Canadian Association of Neuropathologists

Abstracts of papers and cases presented at the 44th Annual Meeting

October 13-16, 2004

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The Forty-Fourth Annual Meeting of the Canadian Association of Neuropathologists was held from October 13-16, 2004 at the Fort Garry Hotel in Winnipeg, Manitoba. The co-ordinator for local arrangements was Dr. Marc DelBigio. The scientific sessions were comprised of 19 platform presentations and seven diagnostic case presentations. The sessions were organized under the following headings: Tumours (two sessions), Neurodegenerative Diseases, Miscellaneous Disorders, Pediatric Neuropathology, and Autoimmune and Neurovascular Disorders.

Special lectures were given by invited guests. **The Royal College of Physicians and Surgeons of Canada Lecture** was given by Dr. David I. Graham, Professor at the Academic Unit of Neuropathology, Division of Clinical Neuroscience, Southern General Hospital, Glasgow, Scotland. His talk was entitled: "Traumatic Brain Injury – What is New?" An **Invited Member Lecture** was provided by Dr. Yves Robitaille from The University of Montreal. His lecture was entitled: "The Neuropathology of Recessive Ataxias in the Light of Recent Gene Discoveries."

The meeting included a **Symposium on Pediatric Neuropathology**, chaired by Dr. Sukriti Nag, President. This included the J**erzy Olszewski Lecture** presented by Dr. Rebecca Folkerth from Brigham and Women's Hospital and Children's Hospital and Harvard University. Dr. Folkerth's presentation was entitled: "Perinatal Brain Injury: Overview and Recent Findings." This was followed by addresses by Dr. David Eisenstat and Dr. Lorna Jakobson, both from The University of Manitoba. Their lectures were entitled: "Early Development of the Brain" and "Behavioural Consequences of Periventricular Brain Damage" respectively.

PLATFORM PRESENTATIONS

1. Nuclear gigantism in spinal ependymomas

A.W. Clark, H. Li, G. Sutherland (Departments of Pathology and Laboratory Medicine and Clinical Neurosciences, University of Calgary).

At least five case reports of "giant cell ependymomas" – three of them in the spinal cord or filum terminale – have been published. We recently encountered a "giant cell ependymoma" in the filum terminale of a 36-year-old man. The tumor had characteristic non-myxopapillary histologic features of ependymoma, but also prominent multifocal nuclear gigantism, including nuclei measuring more than 50 micra in major dimension and occasional nuclear pseudoinclusions. There were no features of anaplasia, and Rosenthal fibers were focally extremely abundant. To clarify the relationship of this tumor with other ependymomas, we compared the histologic findings with those in twelve other ependymomas of the spinal cord and filum, of which three were myxopapillary. Among these twelve comparison cases, none had such conspicuous nuclear gigantism as the index case. However, two (both non-myxopapillary) had rare to occasional nuclei measuring more than 50 micra in major dimension; and rare nuclear pseudoinclusions. Among the remaining ten ependymomas studied, there was moderate nuclear pleomorphism (occasional to frequent nuclei measuring 25 micra or more in major dimension) in more than half. One or more nuclear pseudoinclusions were found in two. "Giant cell ependymomas" are apparently not a homogeneous entity. Moderate nuclear pleomorphism is relatively common in spinal ependymomas, and nuclear gigantism of variable extent is seen occasionally.

2. Congenital basal skull teratoma

J.L. Keith, J.C. Walton, J.G. Heathcote, W. Romano, R. Hammond (Departments of Laboratory Medicine & Diagnostic Imaging, University of Western Ontario).

A 20 week gestational age female was stillborn to a healthy 23-year-old woman. Examination of the fetus revealed swelling and distortion of the left side of the head with proptosis and displacement of the left ear. Opening the cranium revealed a large, firm, bosselated extra-axial tumour that appeared to arise from the left middle cranial fossa. The lesion extended into the left anterior cranial fossa and posterior fossa displacing left orbital structures and compressing the brainstem.

