Canadian Association of Neuropathologists

Abstracts of papers and cases presented at the 38th Annual Meeting

September 16 - 19th, 1998
Saskatoon, Saskatchewan

The 38th annual meeting of the Canadian Association of Neuropathologists was held from September 16 - 19th, at the Delta Bessborough Hotel in Saskatoon, Saskatchewan. Local arrangements were made by Drs. David George and Robert Macaulay.

The scientific session consisted of 22 platform presentations and 12 cases for diagnosis. The Royal College of Physicians and Surgeons of Canada speaker was David N. Louis, MD, Associate Neuropathologist, Massachusetts General Hospital and Associate Professor of Pathology, Harvard Medical School. His talk was entitled "Toward a Molecular Genetic Classification of Malignant Gliomas". The Jerzy Olszewski lecturer was Alan Boulton, Ph.D., D.Sc., FRSC, Director of Neuropsychiatry Research Institute & Professor, Department of Psychiatry, University of Saskatchewan. His talk was entitled "Can We Stop the Brain from Aging?"

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Abstracts of Papers Presented at the 37th Annual Meeting of the Canadian Association of Neuropathologists

PLATFORM PRESENTATIONS

1.

In Vitro Neuroprotection from Ionizing Radiation by Metallothionein Induction.

R.R. HAMMOND, L. CAI, M. LEBLANC and M.G. CHERIAN (London Health Sciences Centre and University of Western Ontario, London, ON)

Metallothioneins (MT) are a family of ubiquitous cysteine-rich intracellular proteins. They have a high affinity for metal ions and serve to protect cells from heavy metal toxicity. There is also evidence to show that the induction of MT is associated with cytoprotection from a variety of oxidative stresses, including ionizing radiation. Isoforms MT-I and MT-II are widely expressed throughout the body. MT-IV is expressed in squamous epithelia and MT-III is brain specific. Among the known inducers of MT production are cadmium (Cd) and zinc (Zn). Primary serum-free human CNS cultures were exposed to high dose ionizing radiation with or without preincubation with Cd or Zn. The cultures were sacrificed to examine for apoptosis, neuronal damage and astroglial hypertrophy. Metallothionein was induced above baseline levels by Cd and Zn. Furthermore, in those cultures preincubated with Cd or Zn, there was morphologic and biochemical evidence of neuroprotection in the form of reduced apoptosis, neuronal damage and astrocytosis. These preliminary experiments suggest that MT can be induced in CNS cells and that its induction is cytoprotective. Likewise, it suggests a role for MT expression in the protection of CNS cells from ionizing radiation and other forms of oxidative stress.

2.

Fatal Vertebral Artery Rupture Following Chiropractic Neck Manipulation.

R.J.B. MACAULAY (Department of Pathology, University of Saskatchewan, Saskatoon, SK)

Although neurologic sequelae following chiropractic manipulations are seen occasionally, only rarely has death been attributed to such procedures. This previously healthy 20 year old woman had received approximately 20 cervical 'adjustments' over several months. The day before admission she complained of pain and a 'catch' in her neck, and chiropractic neck rotation was administered on that day, and again on the following day, after which she collapsed, convulsed for 10-15 minutes, and did not recover consciousness. Neurological examination showed evidence of brainstem dysfunction. Angiographically, an intraluminal obstruction was noted in the left vertebral artery at C1-C2, with occlusive thromboemboli in several posterior circulation branches. Urokinase administration cleared the C1-C2 obstruction and partly dissolved distal thromboemboli. The next day she decompensated due to a large left cerebellar infarct. She 'coned' and died approximately 2 1/2 days after admission. At autopsy, the left vertebral artery was lacerated adjacent to the C1-C2 facet joint, with a small surrounding hematoma. There was evidence of mild chronic irritation near the laceration, but not elsewhere. The left vertebral artery was significantly larger than the right (5mm vs 1mm in diameter respectively), and the close proximity of the vessel to the CI-C2 facet joint may have resulted in repeated distortion, possibly exacerbated by passive neck manipulations. However, asymmetry of the vertebral arteries is a common variant of normal, implying additional unknown factors may have been operative.

3.

Pseudoglandular Elements in Schwannomas .

