Canadian Association of Neuropathologists

ABSTRACTS

October 14th - 16th, 2010
Toronto, Ontario
Abstracts and unknown cases presented at the Fiftieth Annual Meeting

Can. J. Neurol. Sci. 2011; 38:172-182

The Canadian Association of Neuropathologists held its Fiftieth Annual Meeting at the Yorkville Bloor Marriott Hotel in Toronto, October 14-16th 2010. Local arrangements, coordinated by Dr. Cynthia Hawkins, Dr. Bill Halliday, and CANP President Dr. David Munoz, were exemplary. The 50th Anniversary Banquet, held in the Gardiner Museum, featured celebrity chef Jamie Kennedy, and was attended by founding members Drs. Stirling Carpenter and Gorden Mathieson, as well as numerous retired members and Past Presidents by invitation. It was a night to remember.

The scientific program was assembled by CANP Secretary/ Treasurer Dr. Rob Macaulay; it comprised a record 33 scientific presentations and 11 unknown case submissions, organized into Sessions of Brain Tumours (two sessions), Degenerative Neuropathology, Inflammatory Neuropathology, Vascular and Neuromuscular Neuropathology, as well as Pediatric Neuropathology and CNS Repair. Session Chairs were Drs. Hawkins, Jeffrey Joseph, Jean Michaud, Chris Dunham, Juan Bilbao and Patrick Shannon.

A Symposium focussed on Stem Cells in Neuropathology was chaired by CANP President Dr. David Munoz. Fascinating basic cellular and neurobiology issues were explored by Dr. Sebastian Jessberger from Zurich, whose talk ("Molecular Mechanisms and Functional Significance of Adult Neurogenesis") constituted the Jerzy Olszewski Guest Lecture; and by Dr. Jenny Hsieh ("Signaling to the Neuronal Stem Cell Genome and Epigenetic Control of Adult Neurogenesis") of Dallas, Texas. Dr. Peter Dirks from the University of Toronto delved into "Stem Cells in Brain Tumours".

The Gordon Mathieson Invited Member Lecturer for 2010 was Dr. Harvey Sarnat from the University of Calgary, who captivated the attendees with his studies on "Markers of Neuronal Maturation in Developing Human Brain and Malformations." A special 50th anniversary guest lecture was provided by Dr. Peter St. George-Hyslop, entitled "Molecular Mechanisms of Dementia."

The Resident Awards Committee, chaired by Dr. Arthur Clark had a difficult time choosing the best presentations, due to the copious excellent submissions by trainees. Congratulations to the Mary Tom Award winner Dr. Zahra Al-Hajri (supervisor: Dr. S. Krawitz) for unknown case 3 "Malakoplakia"; the Morrison H. Finlayson Award winner was Naomi Visanji (Dr. L-N Hazrati) for "Dysregulation of Iron Storage in Multiple System Atrophy".

Scientific Papers

1. Rosette-forming glioneuronal lesion of 4th ventricle in a patient with NF1: hamartoma vs tumour?

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Rosette-forming glioneuronal tumor (RGNT) of the fourth ventricle has been identified as a distinctive type of primary central nervous system neoplasm preferentially affecting young adults and composed of two distinct histological components, one with areas of neurocytic forming rosettes and/or perivascular pseudorosettes and the other with astrocytic areas resembling a pilocytic astrocytoma. This tumour is regarded as low grade (WHO grade I) and to date no high grade progression has been reported. We report the autopsy findings of the brain from a 41-year-old male with clinical diagnosis of NF1 (based on family history and clinical presentation with café-au-lait spots and multiple neurofibromas) who had a glioneuronal lesion of the fourth ventricle biopsied 23 years earlier. The initial diagnosis was pilocytic astrocytoma, but review of the previous biopsy confirms the presence of synaptophysin-positive neurocytic cells forming perivascular rosettes and a glial component resembling a pilocytic astrocytoma. During the many

years of patient's follow-up, the lesion had not progressed and was barely visualized on CT scans and MRI. Patient died of unrelated cause and at autopsy, the lesion was identified at the roof of the 4th ventricle at the rostral pons. Histological examination of this lesion demonstrated the presence of scattered atypical glial cells infiltrating the adjacent pontine tegmentum. In addition, glioneuronal hamartias were noted in the frontal cortex, quite distinct from the 4th ventricle lesion. Although, rare cases of dysembryoplastic neuroepithelial tumour are described in NF1, there is only one case of a RGNT of optic nerve reported in NF1. This case illustrates the indolent nature of this type of glioneuronal lesion and its rare association with NF1.

2. Molecular cytogenetic markers for recurrent versus non-recurrent meningiomas

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Meningiomas are common intracranial tumours in adults, believed to derive from arachnoid cells of the meninges. Meningiomas are divided histologically into three grades: benign, atypical and anaplastic. The 5 year recurrence rate is 7-25% for benign, 29-52% for atypical, and 50-95% for anaplastic tumours. The current methods to predict recurrence rely on histological criteria, such as histological subtype, mitotic index, as well as brain invasion. Previous studies have shown that a co-deletion of 1p/14q, and amplification of the ERBB2 gene are associated with an increased risk of recurrence, and tumour aggressiveness. This study looks at the comparison of recurrence and non-recurrence in meningiomas of the three grades with cytogenetic/genetic markers for deletions of 1p36 and 14q11.2 and ERBB2 (Her2neu) amplification. Paraffin embedded slides from the Canadian Brain Tumour Tissue Bank were reviewed to confirm the tumour grades and subtypes, and the appropriate areas for FISH (fluorescent in-situ hybridization) were selected. For all three grades: seventeen out of 19 (89%) recurrent vs. 7/29 (24%) of non-recurrent tumours exhibited deletion 1p36; twelve out of 19 (63%) of recurrent vs 2/29 (7%) of non-recurrent tumours had deletion of 14q11.2; and seven out of 19 (37%) of recurrent vs 2/29 (7%) of non-recurrent tumours showed amplification of ERBB2. Twelve out of 19 (63%) recurrent meningiomas had co-deletion of 1p/14q, compared to 1/ 29 (3%) of non-recurrent cases; and 6/19 (32%) of recurrent tumours had co-deletion 1p/14q and her2neu amplification compared to 0/29 (0%) for similar non-recurrent samples. For the benign meningiomas, 5 of the 7 recurrent tumours (71%) and only 2 of 15 non-recurrent tumours (13%) showed 1p36 deletion. (Wilcoxon test, $p<0.0005$). The results of this study indicate that 1p36 deletion best characterizes recurrence in the benign meningiomas while 14q deletion and her2neu amplification are rarer events in tumour recurrence.