Microscopically, the tumour demonstrated typical features of a mature teratoma, with predominantly neural tissue. Diagnostic imaging was obtained pre- and postnatally. The neuroradiological and neuropathological features of this congenital skull base teratoma will be described in light of the literature.

3. Genetics of FTD-MND type with neuronal intranuclear inclusions

I.R. Mackenzie[1], B.R. Leavitt[2], M.L. Hutton[3] (Divisions of Neuropathology[1] and Neurology[2], University of British Columbia & Department of Neuroscience, Mayo Clinic[3]).

Many cases of frontotemporal dementia (FTD) are familial. Some are due to a mutation in the tau gene, on chromosome 17, and demonstrate abnormal tau in brain tissue (FTDP-17T). Most of the remaining familial cases have no tau pathology but show the same ubiquitin-immunoreactive (ub-ir) neuronal cytoplasmic inclusions as patients with dementia and motor neuron disease (FTD-MND

type). No tau mutations have been identified in cases of FTD-MND type and the genetic basis is currently not known. Recently, we reported that some patients with familial FTD-MND type also have ub-ir neuronal intranuclear inclusions (NII). We suggested that NII might be a pathological marker for a specific subset of FTD families, which share a common genetic basis. Here, we present some results from our ongoing genetic analysis of these cases. We have found that FTD-MND type with NII (i) is not due to expansion of a CAG trinucleotide repeat region, (ii) links to chromosome 17, (iii) the candidate region is between D17S1787 and D17S931, and (iv) there is no mutation in the tau gene. These results, combined with published data on other families with FTD-MND type, suggest that abnormality in a non-tau gene on chromosome 17q21 is associated with a specific subset of autosomal dominant FTD in which the pathology is MND-type ub-ir cytoplasmic inclusions and the unique finding of ub-ir NII.

4. Dissolution of the cerebellar granule cells may not be solely due to postmortem autolysis

S. Krawitz, M.J. Shkrum, L.C. Ang (Department of Pathology, University of Western Ontario and the London Health Sciences Centre).

Dissolution of cerebellar granule cells is commonly explained as postmortem autolysis. A review of 40 autopsy brains in variable states of decomposition shows clear discrepancies between the state of dissolution of the cerebellar granule cells and that of other parts of the brain. In ten cases the granule cells are intact with evidence of autolysis elsewhere in the brain. Nineteen cases show granule cell dissolution with preservation of the rest of the brain. Of these, eight cases show changes of acute hypoxic-ischemia, five show traumatic brain injury, and in the remaining five, blood supply was otherwise compromised. Eleven cases with longer postmortem intervals prior to autopsy show widespread decomposition of the brain including the granule cells.

Early studies found no correlation between so-called autolysis of the cerebellar granular layer and a particular disease. Granule cell loss was explained by the finding in the cerebellum postmortem of higher acidity, which is known to promote autolysis. It was therefore concluded that granule cell degeneration is a postmortem phenomenon. More recent studies have correlated granular cell autolysis with brain death, and with a greater vulnerability to transient ischemia (Acta Neuropthol, 1986, 70: 75-8).

We have found that postmortem autolysis may not be the sole explanation for dissolution of the cerebellar granule cells. No mechanism is offered to explain the observed discrepancies, but a possible association of granular cell autolysis with hypoperfusion is suggested.

5. Young adult onset parkinsonism with widespread Lewy bodies, cerebellar atrophy and axonal swellings

C.L. Shoesmith[1], D.A. Ramsay[1], J. Maher[2], L.C. Ang[1] (Department of Pathology, London Health Sciences Centre, London[1] and Royal Victoria Hospital, Barrie, Ontario[2]).

