Canadian Association of Neuropathologists

Abstracts Presented

at the 31st Annual Meeting

September 13th - 15th, 1991

London, Ontario

The 31st annual meeting of the Canadian Association of Neuropathologists was held September 13th - 15th, 1991 at the Radisson Hotel in London, Ontario. The scientific session consisted of 26 platform presentations of papers, 1 poster presentation, and 10 cases for diagnosis. The Royal College of Physicians and Surgeons of Canada speaker was Dr. Cedric Raine of the Albert Einstein College of Medicine, Bronx, New York, on the subject of "The Multiple Sclerosis Lesion from the Perspective of the Oligodendrocyte". The Jerzy Olszewski guest lecturer was Dr. Brian Flumerfelt of the University of Western Ontario in London, Ontario, on "Mechanisms of Repair in the Central Nervous System: Reorganization and Transplantation".

Three awards for presentations by trainees were given, namely:

The Mary Tom Award was given to Dr. Henrike Heckman of Saskatoon, for her presentation on "Changes in Opiate Peptide Immunoreactivity in Human Hippocampus in Epileptics". The Morrison H. Finlayson Award was given to Ruth S. Slack of Ottawa, Ontario, for her presentation "The role of Protein Kinase C in the Differentiation of Human Neuroblastoma Cell Lines". An Honorable Mention was given to Dr. Lawrence P. Hudson of London, Ontario, for his paper "Amygdalar Sclerosis in Temporal Lobe Epilepsy".

Social functions included an afternoon trip to Stratford, Ontario, for a viewing of the musical, "Carousel", followed by a banquet at the Elm Hurst Inn in Ingersoll. At the business meeting of the Association a new executive was elected, namely Dr. Joseph J. Gilbert of London, Ontario, for President, and Dr. Sukriti Nag of Kingston, Ontario, for Secretary-Treasurer.

Abstracts of Papers Presented at the 31st Annual Meeting of the Canadian Association of Neuropathologists

1.

Cranial Ectomesodermal Hypoplasia: A New Entity. Report of 2 Cases.

R. HAMMOND and M.G. NORMAN (Vancouver, B.C.)

Two fetuses, 14 and 15 week conceptional age respectively, had their gestation terminated following ultrasound diagnosis of fetal abnormality. At autopsy both were found to have a membrane covering and enclosing the cerebral hemispheres. The membrane seemed mesodermal, but no bone or dura could be found in it. Whether this membrane, which was not covered by squamous epithelium, represents primitive meninx or not is problematic. The superior sagittal sinus had not formed. There were abnormalities in the cerebral hemispheres which probably are deformations, that is, occurred secondary to the fact that the hemispheres were inadequately protected by the membrane which lacked bone. The cervical spine had not closed, leaving the cervical spinal cord exposed.

We believe this to be a newly described entity which is one of the variants seen within the acrania group; there is also a relationship to neural tube defect.

The embryology and proposed pathophysiology will be discussed. One mechanism must be failure of "turning-on" of genes which cause dura and bone to form, though whether the failure is genetic or teratogenic is unknown. One fetus had trisomy 21 which is considered coincidental, and probably not related to the etiopathogenesis of the cranial defect.

2.

Fetal Arterial Insufficiency Defines the Site and Extent of Schizencephaly, Porencephaly, Hydranencephaly and Encephalomalacia

ELLSWORTH C. ALVORD, JR. and CHENG-MEI SHAW (Seattle, U.S.A.)

The MRI of a recent case with a long posterior extension of the lateral fissure dividing the brain into fronto-parietal and temporo-occipital portions, dated at 16 weeks gestation, closely resembled the healed stage of the case reported by Norman (Can J Neurol Sci 7:191, 1980) with 9 weeks survival in utero after a vascular insult estimated at 17 weeks gestation, and prompted the following review of about 2 dozen cases each of schizencephaly-porencephaly and hydranencephaly. Schizencephaly was originally described by Yakovlev and Wadsworth (J Neuropath Exp Neurol 5:116, 169, 1946) as being with lips open or closed but is best reserved to describe narrow clefts ("closed lips" with less than one gyrus destroyed) which may communicate or not with the lateral ventricle. A true "pia-ependyma seam" can be present only in those cases in which the initial lesion communicated with the ventricle but then healed together with neither pia nor ependyma included in the seam between them. By contrast, porencephaly is typically a wide cleft destroying more than one gyrus that communicates with the ventricle and thus cannot have a pia-ependyma seam.

There is a morphologic spectrum of the site and extent of the lesions and degree of the subsequent development of the adjacent cerebral cortex, frequently with polymicrogyria, that can be correlated with the gestational age of apparent onset of the failure of circulation in one or more branches of the major cerebral arteries. The lesions are usually bilaterally symmetric in site but may be asymmetric in size and presence of cortical hyperplasia, polymicrogyria and/or communication with the ventricle.

The presence of many anastomotic channels in the fetal arterial circulation makes it difficult to predict exactly the "watershed" distribution of lesions when arterial blood flow fails. Commonly, however, the clefts of schizencephaly and porencephaly lie in the distribution of single or multiple adjacent fetal arteries, especially branches of the middle cerebral artery. The earlier in gestation that the destructive lesion occurs, the deeper will cerebral cortex appear in the lips of the defect as the preserved cortex continues to grow and "mushrooms" around the defect. The later in gestation that the destructive lesion occurs, the more likely it will present as hydranencephaly or resemble cerebral infarctions in the adult, except that the absorption of the necrotic debris occurs more rapidly.

3.

The Fimbrio-dentate Membrane: Hallmark of Early-Onset Hydrocephalus

JANS MULLER (Indianapolis, U.S.A.)

If there be unusual tension in the fetal ventricular outline — pressure hydrocephalus — most of the stretch will be accommodated in one specific area of least resistance. The ballooning of the hemisphere in and by itself will lead to a specific alteration in the gyral pattern, Stenogyria, of which no more here save the observation that there is a punctilious association between Stenogyria and the typical malformation of the medial hemispheral wall to be described.