3. Differential protein and mRNA expression between invasive and non-invasive meningiomas

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Introduction: We investigated differential protein and mRNA expression profiles in invasive and non-invasive meningiomas .

Methods: Data was collected on 57 patients with invasive (IM) and non-invasive (NIM) meningiomas. A tissue microarray (TMA) including these tumors was generated and immuno-histochemical analysis for osteoponin (OPN), integrin-beta-1 (ITG-ß1) and matrix metalloproteinase-2 (MMP-2) performed. RNA expression was profiled in a small subset (spheno-orbital IM and sphenoid wing NIM) using the DASL platform.

Results: Immunohistochemistry: ITG-ß1: Tumor ITG-ß1 expression was higher in NIM skull-base tumors than IM. Vascular ITG-ß1 immunoreactivity was higher than tumor cell reactivity in all meningiomas. Striking perivascular expression pattern was noted in tumor cells, in keeping with an ITG-ß1 role in neovascular remodeling. MMP-2: Vascular and tumor MMP-2 expression was higher in NIM compared to IMs. OPN: There was not a significant difference between IM and NIM. No correlation was found between ITG-ß1, OPN, MMP-2 immunoreactivity and patient age, sex, tumor size, recurrence, or grade. RNA Microarray: Increased expression of the RNAs for MMP-12, MMP-16, and PDGFR-A was noted between sphenoid wing NIM compared to IM.

Conclusion: We have demonstrated key differentially expressed proteins between IM and NIM that may lead to greater understanding of the biological substrate for invasive behavior in these tumors.

4. Giant cell change/transformation in pituitary adenoma

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Pituitary adenomas with prominent giant cell change are rare. The presence of mild pleomorphism and cellular atypia has been described in the literature and is not uncommon. We report a case of pituitary adenoma with numerous atypical giant cells. A 78-year-old male presented with several month history of emotional lability, decreased motivation and overall depressed mood. There was bitemporal hemianopsia on examination. MRI head showed an intrasellar mass (2.6 x 1.1 cm) with suprasellar extension and compression on the optic chiasm. During intraoperative consultation, the smear preparation revealed the presence of numerous bizarre giant cells which called into the differential diagnosis of giant cell lesions of the sellar region. On the permanent sections, the lesion was composed of monomophohous population of round cells with faint eosinophilic cytoplasm, intermixed with several bizarre giant cells with large hyperchromatic atypical nuclei. Many of the giant cells appeared to have intranuclear pseudoinclusions. Occasionally giant cells were multinucleated. There was no

evidence of granuloma, increased mitotic figures or tumour necrosis. The tumour cells and some giant cells were positive for chromogranin. The Ki-67 immunolabeling was low (about 1% or less), and the giant cells were hardly labelled at all. Ultrastructurally, the giant cells as well as the smaller tumour cells showed dense collection of mitochondria and sparse neurosecretory granules. The morphological studies of the pituitary adenoma with giant cells will be reviewed, together with the differential diagnosis of giant cell lesions of the sellar region.

5. Glomus tumors related to peripheral nerves: Report of two cases

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Glomus tumors are rare benign tumors characterized clinically by their small size and pain as a primary complaint. They are usually found beneath the fingernails, but may occur in many other locations. Occasional glomus tumors display unusual features, such as large size, deep location, infiltrative growth, mitotic activity, nuclear polymorphism, and necrosis. Here we report two unusual cases of glomus tumors involving peripheral nerves. Both cases presented with a long history of a painful mass. In the first case, clinical suspicion was that of a schwannoma arising from the lateral cutaneous nerve of the forearm but the histopathology proved to be that of a glomus tumor. The second case was clinically thought to be a synovial cyst arising from the femoral nerve. However, the lesion showed the histopathologic and ultrastructural features of a variant of glomus tumor, glomangiomatosis that was associated with a traumatic neuroma of the femoral nerve. The lesions were completely and subtotally resected, respectively. Marked reduction in pain was achieved in both cases with uneventful postoperative course. These cases illustrate that glomus tumors arising from or associated with peripheral nerves are very rare, as elsewhere in the body, and present clinically as relatively small masses with pain as a major feature.

6. Synaptic plasticity in Parkinson's disease as revealed by the study of trans-synaptic cell adhesion molecules

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It is known that Parkinson's disease (PD) pathophysiology involves loss of dopaminergic striatal projections with subsequent neuronal discharge abnormalities in the entire motor circuit. The classical "basal ganglia-thalamocortical circuitry" model posits that striatal dysfunction in PD leads to imbalances in neuronal firing rates in direct and indirect pathways. However, the predictions made by the model are not fully supported by numerous electrophysiological and metabolic studies. The limits of this model suggest that more complex changes occur at the molecular level in extra-striatal neurons. Cell-adhesion proteins neurexins and neuroligins mediate synaptic maturation, synaptic neurotransmission and neuronal activity. We report preliminary studies in post-mortem human brains that demonstrate extensive neuroligin-1 (NLGN1) expression in pallidal segments of normal brains, but dramatic decreases in NLGN1 levels in pallidal segments of brains from PD patients. Three human brains with PD and age-matched controls were studied. Immunohistochemistry and western blots demonstrated decreased NLGN1 levels in the globus pallidus interna and externa (GPi and GPe) of PD patients compared to control patients. Semi-quantitative reverse transcriptase polymerase chain reaction experiments confirmed decreased NLGN1 expression in the GPi and GPe of PD patients. Thus, we provide evidence for a specific molecular change at extra-striatal synapses that may contribute to alteration of neuronal firing and circuitry in PD.

7. A case of adrenomyeloneuropathy with frontal lobe type dementia

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Adrenomyeloneuropathy is a phenotype of X-linked adrenoleukodystrophy, a disorder of peroxisomal β oxidation. It is characterized by accumulation of very-long-chain fatty acids leading to damage of central and peripheral myelin, adrenal glands and gonads. We describe an interesting case of adrenomyeloneuropathy with frontal lobe type dementia who presented at the age of 23 with features of hypogonadism, adrenal insufficiency and developed gait abnormality and dementia late in the disease course. His two brothers died of adrenoleukodystrophy at an early age. Our patient died at 68 years of age and an autopsy revealed bilateral adrenal atrophy and marked atrophy and demyelination of brain predominantly involving centrum semiovale, parieto-occipital white matter, thalamus, brainstem and spinal cord.