Lewy bodies are commonly associated with Parkinson's disease and diffuse Lewy body disease. However, widespread Lewy body pathology is very rare in brains of individuals before the fifth decade. A 30-year-old man died after a two year history of progressive parkinsonism associated with tremor, rigidity, postural instability, dysarthria, ataxia, cognitive decline and terminal akinetic mutism. At autopsy, there was atrophy of the cerebral hemispheres and severe atrophy of the cerebellum. The basal ganglia, pons and medulla were grossly normal, but there was marked pallor of the substantia nigra (SN). Microscopic examination showed numerous Lewy bodies in the deep neocortical layers, hippocampus, amygdala, SN, and locus ceruleus. Axonal swellings were also frequently encountered in several grey matter regions including the cerebellum. Granulovacuolar degeneration was apparent in CA1. No significant iron deposition was noted in the basal ganglia. Although there were Lewy neurites present, neither neurofibrillary tangles nor neuritic plaques were found. The cerebellum showed moderately severe granule cell loss in the hemispheres and relative preservation of Purkinje cells. This is an unusual, sporadic case of early onset, rapidly progressive parkinsonism, associated with widespread Lewy bodies, axonal swellings, and cerebellar granule cell atrophy that has been only rarely reported (Clin Neuropath, 1993, 12:147-152; Ann Neurol, 1982, 11:335-343).

6. Interactions between nuclear bodies in neurons of the human substantia nigra

J. Woulfe[1], D.A. Gray[1], W. Prichett[1], D.G. Munoz[2] (University of Ottawa and The Ottawa Health Research Institute[1] and St. Michael's Hospital and The University of Toronto[2]).

Recent studies have revealed that the cell nucleus is organized into discrete structural domains, each subserving a specific function. These functional nuclear bodies are to be distinguished from pathological intranuclear inclusions which have been described in a variety of neurodegenerative diseases. Marinesco bodies (MBs) are eosinophilic ubiquitinated intranuclear inclusions present in pigmented neurons of the human substantia nigra and locus coeruleus. Although they have traditionally been considered non-pathological entities, more recent studies have indicated that MBs are associated with the age-associated degenerative changes in the substantia nigra and striatal loss of dopaminergic terminals. In this immunohistochemical double-labeling study, we demonstrate colocalization, contiguity, and focally shared immunoreactivity between MBs and neuronal intranuclear rodlets (INRs) in the nuclei of pigmented neurons of the human substantia nigra. The latter nuclear structures of uncertain function are markedly decreased in the cortex of Alzheimer's disease. INRs also displayed a consistent association with the nucleolus of nigral pigmented neurons. In addition, we demonstrate an interaction between INRs and promyelocytic leukemia (PML) protein, the signature protein of PML nuclear bodies. These results indicate spatial interactions between INRs, nucleoli, PML bodies, and MBs in the human substantia nigra. These interactions may be relevant to elucidating cellular mechanisms of age-related motor dysfunction. (This study was supported by The Alzheimer's Society of Canada).

7. Colchicine, myopathy and fatality

E.S. Johnson[1], T. Kovithavongs[2], A.S. Easton[3] (Departments of Laboratory Medicine and Pathology[1], and Medicine[2], University of Alberta; Department of Pathology, Dalhousie University[3]).

Vacuolar myopathy induced by colchicine intoxication is ascribed to accumulation of autophagosomes and is usually non-fatal. This report questions these assumptions. A 63-year-old man, immunosuppressed by cyclosporine and prednisone for 19 years postrenal transplantation, had been treated seven years for gout with colchicine and allopurinol, and ten years for hypercholesterolemia

with statins. Subacute illness heralded by abdominal pain prompted admission to hospital and, over a 40 day period, he developed other multisystem manifestations of severe colchicine toxicity. Early onset of a proximal myopathy progressed within two weeks to a bedridden state with diminished pulmonary function. A left anterior tibialis muscle biopsy showed a necrotizing vacuolar myopathy in which approximately 20% of the fibers contained clear sarcoplasmic vacuoles that ultrastructurally were empty but bounded by a limiting membrane enfolded into saccular invaginations. However, only an estimated 3% of fibers displayed acid hydrolase reactive autophagocytic vacuoles that immuno-expressed dystrophin and spectrin. Both types of vacuoles were associated with desmin and ubiquitin immunoreactivity. No improvement occurred with discontinuance of colchicine and the statin; the patient died of pneumonia. Nonetheless, postmortem examination of the quadriceps muscles revealed reversion of previous findings. These types of vacuolar changes observed have relevancy to the recently recognized role of microtubules in the transport mechanisms of the sarcoplasmic reticulum and lysozomes. Furthermore, post-transplant patients entail greater risk of chronic colchicine toxicity, including fatality.