C.A. ROBINSON, B. CURRY and N.B. REWCASTLE (Department of Pathology, University of Calgary, Foothills Hospital, Calgary, AB)

The pseudoglandular schwannoma is a recently described variant in which cystic spaces are lined by pseudocolumnar or cuboidal-like neoplastic Schwann cells exhibiting an epithelial-like appearance. Because the incidence and significance of pseudoglandular elements within schwannomas is unclear, we screened 215 schwannoma cases for the presence of these elements. Sixteen cases (7.4%) were found to contain pseudoglandular elements, and these were subsequently examined with light microscopy, immunohistochemistry, and electron microscopy. The pseudoglandular elements ranged from poorly to well-organized in appearance, and were found in schwannomas exhibiting a wide range of morphological appearances. To one extent or another, the pseudoglandular elements were almost always found in association with Antoni B tissue. The Schwann cell nature of the cells comprising these elements was apparent both immunohistochemically and ultrastructurally. The frequency of proliferative activity within these elements was similar to that observed throughout the remainder of the respective schwannomas. Our observations suggest that, rather than representing a distinct histologic schwannoma variant, pseudoglandular elements likely arise secondarily as a degenerative phenomenon. These elements may be found within a variety of schwannoma variants, and do not appear to possess a unique growth potential. Degeneration within tumor areas exhibiting different growth patterns may contribute to the variable appearances seen within the pseudoglandular elements.

4.

Neuronal Intranuclear Rods Come of Age.

J.M. WOULFE, D. MUNOZ and R. HAMMOND (Department of Pathology, Division of Neuropathology, London Health Sciences Centre, London, ON)

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Rod-shaped neuronal intranuclear inclusions were known to light microscopists of the classical period and were described as early as 1894. Subsequent electron microscopic studies confirmed the existence of these structures and elucidated details of their ultrastructural morphology. However, the biochemical composition of these structures as well as their functional significance and possible pathological relevance have remained elusive. In addition, their localization in the human brain remains to be described. Much of the difficulty stems from unreliable methods of demonstrating intranuclear rods at the light microscopic level.

We discovered, serendipitously, that immunostaining for the selective neuronal cytoskeletal protein, class III beta tubulin, intensely labels morphologically similar rod-shaped intranuclear structures within the nuclei of neurons in the human temporal lobe. Consequently, we exploited the expression of class III beta tubulin in these structures to examine the topographic and intracellular distribution of neuronal intranuclear rods in the human brain using immunohistochemistry. Multiple sections through several regions of the human brain were processed immunohistochemically for the demonstration of class III beta tubulin. Intensely-immunoreactive intranuclear rods displayed a highly selective pattern of distribution within the human brain. Areas containing large numbers of these structures included layers II and VI of the insular and temporal cortices, the substantia innominata, dentate hilum, substantia nigra pars compacta, inferior colliculus, inferior olivary nucleus, and cerebellar dentate nucleus. This anatomically-selective pattern of distribution of neuronal intranuclear rods suggests region-specific functions for these structures in the human brain and implicates them in some of the many pathologic processes that affect the brain in a regionally selective manner.

5.

Cell Cycle-related Expression of Ki67 Antigen and H3 Histone Messenger RNA in Human Fetal Brains.

M.R. DEL BIGIO (Department of Pathology, Health Sciences Centre and University of Manitoba, Winnipeg, MB)

Most information concerning cell proliferation in the developing brain is derived from animal experiments that have utilized pulse-labeling with thymidine analogs. Cell cycle-related markers were studied in the frontal cerebrum of fourteen human fetuses aged 15-28 weeks gestation. Ki67 antigen is expressed beginning in late G1 phase and maximally in G2 and M phases. H3 histone mRNA is expressed during S phase. Immunohistochemistry and in situ hybridization revealed a laminar organization of ventricular zone cells in different stages of the cell cycle. Most S phase cells were located 60-100μm from the ventricular lumen, supporting the concept of interkinetic nuclear migration. The ventricular zone dissipated gradually between 20 and 26 weeks. Proliferative cell populations were also observed in the subventricular and intermediate zones. Dorso-ventral partition of proliferating cell populations within the ganglionic eminence reflects differences in the developmental timing of its target structures; the ventral portion supplies cells to the thalamus which develops later than the striatum. [Funded by the Health Sciences Centre and the Manitoba Health Research Council]

6.

Farnesylation Inhibition is More Efficient than Lovastatin in Inducing Apoptosis of Medulloblastoma Cell Lines *In Vitro*.