8. Overexpression of LCAT and ABCA1 influence brain apoE levels in a region-specific manner

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Brain apoE levels and, more importantly, the lipidation status of apoE are critical for the development of amyloid in animal models of Alzheimer Disease (AD). Poor lipidation of apoE due to the absence of the cholesterol transporter ATP-binding cassette A1 (ABCA1) reduces brain apoE levels and worsens amyloid pathology. Conversely, overexpression of ABCA1 increases apoE lipidation and reduces amyloid burden. Lecithin cholesterol acyltransferase (LCAT) may also modulate lipidation of apoE, as it esterifies free cholesterol on plasma lipoproteins. LCAT is synthesized within the brain and LCAT-deficient mice have an altered CSF lipoprotein composition. To further investigate the effects of LCAT and ABCA1 on brain apoE metabolism, we evaluated the effects of LCAT overexpression and deficiency, as well as ABCA1 overexpression in the presence and absence of LCAT, on regional brain apoE levels. We found that the expression levels of apoE in cortex, hippocampus and cerebellum were affected differently by the overexpression of LCAT and ABCA1. Both led

to increased cerebellar apoE and no changes in cortical apoE, but only ABCA1 overexpression reduced hippocampal apoE levels compared to controls. In contrast, LCAT deficiency had no effect on regional apoE levels. These data suggest that LCAT and ABCA1 may not only influence the lipidation status of brain apoE, but also the region-specific metabolism of this lipoprotein and its effect on local amyloidogenesis.

9. Dysregulation of iron storage in multiple system atrophy

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Increased iron has long been associated with neurodegenerative disease, yet the role of iron in neurodegeneration remains elusive. Iron is vital for many processes. However, excess leads to free radical production. Thus, iron homeostasis is tightly regulated. We investigated the relationship between iron homeostasis proteins and the levels, distribution and form of iron in control, multiple system atrophy (MSA) and Parkinson's disease (PD).

In MSA pons, ferritin was increased by ~247±20% ($p<0.01$ cf control) and unaltered in PD. Immunohistochemistry confirmed elevated ferritin was localized to oligodendrocytes and dysmorphic microglia. Ferritin contains iron oxide cores producing an isothermal remanent magnetisation (IRM) at low temperature. Superconducting quantum interference device (SQuID) measurement of IRM indicated elevated concentrations of ferritin cores in MSA compared to control. This is supported by graphite furnace measurement of total iron. The relationship between IRM and total iron enables estimation of non-ferritin-bound iron, assuming that IRM signal is due to ferritin cores, and that the cores are identical in nature. This estimate indicated a lower proportion of non-ferritin-bound iron in MSA compared to control.

Conventional opinion holds that excess iron is involved in neurodegeneration via free radical production; however, our data suggest that in MSA elevated iron is sequestered by elevated ferritin, which may be detrimental to the cell due to a deficit in bioavailable iron.

10. Clinical, pathological, and molecular aspects of a patient with Gerstmann-Straüssler disease and a novel mutation

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We present the clinical aspects, brain biopsy pathology, and molecular analysis of a patient with a slowly progressive neurodegenerative disease and a novel prion gene mutation. The patient is a 39-year-old father of three who presented at age 34 years with seizures and night terrors. Over 4-5 years, he experienced cognitive decline in all domains, including orientation, language, attention, and memory. Gait instability is also limiting. He displays little insight into his impairments. A brain biopsy in Spring 2009 revealed the presence of amyloid plaques, gliosis, and only mild spongiform changes. Immunoperoxidase stains showed the plaques contained abnormal prion protein. Silver stains revealed a few neurofibrillary tangles. Molecular genetic analysis on peripheral blood did not show point mutations in the PRNP gene. However, additional testing demonstrated a PRNP allele (365–388dup) containing 24 extra nucleotides inserted between nucleotides 388 and 389 of the PrP-coding region and encoding an 8-amino acid insertion (Leu-Gly-Gly-Leu-Gly-Gly-Tyr-Val) between PrP amino acids 129 and 130. The mutation disrupts and lengthens a PrP hydrophobic region (codons 113–135), the literal amino acid sequences of which are almost perfectly conserved across 18 orders of placental mammals and which is thought to serve as a transmembrane domain for abnormal topological species of PrP favored by known GSS mutations.

11. Non-infectious intracranial caseating granulomas

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Caseating granuloma is a classic histopathological feature of mycobacterial infections. Occasionally, no infectious organism is demonstrated despite extensive examination of intracranial caseating granulomas. The pathogenesis of such non-infectious intracranial caseating granulomas (NICGs) remains unclear. To elucidate the clinical pathology of NICGs, we reviewed the clinicopathological data of patients with intracranial caseating granulomas in whom no infectious cause was identified after rigorous investigations. The study was a retrospective case-series design in a referral hospital setting. We identified 8 patients with NICG (4 females and 4 males) with average age on presentation of 46 years (range 21-69). Seizure was the most common presentation. None had any prior systemic inflammatory history, although one patient reported malaise and weight loss. CSF showed elevated cells and protein and decreased glucose. ANCA (available in 4), ANA and ACE were negative. On imaging, gadolinium-enhancing intraparenchymal multiple or single lesions were often accompanied by meningeal enhancement. Immuno-modulation was tried in five patients and resulted in clinical improvement. Anti-mycobacterial therapy was tried in four patients with no improvement or worsening of clinical or radiological features. Two of these patients had excellent responses to subsequent immunomodulation treatment. This excellent response to immunomodulation and lack of response to anti-mycobacterial therapy suggest that NICG represents an inflammatory rather than infectious process. Caseating granulomas and normal ACE levels in all our patients argues against classical sarcoidosis, although atypical presentation cannot be ruled out. Nonetheless, when no infectious cause is identified after rigorous tissue investigations in patients with intracranial caseating granulomas, an inflammatory etiology is likely.

https://doi.org/10.1017/S0317167100011276 Published online by Cambridge University Press