8. A clinico-biological model predicting survival in medulloblastoma

A Ray[1], M Ho[3], J Ma[3], R Parkes[4], J Mc Laughlin[4], R Bouffet[2], JT Rutka[1], CE Hawkins[3] (Divisions of Neurosurgery[1], Oncology[2] and Pathology[3], The Hospital for Sick Children, Toronto and Department of Epidemiology and Biostatistics[4], Mount Sinai Hospital, Toronto).

Objective: To develop a model predictive of outcome for patients with medulloblastoma (MB) based on both clinical and biological markers.

Methods: Clinical presentation and survival information were obtained for 120 Hospital for Sick Children patients and a tissue microarray constructed from their tumour samples. The arrays were immunohistochemically assayed for expression of MYC, p53, PDGFR, ErbB2 and TrkC and their ability to predict survival tested.

Results: The percentage of immunopositive MBs for each of the markers was as follows: MYC 16%, ErbB2 16%, p53 12%, TrkC 33% and PDGFR 97%. The four strongest predictors of survival based on univariate and multivariate analysis were the presence of metastatic disease at presentation (HR 2.03) and p53 (HR 2.24), TrkC (HR 0.65), and ErbB2 (HR 1.51) immunopositivity. Scaled coefficients were then calculated and a survival estimate determined based on the sum of the coefficients for the markers present in a particular tumour.

Conclusions: We present one of the largest single institution studies of pediatric MB and the first attempt at combining both clinical and biological markers to stratify MB patients into risk groups. Further, the fact that the biological markers studied are all immunohistochemistry-based should make this method widely applicable.

9. A case of metastatic cystosarcoma phyllodes to the brain

H. Reddy, S. Krawitz, J. Megyesi, D. MacDonald, L.C. Ang (Departments of Pathology and Clinical Neurological Sciences, London Health Sciences Centre, and University of Western Ontario, Ontario).

Cystosarcoma phyllodes is an uncommon fibroepithelial breast neoplasm which very rarely metastasizes to the brain. Less than fifteen cases are reported in the literature, few in detail (Hlavin et al., Cancer. 1993 1; 72 : 126 –30). A 47-year-old woman had two years previously been diagnosed with breast cystosarcoma phyllodes, treated with surgical excision and radiation. Subsequently she had a mediastinal cystic mass and multiple pulmonary metastatic nodules removed. She then developed increasing confusion and word finding difficulties. A CT and MRI scan of the head revealed a large left temporal heterogeneous enhancing brain lesion with minimal edema. The mass was resected. Macroscopically, the mass was variably firm and rubbery with gelatinous areas. Microscopic examination showed a mesenchymal neoplasm forming interlacing fascicles with necrotic areas and up to 28 mitotic figures per 10 hpf. No epithelial elements were identified in the tumour. The histological features were consistent with a high grade sarcoma. Cystosarcoma phyllodes characteristically contains both epithelial and stromal elements at the primary site. However, as is seen in this case, metastases are composed only of the sarcomatous component. As in most previous cases, this patient had widespread metastases at the time of central nervous system involvement.

10. Bilateral, multifocal dysembryoplastic neuroepithelial tumor (DNT): case presentation and discussion of possible pathogenesis

S. Yip[1], R. Nugent[2], W.B. Woodhurst[3], I.R. Mackenzie[1] (Divisions of Neuropathology[1], Neuroradiology[2], Neurosurgery; University of British Columbia).

