Canadian Association of Neuropathologists Abstracts of papers and cases presented at the 39th Annual Meeting

October 13 - 16th, 1999
Québec City, Québec

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The 39th annual meeting of the Canadian Association of Neuropathologists was held from October 13 - 16th, 1999 at the Quebec Hilton Hotel in Quebec City. Local arrangements were made by Dr. Peter Gould.

The scientific session consisted of 14 platform presentations and 13 cases for diagnosis. The Royal College of Physicians and Surgeons of Canada speaker was Dr. Valerie Askanas, M.D. Ph.D., Professor of Neurology and Pathology, University of Southern California School of Medicine and Hospital of the Good Samaritan, Los Angeles. Her talk was entitled "Inclusion Body Myositis: Current Concepts of Pathogenesis in Relation to Aging, Oxidative Stress and Alzheimer's Disease". The Jerzy Olszewski lecturer was Dr. André Parent, Ph.D, FRSC, Professeur, Département d'Anatomie et Physiologie, Université Laval. His talk was entitled "The Basal Ganglia and Neurodegenerative Diseases".

PLATFORM PRESENTATIONS

1.

Parvovirus B19 myositis as a cause of arthrogryposis multiplex congenita.

J. MICHAUD, M. BLAYNEY, J. ALLANSON and F. DIAZ-MITOMA (Children's Hospital of Eastern Ontario, Ottawa, ON)

The post-mortem investigation of arthrogryposis multiplex congenita remains a challenge. We report the case of a 2.1 kg female infant born at 36 week gestation. The pregnancy was closely followed because amniotic bands were seen at 15 weeks, without entrapment. Arthrogryposis multiplex congenita was noted at birth along with a small for gestational weight, dolichocephaly and severe hypotonia. There was no evidence of constriction rings. The creatine kinase was at 1892 units and the lactate dehydrogenase at 2447 units. She died at 69 hours of age. The autopsy revealed a myositis of variable severity. The changes varied from mild perivascular chronic inflammation to diffuse involvement with muscle fiber degeneration and loss. No infectious organisms or viral inclusions were found. Non-specific central nervous system changes with neuronal loss and gliosis were also seen. A review of the maternal history revealed exposure to parvovirus at 17-18 week gestation without maternal clinical manifestations. PCR testing was then performed on liver and muscle and was found positive only in the muscle for parvovirus B19.The usual fetal parvovirus B19 manifestations are hydrops fetalis, fetal anemia and, at autopsy, hepatitis. It is also known that skeletal and cardiac muscle cells may harbor the virus, which sometimes causes a true myositis. This case appears to be the first reported case of intrauterine myositis and secondary arthrogryposis multiplex congenita associated with a parvovirus infection.

2.

A comparative study of the neurofibrillary tangle pathology in the posterior cingulate gyrus versus the anterior cingulate gyrus in Alzheimer's disease.

M. KAHIL, M. SAPP, B. YOUNG, H. BEGLEY and L. ANG (Sunnybrook & Women's College Health Science Center, University of Toronto, ON)

Fifteen autopsy cases diagnosed with Alzheimer's disease (AD) using CERAD criteria and three control cases were studied. The aim of the study was to compare the neurofibrillary tangle density in the posterior cingulate gyrus and the anterior cingulate gyrus in AD patients. The cerebral hemispheres were sectioned coronally from anterior to posterior and two blocks were taken from each of the most anterior 1 cm and most posterior 1 cm of the cingulate gyri. The blocks were fixed in formalin, embedded in paraffin, sectioned at 6 μm thickness and immunostained with tau antibody (Dako, dilution 1/300) using the avidin biotin method. The prevalence of neurofibrillary tangles was assessed with the light microscope at magnification of x100. The neurofibrillary tangle prevalence was significantly higher ($p<0.03$: Student's 1-tailed t-test) in the posterior cingulate gyrus (mean 40.14/sq mm ± 4.11 SEM) as compared to the anterior cingulate gyrus (27.48 ± 4.11 SEM). This study

provides neuropathological support for the metabolic and radiological studies suggesting that the posterior cingulate gyrus is more severely involved than the anterior cingulate gyrus in AD.