12. IgG4-related sclerosing pachymeningitis

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IgG4-related sclerosing disease is a systemic disorder in which IgG4-positive plasma cells and T lymphocytes extensively infiltrate various organs often producing a mass lesion. Recently a case of IgG4-related sclerosing pachymeningitis was reported in a patient with other IgG4-related lesions (Chan et al. Am J Surg Pathol 2009). The authors suggested that some of the previously reported cases of idiopathic hypertrophic pachymeningitis might be IgG4-related. Review of such a case from our files confirmed IgG4-related disease. A previously healthy 64 year old man had presented with acute onset of severe neck pain radiating into the right face. Except for neck pain and stiffness, the physical exam was normal. Neuroimaging revealed findings consistent with epidural blood at cervical levels 1-4. At surgery, an epidural mass was removed. Histopathologically, it was characterized by dense connective tissue with an extensive inflammatory infiltrate dominated by plasma cells. It was interpreted as consistent with hypertrophic pachymeningitis. Our recent review of the case confirmed immunopositivity for IgG4 in more than 70% of the plasma cells. To our knowledge this is the first description of a case of IgG4-related sclerosing pachymeningitis presenting in the absence of other lesions attributable to IgG4-related sclerosing disease. In our opinion immunostaining for IgG4 should always be included in the evaluation of cases of hypertrophic pachymeningitis.

13. Novel insights into the regulation of angiogenesis and its relationship to blood-brain barrier disruption in experimental allergic encephalomyelitis

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There is increasing evidence that angiogenesis plays a role in multiple sclerosis and its murine animal model, experimental allergic encephalomyelitis (EAE). However, little is known of its regulation and relationship to permeability alterations across the blood-brain barrier (BBB). We have used the EAE model induced by myelin oligodendrocyte glycoprotein (MOG peptide 33-55) in adult female C57/BL6 mice to explore these issues. The mice develop a progressive increase in clinical score (based on distal paralysis) and pathological features in lumbosacral spinal cord (inflammation, demyelination, axonal loss) which begin at day 8 after induction and peak at day 21. The density of blood vessels did not increase at day 7 or day 14 from disease onset, but increased by 160% over the control ($P<0.001$) at day 21. Increases were confined to grey matter, with no increase in white matter. Vessel density correlated with clinical score ($r^2=0.94$) and pathological score ($r^2=0.91$). We performed immunohisto-chemistry to detect changes in expression of key regulators. Vascular endothelial growth factor (VEGF) was expressed in the cell body of dorsal root ganglion cells and also in axons within the dorsal columns, and its expression increased significantly ($P<0.05$) at day 14 and began to decrease markedly ($P<0.05$) in 3/5 mice at day 21. VEGF receptor 2 levels were constant. Angiopoietin-(Ang)1 was also constantly expressed by both neurons and glia, as well as infiltrating neutrophils. Ang-2 expression increased at day 14 in neurons and glia and showed widespread expression by inflammatory cells at day 21. Levels of the Tie receptors Tie-1 and Tie-2 were constant throughout. We also detected increases in BBB permeability at day 7, peaking at day 14 (maximum ca 80 X 10-6 ml/s/g) and then declining significantly at day 21. Changes were noted in both grey and white matter. In contrast to vessel density, there was no correlation between BBB permeability and clinical score, pathological score or vessel density ($r^2<10$). These data provide insights into the regulation of angiogenesis and its relationship to BBB permeability in an animal model of multiple sclerosis.

14. CNS Rosai-Dorfman disease and multiple sclerosis

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Rosai-Dorfman disease involving the central nervous system (CNS) is rare. Of those cases that involve the CNS, the majority presents with focal, dural-based hemispheric brain lesions mimicking meningioma. We describe the case of a 63-year-old woman, who suffered a 10-month history of progressive diarrhea, anasarca, vertigo, gait ataxia, and right thalamic stroke. MRI of the brain revealed extensive T2/FLAIR hyperintense lesions in the periventricular white matter, as well as diffuse dural thickening and gadolinium enhancement. An autopsy revealed widespread dural infiltration by inflammatory cells, principally large, epithelioid histiocytes, many of which exhibited emperipolesis, the characteristic finding in Rosai-Dorfman disease. The same process invaded the right vertebral arterial wall, causing dissection. In addition, we found demyelinating plaques (with preservation of axons), located in the corpus callosum, periventricular white matter, and multiple brainstem segments. These were consistent with a diagnosis of unrecognized multiple sclerosis. This case represents the first report of intracranial vascular dissection complicating CNS Rosai-Dorfman disease. Our case is the second report of diffuse dural histiocytic infiltration, mimicking idiopathic hypertrophic pachymeningitis. Finally, the co-existence of CNS Rosai-Dorfman disease and multiple sclerosis has never been described; one could speculate that the two disorders may have been triggered by the same underlying dysimmune state.

15. Anti-angiogenic effects of a red wine polyphenol, resveratrol, on an in vitro cerebral angiogenesis model

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Angiogenesis plays a role in many pathological processes of the CNS. Resveratrol, a natural polyphenol compound found in several plants (abundant in red grapes/wine), has been increasingly recognized for its anti-inflammatory and anti-angiogenic properties. However, the effect of resveratrol on human brain endothelial cells and cerebral angiogenesis is

unclear. The impact of resveratrol on cerebral angiogenesis was modeled in vitro with the human brain endothelial cell line hCMEC/D3, and also tested on two primary endothelial cell cultures, HUVEC (human) and BBMEC (bovine brain). Three critical steps of angiogenesis, including cell proliferation, migration, and tube formation, were investigated. In all cell models tested, resveratrol induced a dose-dependent suppression of cell proliferation and a reduction of cell numbers after 24 hours of treatment. Endothelial migration and tubule formation was inhibited by resveratrol treatments in a dose-dependent manner as assessed by two image-based assays, a scratch wound healing assay and an *in vitro* Matrigel matrix assay. Results from the LDH-cytotoxicity assays suggest that only cell models treated with a high dosage (100uM) of resveratrol exhibited some degree of cytotoxicity. To elucidate the possible modulation of signaling pathways (Akt, NF-kB, and MAPK) by resveratrol, western blot analyses are currently being conducted. We present evidence that cerebral angiogenesis may be inhibited by resveratrol. However, to use resveratrol as a potential anti-angiogenic agent, dosage may be critical.