Dysembryoplastic neuroepithelial tumor (DNT) is an indolent neoplastic process associated with dysembryogenesis. Affected patients tend to be younger and present with chronic epilepsy. The tumor does not cause any significant mass effect and prognosis is good, even with just partial resection. We present a 48-year-old woman with chronic seizures and gradual neurologic decline. Radiologic investigations revealed bilateral mesial temporal cystic lesions as well as smaller circumscribed cysts within both basal ganglia and thalami. MRI characteristics were consistent with a low-grade glioma. A stereotactic biopsy of the left temporal lesion demonstrated well-defined tumor nodules composed of numerous oligodendroglial-like cells (OLCs), arranged in cords with a delicate fibrillar stroma. Normal appearing pyramidal neurons were identified within the intervening mucus-filled spaces. The histopathologic diagnosis was DNT. The lesions in the contralateral temporal lobe and deep grey nuclei were not sampled. The bilateral, multifocal nature of this case supports the theory of a germinal origin for DNT, with the final locations of the lesions being determined by the migratory patterns of germinal matrix cells from the subependymal plate.

11. A nodular lesion involving the 7th and 8th cranial nerves, suspicious of glial heterotopia or ectomesenchymal choristoma

E. Kadota[1], S. Hashimoto[2] (Division of Pathology, Kishiwada City Hospital, Osaka, Japan[1], Department of Pathology, PL Hospital, Osaka, Japan[2]).

A 33-year-old female was admitted to the hospital because of hearing-loss affecting her right ear. There was nothing particular in her past history. Radiologically, a nodular lesion involving the right 7th and 8th cranial nerves and an enlargement of the right internal acoustic meatus were noted. The lesion was resected surgically. Histologically, the nodule consisted of white matter-like tissues lacking ganglion cells, arachnoidal cell nests, parts of proliferated

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perineurium and amianthoid collagen fibres. Each component looked well-differentiated and displayed no atypia. The arachnoidal cells formed scattered small nests and did not show meningioma-like formations. The proliferation of the perineurium was considerable. However, perineurioma seemed unlikely because of the coexistence of the white matter-like tissues. The glial cells of the white matter-like tissues appeared paucicellular and lacked the character of glioma. There have been reports of heterotopia, choristoma, and hamartoma of the 7th and/or the 8th cranial nerves. Therefore, glial tissue heterotopia with reactive proliferation of arachoidal cells and perineurium or ectomesenchymal choristoma composed of glial tissues, arachnoidal cells and perineurium was suspected. The question remains as to whether heterotopia or choristoma can be causative of internal acoustic meatus enlargement. We will discuss the differential diagnosis and more.

12. A rat model of neonatal brain hemorrhage with persistent motor deficit: an animal model for human cerebral palsy

J. Balasubramaniam, M.R. Del Bigio, M. Xue (Department of Pathology, University of Manitoba).

Periventricular hemorrhage (PVH) in the premature infant brain is often associated with persistent deficits in motor and cognitive function (cerebral palsy). Using a neonatal rat model of periventricular hemorrhage, we hypothesized that damage to periventricular germinal tissue would lead to immediate and long-term behavioural changes.

Tail blood from newborn rats (one day old) or saline was injected into the periventricular region of the cerebrum. Magnetic resonance imaging (MRI) was used to define the extent of the hematoma. Rats with hemorrhage, as well as saline and intact controls underwent behavior tests until 10 weeks of age by a blinded observer. Brains were subjected to histological and biochemical tests.

The PVH group displayed significant impairment ($P<0.05$) in all tests of motor development (ambulation, righting response, and negative geotaxis). In maturity they demonstrated impaired ability to stay on a rotating rod and skilled reaching. MRI at the end of the experiment demonstrated subsets of rats with focal cortical infarction (n=4) or mild hydrocephalus (n=3) and these structural defects were associated with greater behavioral deficits. There was a good correlation between MR imaging and histological appearance. Many of the rats exhibited periventricular heterotopia. Blood injection into the periventricular tissue of the neonatal rat results in both immediate and long-term behavioral abnormalities. PVH is a good model of human cerebral palsy and it could be used for testing of specific biological hypotheses.

13. Prospective histologic study of blocked hydrocephalus shunt catheters

M.R. Del Bigio, P.J. McDonald (Departments of Pathology and Surgery, University of Manitoba).