3.

Morphologic evidence for oligodendroglial proliferation in the CNS of adult Long Evans Shaker (LES) rats.

J.M. KWIECIEN, A.L. FLETCH and K.H. DELANEY (Central Animal Facility, McMaster University, Hamilton, ON)

The LES rat is a severely dysmyelinated mutant of myelin basic protein (MBP) gene with a lifespan (>16 months) similar to that of a normal laboratory rat. Histological and ultrastructural examination of the optic nerve and spinal cord of LES rats 1-40 weeks old revealed abnormally high numbers of glial cells in the white matter. For example, there were 2-3 times more glial cells in the optic nerve of adult LES rats (>8 weeks of age) than in age matched Long Evans (LE) rat controls. Autoradiography of both regions of the CNS indicated proliferation activity in glial cells after the age of 16 weeks. Ultrastructural examination revealed numerous immature and young oligodendrocytes with futile attempts to myelinate naked intact axons. Also, nests of immature oligodendroglial cells are commonly observed in adult LES rats, further supporting the notion of oligodendroglial proliferation in the CNS of this exceptionally long-lived dysmyelinated animal.

Supported by Multiple Sclerosis Society of Canada.

4.

Patterns of EAAT2 immunoreactivity in the human hippocampus and neocortex.

P.V. GOULD and R. DESBIENS (CHA pavillon Enfant-Jésus, Québec, PQ)

The glial glutamate transporter EAAT2 (GLT-1) is found throughout the neocortex and hippocampal grey matter, where it is thought to protect against excitotoxicity by removing excess glutamate from the extracellular space. Disruption of the EAAT2 gene leads to lethal spontaneous seizures in mice, but studies of human epileptic hippocampi thus far fail to show significant changes in EAAT2 immunoreactivity in the absence of neuronal loss. Analysis of 20 surgical resections performed in this hospital for temporal lobe epilepsy between 1997 and 1999 largely confirmed these previously reported findings. In contrast, a more variable pattern of immunoreactivity was found in control autopsy sections, including cortical mosaicism and prominence of individual protoplasmic astrocytes. Immunostaining of adjoining sections for GFAP revealed that foci of strongly EAAT2-immunoreactive astrocytes corresponded to foci of GFAP-immunoreactive cortical astrocytes. Foci of subcortical GFAP-immunoreactivity did not reveal significant EAAT2-immunoreactivity. We conclude that cortical and hippocampal grey matter astrocytes can modulate EAAT2-immunoreactivity in reaction to external stimuli, even if such changes are not evident in chronic temporal lobe epilepsy.

5.

Cerebral myxopapillary ependymoma.

E.S. JOHNSON and D.E. STEINKE (University of Alberta, Edmonton, AB)

Documented in this report is the rare occurrence in the cerebrum of an ependymoma having a myxopapillary pattern of growth. In a 31-year-old man, who presented with headaches and an upper quadrantanopsia, CT and MRI studies disclosed within the right parieto-occipital region a 7 x 4 x 4 cm cyst that was focally enhanced along its medial posterior wall and compressed the ventricular trigone. At surgery the cyst was found to contain a nodular mass, which upon biopsy was an ependymoma wherein the neoplastic neuroglial cells were aligned along arborizing, stout, hyalinized vascular pedicles. Pools of Alcian blue staining mucoid material were deposited in extracellular spaces and the vascular stroma. Consistent with an ependymal derivation, immuno-histochemistry showed strong expression for GFAP and absent reactivity for synaptophysin, epithelial membrane antigen, and cytokeratin. Electron microscopy confirmed the presence of microvilli, abundant 10 nm diameter filaments, and occasional gap junctions, but not cilia, centrioles or basal deposition of basement membrane. The clinicopathologic features of this tumor are similar to that of the three cases of cerebral myxopapillary ependymoma reported in the literature: proximity to the ventricles (three cases); location in the parieto-occipital region (two cases); association with a cyst (one case); and mucinous degeneration of hyalinized vascular pedicles (three cases). Absence of deposited basement membrane material need not exclude the diagnosis, as this finding was inconstant in the one case with electron microscopy.

