurites, also seen in nucleus basalis and brainstem.

Some progranulin mutations carriers develop clinical Parkinson disease with AS pathology in addition to TDP-43 pathology. Similarly, the process leading to the formation of non-TDP-43 inclusions can produce AS pathology of IPD anatomical distribution. Thus AS pathology and IPD may represent secondary phenomena to several pathogenic processes.

17. Reactive microgliosis in Rasmussen's syndrome

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In a disease complex of unknown etiology mainly observed in childhood encompassing progressive and intractable focal seizures and hemiparesis recognized as Rasmussen's encephalitis (RE), considerable microglial activation is often present throughout the affected cerebral hemisphere.

To investigate the inflammatory nature of the disease we determined the extent of microglial reactivity within areas of brain specimens removed during surgical treatment of children suffering from RE. Cortical areas of severe and minimal reactivity within the same brain regions and cortical areas from patients suffering from other CNS diseases such as cortical dysplasia (CD) or tuberous sclerosis complex (TSC) known for having a less inflammatory CNS pathology were compared. Microglial reactivity visualized by Iba1 immunolabeling was significantly increased in severely affected areas (one-way ANOVA, $p<0.05$) in brains from RE cases (29% labeled area) compared to minimally affected areas (15% labeled area) within the same cases and control cases (13% labeled area). Of interest were patients thought clinically to have RE but in whom the neuropathologic features were not observed; these individuals showed an absence of microglial activation comparable to TSC and CD controls. RE a serious and debilitating inflammatory disease of the brain still of unknown origin includes as demonstrated here a component of diverse and often intense microglial activation.

Titles of Diagnostic Case Presentations

1. Astroblastoma

D.G. Munoz[1], L. Noel De Tilly[2], R. Perrin[3]

[1]Department of Laboratory Medicine and Pathobiology, [2]Department of Radiology, [3]Department of Surgery, St. Michael's Hospital and Li Ka Shing Knowledge Institute, University of Toronto, Ontario, Canada

2. Intracerebral amyloidoma

Ana Maria C. Tsanaclis[1], Peter V. Gould[2], David Fortin[1], Geneviève Ricard[1]

[1]Departments of Pathology, Neurosurgery and Neurology, University of Sherbrooke School of Medicine, and [2]Univeristy of Laval

3. Melanocytic neoplasm, intermediate grade

J.S. Krawitz, S. Hamza

Department of Pathology, University of Manitoba, Winnipeg, MB

4. Myopathy as the initial manifestation of primary systemic amyloidosis (lambda)

Z. Afshar-Ghotli[1], J.M. Bilbao[1], S. Deodare[2], B. Young[1]

[1]Division of Pathology, Sunnybrook Health Science Centre, Toronto, ON; [2]Division of Pathology, Credit Valley Hospital, Mississauga, ON

5. CAP myopathy

C.E. Hawkins[1], J. Vajsar[2], G. Yoon[3] W. Halliday[1]

[1]Divisions of Pathology, [2]Neurology and [3]Genetics, The Hospital for Sick Children, Toronto

6. Caveolin-3 inclusion body myositis (myopathy with hexagonally linked crystalloid inclusions)

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[1]Department of Pathology & Molecular Medicine, Hamilton Health Sciences, Hamilton General Site, Hamilton, Ontario, Canada; [2]Department of Medicine and Pediatrics, McMaster University, Hamilton, Ontario

7. Pelizaeus-Merzbacher disease

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8. Focal cortical dysplasia with diffuse oligodendroglial proliferation

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9. Melanotic neuroectodermal tumour of the pineal region

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10. Desmoplastic infantile ganglioglioma

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11. Amyloid beta-related angiitis

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12. Cerebrotendinous xanthomatosis

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