At one point during development three structures — the posterior corpus callosum, the fornix and the fasciola cinerea or gyrus fasciolaris, meet at one point, called the fimbrio-dentate point by Max Clara. This structure is held to point dimension in a wide variety of mammalian brains, usually by various contortions of the fasciolar gyrus; it is precisely this abhorrence of Nature which is transcended in intra-uterine hydrocephalus with the formation of a stretched, fimbrio-dentate membrane. Its limits are: the corpus callosum above, the un-rolled fasciolar gyral complex behind (often still bowing forward, as if to obviate the membrane), the fornix below, and a new structure, the suture where the fimbrio-dentate membranes from each side meet, in front. The reluctant development of this de-novo structure exposes priorities of the morphogenetic program: the fornix always stays low and the dorsal hippocampus vestigializes (Striae Longitudinales of Lancisi, Indusium Griseum) only

where the corpus callosum is close by, assumes its predestined full bloom as soon as it is free of callosal inhibition.

In addition, the presence of this structure, the development of which is only possible in a fairly narrow window, say 20 to 30 week gestation, dates the onset of the hydrocephalic process. In later-onset hydrocephalus, the corpus callosum no longer distances itself from the fornix, and the gyral pattern now will be of the expanded gyrus pattern.

4.

Hypothalamic Neurocytoma with Vasopressin Immunoreactivity: Immunohistochemical and Ultrastructural Observations

J. MAGUIRE, J. BILBAO, K. KOVACS and L. RESCH (Toronto, Ontario; Halifax, Nova Scotia)

Hypothalamic tumors of neuronal derivation are extremely rare. We describe the case of a 55-year-old woman with visual disturbance who was found by magnetic resonance imaging (MRI) to have an intrasellar mass with suprasellar extension. She underwent subtotal surgical resection of a firm homogenous mass by a transsphenoidal approach. Light microscopy showed tumor tissue composed of a uniform population of short spindle cells with round to oval nuclei, arranged in bundles. Cellular outlines were indistinct, the tumor cells being separated by an abundant ground substance with the appearance of neuropil. Fine axonal processes were demonstrated by the Bodian stain. The neoplastic cells were immunoreactive for neuron specific enolase (NSE), synaptophysin and vasopressin. Immunostainings were negative for glial fibrillary acid protein (GFAP), VIP, bombesin, chromogranin, neurofilament, high and low molecular weight cytokeratin, vimentin, β-endorphin, GRH, galactosamine, neurophyin, serotonin, arterenol, CRH, and somatostatin. Electron microscopy revealed axonal processes containing neurosecretory granules. Synapses and glial stroma were not seen. This is the first case of a vasopressin immunoreactive neurocytoma occurring in this location. The light microscopic, immunohistochemical and ultrastructural observations of this unique tumor are indicative of primary hypothalamic derivation.

5.

Cowden Syndrome and Lhermitte-Duclos Disease: Report of Two Cases

S. ALBRECHT, R.M. HABER, J.C. GOODMAN and M. DUVIC (Toronto, Ontario; Houston, U.S.A.)

Cowden syndrome (CS) is a rare but underdiagnosed autosomal dominant condition also known as "multiple hamartoma-neoplasia syndrome". Patients develop multiple tricholemmomas (a type of benign skin appendage tumor), oral papillomatosis and cutaneous keratoses. They also often have goiter, gastrointestinal polyps and hamartomatous soft tissue lesions. Breast cancer affects about one-third of women with CS. Lhermitte-Duclos disease (LDD) is a peculiar proliferation of abnormal neuronal elements of the cerebellum that has features of a hamartoma and of a neoplasm; only about 60 cases have been reported since 1920. We describe two patients who have both CS and LDD. The first patient is a 48-year-old women who developed hydrocephalus in 1972, for which no cause could be identified. She was treated with a shunt. In 1975, brain scan demonstrated a right cerebellar mass which was partially resected. The histology was typical of LDD. A recurrence in 1981 was resected and irradiated. She also had a multi-nodular goiter and an ovarian cyst. When seen in 1985 for "plantar warts", examination revealed multiple facial papules which were typical tricholemmomas histologically. She also had papillomatosis of the tongue and gingiva as well as acral, palmar and plantar keratoses. In 1988, she underwent a lumpectomy for carcinoma of the right breast. When last seen in 1989, she had developed bony metastases. The second patient is a 50-year-old woman with a history of thyroidectomy for goiter, gingivectomy for gingival papillomatosis, endometriosis, and fibrocystic changes of the breast. She had multiple facial, acral, palmar and plantar keratoses, as well as inflammatory and fibrous polypoid lesions in the esophagus, stomach, duodenum and colon and a tubular adenoma of the colon. She presented in December 1990 with a one-year history of headaches and positional syncope. Imaging investigations showed hydrocephalus and a right cerebellar lesion. Biopsy was typical of LDD. Only three other patients in whom both LDD and CS were recognized have been reported in the literature. Given the rarity of these two entities, we believe that their association is not fortuitous. LDD fits into the concept of CS as a hamartoma-neoplasia syndrome. Furthermore, a number of patients with LDD who had other neoplasms and/or thyroid lesions have been reported, raising the possibility that CS and LDD are more closely linked than is generally appreciated. We suspect that there are more patients with LDD who have unrecognized CS. Patients with either of the two conditions should be examined and followed for evidence of the other.

6.

Golgi Studies of the Brain in Rett Syndrome

DAWNA DUNCAN ARMSTRONG, BARBARA ANTALFFY and STEPHEN C. WARING (Houston, U.S.A.)