6.

Nestin expression and anaplasia in dysembryoplastic neuroepithelial tumours.

N. DUGGAL, J. GIRVIN, L. CAI and R. HAMMOND (London Health Sciences Centre, (LHSC) and University of Western Ontario, London, ON)

The recognition of dysembryoplastic neuroepithelial tumours (DNT) as a distinct clinicopathological entity was first established by Daumas-Duport et al. in 1988. The biology of these lesions has been debated with increasing evidence in support of a neoplastic nature. Still, other authors point to undeniable developmental and hamartomatous features. We recently reported the first example of malignant transformation in a DNT. The unique case raised several questions about the neoplastic potential of these lesions. Do histological features determine the risk of malignant transformation? In the pre-DNT era, how many such lesions were "misdiagnosed" as gliomas and underwent malignant transformation?

The LHSC files from 1988 to 1998 contain 13 additional cases of DNT. The lesions were reviewed to confirm their diagnosis and to be subclassified as simple (4) or complex (9). Anaplastic features were tabulated and the lesions were also examined for MAP2, NF, nestin, GFAP, Ki67 and TUNEL positivity by two blinded observers (RH, ND). Complex DNTs harbour greater anaplastic features, Ki67 indices and nestin expression. The degree of anaplasia, Ki67 labeling and

expression of immature neuroepithelial markers is alarming in some cases and lends further support to the neoplastic nature and potential of these lesions. Of note, the lone malignant example was also of the complex form. These findings suggest that DNTs (particularly the complex form) deserve follow-up appropriate for any low grade glioma. As the collective experience with DNTs continues and patients are prospectively followed beyond 10 years, their potential for malignant degeneration will become better defined.

7.

Cerebral arteriopathy and protein C resistance.

J. R. BARRON and D. G. MUNOZ (University of Western Ontario, London, ON)

Activated protein C resistance is a hereditary coagulation disorder most commonly caused by a mutation in factor V. The resulting poor anticoagulant response is associated with familial venous thrombosis and stroke in young patients. We are reporting the case of a heterozygous carrier of a factor V mutation, who experienced multiple cerebral infarctions starting at age 37 years and who passed away at 60 years of age. Postmortem examination of his brain showed an arteriopathy characterized by deposition of basophilic loose granular material in the intima and media of small and medium sized arteries within the leptomeninges, white matter and to a lesser degree the grey matter of the cerebral hemispheres, brainstem and cerebellum. This process was largely restricted to the brain. There were no other risk factors for cerebrovascular disease and therefore we conclude that this unusual arteriopathic process is likely related to both this patient's coagulopathy and the development of cerebral infarction at an early age.

8.

Paired helical filaments (PHF): a new twist.

M. S. POLLANEN and C.BERGERON (Centre for Research in Neurodegenerative Disease and Department of Pathobiology and Laboratory Medicine, University of Toronto, Toronto, ON)

Since our atomic force microscopic images of PHF were published in 1994, the concept that PHF is best thought of as twisted ribbons has become more widely accepted. In the late 1990s the three generally agreed upon features of PHF are: (i) composition by two subfilaments; (ii) overall structure of a twisted ribbon; and (iii) the twist has a magnitude of about 80 nm. In this presentation, the evidence from our studies, and those of other investigators, is synthesized to provide a unified model of PHF structure. The model of PHF structure that emerges from this analysis is a twisted ribbon with a highly ordered (translationally) symmetric longitudinal profile. In addition, the ribbon is divided into parallel subfilaments that twist together around a central point with the same surface in contact along the filament length. This is in contrast to a competing model that suggests that PHF are composed of a random polymer aggregation. The latter proposal is paradoxical and suggests that the long-range twisted structure of the PHF is not formed by the regular alignment of its components. Our proposed model predicts that PHF are composed of a hierarchy of structural subunits that form oligomeric intermediate species in PHF assembly. Kinetic assembly studies, and ultrastructural computational modeling will ultimately be used to test prevailing models of PHF structure.