16. Extramedullary hematopoiesis involving the CNS and surrounding structures

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Extramedullary hematopoiesis (EMH) in CNS is a rare condition that can present in association with hematologic conditions (e.g. idiopathic myelofibrosis, thalassemia, bone marrow transplantation, etc.). Some EMH/CNS cases can be incidental findings, while others cause symptomatic mass effect. We present 9 cases of EMH involving the CNS or meninges. Three individuals (2 with polycythemia vera and 1 with inflammatory pseudotumor) presented with symptomatic cranial dura-based (age 67 and 68 years) or spinal canal tumors (age 78 years). The others were incidental autopsy findings, usually microscopic collections of cells in the meninges of infants (4 cases, age 10 days to 5 months), in 1 young child (6.5 years with marked anemia) and 1 adult (81 years with idiopathic myelofibrosis). Characteristic morphology and appropriate immunohistochemistry assessed by an experienced hemato-pathologist was the method for diagnosis. The precise pathogenesis of EMH in CNS is unknown. In the early pediatric population, meningeal EMH is unlikely to be pathological and most likely represents a resolving fetal state. The late pediatric population and adults with incidental EMH usually have an underlying hematologic condition. After infancy, the presence of EMH should cause the clinician or autopsy pathologist to search for an underlying hematologic condition.

17. History of Neuropathology in Canada (1870-c1970)

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We describe the evolution of neuropathology in Canada, beginning with William Osler who began working in Montréal in 1874 and finishing with the major period of expansion in the 1970s. Organized services began in the 1930s, in Montréal with the neurosurgeons Wilder Penfield and William Cone, and in Toronto with Eric Linell and Mary Tom, who both began their careers as neuroanatomists. Jerzy Olszewski and Gordon Mathieson, who trained in Montréal and Toronto in the 1950s, drove the creation of the Canadian Association of Neuro-pathologists in 1960. This historical analysis highlights the evidence that the roots of neuropathology include the clinical neurosciences and laboratory medicine, and that neuropathology is not simply a derivative of surgical pathology. This was recognized long ago and was the incentive to create a specialty training program under the auspices of the Royal College of Physicians and Surgeons of Canada, which was formalized in 1965. The first certifying examination was in 1968 with the subsequent recognition of structured training programs. The number of neuropathologists in Canada increased rapidly through the 1960s and 1970s, with individuals coming from both clinical neuroscience and anatomic pathology backgrounds, a pattern that persists to the present day.

18. Cellular solitary fibrous tumor (hemangiopericytoma) with anaplasia at cerebellopontine angle (CPA), a case report

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Cellular solitary fibrous tumor is currently considered synonymous with hemangiopericytoma, as it became increasingly clear that the morphological and immuno-histochemical features that separate the two entities have become tenuous, and evidence for a unifying concept emerged. Furthermore, as no evidence of pericytic differentiation is seen in most cases of hemangio-pericytoma, this diagnostic term is waning in popularity.

We present here a case of cellular solitary fibrous tumor in a 22-year-old male who on neuroimaging revealed a right cerebellopontine angle tumor, upon work up for headaches.

Most of the tumor was cellular though some less cellular areas were seen. Sinusoidally dilated large vessels including staghorn type were seen. Nuclear pleomorphism and increased mitotic activity (5/10 HPF) were seen as evidence of anaplasia. Diffuse CD34 immunoreactivity and focal positivity for Factor XIIIa were seen in the tumor which was negative for EMA and S100. The tumor displayed a rich reticulin network.

Solitary fibrous tumor at the cerebellopontine angle is rare and nine such cases (3 reported as hemangiopericytoma) were found on literature search.

19. Diffusion weighted imaging in pediatric medulloblastomas: An unreliable radiologic feature possibly related to reticulin deposition

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Introduction: Medulloblastomas typically present as solid contrast enhancing masses on Magnetic Resonance Imaging (MRI). Some investigators have suggested that medulloblastomas can be distinguished from other cerebellar neoplasms via demonstration of "restricted diffusion" on the Apparent Diffusion Coefficient (ADC) map obtained from Diffusion Weighted MRI (DWI) sequences. Restricted diffusion has been postulated to be a reflection of very high cell density.

Methods: The DWI characteristics of pathologically confirmed medulloblastomas diagnosed at our institution were retrospectively reviewed. Transverse diffusion imaging was performed on a 1.5 T Magnetom Avanto MRI using a single shot sequence with subsequent generation of the ADC map. A solid, non-hemorrhagic and non-necrotic region of tumor was assessed twice and an average ADC value was obtained. ADCs below 1000 (x 10^{-3} mm^2/s) were considered to represent restricted diffusion. A detailed pathologic review of each tumor was conducted.

Results: Ten cases of medulloblastoma were reviewed, of which 2 demonstrated an average ADC above 1000 (1223 and 1169 respectively), indicating a lack of restricted diffusion. Pathologic review revealed that both of these non-restricting cases exhibited a lack of histologic reticulin.

Conclusion: DWI does not appear to be a reliable means of distinguishing medulloblastomas from other cerebellar neoplasms. Microscopically, restricted diffusion in medulloblastomas may be related to reticulin deposition.

20. Extraventricular anaplastic ependymoma with metastasis to scalp and neck

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We report a case of anaplastic ependymoma with extracranial metastases in a 22-year-old female. The patient originally presented with headaches and dysarthria. Neuroimaging revealed a large solid and cystic right frontotemporal lesion. It was located completely extraventricularly and a glioblastoma was suspected based on the neuroimaging findings. A gross total resection was achieved. Histopathologic examination revealed an anaplastic ependymoma. The patient was treated with radiotherapy. Approximately one year after the initial surgery, the patient presented with metastatic disease to the scalp. Approximately 2 years after the initial surgery, an intraparotid metastasis was detected. A subsequent neck dissection revealed positive lymph nodes at several levels. It was followed by radiotherapy to the neck. At nearly 4 years after the initial surgery now, the patient has residual metastatic disease and dissemination to the vertebral column.

21. Mitotic counts and the accuracy of tumour grading

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While important for grading, the methodology for counting mitoses has not been standardized. Accurately grading an individual tumour is fundamentally different from the methodology used to derive statistically significant mitotic thresholds in large population studies. Assuming mitoses occur at random imposes mathematical limitations on the confidence of mitotic counts. Using this assumption, this paper examines three questions:

1. Given an actual tumour mitotic index and assuming mitotic frequencies follow a Poisson distribution, what is the probability that a measured mitotic count is in error (defined as a pathologist's count that undergrades a higher-grade tumour or overgrades a lower-grade tumour)?