W. WANG and R.J.B. MACAULAY (Department of Pathology, University of Saskatchewan, Saskatoon, SK)

Medulloblastoma is a malignant cerebellar tumour usually manifesting in childhood. We have previously shown that blocking the mevalonate pathway with lovastatin, a competitive inhibitor of 3-hydroxy-3methylglutaryl coenzyme A (HMG-CoA) reductase, induces MB cell line apoptosis *in vitro*. We also observed that lovastatin resulted in the inhibition of p21 ras farnesylation, and suggested that blocking protein farnesylation is important in lovastatin-induced apoptosis. We tested this hypothesis using manumycin A, an antibiotic which inhibits farnesyl protein transferase. We found that blocking protein farnesylation with manumycin A is followed by medulloblastoma cell apoptosis in a time- and dose-dependent manner. However, cell death induced by manumycin A was more rapid and efficient, requiring only 12 to 24 hrs of treatment, than lovastatin-induced apoptosis, which required 36 to 96 hrs, depending on the cell line tested. In addition, unlike lovastatin which caused cell cycle arrest in G I and HMG-CoA upregulation, manumycin A had no effect on the cell cycle and resulted in downregulation of HMG-CoA. In both lovastatin- and manumycin A-treated cells, cellular cysteine protease precursor CPP32 was activated, confirming the occurrence of apoptosis in both phenomena. Further studies on the induction of apoptosis in MB may lead to the development of new therapeutic approaches. [Supported by a Grant from the Brain Tumor Foundation of Canada]

7.

Caspase-cleaved Actin (Fractin) Immunolabeling of Apoptotic Neurons in Acute Perinatal Hypoxic-ischemic Brain Injury.

J.P. ROSSITER[1], L.L. ANDERSON[1], F. YANG[2] and G.M. COLE.[2] (Dept. of Pathology, Kingston General Hospital,[1] ON and Sepulveda VAMC GRECC,[2] CA)

Activation of a family of aspartate-specific cysteine proteases (caspases) is a central feature of apoptotic cell death. Caspase activation results in cleavage of multiple substrates, including cytoskeletal actin microfilaments. Caspase cleavage of actin into N-terminal ~ 32 kD and C-terminal ~ 15 kD fragments has been identified in apoptotic cell extracts. This has led to the development of a rabbit polyclonal antibody specific for caspase-cleaved actin, directed to the last five C-terminal amino acids of the ~ 32 kD fragment (= fractin) (Am. J. Pathol. 1998, 152:379-389). In this study we have examined the pattern of fractin immunolabeling in postmortem brain tissue from 10 premature to term infants with acute perinatal hypoxic-ischemic brain injury.

There was strong fractin immunolabeling of the cytoplasm of apoptotic neurons in vulnerable regions, including the basal pontine nuclei, hippocampal formation and cerebral isocortex. There was prominent fractin-labeling of the dendrites of some

apoptotic cells. Many long fractin-positive axonal segments, frequently with a beaded appearance, were seen in the grey matter and adjacent white matter of vulnerable areas in several cases.

These findings support a role for catalytic caspase-like activity in neuronal apoptosis, including possible activity in axons, in perinatal hypoxic-ischemic brain injury. They also further demonstrate the utility of fractin immunolabeling for highlighting apoptotic neurons and their processes.

8.

Autophagic Myopathy Induced by Omeprazole Therapy.

J.M. BILBAO and G. MODDEL (St. Michael's Hospital, Toronto, ON)

Omeprazole inhibits gastric ATPase (the proton pump) which catalizes the exchange of H+ and K+. Rarely muscular weakness and myalgia have been reported as an adverse effect of this treatment. This is the first report of a vacuolar myopathy induced by a proton pump inhibitor.

A 71-year-old male presented with a two year history of increasing difficulty in walking. Two years previously, he had started treatment with 20 mg of omeprazole and 10 mg of cisapride per day for gastric complaints. Examination revealed mild generalized weakness and no neuropathic signs. CPK was 170 and EMG indicated a myopathic process. Muscle biopsy revealed a non-necrotizing vacuolar myopathy associated with accumulation of intrasarcoplasmic lamellar-osmiophilic bodies and exocytosis of lysosomal debris. After cessation of treatment, the patient's strength returned to normal within 4 months. Repeat EMG showed no abnormality. The exact mechanism of omeprazole-induced myopathy is not known. Cisapride does not cause muscle symptoms.

Conclusion: The myopathy induced by omeprazole should be added to the list of autophagic myopathies caused by drugs such as chloroquine, perhexiline, amiodarone, vincristine and colchicine.