Rett syndrome is a disease of the nervous system affecting girls, beginning in infancy, and characterized by deceleration of head growth, loss of purposeful hand movements, acquisition of sterotypic hand movements, psychomotor retardation, spasticity and a breathing and movement disorder. The pathogenesis of the disorder is not understood. A genetic factor, possibly encoded on the X chromosome is being sought, and morphologists are searching for a morphologic marker of this unknown factor. The decreased size of the brain, and of most other organs, is a consistent finding, but the brain shows no obvious site of neuronal loss, myelin deficiency or hydrocephalus to account for its 30% reduction in weight. Gross examination of the brain does not define obvious sites of selective atrophy, although there is one report of CT examination suggesting that the brain stem, thalamus, and medial frontal lobes are more involved. There is a recent report of a generalized decrease in neuronal size in Rett syndrome. We have studied selected cortical areas of six girls with Rett syndrome, ages 6-30 years, using the Golgi technique

and the Scholl analysis of dendritic fields. The frontal, motor, temporal, and occipital cortex show decreased size of neurons. There is a decrease in the dendritic fields of selected layers, which is not age related. The sibiculum and CA1 appear to be involved before other cortical areas, and in some areas the layer V neurons appear to be involved before the layer III neurons. These initial and selected studies suggest that limbic and cortical efferent systems may be arrested or delayed in development before other systems.

7.

Intracapillary Gaucher Cells - A Possible Cause of Neurological Symptoms

R. MACAULAY and J.H.N. DECK (Toronto, Ontario)

Gaucher's disease, the result of deficiency of the lysosomal enzyme B glucocerebrosidease is characterized by the accumulation of sphyngolipid within macrophages of the reticuloendothelial system.

Our patient, diagnosed at age 18 months had a splenectomy at age 9 years, developed seizures at 18 and died at 25.

The brain showed widespread perivascular Gaucher cells as has been previously reported. In addition, Gaucher cells were frequently identified within capillary lumina. Similar intraluminal Gaucher cells were present in pulmonary and glomerular capillaries as has been reported previously.

Electron microscopy of formalin fixed autopsy tissue confirmed the presence of Gaucher cells with cytoplasm swollen by typical tubular aggregates obstructing the lumina of many capillaries. The Gaucher cells were distinguishable from endothelial cells and pericytes. Their presence also in pulmonary and glomerular capillaries suggests that Gaucher cells may spill from bone marrow and liver and may enter the circulation and embolize to pulmonary and eventually to cerebral capillaries. Their large size and the numbers of capillaries affected suggest that they have become arrested within capillaries, however, slow passage through the capillary bed with more transient obstruction cannot be excluded by the EM appearances. Despite the absence of demonstrable cerebral infarcts, the substantial portion of cerebral capillaries affected suggests that ischemia may have contributed to neurological symptoms. Intraluminal Gaucher cells are easily overlooked and it is not known in what proportion of cases of Gaucher's disease, this phenomenon is present as a possible cause of neurological symptomology.

8.

Fahr's Disease Associated with Astrocytic Proliferation and Intracranial Neoplasia

L.C. ANG, B. ROZDILSKY, E.C. ALPORT and S. TCHANG (Regina; Saskatoon, Saskatchewan)

Although Fahr's disease (idiopathic progressive strio-pallido-dentate calcification) may have variable clinical presentations, it is well characterized pathologically by extensive bilateral symmetrical calcification in the basal ganglia, sulcal depths of the cerebral cortex and the dentate nuclei of cerebellum. In this report we document the occurrences of astrocytic proliferation and intracranial neoplasms in 2 relatives, both afflicted with Fahr's disease. The first patient, a 36-year-old man presented with convulsions. CT scan showed a hypodense mass in the left parietal lobe as well as extensive calcifications in the basal ganglia and cerebral cortex. His serum alkaline phosphatase, calcium and phosphate were normal. He died of acute pulmonary edema and the neuropathological examination confirmed a low grade strocytoma in the left parietal lobe and massive cerebral calcification. His paternal uncle who died at the age of 52 years, 26 years earlier, presented with ataxia and extrapyramidal signs. He died of acute bronchopneumonia and the neuropathological examination also revealed massive cerebral calcification of similar pattern. A small meningioma was also noted in the basal meninges of the frontal lobe. In both cases the GFAP demonstrated astrocytic proliferation in the areas of early calcification and at margins of the large calcareous deposits. Except for a handful of reports like those of Denny-Brown (1962) and Galatioto et al. (1976), the association of calcification and astrocytosis in this disease has rarely been discussed. Since calcifications take place initially in the vessel walls and perivascular areas, the astrocytosis has been interpreted as a response to the breakdown of blood-brain-barrier (Denny-Brown, 1962). The association of astrocytic neoplasm in Fahr's disease was only reported once previously in a boy with a cerebellar pilocytic astrocytoma (Morimoto et al., 1984). While the presence of astrocytoma in the first case could be related to extreme progression in astrocytic proliferation, the meningioma in the 2nd case is likely to be incidental.

9.

Transneuronal Degeneration in Human Inferior Olive: An Immunohistochemical Study

KEVIN D. BARRON, S. NAJJAR and A.H. KOEPPEN (Albany, New York, U.S.A.)

Transneuronal degeneration (TND) in human inferior olive follows interruption of the dentato-olivary pathway (DOP) at the cerebellar or brain stem (Pontine tegmentum) loci and is accompanied by neuronal and astroglial hypertrophy and grossly visible enlargement of the olive. We have examined histologically and immunohistochemically 12 autopsy cases where 6 weeks to several years elapsed between death and DOP interruption. Olivary TND presents striking neuronal accumulation of phosphorylated 200 kD neurofilament (NF) protein, in some nerve cells as soon as 6 weeks after injury. Dendritic expansions and "glomeruli" are prominently displayed. The 160 kD NF antigen, tyrosinated and beta tubulins and neuron specific enolase accumulate in neurons also, though to a lesser degree. These changes persist for several years and their degree varies greatly from neuron to neuron. Interestingly, affected nerve cells show marked hypertrophy and increased staining of the Golgi apparatus in preparations made with monoclonal antibody A2B5. To date we have not observed similar alterations in pontine nuclei and lateral geniculate body undergoing TND. The results may reflect a piling-up of products of neuronal synthesis due to a failure of secretion by deafferented cells (Barron et al., 1982).

10.