2. Given a pathologist-measured mitotic count and again assuming a Poisson distribution, what are the confidence windows on the actual tumour mitotic index?

3. Given a measured mitotic count and a known grading mitotic threshold, again assuming mitoses follow a Poisson distribution and using the gamma function for the calculation, what is the probability that an error has occurred in grading? (What is the probability that the measured count is above the threshold when the real tumour index is below the threshold? What is the probability that the count is below the threshold when the real tumour average lies above the threshold?

Grading accuracy, especially near a threshold mitotic count, requires either counting of numerous fields to reduce stochastic noise, use of markers that provide greater sensitivity to proliferation, or modification of grading criteria to include more tumour characteristics than mitotic counts alone.

22. Fatal cerebral infarctions in a 24-year old man secondary to systemic granulomatous vasculitis

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Cerebral infarction secondary to granulomatous vasculitis involving the central nervous system is extremely rare in the young. We report the case of intracranial giant cell arteritis causing catastrophic cerebral infarctions in a previously healthy 24-year-old man who collapsed following a 10-day history headache.

CT angiography showed multiple filling defects involving both middle cerebral arteries, left ACA and left PCA; and CT perfusion revealed infarcts in multiple arterial territories. Recanalization failed and the patient died of multiple cerebral infarctions. Blood and CSF cultures and serologies disclosed no obvious infection. Autoimmune and hypercoagulability workups were negative.

Histological examination showed a giant cell arteritis causing occlusive thrombosis that involved segments of the cerebral arteries just distal to the circle of Willis. The arteritis was circumferential, displayed fragmentation of the elastica by

invading giant cells with CD4 and CD8-positive lymphocytes in the adventitia. Vessel diameter ranged from 2 to 3.5 mm and all lesions were of the same age with scanty necrosis. Carotid siphons and one renal artery were focally affected. Stains for fungi, bacteria and β-amyloid were negative as was ISH for varicella-zoster virus. The dura exhibited patchy areas of chronic inflammation.

Findings represent a unique case of disseminated giant cell arteritis with preferential involvement of intracranial arteries in a young male. The differential diagnosis includes an unusual manifestation of temporal arteritis.

23. A comparative autopsy study of vasculopathy in CADASIL and in subcortical arteriosclerotic leukoencephalopathy (SAL)

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Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is not associated with hypertension, but shares certain neuropathologic features with cases of subcortical arteriosclerotic leukoencephalopathy (SAL), which is associated with hypertension. SAL has also been called "ischemic white matter degeneration" or "Binswanger's disease." We compared two autopsied cases having clinical and pathologic features of CADASIL with an autopsied case of SAL. The two cases of CADASIL, males 61 (Case 1, C1) and 68 years (C2) of age at death, were not related but C2 had a similarly affected brother. C1 and C2 both had dementia but not hypertension. Subcortical pathology characteristic of CADASIL was found in each of the two: infarcts and multifocal leukoencephalopathy with small sclerotic intralesional vessels. The pathologic feature that distinguished these two cases most clearly from a case of SAL (C3), which had grossly and microscopically similar subcortical lesions, was disintegration of the media in leptomeningeal arteries of the CADASIL cases, which was not found in C3. Degeneration of vascular smooth muscle in CADASIL is well recognized and in accord with localization of the Notch3 gene product. The findings in these two autopsies emphasize the value of this degeneration in leptomeningeal arteries of CADASIL in making the distinction from SAL.

24. A case of familial syringomyelia

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This is a case of an 80-year-old woman of Japanese descent who presented at age of 46 with urinary bladder instability, bilateral leg drop and intermittent motor weakness in her right arm. Physical examination revealed sensory loss at level T10. The magnetic resonance imaging of the spinal cord revealed cervical stenosis, atrophy of cervical cord and a large syrinx extending from C7 to the conus. The patient was diagnosed with syringomyelia secondary to arachnoiditis and within two years, she became paraplegic and ambulating in a wheelchair. In late 2004, the patient underwent C3-C5 laminectomy, posterior decompression and segmental fusion after progressive decline in her upper limbs function due to disk herniation. In 2009, the patient died at age of 80 due to complications of acute bacterial pneumonia and stroke. Post mortem examination showed significant thinning of the cervical and thoracic spinal cord with dural fibrosis and spinal cavernous hemangioma

Interestingly, the patient's brother had also been diagnosed with syringomyelia secondary to arachnoiditis at age of 56 and died at age of 74. Autopsy examination also revealed a spinal cavernous hemangioma and an extensive syringomyelia.

25. Unusual case of extracranial vertebral artery thrombosis

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Extracranial vertebral artery after blunt cervical trauma has been considered to be uncommon. Most patients remain asymptomatic with sudden unexpected deterioration taking place hours to days after the insult. Distraction/extension, distraction/flexion, and lateral flexion injuries are the major mechanisms of injury. Dissection and occlusion are the frequent vascular injury patterns. We report a case of previously healthy 12-year-old boy who sustained a mild impact to the right ear region. Over a 4 months period he had vague history of slightly unsteady gait, slurring of speech and some decrease in school performance. He had a sudden decrease in level of consciousness and brain imaging showed multiple foci of thrombo-embolic brain infarction. Imaging also showed occlusion of the right extracranial vertebral artery and acute thrombus in the upper basilar artery. He died 5 days after the acute presentation despite anticoagulation. Autopsy showed a small defect in the right vertebral artery wall at the 2nd cervical level and thrombus of at least two ages. It appears that the initial thrombotic narrowing became a site of secondary thrombosis from which emboli were released into the basilar artery. Such consequences in this age group are extremely rare. Traumatic injuries of the vertebral artery often resolve spontaneously and seldom result in serious neurological sequelae unless embolic propagation occurs.

26. Hypertonic muscular dystrophy: recent cases and review

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Two infants aged 2 and 2.5 months respectively presented with respiratory distress and muscular rigidity. Their antenatal and postnatal histories were otherwise unremarkable. Apart from marked muscular hypertonia their neurological examinations were normal. Serum CPK levels were elevated. CT, MRI and nerve conduction studies were unremarkable.

Skeletal muscle biopsies were obtained to reveal nonspecific myopathic findings and irregular sarcoplasmic aggregates of

granular material that were reddish-purple on modified Gomori trichrome stains and dense blue on toluidine blue stains. The aggregates corresponded to collections of granular, electron-dense material in the vicinity of z-bands of affected sarcomeres.