9.

Neuropathology of Bouncer Long Evans Rat: A Novel Dysmyelinated Mutant.

J.M. KWIECIEN, M.C. BLANCO, J.G. FOX, S.U. KIM, K.H. DELANEY, A.L. FLETCH (McMaster University, ON, Mayo Clinic, MN, University of British Columbia, BC)

Dysmyelinated rodents serve as useful models for studying mechanisms involved in myelinogenesis or as recipients of oligodendroglial cells to study remyelination. Recently, a Long Evans Shaker (LES) rat, which is a severely dysmyelinated, long lived model with a functional mutation in the myelin basic protein (MBP) gene, has been described. In this presentation, results of histologic, ultrastructural and immunocytochemical studies of the Bouncer Long Evans (BLE) rat, a novel mutant, are shown. The BLE mutation is transmitted in an autosomal recessive fashion and is associated with lack of myelin in the CNS but myelin sheaths in the peripheral nervous system appear morphologically normal. Electron microscopic studies of rats 1-14 weeks old reveals severe dysmyelination with scattered, thin, up to 4-5 lamellae-thick sheaths wrapped around axons which are uncompacted and lack the major dense line. Oligodendrocytes (OL) degenerate in a progressive fashion with accumulation of a membranous material, presumably of a lipid nature, in the perikaryon. OL necrosis is evident and at 8-14 weeks there are numerous immature glial cells of OL type in the optic nerve and spinal cord. Astrogliosis is severe and diffuse, microgliosis is diffuse but not intense. Specific antibody labelling of paraffin embedded sections of the CNS revealed no detectable MBP and proteolipid protein. The BLE rat survives beyond 19 weeks and may prove a useful model for studying mechanisms of myelinogenesis and glial proliferation in the adult CNS. While definite molecular experiments elucidating the nature of the mutation are pending, the BLE rat is presumed to be affected by a functional mutation in the MBP gene. [Funded by the Myelin Project of Canada].

10.

Approaches to Inhibiting Cell Proliferation in Malignant Gliomas: Histopathological Observations.

N.B. REWCASTLE, M. LAFLEUR, L.L.GROFT, M.E.WILCOX, H.MUZIK, S.Q. SHI, D.EDWARDS, P. LEE and P. FORSYTH (University of Calgary, Calgary, AB)

Human malignant gliomas are characterized by profuse vascular proliferation and cell invasion of adjacent tissues. It is hypothesized that imbalances between tissue metalloproteinases and the tissue inhibitors of metalloproteinases (TIMP's) may allow for such tumor growth. In-situ hybridization localized TIMP's to glioma cells but in addition TIMP's 1 & 4 localized to proliferating blood vessels suggesting a role in angiogenesis regulation. In contrast to gelatinase A, gelatinase B was highly expressed in vessels at the growing tumor margin again suggesting a role in angiogenesis. Using a subcutaneously implanted human malignant glioma cell line (U87) in SCID-NOD mice, the synthetic matrix metalloproteinase inhibitor AG3340 produced a marked impediment to tumor cell proliferation compared to controls. Viral therapy as a means of interfering with cell proliferation has been applied to gliomas. Reo virus selectively infects Ras-activated cells that includes glioma cells but not normal cells. Using the same experimental mouse model with intra-tumor and remote administration, Reo virus produced a striking inhibition of tumor growth compared to controls ($p=0.0001$). Morphological findings supporting these observations will be presented. (Funded in part by the Alberta Cancer Board).

11.

Dysproteinemic Polyneuropathy.

J.M. BILBAO and S. COHEN (St. Michael's Hospital, Toronto, ON)

Paraproteinaemia is found in about 5% of patients with cryptogenic peripheral neuropathy. In 771 consecutive cases of peripheral nerve biopsy collected over a 26 year period, we identified 6 cases of polyneuropathy associated with non-amyloidgenic paraproteinemia. Four of the patients had IgM mono-

clonal gammopathy. Non-specific histologic changes included patchy and perivascular mononuclear cell infiltrates, axonal degeneration, segmental demyelination, and remyelination with onion bulbs. Specific changes were congo-red negative amorphous deposits (one case) and widely spaced myelin (3 cases). Immunohistochemistry demonstrated the preeminence of immunofluorescence (frozen tissue) and immunogold (on etched plastic sections) over immunoperoxidase (on paraffin section) for the identification of deposits of clonal immunoglobulin in peripheral nerve.