Automated Nerve Biopsy Morphometry on a Personal Computer

ROLAND N. AUER (Calgary, Alberta)

In the past, nerve biopsy morphometry was performed using manual counting and measuring devices. Recently, digitizing tablets and personal computers (PCs) have allowed tracing of nerve fibre data from enlarged photomicrographs into PCs. However, full automation of the process would be ideal, obviating the need for individual attention to each nerve fibre. With the advent of low cost personal computers of considerable power, and low cost image analysis systems, analysis of an image obtained at the microscope should allow automated counting, sizing, and graphing of myelinated nerve fibre data. We have developed such a method using commercially available, undifferentiated software. Macros written within the software packages give a standalone application customized for the requirements of nerve biopsy analysis, equivalent to a turnkey system.

With a 100X oil immersion lens attached to a microscope fitted with a video camera, it is possible to measure the finest (< 3 μm) myelinated nerve fibres in Epon embedded, toluidine blue stained sections, routing the data to an image analysis system. Black objects (myelin rings) having a grey scale density difference even from Schwann cell nuclei, are sized and counted. Small groups of pixels representing the darker heterochromatin of Schwann cell nuclei, are generally eliminated by the size thresholds given for counted objects. Any remaining spurious objects can be eliminated manually by clicking the mouse on them. For each object, total perimeter and area are measured, allowing calculation of nerve fibre and axon diameter. From this, myelin sheath thickness can be calculated, with the mean and variability expressed as mean and standard deviation, respectively. The results can be automatically graphed for output to paper hardcopy or 35 mm color slides, making presentation of data on a patient chart and at clinical rounds relatively simple and routine.

Advantages of the method include: 1) the ability to acquire data on hundreds of nerve fibres in a reasonable amount of time; 2) the relatively low cost; 3) the undifferentiated nature of the image analysis system (allowing other uses than nerve biopsy analysis), and 4) the independence of the data generated from the operator, if the latter is well trained. The method allows virtually every neuropathology laboratory handling nerve biopsies to routinely add morphometric data to the biopsy report in a timely manner. The procedure is also applicable in research settings. Disks containing the required macro files and instructions can be provided by the author. The method allows large quantities of data to be generated easily, and will possibly lead to increased insight into changes in peripheral nerve in aging and disease.

11.

The Neuropathology of Domoic Acid Intoxication in Man

P. GOULD and S. CARPENTER (Montreal, Quebec)

Five individuals, all male, who ingested toxic mussels in November 1987 and developed clinical signs of domoic acid poisoning came to autopsy. Three patients died within a month of their intoxication. Two patients survived 3 months, and 3 years respectively with severe memory impairment. All patients showed extensive neuronal necrosis or loss in the hippocampus and other limbic structures. Domoic acid is known from animal experiments to be an extremely potent excitotoxin. These five cases allow us to correlate the extensive experimental literature on excitotoxins with human neuropathology.

12.

Changes in Opiate Peptide Immunoreactivity in Human Hippocampus in Epileptics

H.HECKMAN, L.C. ANG, D.H. GEORGE and D. SHUL (Saskatoon, Saskatchewan)

The changes in opiate neuropeptides in seizure activity have been well studied in animals. There are increased enkephalin and dynorphin immunoreactivities in the hippocampus of seizure sensitive Mongolian gerbils (R.J. Lee et al., 1987). Such changes were interpreted as seizure induced mossy fibre sprouting. We studied the hippocampi from 5 patients with longstanding grand mal seizures using frozen sections immunostained with four antibodies against: a) dynorphin A; b) leu-enkephalin; c) met-enkephalin; d) β-endorphin. Parallel tissue sections from these hippocampi were also stained with Nissl preparations. The ages of patients ranged from 33 to 60 years with mean age of 45.6 years. Another 5 hippocampi were obtained from patients with no history of epilepsy or chronic neurological disease. One exception was a 35-year-old female who had generalized convulsions 1 day prior to death due to hepatic encephalopathy. The ages of the control patients ranged from 32 to 69 years with a mean of 48.6 years. The controls were immunostained in the same manner. There were no significant differences between the epileptic and normal hippocampi with β-endorphin and met-enkephalin immunostaining. With the dynorphin and leu-enkephalin there were increased immunoreactivities in the hippocampal formation within the CA4 and CA3 fields with staining ending in the junction between CA3 and CA2. Though there was some variability in staining between different epileptic cases it appeared that staining was mainly concentrated in clumps of punctate as well as fibre-like structures. In the CA4 field the staining was most prominent in the molecular layer. In all the control hippocampi there was no accentuation of leu-enkephalin staining. In 4 of these cases there was also no accentuation of the dynorphin A immunoreactivity. It is interesting

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that the patient with convulsions of 1 day duration resulting from hepatic encephalopathy showed no accentuation of immunoreactivity with either leu-enkephalin or dynorphin A. Previous studies have demonstrated an increase in dynorphin A immunoreactivity in temporal epilepsy in surgically removed hippocampi. However, similar changes with dynorphin A in generalized epilepsy in humans have not been demonstrated before. In spite of the evidence of increased leu-enkephalin immunoreactivity in hippocampi of experimental animals with seizures, this is the first study we are aware of that confirms such changes in the human hippocampus.

13.

Neuropathologic Findings in Cortical Resections Performed for the Treatment of Intractable Childhood Epilepsy

M.A. FARRELL, M.J. De ROSA, D.L. SECOR, M.E. CORNFORD and H.V. VINTERS (Los Angeles, U.S.A.)