Proximal catheter obstruction in shunts remains the most common complication in the treatment of hydrocephalus. The histopathologic reactions of brain tissue to shunt catheters were described 20-30 years ago. However, the construction and composition of shunt catheters has changed and we therefore decided to revisit the histopathology of shunt obstructing material. Since late 2002, obstructed ventricular shunts from hydrocephalic children have been submitted for histopathologic examination rather than microbiology culture studies or disposal. We have prospectively examined 12 specimens from 11 children. Acute and subacute obstructions included necrotic brain debris and choroid plexus (1), bacteria and necrotic debris (1), clotted blood (1), and eosinophilic / mixed inflammatory cell collection (2 in same patient one year apart). The latter patient had had many rapid obstructions and was given steroids in an attempt to reduce the reactive response. Chronic obstructions included glial and collagenous material from choroid plexus (5 including 1 Bioglide catheter), sometimes with mild chronic inflammation with foreign body giant cells (2). We conclude that shunt obstructions in the current era of neurosurgical hardware are caused by generally the same types of tissue reactions as in the past. Histopathological examination of obstructed catheters might be useful in the management of some patients with frequent obstructions. The mechanism of these inflammatory obstructions remains to be determined. (Funded by the Canada Research Chairs program).

14. Characterization of structural and behavioral abnormalities in kaolin-induced neonatal rat hydrocephalus

O.H. Khan, M.R. Del Bigio (Department of Pathology, University of Manitoba).

Hydrocephalus is characterized by obstruction of cerebrospinal fluid (CSF) flow leading to enlargement of CSF-containing ventricular cavities in the brain. We characterized the structural changes and behavioral outcomes of a neonatal model of kaolin-induced hydrocephalus in rat. In situ evidence of tissue hypoxia in hydrocephalic rat was completed by administration of pimonidazole hydrochloride. We also compared vascular endothelial growth factor (VEGF) expression in hydrocephalic and control rat brains by immunohistochemistry and ELISA. Sprague-Dawley rats injected with kaolin at postnatal day one had enlarged ventricles by one week and severe dilatation by three weeks as assessed by magnetic resonance imaging (MRI) and histology. Hydrocephalic rats had decreased weight gain, reduced time for geotactic orientation, and rotorod (endurance and accelerating). Enzyme assays and western blots revealed decreased expression of myelin associated proteins including myelin basic protein (MBP). Following pimonidazole administration, immunohistochemistry demonstrated hypoxia-associated pimonidazole adducts in periventricular glial cells. VEGF immunohistochemistry in normal rats revealed positive cortical neurons that diminished with age. The pattern of expression shifted to more white matter glial cells in hydrocephalic rats. VEGF expression determined by ELISA supports those findings. We conclude that hypoxia in brain white matter might contribute to vascular changes in hydrocephalus.

15. Inhibition of thrombin activation reduces brain damage following intracerebral blood injections in neonatal mice

M. Xue, J. Balasubramaniam, K. Parsons, I. Mcintyre, J. Peeling, M.R. Del Bigio (Department of Pathology and Radiology, University of Manitoba and Manitoba Institute of Child Health).

The mechanisms of brain injury following intracerebral hemorrhage (ICH) may be in part related to proteolytic activities in the brain. We hypothesized that activities of thrombin and plasmin (serine proteases) are responsible for damage following neonatal ICH and that inhibition of their activation would reduce brain

damage and improve the neurological impairment following ICH in the neonatal mice. Neonatal rat brain cells were cultured for MTT [3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H tetrazolium bromide] colorimetric viability assay. Rats received injection of blood and brain slices were tested with enzyme overlays (using thrombin and plasmin fluorogenic substrates). Mice at 2 and 10 days ages received intracerebral injections of blood in combination with hirudin, α2macroglubulin, and PAI-1. After two days survival, H&E, Fluoro-Jade, histochemistry, and TUNEL staining were performed. The long-term study used low and high doses of hirudin mixed with blood. MRI, H&E, solochrome cyanine staining, ELISA, and behavioural testing were done. Blood decreased cultured brain cell viability more than thrombin or plasmin alone, enzyme overlays showed increased serine protease activity around the hematoma immediately after the blood injection. Hirudin significantly reduced the brain damage 48 hours following ICH. Ten weeks after neonatal ICH, high dose hirudin exhibited a trend to mild brain protection. These results indicate that thrombin plays a role in neonatal brain damage following ICH.