This rare muscular disorder leads to progressive generalized hypertonia and eventual respiratory failure. Inheritance is autosomal recessive with onset in early infancy and an average life expectancy of less than one year according to the largest published case series (Lacson et al, CJNS, 1994;21:203-212). The present cases are typical of the clinical and pathological features.

27. Isolated paraspinal myopathy with novel shard-like compact aggregates of thin filaments

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An 83-year-old woman presented with a six week history of constant aching posterior neck pain, "neck heaviness", and severe pain in her left shoulder. On examination she had isolated weakness of her neck extensors. MRI of the cervical spine showed no significant spinal or foraminal stenosis and electrophysiological studies were consistent with an active myopathic process isolated to the neck extensor muscles. A diagnosis of dropped head syndrome was made and the differential diagnosis was isolated neck extensor myopathy versus polymyositis, while the most common causes of head drop, myasthenia gravis and motor neuron disease, were essentially ruled out. A paraspinal muscle biopsy showed myopathic features reminiscent of inclusion body myositis, including congophilic sarcoplasmic inclusions. Ultrastructural examination failed to demonstrate the pathognomonic intra-nuclear filamentous inclusions associated with inclusion body myositis, but rather revealed novel sarcoplasmic inclusions which were elliptical and composed of compacted thin four nanometer diameter filamentous structures with periodicity. No reports on normal or diseased paraspinal muscles to date have described inclusions resembling those seen in the present case. In recognition of the paucity of investigation into this uncommonly biopsied muscle, it remains possible that these inclusions are a normal, possibly age related component of the paraspinal musculature; however we favor that this case represents a hitherto undescribed form of isolated paraspinal myopathy.

28. Usefulness of superficial peroneal nerve/peroneus brevis muscle biopsy in diagnosis of vasculitic neuropathy

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Objectives: 1. To determine the sensitivity, specificity and diagnostic yield of superficial peroneal nerve (SPN)/peroneus brevis (PBM) biopsy in 43 patients with clinically suspected vasculitic neuropathy. 2. To analyze pathological features which attain statistical significance as markers of vasculitis. *Methods:* The clinical, laboratory and pathologic data for all patients undergoing SPN/PBM biopsy from 1999-2008 was analyzed. Biopsies were classified histopathologically as "definite" if they had necrotizing vasculitis or microvasculitis and "suspicious" or "possible" in accordance with previously established criteria. Patients were divided into vasculitis and non-vasculitis cohorts based on clinico-pathologic criteria. We have favored SPN/PBM biopsy in patients in whom we suspected vasculitis. *Result:* Of the 43 people who underwent SPN/PBM biopsy, vasculitis was detected in twenty-seven cases [21-non systemic vasculitic neuropathy (NSVN), 6 – systemic vasculitis (SVN)]. Thirteen patients (48.1%) had definitive evidence of vasculitis in the biopsy (2 - necrotizing vasculitis, 11- microvasculitis). The overall diagnostic yield of SPN biopsy in definite vasculitis category was 76.9% (10/13) and 53.8% (7/13) for PB biopsy. The addition of muscle biopsy enhanced the diagnostic yield by 23%. Employing definitive criteria for diagnosis, sensitivity of SPN/PBM biopsy was 76.4% with 100% specificity. By including cases suspicious or definitive for vasculitis, sensitivity increased to 85.1% but specificity dropped to 87.5%. Asymmetric nerve fiber loss (odds ratio 9.16 95%CI 1.49- 56.29, p = 0.01), wallerian degeneration (odds ratio 8.16 CI 1.29-51.4, p=0.02) and Perl's stain for hemosiderin (odds ratio 4.95 CI 1.01-24.09 p=0.04) had statistical significance as markers of 'suspicious' vasculitis. *Conclusion:* Combined superficial peroneal nerve/peroneus brevis biopsy offers better diagnostic yield, with aid of supportive features of vascular damage in diagnosis of vasculitic neuropathy.

29. Radial columnar cortical architecture: maturational arrest or cortical dysplasia?

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The fetal cerebral cortical plate at mid-gestation and earlier exhibits radial columnar architecture rather than histological layering. Lamination is superimposed later in gestation, but traces of the residual columnar pattern may persist at the crowns of gyri and in the depths of sulci. In neonatal and mature brains, prominence of columnar architecture is abnormal. Standard classifications of focal cortical dysplasias in epileptic patients do not include this as one of several described patterns. Neuropathological examination was performed in 38 resections of epileptogenic neocortex in children and 10 postmortem cases of chromosomal disorders, the rim of porencephalic cysts and genetic malformations. Radial columnar architecture was a component of 24 focal cortical dysplasias. Inhibitory interneurons by tangential migration were abnormally distributed. An infant with DiGeorge syndrome exhibited columnar architecture in all cortical regions. In hemimegalencephaly the pattern in the dysplastic enlarged hemisphere also was noted in contralateral "normal" cortex. In polymicrogyria, pachygyria, schizencephaly, the polymicrogyric margins of porencephaly, and dysplastic cortex adjacent to DNETs, columnar architecture was mixed with other patterns of dysgenesis. Synaptophysin demonstrated a laminar synaptic

pattern, but maturation was delayed. Columnar neocortical architecture may persist as a maturational arrest in development and is frequent in focal dysplasias. We propose that it be classified as another distinct form of cortical dysplasia and, furthermore, that it be categorized with other neuroblast migratory disorders associated with abnormal architecture of the cortical plate, as in lissencephalies.

30. Vascular changes in patients with multiple resections for Rasmussen's encephalitis

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From 2008-2010, 4 patients underwent revisions of previous resections which had originally been diagnosed as showing changes of Rasmussen's encephalitis (RE). In 3 of these cases we observed marked atherosclerotic changes in leptomeningeal vessels. These changes principally manifested as moderate to moderately severe intimal hyperplasia and were limited to large leptomeningeal arteries. The intervals between original resection and revision for the cases with atheromatous changes were 13 months (2/2009 - 3/2010), 24 months (6/2008 - 6/2010), and 10 years (6/1998 - 6/2008). The ages of the patients at primary resection ranged from 9-12 and was 12-19 years at the time of revision. Four cases from 2006 - 2010, with a single surgical resection diagnosed as consistent with RE (age range 5-21 years), as well as 2 surgical revisions for severe cortical dysplasia, one for mild cortical dysplasia and one for recurrent dysembryoplastic neuroepithelial tumor did not show significant vascular changes (ages 4 months - 9 years at primary and 4-18 years at revision; interval of 10 months - 16 years). This observation may suggest that leptomeningeal atheromatous disease may be a potential complication in children undergoing surgical resection for Rasmussen's encephalitis, and may contribute to the neuropathologic features of the lesion. (Harry V. Vinters supported by the Daljit S and Elaine Sarkaria Chair in Diagnostic Medicine).