12.

Education and Socio-economic Status in Confirmed Alzheimer's Disease and Autopsy Controls.

D.G. MUNOZ, G.R. GANAPATHY, M. ELIASZIW and V. HACHINSKI (The University of Western Ontario, London, ON)

A number of epidemiological studies in several countries, including Canada, have reported that low educational attainment is a risk factor for Alzheimer's disease (AD). However, diagnosis was obtained by clinical observation only, without pathological confirmation. We have previously reported that educational attainment did not influence the rate of cognitive decline in patients with pathologically confirmed AD. Moreover, less educated patients were older at onset, contrary to the predictions of the "brain reserve" hypothesis on the mechanism of action of education. In the present study we have obtained through telephone interviews with relatives the educational attainment and socio-economic status of 115 patients with Alzheimer's disease enrolled in the University of Western Ontario Dementia Study and 181 non-demented individuals over the age of 65 autopsied at the University Hospital of London, Ontario. All results were adjusted for sex, age at death, and year of birth. There were no statistically significant differences in education or socio-economic level between the two groups. Similar results were obtained when analysis was repeated for the subgroup of patients in the work force.

13.

Exon 5 Mutation and Malignant Glioma: Case Report and Molecular Genetic Study.

M.D. TAYLOR,[7] J. PERRY,[4,7] M.C. ZLATESCU,[1,8] A.O. STEMMER-RACHAMIMOV,[2,6] L.C. ANG,[3,7] Y. INO,[2,6] M. SCHWARTZ,[7] L.E. BECKER,[5] D.N. LOUIS[2,6] and J. G. CAIRNCROSS[1,8] (London Regional Cancer Centre1, Massachusetts General Hospital,[2] Sunnybrook Health Sciences Centre,[3] Sunnybrook Regional Cancer Centre,[4] Toronto Hospital for Sick Children,[5] and Universities of Harvard,[6] Toronto[7] and Western Ontario[8])

Patients with Turcot syndrome (TS) are predisposed to colon tumours and primary brain tumours, typically glioblastomas or medulloblastomas. We describe a TS patient with a known germline mutation of exon 5 of the hPMS2 mismatch repair gene who developed two metachronous glioblastomas, both having distinct oligodendroglial features. Molecular genetic analysis showed that the patient's second tumour had allelic loss of chromosome 19q but lacked allelic loss of chromosome 1p. The tumour also had prominent microsatellite instability, consistent with a germline mismatch repair defect. Because this patient had an unusual underlying condition and his tumour had a unique histological appearance for TS, we hypothesized that this genetic defect may predispose to malignant gliomas with oligodendroglial features. We therefore evaluated whether sporadic glioblastomas and oligodendrogliomas undergo mutations of this region of the hPMS2 gene. Single strand conformation polymorphism analysis of hPMS2 exon 5, however, failed to reveal mutations in 20 sporadic glioblastomas and 16 sporadic oligodendroglial gliomas. Thus, while it is possible that germline hPMS2 exon 5 mutation may predispose to glioblastomas with an oligodendroglial component, the same genetic defect is not commonly involved in sporadic oligodendrogliomas or glioblastomas.

14.

Peritumoral Brain Edema on CT Scan Predicts Recurrence of Meningioma.

R. MANTLE, B. LACH, M. DELGADO, S. BAEESA and G. BELANGER (Ottawa Civic Hospital, Ottawa, ON)

Approximately 10% of meningiomas recur after gross total resection, presumably due to residual tumor cells in the meninges or brain parenchyma. Our objective was to determine whether peritumoral edema on CT could be correlated with pathologic brain infiltration and clinical recurrence.

Methods: 132 cases of intracranial meningioma resected at our hospital from 1980-92 were assessed and followed to the present day. Blinded grading of edema on initial CT scan and pathologic determination of brain infiltration were done by a neuroradiologist and a neuropathologist respectively. Linear regression with Spearman rank correlation analysis was used to compare the degree of edema graded in subjective average radial cm with brain infiltration and recurrence.

Results: The recurrence rate was 22% overall and 11% after gross total resection. Mean time to recurrence was 6y (SD ± 4), mean follow up was 11y (SD ± 4 yrs). The quantity of peritumoral edema correlated linearly with the chance of brain infiltration ($r_S = 0.95$, $p = 0.002$), and recurrence ($r_S = 0.98$, $p < 0.0001$).