16. Cervical spine in forensic neuropathology: vertebral artery dissection

J.M. Bilbao, T. Feltis, B. Young (Sunnybrook Hospital and The Office of The Chief Coroner For Ontario, University of Toronto).

Report of two cases:

In the younger adult population, about 20% of strokes are associated with cervical artery dissection. The increasing number of reported patients lately reflects a growing familiarity with this complex clinical entity. The first patient was a 25-year-old man who, after a weekend of partying, returned home, began to vomit, became confused and walked into a wall. Thereafter he was found moribund by his partner. Imaging showed absence of flow void in left vertebral and basilar arteries and infarction in brainstem and thalamus. At autopsy, there was thrombotic occlusion of the left vertebral and basilar arteries and a focal dissection of the left VA at C4.

The second patient was a 40-year-old female, with a history of migraine. Following neck manipulation she developed agitation, hearing loss and stabbing headaches. Five days later she collapsed in the ER. Imaging showed a pseudoaneurysm of the intracranial portion of the left VA distal to pica and beading of the right vertebral artery (V3 segment). At autopsy, there was a dissection of the right VA at C1-C2 and a pseudoaneurysm of the left VA. Brainstem exhibited infarction. We will discuss the methods for the postmortem examination of the cervical spine and the possible mechanisms complicating dissection of the cervical arteries following minor trauma. We emphasize that chiropractic manipulation may be associated with bilateral VA dissection.

17. Neuropathologic correlation with clinical presentation in a patient with antiphospholipid syndrome and Libman-Sacks endocarditis

B.I. Germin, J.M. Powers, R. Han, S. Vella (Department of Pathology and Laboratory Medicine, University of Rochester Medical Center, Rochester, NY).

We report a case of a 29-year-old Caucasian female with a complicated history consisting of mental retardation, systemic lupus erythematosus (SLE) and organic brain syndrome. Her predominant symptoms during the last days of her life were related to the SLE with evidence of an antiphospholipid syndrome (APS). She presented with lethargy and mental status changes on 3/19/04. On 3/26 she developed respiratory failure, treated by intubation. An MRI suggested bilateral watershed infarcts. She died on 4/19. At autopsy she was found to have Libman-Sacks non-bacterial verrucous endocarditis involving her mitral valve and multiple microinfarcts in virtually all parts of the central nervous system examined. The microinfarcts were of both an embolic and a thrombotic nature. Libman-Sacks vegetations were found in 35% to 65% of lupus patients in early autopsy studies but routinely were clinically silent and of minor hemodynamic importance. The association between Libman-Sacks endocarditis and antiphospholipid (aPL) antibodies was first noted in 1985 in a young woman with SLE. Similar observations in four patients with SLE and one with primary APS soon followed. In 1989, four groups highlighted a probable role of aPL antibodies in the pathogenesis of valvular heart disease in patients with SLE. Other authors have reported cerebral embolism and multiple brain infarcts complicating Libman-Sacks endocarditis.

18. Comparison of Notch3 immunostaining and molecular analysis of Notch 3 gene as diagnostic strategies in CADASIL

D.G. Munoz, I. Ampuero, A. España, A. Rebolledo, J. Hoenicka, J. Garcia De Yebenes (Banco de Tejidos para Investigacion Neurologica, Madrid, and St. Michael Hospital, University of Toronto).

The best diagnostic strategy for CADASILis disputed because of lack of clinical specificity, length of the Notch 3 gene, and low sensitivity of electron microscopic examination of skin biopsies.