31. Third trimester stillbirths: Correlative neuropathology and placental pathology

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Placental pathology has recently been the subject of detailed descriptions and diagnostic categorization, but systematic correlation with the neuropathology of stillbirth has not been attempted. We examine the relationship of specific inflammatory, maternal and fetal vascular pathologies in the placenta with indicators of fetal compromise in the central nervous system (CNS), in 37 third trimester intrauterine fetal deaths without fetal structural or chromosomal abnormalities. Mixed placental pathologies were the rule: 3/4 of the placentas demonstrated combinations of maternal vascular, fetal vascular, umbilical cord or inflammatory pathologies. The usual brain pathology was acute, severe congestion, white matter edema and neuronal karyorrhexis. Periventricular leukomalacia was present in 2 cases. Neuronal karyorrhexis or gliosis correlated with the presence of a high grade inflammatory lesion and with fetal thymic involution. Neuronal karyorrhexis, but not gliosis correlated with histologically established fetal vascular lesions in the placenta even once the effect of inflammation was accounted for. Gliosis correlated with inflammation, meconium staining, and thymic involution. We conclude that CNS injury may be the end result of complex placental pathologies, and neuronal injury may be a consequence of the fetal inflammatory response. The correspondence between the time courses of histological features of chorioamnionitis, neuronal karyorrhexis and thymic involution point to irreversible CNS injury being common 12-48 hours prior to demise.

32. Dorsal spinal column crush in the LES rat; a surgeon's angle on neuroregeneration

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Animal models of spinal cord injury often involve adult, normally myelinated rodents that are not suitable for studying cellular mechanisms of CNS regeneration for two main reasons; (1) damage to myelin induces severe and sustained phagocytic response effectively precluding required morphologic studies of the injury area, and any cellular implants are destroyed; (2) myelin inhibits axonal regeneration.

We used an adult myelin-lacking rat, the Long Evans Shaker (LES) where axonal regeneration and other cellular events participating in formation of new white matter tissue can be studied. Injury in the spinal cord was performed for its easy accessibility and morphologic analysis. In the dorsal column crush, the dorsal spinal cord is accessible via a window created by laminectomy. While most or all axons in the dorsal column are transected, the surgery does not result in paralysis of urinary bladder or in major motor deficits. The LES rats tolerate the surgery well and can be maintained in good health for several months post-op.

Choroid plexus cells (CPlx) are harvested from euthanized, normal donor rats during the surgery for immediate implantation in LES rats. Although CPlx are very effective in supporting axonal regeneration and in creating new white matter tissue at the current, experimental stage, we do not anticipate their use as viable strategy for human applications. Studies are already under way to test stem cells from non-CNS tissues for supporting axonal regeneration and neuroregeneration in our crush model. This will be followed by testing of human cells.

33. Animal model of CNS regeneration

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In adult dysmyelinated Long Evans Shaker (LES) rats (see Abstract 21), we used the dorsal spinal column crush as a model of CNS injury and implanted the acute lesion with green fluorescent protein (GFP) rat choroid plexus cells (CPlx).

Regeneration of ascending axons in the fasciculi cuneatus and gracilis across the injury site was visualized with dextran 3,000 TexasRed™ (Invitrogen) injected into both sciatic nerves. A 3-14 days post-op the animals were overdosed, perfused and longitudinal sections of the spinal cord including the site of the crush injury and the caudal brain stem, 7 cm rostral, were cut and examined under a confocal microscope for green (GFP cells) and red (TexasRed axons) fluorescence. For the light and electron microscopy, LES rats with the crush injury were implanted with rat CPlx and the site of injury examined 3 days to 8 weeks post-op. While crush injury in the myelinated, LE-control rat spinal cord caused severe, sustained, expanding macrophage-rich inflammatory response, in the LES rats it caused transient infiltration of the crush cavity by macrophages that cleared by day 7 post-op and resulted in a fluid-filled cavity surrounded by the spinal cord tissue with scattered erythrocyte-laden macrophages. At the interface of the fluid cavity and the surrounding tissue there was a discontinuous, 200 μm thick layer of edema widely separating small clusters of large, fusiform cells often forming rich microvilli and each encasing multiple axons. Such cells were interpreted as immature ependymal cells derived from implanted CPlx, that persisted in the zone of neuroregeneration for 4 weeks and were not found at 8 weeks post-op. Instead, the zone of axonal regeneration, with less but still considerable edema, was populated by astrocytes, Schwann cells and scattered oligodendrocytes, some forming well compacted myelin sheaths. Numerous swollen axonal endings were observed caudal to the crush lesion on light and electron microscopy indicating that not all axons crossed the crush lesion. On confocal microscopy in GFP-CPlx implanted spinal cords of LES rats there was abundant and long distance axonal regeneration across the lesion site and into the dorsal column proximal to the lesion. Numerous axons formed large, onion bulb-like swollen endings abutting the caudal margin of the lesion indicating that large proportion of axons did not cross the lesion. Here, we introduce an adult animal model of white matter regeneration with integration of a proportion of implanted cells and abundant and long distance axonal regeneration.

Titles Of Diagnostic Case Presentations

1. Complex dysembryoplastic neuroepithelial tumour

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2. Tumour-tumour metastasis (carcinoma to meningioma)

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3. Malakoplakia

Z. Al-Hajri, S. Krawitz

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4. Late-onset Friedreich's Ataxia

A.H. Koeppen, J.A. Morral

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5. Cribriform Neuroepithelial Tumour

N. Basahel, C. Hawkins, W. Halliday

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6. Atypical Teratoid/Malignant Rhabdoid Tumour

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7. Medullomyoblastoma

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8. Pleomorphic xanthoastrocytoma/glioblastoma

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9. Microangiopathy and white matter lesions

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10. Myofibrillar myopathy with filamen C mutation

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11. Contronuclear myopathy

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