Despite the use of hemispherectomy in the treatment of medically refractory seizures since the early 1950's, few published studies have documented neuropathologic findings in the resected specimens. We report the neuropathologic findings in 38 children who underwent either hemispherectomy or multilobar cortical resection as treatment for medically intractable epilepsy between 1986 and 1990. Examination of the resected specimens revealed a variety of abnormalities which fell into four broad categories. Malformations or hamartomatous lesions were the dominant finding in 15 patients. Characteristic of this group were coarse neuronal cytoplasmic fibrils and large "balloon cells" which displayed variable GFAP immunoreactivity. The proliferative potential of the "balloon cells" was assessed using a silver impregnation technique to demonstrate nucleolar organizer regions (AgNORs). When corrected for nuclear area, giant neurons and "balloon cells" had similar numbers of AgNORs and both had significantly ($p < 0.001$) fewer AgNORs than reactive astrocytes. This result suggests that "balloon cells" are non-proliferative. Encephalomalacic lesions were the most prominent abnormality in 16 patients. Chronic pathogen-free encephalitis (Rasmussen's encephalitis) was present in three patients. Using immunohistochemistry and *in situ* hybridization we were unable to demonstrate cytomegalovirus in brain tissue resected from patients with Rasmussen's encephalitis. Three children had Sturge-Weber-Dimitri syndrome. There were no gross or microscopic abnormalities in one patient. This report provides the first comprehensive description of the pathologic findings in a series of children with refractory epilepsy of varying types treated by hemispherectomy-multilobar resection. Correlations between specific neuropathologic abnormalities and efficacy of surgical treatment of a given type of epilepsy will eventually be of therapeutic value but are as yet not possible.

14.

Effects of Hippocampal Sclerosis on Neuropsychological Test Performance

L.A. MILLER, D.G. MUNOZ and M. FINMORE (London, Ontario)

Thirty-nine patients in whom unilateral temporal lobectomies had been carried out for the relief of intractable seizures were classified into four groups on the basis of: 1) side of excision, and 2) presence or absence of hippocampal sclerosis. Excluded from the study were patients with ages < 16, IQs < 80, evidence of atypical speech representation, or hippocampal pathology other than sclerosis. Hippocampal sclerosis was identified by loss of neurons and gliosis involving the CA_1 and CA_3 hippocampal sectors, in the presence of partial sparing of the CA_2 sector. The extra-hippocampal pathology in patients without hippocampal sclerosis included 5 cases of isolated gliosis of the amygdala, 2 gangliogliomas, 1 oligodendroglioma, 2 cavernous angiomas, 1 arterio-venous malformation, and 3 cases with minimal changes, best expressed by subpial gliosis.

A chi-squared test comparing groups on the basis of age of initial seizure showed that whereas only 1/14 without hippocampal sclerosis had experienced their first seizure prior to the age of 3, 19/25 of the patients with hippocampal sclerosis had had a seizure by this age. Pre-operative neuropsychological test results revealed that patients with hippocampal sclerosis did not differ from those without sclerosis on tests of immediate recall, problem solving, fluency, visual perception, or attention span. They were, however, impaired on two tests requiring material to be recalled after a delay interval. On the delayed recall of a complex geometric drawing, patients with either left- or right-sided hippocampal sclerosis achieved significantly low scores. For the recall of short verbal passages, only patients with left-sided sclerosis were impaired. The results are taken as further evidence that mesial temporal-lobe structures are necessary for long-term retention.

15.

Extensive Acute Infarct of the Spinal Cord: Complication of Disseminated Leptomeningeal Gliomatosis

K.L. HO, D.V. CACCAMO and J.H. GARCIA (Detroit, U.S.A.)

Although leptomeningeal gliomatosis from a primary intraparenchymal glioma is well recognized, extensive acute infarct of the spinal cord as a complication of disseminated leptomeningeal gliomatosis has not been reported. We presented the case of a 55-year-old man who developed progressive deterioration of mental status and gait due to hydrocephalus for which bilateral VP shunts were placed. Two weeks prior to death, he became lethargic, dysphasic and paraplegic. CT scan suggested an intraventricular tumor involving the posterior portion of the third ventricle. He died of massive acute pulmonary embolism. Neuropathologic examination revealed a diffuse periventricular glioblastoma multiforme involving the entire ventricular system including the 4th ventricle. Gliomatous extension into the leptomeninges was noted in the cerebrum, cerebellum, brainstem, spinal cord and cauda equina. The cervical and upper thoracic cords were encircled by a thick gliomatous tissue whose astrocytic lineage was confirmed by the positive stains for GFAP and S100 protein. The cord in this region was almost totally necrotic due to acute infarction, with only small rim of intact parenchyma at the periphery. The surrounding gliomatous tissue exhibited prominent vasculatures and various vascular changes including endothelial proliferation and hyperplasia, glomeruloid formation, recent and organizing thrombosis with recanalization. Some of the intrinsic small vessels of the cord also appeared to be occluded. The gliomatous tissue was limited to the subarachnoid space and the cord was not invaded by the

tumor. The findings suggest that: 1) examination of spinal cord is necessary in all brain tumor cases, and 2) acute necrotizing myelopathy due to thrombosis may complicate leptomeningeal gliomatosis.

16.

Chromogranin A, A Synaptic Vesicle Protein, is Found in Cortical Neurons Other than Previously Identified Peptidergic Neurons

LAURIE A. ADAMS and DAVID G. MUNOZ (London, Ontario)

Only one broad morphological class of peptidergic neurons has been identified in the cerebral cortex to date: the bitufted neuron (Jones, 1986). Chromogranin A (CgA) is a soluble protein of large dense core synaptic vesicles. The distribution of CgA immunoreactivity in the calcarine cortex (Broadmann's area 17) was compared with that of two calcium binding proteins, calbindin-D28K (CaBP) and parvalbumin (PV), using a sequential double immunolabelling method. Virtually all PV-immunoreactive neurons were found to be co-localized with CgA. PV has been found by previous investigators to be a marker for basket cells, chandelier cells and other less well-defined cell types, thus, the concurrent localization of CgA to these cell types marks the first discovery of a synaptically active neuropeptide outside a single class of cortical peptidergic neurons. Additionally, the sum of PV-immunoreactive plus CaBP-immunoreactive neurons is known to encompass the entire population of non-pyramidal neurons. In this study, CgA-immunoreactive neurons formed a larger group than PV and CaBP neurons combined, therefore CgA-immunoreactive neurons appear to make up a diverse neuronal population encompassing both pyramidal and non-pyramidal cells.

17.