9.

Damage and repair of DNA in HIV encephalitis.

C. A .WILEY, C. L. ACHIM, R. HAMMOND, S. LOVE, E. MASLIAH, L. RADHAKRISHNAN, V. SANDERS and G. WANG (University of Pittsburgh Medical Center, PA; University of Western Ontario, ON; Frenchay Hospital, UK; University of California, San Diego, CA)

Clinical dementia and neuronal damage are common sequelae of HIV encephalitis. The mechanism by which HIV infection of CNS macrophages results in neuronal damage is unknown. We examined the brains from 16 AIDS autopsies for the presence of DNA strand breaks. Abundant DNA damage was observed with TUNEL labeling, however, there was no morphologic evidence of significant neuroglial apoptosis. DNA repair enzymes were present in neuronal and glial cells in autopsies with and without HIV encephalitis. No clear spatial relationship existed between expression of DNA repair enzymes and the presence of microglial nodules or HIV infected macrophages. There was no difference in DNA repair enzyme immunostaining in oligodendroglia from autopsies with and without encephalitis. Greater cortical neuronal amyloid precursor protein (APP) staining was observed in cases without HIV encephalitis, however, staining of deep gray matter neurons was similar irrespective of the presence or absence of encephalitis. While foci of intense APP staining was not related to HIV infection, it was associated with foci of opportunistic infections (e.g. CMV or PML). We conclude that damaged DNA and expression of reparative proteins are more common in the brains of AIDS autopsies, but they do not have a spatial relationship to HIV infected macrophages.

10.

Anti-inflammatory drugs and Alzheimer-type pathology in aging.

I.R.A. MACKENZIE and D.G. MUNOZ. (Vancouver General Hospital, Vancouver, BC and London Health Sciences Centre, London, ON)

Epidemiologic studies and the results of a single clinical trial indicate that anti-inflammatory drugs may be useful in treating Alzheimer's disease (AD). The association of immune proteins and immune-competent microglial cells with senile plaques (SP) suggests that these drugs may be able to modify the course of AD, either by interfering with SP formation or by suppressing the inflammation associated with SP. To investigate these possibilities, we have examined the Alzheimer-type pathology in post-mortem brain tissue from elderly non-demented individuals, exposed to various classes of anti-inflammatory drugs. We have previously reported that patients with a history of chronic nonsteroidal anti-inflammatory drug (NSAID) use showed a similar degree of SP and neurofibrillary tangle (NFT) pathology, compared with controls, but that NSAID use was associated with significantly less microglial activation; controls with SP had almost four times the number of activated microglia

as NSAID-treated patients (P<0.02). More recently, we have completed a similar analysis on the effect of glucocorticoid steroids. As with NSAIDs, chronic steroid exposure did not affect the degree of SP or NFT pathology. Unlike NSAIDs however, steroids caused *no* reduction in the number of activated microglial cells associated with SP. These results suggest that (i) anti-inflammatory drugs do not inhibit the formation of SP or NFT, and (ii) NSAIDs may be more effective than steroids in treating AD by virtue of their ability to suppress SP-associated microglial activation. [Supported by the Alzheimer Society of Canada.]

11.

Hippocampal abnormalities preceding hippocampal sclerosis in epileptic patients.

