Canadian Association of Neuropathologists

ABSTRACTS

October 14th - 17th, 2009
Ingonish, Nova Scotia
Abstracts and unknown cases presented at the Forty-Ninth Annual Meeting

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The Canadian Association of Neuropathologists held its Forty-Ninth Annual Meeting at the Keltic Lodge in Ingonish, Cape Breton Island, Nova Scotia, October 14-17th 2009. Local arrangements were coordinated by CANP Secretary Treasurer Dr. Rob Macaulay and by Dr. Alex Easton; highlights were the informal Lobster Dinner, the exquisite banquet at the Purple Thistle Dining Room and the incredible views of the Atlantic Ocean.

The scientific program, assembled by Dr. Macaulay, comprised 24 scientific presentations and 13 unknown case submissions, organized into Sessions of Muscle Pathology, Inflammatory Neuropathology, Pediatric Neuropathology, Degenerative Neuropathology, Brain Tumours, and Toxicology/Vascular Neuropathology. Session Chairs were Drs. Lee Cyn Ang, Samuel Ludwin, Harvey Sarnat, Ian Mackenzie, Marc Del Bigio, and Peter Gould.

Three excellent invited lectures comprised a Symposium entitled "The Spinal Cord, Muscle and that to be Dreamed", organized and chaired by outgoing CANP President Dr. Edward Johnson. Dr. James Fawcett from Dalhousie's Pharmacology Department delved into spinal cord anatomy and physiology in his talk entitled "Understanding Spinal Circuits Involved in Walking", which constituted the Jerzy Olszewski Guest Lecture. Dr. Rob Brownstone, a Professor of Neurosurgery at Dalhousie, entertained and informed in his address entitled "There and Back Again: A Midle Earth View of Stem Cells in Treating Neurologic Diseases". This year's Speaker of the Royal College of Physicians and Surgeons of Canada was Dr. Stephen Moore, who explored "Limb Girdle and Congenital Muscular Dystrophies: Mechanistic and Diagnostic Considerations". The Gordon Mathieson Invited Member Lecturer for 2009 was CANP past-President Dr. Sukriti Nag, University of Toronto; her address was entitled "Molecular Pathogenesis of Blood-Brain Barrier Breakdown in Brain Injury".

Dr. John Woulfe, Chair of the Trainee Awards Committee, presented the Mary Tom Award to Dr. Joanne Sy (supervisor: Dr. LC Ang) for "Cytological, Histological and Ultrastructural Findings of Two Variants of Mixed Pituitary Adenoma-Gangliocytoma." The Morrison H. Finlayson award went to CJ MacMillan (Dr. A. Easton) for "In Vivo Effects of Neutrophils on the Blood Brain Barrier."

Scientific Papers

1. Ultrastructural changes in dysferlinopathy

S. Krawitz

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Dysferlin is a sarcolemmal protein involved in the repair of skeletal muscle membranes. Mutations in the dysferlin gene result in dysferlin deficiency and cause limb-girdle muscular dystrophy type 2B, Miyoshi myopathy, and other myopathies. While histologic features are shared with other limb girdle muscular dystrophies, subtle ultrastructural features that may be specific to dysferlin-deficient myopathies have been described. A cluster of dysferlin mutations has been identified in a Metis community of Manitoba and includes a case with striking sarcolemmal changes. The aim of this review of Manitoban cases is twofold, to show a gradation of pathologic changes and to identify possibly distinctive ultrastructural changes of dysferlinopathy.

Skeletal muscle biopsies from five patients with genetically confirmed dysferlinopathy were examined histologically, immunohistochemically, and by electron microscopy. The light microscopic findings (fatty replacement, fibrosis, inflammation, fibre size variation, degeneration, regeneration) are variable but not surprising with the exception of dense clumps at the sarcolemma on toluidine blue-stained semithin plastic sections. The ultrastructural findings include redundant and splitting basal lamina, papillary and bridging projections, dense globules decorating the sarcolemma, subsarcolemmal vesicles, and subsarcolemmal vacuoles. The extent of change varies among cases and within the same case, some structures may represent transitional forms. Blinded studies including other muscular dystrophies are underway in order to determine the specificity of ultrastructural features in dysferlinopathy. The significance of the ultrastructural changes will be discussed with reference to possible mechanisms of membrane damage.

2. Myonuclear changes in sporadic inclusion body myositis

J.M. Bilbao, B. Young, S. Cohen

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We have reviewed our experience with over 250 cases of inclusion body myositis collected over the period of 1979 to 2009 from St. Michael's and Sunnybrook hospitals in Toronto. We analyzed the pattern of the myonuclear changes as detected by light microscopy and electron microscopy.

All cases were diagnosed by the same pathologist using histostains, muscle histochemistry, immunohistochemistry and electron microscopy from a standard open biopsy procedure.