Microtubule Associated Protein Tau is a Component of the Lewy Body Fibril Core

M.S. POLLANEN, C. BERGERON and L. WEYER (Toronto, Ontario)

Cortical Lewy bodies were isolated from brains with diffuse Lewy body disease using non-ionic detergent-high salt buffer extraction, gradient centrifugation, and extraction into urea. Purified Lewy bodies maintain the characteristic histologic and immunochemical profile and are composed of straight unpaired filaments. Neurofibrillary tangles-paired helical filaments did not copurify in significant amounts with Lewy bodies. Treatment of isolated Lewy bodies with sodium dodecyl sulphate/dithiothreitol solubilized much of the Lewy body contaminants which copurified on sucrose gradients and the non-covalently bound proteins of the Lewy body fibril, which on electrophoresis were characterized by several high molecular weight polypeptides. The detergent insoluble Lewy body fibril core was largely soluble in formic acid. Electrophoretic studies of formic acid solubilized Lewy body fibrils revealed polypeptides in the 68 kD range. Western transfers of the 68 kD Lewy body polypeptide were probed with antisera to microtubule associated protein tau which reacted with the 68 kD band. Immunohistochemical studies with a monoclonal antibody which recognizes the tau-l epitope of human tau, however, did not stain cortical Lewy bodies in dephosphorylated formalin fixed histologic sections. We conclude that tau is a component of the Lewy body fibril but exists in a conformation in which the tau-l epitope is inaccessible. The results suggest that tau of Lewy bodies is post-translationally distinct from that in Alzheimer neurofibrillary tangles.

18.

Dystrophic Neurites in Alzheimer's Disease are not Necessarily Associated with B-Amyloid Protein

D. WANG and D.G. MUNOZ (London, Ontario)

Senile plaques of Alzheimer's disease consist of a crown of dystrophic neurites around extracellular deposits of amyloid. B-amyloid protein (B/A4), a major component of plaque amyloid, shows both neurotrophic and neurotoxic effects *in vitro*. These facts have prompted several authors to postulate that B/A4 is the factor inducing the development of dystrophic neurites. We recently described a new lesion in Alzheimer's disease, tangle-associated neuritic clusters (TANCs). TANCs are seen in the hippocampus in all patients with Alzheimer's disease. They consist of multiple dystrophic neurites, identified by their chromogranin A immunoreactivity, in intimate association with an extracellular neurofibrillary tangle. We now report that the neurofibrillary tangles associated with dystrophic neurites in TANCs are consistently decorated by antibodies to paired helical filaments, but not tau. Conversely, only a subset of these tangles is labelled by three different antibodies to B/A4. We conclude that the presence of B/A4 is not necessary to induce dystrophic changes in neurites.

19.

Amygdalar Sclerosis in Temporal Lobe Epilepsy

L.P. HUDSON, D.G. MUNOZ, J.P. GIRVIN, H. REICHMAN, R.S. McLACHLAN, L. MILLER and W.T. BLUME (London, Ontario)

Hippocampal sclerosis (HS), a stereotyped pattern of hippocampal cell loss and gliosis, is the sole pathological abnormality in approximately 65% of temporal lobectomies for intractable temporal lobe seizures (Babb and Brown, 1987). Although a small proportion of the remaining cases can be related to vascular, malformative or neoplastic lesions, up to 22% of these resections demonstrate no recognizable pathology (Duncan; Sagar, 1987; Burton, 1988). We have encountered severe amygdalar gliosis and cell loss, in the absence of HS or other temporal lobe pathology, in 8 patients treated with en bloc unilateral resection of temporal neocortex, hippocampus and amygdala for temporal lobe seizures. This group of patients exhibited significant preoperative clinical differences from those found to have HS in terms of age at onset of seizures, and performance on standard neuropsychological tests. These findings suggest that amygdalar pathology may be independently associated with the development of temporal lobe seizures.

20.

Microglial Activation and Astrocytic Hyperplasia in Neuritic Plaques of Alzheimer's Disease

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Recent analyses of the neuritic plaque (NP) of Alzheimer's disease (AD) indicate that the microglial cell may play a role in the formation of these lesions. The objectives of this light microscopic study were to examine the presence of microglia within neuritic plaques, and to identify any correlation with astrocytic hyperplasia. Hippocampal (HC) and superior temporal gyral (STG) tissue from ten clinico-pathologically diagnosed cases of AD, and five aged-matched controls, were studied using primary antisera against LN5 (antimacrophage) and glial fibrillary acid protein (GFAP). LN5 immunoreactive cells with microglial morphology were found in 8/10 cases, usually in both STG and HG; and often occurring in plaque-like clusters. Hyperplastic astrocytes immunoreactive to GFAP were identified in 7/10 cases in similar clusters, most in STG. No such changes were seen in control brains. Microglial activation and astrocytic hyperplasia appear to be equally involved at some stage of neuritic plaque formation. A common synchronous response by both microglia and astrocytes to an as yet unidentified single immunogenic stimulus may be implicated.

21.

The Temporal Response of Astrocytes to Injury. An Experimental Study Utilizing Molecular Immunohistochemical Probes

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Our laboratory has been interested in defining the sequence of events that take place within the vasculature of the Central Nervous System after injury; that lead to its regeneration; and that re-establish its blood brain barrier properties. The astrocyte has been shown to be an important contributor to this process. Our earlier studies, utilizing a freeze-injury model in the mouse have shown that around four days after injury the astrocyte enters the mitotic pool in response to injury, and that glial fibrillary acidic protein becomes demonstrable in the cytoplasm of the cells. The present study was undertaken to determine whether or not a messenger RNA for GFAP was present in normal or increased amounts in astrocytes as a response to injury and if so, how was its temporal expression related to the demonstration of GFAP by immunohistochemical techniques.

A cerebral freeze-injury was produced in mice, and at intervals thereafter, the animals were anesthetized, perfused with formalin and histological sections of the brain through the injured area were prepared. A riboprobe for messenger RNA labeled with S35 and an immunohistochemical probe for GFAP were utilized to demonstrate mRNA and the GFAP epitope respectively. For mRNA studies, the histological slide with either sense or antisense probe was overlayed with X-ray film. The developed image was quantitated by a computer-enhanced technique. The results indicated that mRNA for GFAP is increased in astrocytes in the environs of the injury by 8-12 hours, and that it increases dramatically in amount up to 7 days. GFAP is demonstrable in the astrocytes at 3-4 days after injury. Thus there is a rapid response of astrocytes with increased mRNA expression that is followed temporally by GFAP expression.