Discussion: The strong correlation between degree of edema and chance of brain infiltration suggests that infiltration causes peritumoral edema. Edema also predicted recurrence according to a 15% rule: the chance of recurrence (assuming complete resection) increases by 15% for every cm of peritumoral edema. Edema on CT could provide a guide to surgeons with respect to the need for a peritumoral resection margin.

15.

Withdrawn

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16.

Fatal Tumor Embolization to Middle Cerebral Artery: An Unusual Complication of Osteogenic Sarcoma.

C. RAO, F. SCHNEIDER, C. AKMAN, V. ANDERSON and S. AHMED (Kings County Hospital Center and State University of New York Health Science Center at Brooklyn, NY)

Intracranially osteogenic sarcoma is a rare tumor either as a primary or as a metastasis. Tumor emboli from an osteogenic sarcoma occluding the middle cerebral artery resulting in infarction of the distribution territory has not been reported. We present such a case of a 17 year old girl who was diagnosed having osteogenic sarcoma of right fibula for which she underwent amputation and chemotherapy. She developed pulmonary metastases which were resected. She appeared to be in remission with a normal chest CT in early 1998. Her final admission to the hospital was with generalized tonic clonic seizures and a left focal tonic seizure. Twelve hours after admission her neurological examination revealed dilated and fixed pupils, non reactive to light. Her extremities were flaccid with absent deep tendon reflexes and plantar response. CT scan was consistent with hypoxic encephalopathy. Autopsy revealed extensive metastases in the lungs and in the inferior vena cava. The brain showed evidence of permanent global ischemia and non perfusion. The right middle cerebral artery revealed occlusion by tumor embolus and it's distribution territory showed evidence of acute infarction by presence of polymorphonuclear margination and migration into the infarcted tissue. Sections from other areas of the brain showed acutely hypoxic neurons only. Pituitary gland showed acute infarction.

17.

Hippocampal Sclerosis in Two Sisters with 22-Derived Marker Chromosome and Late-Onset Dementia of Alzheimer Type.

A.W.CLARK,[1] M.E.PERCY,[2] P.ST.GEORGE-HYSLOP[2] and D.A.RAMSAY[3] (University of Calgary,[1] University of Toronto,[2] and University of Western Ontario,[3] ON)

Percy and colleagues reported a family in which two sisters with probable dementia of Alzheimer type were found to have an unusual 22-derived marker chromosome, containing an expanded region coding for ribosomal RNA (Am J Med Genet 1991; 39:307-13 and 1993; 47:14-19). We here report the neuropathologic features and further genetic information in these two sisters. In III-3 and III-4 of the 1991 report, the age at death was 88 and 83 years, duration of dementia about 17 and at least 20 years, and brain weights 1061 and 954 grams, respectively. Each case had severe frontal, parietal, and temporal atrophy. Microscopically, both cases had hippocampal sclerosis, with extreme cell loss in CA1 and subiculum. Neurofibrillary tangles were found in neocortex of both cases, rarely in III-3 and more frequently in III-4. Cortical plaques were common in both. Severe neuronal loss and gliosis in cortex, and neuronal loss in substantia nigra, were found in both cases. Both sisters were of ApoE 3/4 genotype, and neither carried any of the known mutations for APP, presenilin 1, or presenilin 2.

Hippocampal sclerosis is recognized as a common pathologic substrate of dementia in the elderly, with variably associated Alzheimer pathology. To our knowledge familial cases are uncommon, and the present subjects represent the first with extensive genetic investigation.

18.

Ganglioneuroblastoma of the Spinal Cord: A Unique Case.

D. H. GEORGE and R. GRIEBEL (Royal University Hospital, Saskatoon, SK)

Background: Ganglioneuroblastomas (GN) are well defined neoplasms of the peripheral sympathetic nervous system (PNS). GNs of the central nervous system (CNS) are even more uncommon, and less well characterized. They have been described in the brain, and have been variably categorized as forms of neuroblastoma or ganglion cell tumor; behaviour is unclear. GNs are almost unknown in the spinal cord, however. By contrast, the fully differentiated ganglioglioma (GG) is a recognized entity in the spinal cord. Spinal GGs develop most commonly in children, usually in cervico-thoracic segments, and sometimes form dramatic masses extending along most or all of the cord. The behaviour of GGs is generally benign, and treatment is surgical resection, facilitated by a usual tissue plane.