Patients residing in Spain clinically suspected of suffering from CADASILwere referred to us for diagnosis. Punch skin biopsy was immunostained with monoclonal antibody anti-Notch3 1E4 (donated by Dr. Joutel) and scored as B+ if 2 or more vessels were labeled, and otherwise as B-. Standard diagnostic strategy (SDS) was sequencing exons 3, 4, 11 & 18 of the Notch 3 gene, and results expressed M+ (mutation found) or M- (not found).

A mutation was present in 13 cases in exons 3 (2 cases), 4 (10 cases), 11 (1 case) and 18, and 1 in exon 19. All were B+, and no B- cases showed mutations. Of 17 M- cases, 9 were B- and 8 were B+. Against SDS skin biopsy as a gold standard, immunostaining has a sensitivity of 100%, a specificity of 50%, a positive predictive value of 59%, and a negative predictive value of 100%. M –, B+ cases may represent mutations in other exons (at least one in this sample), other genes, or false positives. Three mutations encountered (Cys155Ser, Cys162Arg, Cys1004Tyr) had not been previously described.

19. Granulomatous inflammation associated with cerebral arterial stents and aneurysmal coils: a case report

S. Krawitz, D.A. Ramsay (Department of Pathology, University of Western Ontario).

A 62-year-old woman with a large, intact basilar bifurcation aneurysm was treated by inserting stents in the basilar artery and posterior cerebral arteries and coils in the aneurysm sac. Six to eight hours after the procedure an upper brainstem (and cerebellar) haemorrhage was demonstrated. Further neurological deterioration occurred over the next six weeks. She died of acute peritonitis, related to a ventriculoperitoneal shunt apparatus.

The neuropathological examination confirmed organising right cerebellar and pontine haemorrhages and multiple foreign body-type

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granulomas in the wall of the treated vessels and aneurysm and in the vascular distribution of these vessels (right and left thalamus, associated with the haematomas, and free in a small cerebellar leptomeningeal artery adjacent to the cerebellar haemorrhage). The majority of the granulomas contained non-refractile basophilic or eosinophilic material or, rarely, silvery refractile material.

The granulomas in the stented vessels and coiled aneurysm formed in situ, either in response to the metal or its coating. The granulomas in the cerebellum, thalamus, and associated with the haemorrhages could have formed locally in the brain in response to foreign material dislodged at the time of surgery and/or as a consequence of embolisation of granulomas from the treated vessels. The granuloma in the small cerebellar artery originated from the treated vessels shortly before death. The significance of the granulomatous reaction with respect to the haemorrhages is uncertain.

TITLES OF DIAGNOSTIC CASE PRESENTATIONS

1. **Metastatic tumor with mixture of neuroendocrine carcinoma, embryonal mesenchyme, and chondrosarcoma: most consistent with biphasic pulmonary blastoma**

   C. Dunham[1], D. George[1], D. Louw[2] (University of Calgary/ Calgary Laboratory Services[1], University of Calgary Dept of Neurosurgery[2])

2. **Hemangiopericytoma-like tumor of the nasal cavity.**

   M.-C. Guiot, J. Richardson (Montreal Neurological Hospital and Institute, McGill University)

3. **Marchiafava-Bignami disease**

   D.F. Uphoff[1], J. Pacelli[2] (Department of Pathology, Hartford Hospital, Connecticut[1], Senior Resident in Neurology, University of Connecticut and Hartford Hospital[2])

4. **Meningioangiomatosis**

   Wm. Halliday (Division of Pathology, The Hospital for Sick Children, Toronto)

5. **Malignant tumor arising in ganglioglioma**

   R. Perrin, A. Pandita, A. Guha, P. Shannon (Divisions of Neurosurgery and Neuropathology, The University of Toronto)

6. **Lafora disease**

   J. Barron, C. Pushpanathan (Janeway Children's Health and Rehabilitation Centre, St. John's, NL)

7. **Perivenous encephalomyelitis / acute disseminated encephalomyelitis (ADEM), with predominant pattern of spinal cord involvement**

   J.P. Rossiter (Department of Pathology and Molecular Medicine, Kingston General Hospital and Queen's University, Kingston, Ontario)

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