K. MEAGHER-VILLEMURE and J.-G. VILLEMURE (Centre Hospitalier Universitaire Vaudois, Lausanne, Suisse)

In temporal lobe seizures, the hippocampal formation is often the site of significant changes, especially to neuronal cells of the Sommer sector. The changes give rise to neuronal cell death in CA1, CA3 and CA4 of the hippocampal formation and are accompanied by a scarring process with subsequent astrogliosis. In some cases of seizure disorder, the hippocampal atrophy and sclerosis are the only neuropathological findings encountered. In other cases, a dual pathology process is found in the hippocampal region, which can explain the origin of the seizure disorder and may be held responsible for secondary damages in the whole structure of the hippocampus. These pathologies are of various natures: slow tumor growth, migrational defects, infectious or post-infectious state or a mixture of tumor growth on a migrational disorder background (DNET). There are few descriptions of abnormalities of the hippocampal formation other than hippocampal sclerosis giving rise to seizure activities. We are illustrating and discussing these various findings encountered within a pediatric population in which a primary lesion was found in the hippocampal formation. Fifteen cases were identified, the age varied from five months to 18 years with a median of four years old. We postulate that the primary hippocampal lesion and subsequent seizures are responsible for the appearance of a severe selective neuronal loss, atrophy and sclerosis which develops secondarily in this formation.

12.

Brain biopsy diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) in a French Canadian family.

A. MUSTAFA, D. ROWED, J. NORRIS and L. ANG (Sunnybrook and Women's College Health Science Centre, University of Toronto, ON)

This 55-year-old French Canadian man presented with a six year history of multiple transient ischaemic attacks that lasted 10 to 30 minutes and caused a speech disorder and right-sided numbness. During this time there was also a gradual deterioration in cognitive function leading to dementia . There was no history of vascular risk factors. His parents are first degree cousins. There is strong family history of early recurrent stroke and dementia. The electrocardiogram, echocardiography, carotid Doppler, cerebral angiogram, VDRL, TSH, vitamin B12 and coagulation factor screening were negative. MRI scan showed multiple bilateral patchy white matter ischemic lesions. The possibility of vasculitis was excluded by brain biopsy (including the leptomeninges and a wedge of the underlying brain parenchyma) in which, however, several vascular abnormalities were noted, including thickening of the blood vessel walls, replacement of the vascular smooth muscle by PAS positive granular material, and, by electron microscopy, thickening of the media with numerous elastin fragments, collagen and granular electron-dense extracellular material. These features are diagnostic of CADASIL and indicate the possibility of the occurrence of this disorder in families of French Canadian origin.

13.

mRNA cytokine and cytokine receptor profile in glioblastoma tumors and cell lines: Th1/Th2/Th3 cytokine dysregulation is not associated with altered p53 gene expression.

C. HAO, D. A. RAMSAY, J. W. ROA, H. CHEN, I. F. PARNEY, M. J. TURNER, and K. C. PETRUK (Department of Laboratory Medicine and Pathology, Oncology and Surgery, University of Alberta, Edmonton, AB; *Department of Pathology, University of Western Ontario, London, ON)*

Current immunotherapies have not enhanced survival for glioblastoma patients. We hypothesize that Th1, Th2 and Th3 cytokine dysregulation may abrogate anti-tumor responses at the tumor site and that such dysregulation may be associated with p53 tumor suppressor gene mutations. To test this, we used Multi-Probe RNase protection assay to examine cytokine and cytokine receptor expression in human glioblastoma tumors and cell lines. Included in this study were 12 glioblastoma tumors (6 wt p53 and 6 mt p53 as determined by immunohistochemistry) obtained from London Brain Tumor Tissue Bank and 6 well-established glioblastoma cell lines (2 wt p53 and 4 mt p53). In both primary tumors and cell lines, the cytokine and their corresponding receptor genes of a Th3 family (TGFb1, 2, 3) and a Th2 family (IL-6, LIF) were expressed. IL-4Ra and IL-13Ra receptor subunit genes were also identified potentially forming a functional receptor for IL-4 and IL-13. In contrast, only some Th1 cytokine receptor genes (TNFRp55, IFN-gRa, IFN-gR) were identified. All the tumors and cell lines shared similar Th1/Th2/Th3 phenotype independent of their p53 status. These results suggest that Th2/Th3 (anti-inflammatory) cytokines may play an important role in tumor immunosuppression and tumor progression through both autocrine and paracrine loops, and that Th1 (proinflammatory) cytokine receptors may also participate in tumor progression through paracrine loops. Therefore, understanding such unbalanced Th1 and Th2/Th3 regulation within the tumor is crucial in the development of more effective immunotherapeutic strategies in the war against glioblastomas.