Case: In this abstract, we present a unique case of a GN of the spinal cord. It presented subacutely in a 3 year old male child with torticollis and mild gait disturbance. It formed an intramedullary mass with an extraordinary length from C3 to T8. Subtotal surgical resection (90%) was achieved with no residual neurological deficit. By analogy to the GN of the PNS, the tumor is favorable histology, intermixed subtype.

Conclusion: Although follow-up is presently too short to determine prognosis, the clinical and radiological features of this tumor suggest a close relationship to the benign GG of the spinal cord, rather than to high grade neuroblastoma.

19.

Chordoid meningiomas in adults.

P, SHANNON, C. BERGERON and L.C. ANG (Division of Neuropathology, Sunnybrook Health Science Center and The Toronto Hospital, Western Division, Department of Laboratory Medicine and Pathobiology, University of Toronto, ON)

Chordoid meningiomas are unusual tumors which, in pediatric patients, are strongly associated with iron-resistant anemia and occasionally hypergammaglobulinemia. These systemic manifestations are thought to be related to the reactive chronic inflammatory response within the tumor. Few studies of chordoid meningiomas in adults are available. This report describes five chordoid meningiomas in patients ranging in age from 29 to 53 years. Three patients were female, two were male; three tumors involved the cerebral convexities, one was parafalcine and one was in the pineal region. All tumors were composed primarily of epithelioid cells in an abundant mucoid matrix. Only one tumor contained a heavy lymphoplasmacytic inflammatory reaction. Two contained only sparse lymphoid aggregates and two lacked any significant inflammation. One patient suffered anemia; she had a mild normochromic anemia

(Hb=112g/L) and her tumor lacked an inflammatory infiltrate. Two tumors contained small areas with unusual patterns of differentiation. One contained small aggregates of cells surrounding PAS (+) material; these aggregates were reactive with immunohistochemical stains for cytokeratin and CEA. Another tumor had distinctly microcystic areas and invaded the underlying brain. The dense inflammatory infiltrate and accompanying anemia in chordoid meningiomas is less common among adults than children. The presence of microcystic and secretory differentiation in this series is unusual and may reflect phenotypic plasticity in these tumors.

20.

Progressive Multifocal Leukoencephalopathy Feigning Brainstem Ischemia.

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

Of the protean manifestations of progressive multifocal leukoencephalopathy (PML), none can be more misleading in presentation than primary involvement of the brainstem and cerebellum. Described in this report is a rare case in an 80 year old woman who had a 40 year history of rheumatoid arthritis controlled by immunosuppressive therapy. Diplopia, vertigo and frequent falling heralded her neurologic disorder, which was later compounded by dysphagia and episodic visual loss in the left eye. Examination disclosed palsies of the right sixth, right seventh, and left eleventh cranial nerves accompanied by ocular bobbing, hypertonia of the left limbs, and unsteadiness. No abnormalities were found in studies of the CSF or CT imaging. An MRI scan, however, showed an increased T2 signal in the brainstem interpreted as ischemia. Death, approximately 12 weeks after presentation, was preceded by precipitous neurologic decline. Patchy demyelination with features characteristic of PML was strewn the length of the brainstem, the tegmentum bearing the brunt. *In situ* hybridization confirmed the presence of DNA sequences of the JC strain of Papova virus in Cowdry A intranuclear inclusions found within several oligodendrocytes in the most recent lesions in the rostral brainstem and cerebellar hemispheres. A few tiny foci of demyelination were noted in the cerebrum. Selection of the brainstem in this patient as the primary site of infection is enigmatic, but attests to the need to consider PML in the differential diagnosis of brainstem syndromes.

21.

Painful Ophthalmoplegia in Rheumatoid Arthritis.

C. RAO, J. SCHNELLER, S. NAJENDRA and M. WRZOLEK (Kings County Hospital Center and State University of New York Health Science Center, Brooklyn, NY)