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22.

Regenerative and Remyelinative Capacity of Long Term Quiescent Oligodendrocytes

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The ability of oligodendrocytes in adult brain to regenerate and remyelinate is of fundamental importance for the recovery from neurological disease. We have previously investigated the survival capacity of oligodendrocytes in long term Wallerian degeneration in the optic nerve of the rat. In these studies it was shown that oligodendrocytes could survive for periods of up to 2 years in the absence of axons. The oligodendrocytes however, displayed abnormal cytological characteristics, with abnormal notched irregular nuclei, and scanty cytoplasm. Their oligodendrocytic nature was determined with certainty only with the use of antibodies to carbonic anhydrase at a light microscopic level, and to myelin oligodendrocytic glycoprotein (MOG) at an ultrastructural level.

We have now tested the capacity of these long term quiescent oligodendrocytes to regenerate and to remyelinate axons. Fragments of rat optic nerves in which enucleation had been carried out between 13 months and 2 years previously, were trypsinized, their meninges removed, and implanted into the brains of neonatal Shiverer mice. Four weeks after implantation, the brains of the Shiverer mice were studied using antisera to myelin basic protein. Although the quantities of tissue implanted and the number of cells were very small, unequivocal evidence of myelination was demonstrated outside and within the implant. The presence of myelin basic protein indicated that the myelin formed had come from oligodendrocytes emanating from the grafted tissue. In addition, numerous oligodendrocytes, both within the graft and outside the graft, displayed myelin basic protein positive cytoplasm, reminiscent of the pattern seen in development and remyelination. Silver stains demonstrated ingrowth of axons from the host tissue into the graft, and often in these situations, oligodendrocytes positive for myelin basic protein were noted within the graft. Some of these axons were subsequently remyelinated by the oligodendrocytes remaining in the graft.

The results indicate a potential for recovery and remyelination by oligodendrocytes even when deprived of axonal stimulus for long periods, and their subsequent responsiveness to the presence of axons. The small numbers of cells involved precludes an accurate assessment of the true migratory potential of these cells for any long distance.

23.

Systemic Microangiopathy in Leber's Hereditary Optic Atrophy

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Leber's hereditary optic atrophy (LHOA) is maternally inherited mitochondrial disease characterized primarily by loss of vision, occasional systemic and/or neurological manifestations and red ragged fibers (RRF) in muscle biopsies. Some patients with mitochondrial DNA (mDNA) point mutation at nucleotide position 11778. Mothers are obligatory carries, fathers do not transmit, while male and female offspring may clinically express the disorder.

We carried out morphological examinations of muscle and skin biopsies as well as tissue culture studies of striated muscle and fibroblasts from three families with LHOA. Each family was also studied for the presence of mDNA 1178 mutation. The patients included clinically affected males and females as well as unaffected females.

Electron microscopy showed subsarcolemmal accumulation of mitochondria (M) in many striated muscle fibers. M frequently showed slight morphological abnormalities in configuration of cristae as well as crystalloid inclusions and significant variability in size and shape. M abnormalities persisted in tissue cultures and they were present in subclinical female carriers as well as in the affected individuals. M changes were present in many cell types, including Schwann cells, fibroblasts, occasional pericytes and few smooth muscle cells of vessels. However, only severely affected individuals showed marked thickening and reduplication of endothelial basal lamina, necrosis of pericytes and accumulation of necrotic debris in walls of affected capillaries. These changes were much less pronounced in clinically unaffected female carriers. All families were negative for 11778 point mutation.

Our studies support the concept of Leber's hereditary optic strophy as a systemic mitochondrial disease. In addition, we demonstrated that all individuals in the maternal line of inheritance, affected as well as subclinical, express mitochondrial abnormalities. Furthermore ultrastructural studies of muscle biopsies indicate that the development of the systemic microangiopathy correlates well with the clinical expression of the disorder.

24.

The Role of Protein Kinase C in the Differentiation of Human Neuroblastoma Cell Lines

R.S. SLACK, B. LACH, A. GREGOR and P. PROULX (Ottawa, Ontario)

Studies on the involvement of protein kinase C (PKC) in retinoic acid (RA) induced differentiation of two sublines of human neuroblastoma were carried out. The SH-F subline when treated with RA demonstrated substantial increase in PKC and differentiated to a flattened, strongly adherent cell type resembling fibroblasts. Under the same conditions, the other, SH-N cell line responded with a marked PKC decrease and formed a neuronal-like phenotype. To test the hypothesis that PKC inhibition is required for the formation of the neuronal phenotype, the PKC inhibitor, staurosporine, was added to cell cultures. When SH-F cells were treated with staurosporine and RA together, a marked decrease in PKC activity was observed. Under these conditions the usual flattened cell type was not formed. Instead, these cells gave rise to a neuronal-like phenotype similar to that produced by RA-induced differentiation of the SH-N subline.

Immunohistochemical and electron microscopic studies confirmed that SH-F and SH-N cells form distinctly different phenotypes following RA treatment. SH-N cells expressed neurofilament and other neuronal markers, and showed ultrastructural features indicative of neuronal differentiation. Many of these neuronal cells demonstrated formation of synaptic-like contacts with other cells. Prolonged maintenance in tissue culture of these cells led to development of striking dystrophic changes in the distal segments of neuritic processes. SH-F cells appeared to loose immunohistochemical and ultrastructural neuronal markers following the RA induced differentiation to fibroblast-like cells. When PKC inhibitor, staurosporine was added together with RA to SH-F cells, they showed striking immunohistochemical and ultrastructural features of neurons, similar to that produced by SH-N in the presence of RA. Staurosporine, when added alone also induced signs of neuronal differentiation in these cells.

These results strongly implicate a key role for the PKC in the phenotype development in neuroblastoma cell line.

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25.