14.

Intracranial hemorrhages in the child abuse-maltreatment syndrome: a retrospective study.

M. S. POLLANEN, C. R. SMITH and J. H. N. DECK (Forensic Pathology Unit, Office of the Chief Coroner for Ontario, and Department of Pathobiology and Laboratory Medicine, University of Toronto, Toronto, ON)

The fatal child abuse-maltreatment syndrome is defined pathologically in cases of child deaths with immediately lethal injuries, and evidence of old (healed or healing) injuries usually involving multiple sites. In this retrospective study, we determined the frequency of old and recent intracranial hemorrhages in 17 cases of classical fatal child abuse-maltreatment syndrome. Cases ranged in age from three weeks to 11 years with most cases less than six months of age. Acute head trauma was the single most common cause of death (14 cases, 82%). In most cases of fatal head injury, subdural, subarachnoid, and retinal hemorrhages were found concurrently usually in the presence of perioptic nerve hemorrhage. In seven cases with fatal head injury, there was evidence of old sublethal head trauma as indicated by old or organizing subdural, subarachnoid, or retinal hemorrhages. Five cases conformed to the standard definition of shaken baby syndrome (subdural, subarachnoid, and retinal hemorrhages in the absence of impact injury to the scalp or skull) representing 29% of all child abuse deaths in this study, or 36% of cases with head injury. All of these cases had evidence of old intracranial hemorrhage indicating previous episodes of significant head trauma. The single most common finding of old trauma was intracranial hemorrhage (41%) which occurred more often than old rib fractures (35%). These results indicate that the neuropathologist can play a major role in defining cases of fatal chronic child abuse since old intracranial hemorrhage may be the only indicator for previous maltreatment.

Titles of Diagnostic Case Presentations

1. **(1) Paraneoplastic encephalomyelitis / sensory neuropathy. (2) Occult oat-cell carcinoma, anterior mediastinum [?thymus]**

   J.M. BILBAO, S.M. COHEN and W. OZANNE (Toronto, ON)

2. **Meningeal sarcomatosis, metastatic Ewing's sarcoma**

   C.E. HAWKINS, J. BILBAO, and W. HARTWICK (Toronto, ON)

3. **Cervical nerve root primary synovial sarcoma**

   K. MEAGHER-VILLEMURE (Lausanne, Switzerland)

4. **Complex focal inflammatory muscle mass of indeterminate nature. Differential diagnosis includes focal myositis (used as a descriptive diagnosis), nodular fasciitis and proliferative myositis**

   N.B. REWCASTLE, K. BROWNELL and M. ABU-HAKIMA (Calgary, AB)

5. **Fronto-temporal dementia with dysphasia, Parkinsonism, mild motor neuron disease and intranuclear/cytoplasmic ubiquitinated inclusion bodies**

   Y. ROBITAILLE (Montreal, PQ)

6. **Olfactory neuroblastoma with extensive olfactory differentiation (esthesioneuroepithelioma)**

   P. SHANNON, F. GENTILI, D. BANERJEE, S. KAMEL-REID, A. KELLER, K. MANCER (Toronto, ON)

7. **Malignant subependymoma with ganglionic component**

   B. LACH (Ottawa, ON)

8. **Third ventricular chordoid glioma**

   A.O. STEMMER-RACHAMIMOV and D.N. LOUIS (Boston, MA)

9. **Juvenile pilocyte astrocytoma with atypical multicentric spread and malignant transformation**

   W. STEFANEK and B. CURRY (Calgary, AB)

10. **Acute multiple sclerosis with features of acute disseminated encephalomyelitis**

    C. HAO, J.M. FINDLAY* and J. M. BILBAO** (* Edmonton, AB and ** Toronto, ON)*

11. **Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)**

    A. H. KOEPPEN (Albany, NY)

12. **Acute lead encephalopathy**

    J. FERREIRA (Montreal, PQ)

13. **Right pallidotomy site**
    W. HALLIDAY (Toronto, ON)