Rheumatoid arthritis (RA) is a chronic multisystemic disease with deforming arthritis as the outstanding feature. Atlanto-axial subluxation resulting in cervical myelopathy is a common neurological complication of RA as is entrapment or angiopathic neuropathy. Rheumatoid vasculitis and rheumatoid granulomas in the central nervous system are uncommon complications of RA. Rheumatoid granulomas involve craniospinal dura and leptomeninges and rarely choroid plexus or cerebral parenchyma. We report an autopsy case of an unusual neurological complication of RA manifesting as painful ophthalmoplegia due to involvement of cavernous sinus structures. This 65-year old male with history of RA presented with diplopia, ptosis, proptosis and severe pain in the left eye. Patient expired of extensive bilateral bronchopneumonia. Autopsy revealed rheumatoid vasculitis in the leptomeninges and many classical rheumatoid granulomas in the dura and leptomeninges. Sections of left cavernous sinus showed rheumatoid granulomas involving the wall of the sinus, perineurium of the cranial nerves and adventitia of internal carotid artery. Trigeminal nerve was involved by endoneurial vasculitis, inflammation, rheumatoid granulomas and changes secondary to compression by the granulomas. Previously a single case of painful ophthalmoplegia in RA is reported without documentation of pathological changes in the cavernous sinus (Dornan. JNNP 1979).

22.

Loss of the *NF2* Gene and Merlin Occurs in the Tumorlet Stage of Schwannoma Development in Neurofibromatosis 2.

A.0. STEMMER-RACHAMIMOV, Y. INO, Z.Y. LIM, L.B. JACOY, M. MACCOLLIN, J.F. GUSELLA, V. RAMESH and D.N. LOUIS (Molecular Neuro-Oncology Laboratory and Molecular Neurogenetics Unit, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA).

Loss of the *NF2* (neurofibromatosis 2) gene-encoded protein merlin is a universal finding in sporadic and *NF2*-associated schwannomas. Certain *NF2* patients may develop numerous minute Schwann cell tumorlets of the spinal nerve roots in addition to larger, frank schwannomas and thereby provide an opportunity to investigate the timing of *NF2*/merlin loss in Schwann cell tumorigenesis. We studied an *NF2* patient with a germline *NF2* gene frameshift mutation who had many Schwann cell tumorlets and schwannomas. Loss of heterozygosity studies of DNA from microdissected specimens showed allelic loss of the *NF2* region of chromosome 22q in tumorlets as well as schwannomas. Immunohistochemistry further demonstrated loss of merlin expression in tumorlets as well as schwannomas, with intact expression in adjacent nerve. Thus, loss of both *NF2* alleles and merlin occur early in Schwann cell tumorigenesis, before the tumorlet stage. The study of tumorlets and schwannomas in such patients may also provide an opportunity to elucidate mechanisms responsible for the subsequent growth of Schwann cell lesions into symptomatic tumors. [Supported by NIB grants NS24279 and CA51410 and by a grant from the U.S. Army.]

Titles of Diagnostic Case Presentations

1. **Hypertrophic brachial plexus neuritis**
   C. HAO, E. S. JOHNSON and J.M. FINDLAY (Edmonton, AB)

2. **Neurotropic melanoma**
   N.B. REWCASTLE, D. SAWYER, S.U. UBANSKI, and J. DORT (Calgary, AB)

3. **Severe degeneration of corpus striatum (The "CAG" repeat expansion on the Huntington gene indicates a normal phenotype. ? A phenocopy of HD or different unique disease process.)**
   B. CURRY (Calgary, AB)

4. **Distinctive, non-Rosenthal eosinophilic inclusion in astrocytes**
   W. C. HALLIDAY and J. K. MACDONALD (Winnipeg, MB)

5. **Familial central nervous system sarcoidosis**
   A.H. KOEPPEN (Albany, NY)

6. **Andermann Syndrome, neuronopathic, with early infantile onset**
   Y. ROBITAILLE and N. LECLERC (Montreal, PQ)

7. **"Angioglioma" (Low grade astrocytoma with hemangioblastoma)**
   B. LACH and N. PERRON (Ottawa, ON)

8. **Pigmented villonodular synovitis**
   A. BRÜCKS and R. J. B. MACAULAY (Saskatoon, SK)

9. **Lhermitte-Duclos disease (Dysplastic gangliocytoma of cerebellum)**
   (Comment: The unusual large dysplastic cells may be gangliocytes, but not decisive Purkinje cells and granular cells. The changes occur as a possible consequence of a primary migration and maturation disorders.)
   S. HASHIMOTO (Osaka, JAPAN)

10. **Spinal ganglioglioma with fecal neurocytoma features**
    J. FERREIRA and Y. ROBITAILLE (Montreal, PQ)

11. **Autosomal recessive fatal infantile hypertonic muscular dystrophy**
    D.H. GEORGE (Saskatoon, SK)

12. **Ruptured intramedullary spinal cavernous angioma (cavernoma)**
    J. BARRON and D. A. RAMSAY (London, ON)

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