Vascular Dementia: Case Presentation and Results of Preliminary Studies

J.H. GARCIA and G.G. BROWN (Detroit, U.S.A.)

There is considerable controversy over the definition and, therefore, the prevalence of dementia that is purely associated with either vascular or circulatory disorders.

A variety of lesions in several locations (cerebral cortex, subcortical white matter, and thalamic nuclei) have been associated with dementing syndromes. The lesions of presumed "vascular" origin are also heterogenous, ranging from hypotensive crises to amyloid angiopathy.

We have studied the brain of a 58-year-old patient whose dementia (clinically classified as Alzheimer's type) had started about 4 years before death. The brain showed none of the lesions of Alzheimer's Disease; instead, there were numerous areas of scarring (gliosis) associated with widespread angiopathic changes of uncertain etiology. Data will be presented from two prospectively evaluated groups of dements. By nuclear magnetic resonance spectroscopy, those with a clinical diagnosis of Alzheimer's Disease have decreased phosphomonoester signals (suggestive of hypometabolism) whereas a second group with a clinical diagnosis of vascular dementia demonstrates increased signal for these same metabolites. We propose that this increased signal is related to hypermetabolic activity associated with astrogliosis.

26.

Fatal Intracranial Hemorrhage Arising From an Acute Traumatic Carotid-Cavernous Sinus Fistula

E.S. JOHNSON (Edmonton, Alberta)

Intracranial hemorrhage is an uncommon and delayed complication of carotid-cavernous sinus fistulas and usually occurs as a sequel to chronic venous hypertension in the venous tributaries of the sinus due to reflux of arterial blood. This report, however, documents the rarer occurrence of hemorrhage as an acute complication of a fistula. A 35-year-old man fell 3 to 4 m from a metal scaffold at work and sustained bilateral skull fractures with loss of consciousness (Glasgow coma score 4/15). A CT scan on entry to hospital showed a left petrous fracture with acute subarachnoid hemorrhage, and a scan the following day revealed an additional finding of a right medial temporal lobe hematoma. To monitor intracranial pressure a right intraventricular catheter was inserted upon admission but had to be removed ten hours later because of clotting by blood. On the third hospital day a right pulsating exophthalmos developed and angiography confirmed the presence of a right carotid-cavernous sinus fistula. The patient's clinical status worsened and he died nine days after the accident. At autopsy there were bilateral severe petrous fractures that extended into the sphenoid bone and were accompanied by multifocal tears and organizing hemorrhages in the trabecular and dural walls of both cavernous sinuses. This damage was greater in the engorged right sinus in which there was a huge fistulous communication with the posterior ascending segment of the carotid artery. A related finding was a giant hematoma arising in the lateral dural wall opposite the fistula and tracking through the dural roof of the sinus into the right medial temporal lobe to rupture into the ventricular horn and produce a broad border of pressure necrosis. Other findings attesting to the severity of craniocerebral trauma included a fracture contusion of the left fusiform gyrus, intermediate coup contusions of the white matter structures and hypothalamus, a right orbital contusion, and acute subarachnoid and subdural hemorrhages. This pattern of injury suggested that the patient fell on his feet or buttocks with the impact ramming the vertebral column into the skull base to cause the petrous and sphenoid fractures, shearing tears of the cavernous sinus, and fistula. Hence, unlike most cases of intracranial hemorrhage arising from a carotid-cavernous sinus fistula, the mechanism in this case was the combination of traumatic laceration of the dural walls of the sinus and acute venous hypertension subsequent to formation of the fistula.

27.

Cutaneous Ganglioneuroma

R. HAMMOND and J. WALTON (London, Ontario)

The occurrence of ganglioneuromas outside of the sympathetic chains of the mediastinum and abdomen in the non-pediatric age group is distinctly unusual. We report the case of a solitary cutaneous ganglioneuroma of the abdomen in a 52-year-old woman. The lesion had been present for approximately 20 years and was located in an abdominal scar. Grossly it measured 1.2 centimetres in greatest dimension. Characteristic unmyelinated axons, Schwann cells and scattered mature ganglion cells were seen microscopically and their presence confirmed using routine histochemical and immunocytochemical stains. Only 3 similar cases have been reported in the literature. They have also been reported as mature components of metastatic neuroblastoma and in association with plexiform neurofibromas, neither of which was present in this case. The pathogenesis of this lesion is unclear, however aberrant embryological migration of neural crest elements would seem to be the most reasonable explanation. Although no follow-up series exist, local excision should be curative considering the small size and histologically benign appearance of the lesion.

Titles of Diagnostic Case Presentations

1. **Arachnoidal cyst with choroid plexus differentiation**
   A.H. KOEPPEN, C.G. HURWIRTZ and J.J. LEE (Albany, New York).
2. **Cytomegalovirus encephalitis with polymicrogyria**
   R.P. HAMMOND and M.G. NORMAN (Vancouver, B.C.).
3. **Kernicterus**
   M. BRENNAN and D.G. MUNOZ (London, Ontario).
4. **Adult onset Hallervorden-Spatz disease**
   W.C. HALLIDAY (Winnipeg, Manitoba).
5. **A. Perineurioma, B. Benign nerve sheath tumor (cellular neurothekeoma)**
   T.-w.E. HUANG (Royal Oak, Michigan).
6. **Melanocytoma (cellular blue nevus) of leptomeninges**
   B. LACH, B. BENOIT and P. PROULX (Ottawa, Ontario).
7. **Neurotropic primary T-cell lymphoma**
   J.B. LAMARCHE (Sherbrooke, Quebec).
8. **Nucleus dentatus nigracans, ?due to deposition of sulphur containing compound from anti-ulcer medication "Carafate" (Sucralfate)**
   M.J. BALL, P. STENBERG, C. MESCHUL and D. PERL (Portland, Oregon; New York, New York).
9. **Request for help with diagnosis, ?toxic disorder of astrocytes**
   V. SANGALANG (Halifax, Nova Scotia).
10. **Inclusion body myositis**
    M.R. Del BIGIO and V.P. JAY (Toronto, Ontario).