Some investigators propose that IBM is a disimmune-inflammatory disease with secondary degenerative changes. Others favor the opposite scenario. A third view is that there is no causal relation between inflammation and degeneration.

Myonuclear abnormalities comprised inclusion bodies identified on H&E, Congo red, UBQ and AT8 preparations and bundles of 18 nm tubulo-filaments and nuclear disintegration with features of apoptosis.

Some myonuclear inclusions were detected in muscle fibers not harboring "rimmed" vacuoles or signs of sarcoplasmic degeneration. Progressive alterations consisted of nuclear degeneration, effacement of nuclear membrane, egression nuclear contents into sarcoplasm with formation of the osmiophilic and myeloid bodies of "rimmed" vacuoles.

Our findings are consistent with the hypothesis that an early alteration of the myonuclear matrix foreshadows the beginning of the cascade of dissolution of the nuclear membrane, nuclear disintegration, the formation of vacuoles and the accumulation of sarcoplasmic tubulo-filaments.

3. Plaque-like, U-fiber Sparing Presentation of Acute Disseminated Encephalomyelitis (ADEM)

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The pattern of demyelination in acute disseminated encephalomyelitis (ADEM) in the scant autopsy literature on is described as perivenous sleeves. We report an unusual presentation of ADEM. A 19-year-old female patient presented with subacute onset of lethargy, confusion, left hemiparesis and dysphasia following a flu-like illness after an interval of 4-5 days. Neurological symptoms remained stable over the length of the hospital stay (1 month) despite aggressive treatment with methylprednisolone i.v. and plasma exchange. The patient passed away due to sepsis and bronchopneumonia.

On autopsy, the brain showed extensive, confluent, plaque-like demyelinating lesions with a striking selectivity for the subcortical white matter, sparing the U-fibers. Histologically, all lesions were of the same age, coupling near complete demyelination with relative preservation of axons, along with perivascular lymphocytic infiltrates, dense infiltration by macrophages, and reactive astrocytes. The morphology of the individual demyelinating lesions is indistinguishable from the lesions in multiple sclerosis (MS), a disease of unknown etiology. However, the monophasic clinical course and histological dating of multiple lesions are inconsistent with MS. The case suggests that immune mechanisms operative in ADEM are capable of producing MS-like plaques. The selectivity of the affected brain regions and the sparing of the subcortical U-fibers may reflect a selective immune attack.

4. In vivo effects of neutrophils on the blood-brain barrier

C.J. MacMillan, A.S. Easton

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Within our province stroke has been identified as a critical health issue, accounting for the death of more Nova Scotians than any other disease. A significant complication of stroke is breakdown of the blood-brain barrier (BBB), a structure that restricts the passage of substances between the bloodstream and brain, resulting in cerebral edema. Although neutrophils are found at the site of inflammation in stroke there has been limited investigation of their role in BBB breakdown, forming the rationale for this work. To induce stroke, a focal infarct was generated by striatal injection of the vasoconstrictor endothelin-1 (ET-1, 400pg) in anaesthetized juvenile Wistar rats. There was a significant increase in permeability at 72h ($55.44 \pm 8.32 \times 10^{-6}$ ml/s/g) compared to control ($10.40 \pm 5.85 \times 10^{-6}$ ml/s/g). To examine the role of neutrophils, the neutrophil chemoattractant CXCL1 (0.5µg) was administered concurrently with ET-1. In another group, CXCL1 was injected 60h after administration of ET-1 into one hemisphere (12h before permeability was assessed). In the first group, 72h permeability was unaffected by co-injection of CXCL1. In the second group, there was a significant reduction in the volume of tissue showing increases in permeability in the hemisphere injected with CXCL1. Additionally, CXCL1 was injected into normal brains and we observed that neutrophil recruitment across healthy blood brain barrier results in an increase in permeability. This suggests that, in a model of acute brain inflammation, neutrophils cause an early reduction in BBB disruption. In contrast, neutrophil recruitment across a healthy barrier results in increased barrier disruption.

5. Ectopic Purkinje Cells in Ataxia-Telangiectasia

A.R. Bottini, R.A. Gatti, G.V. Vinters

David Geffen School of Medicine at UCLA

Ataxia-telangiectasia (A-T) is a heredofamilial syndrome of progressive cerebellar ataxia with onset in infancy, progressive oculocutaneous telangiectasia, and susceptibility to progressive bronchopulmonary disease and lymphoreticular neoplasia. Prominent neuropathologic findings in A-T patients include marked loss of granule cells and Purkinje cells from their respective layers in the cerebellar folia. The presence of ectopic Purkinje cells in the molecular layer of the cerebellar cortex has been studied in a mouse model of A-T and observed, but not quantified, in several A-T patients. In our study the anti-calbindin antibody was used as an immunohistochemical marker for Purkinje cells in cerebellar sections from A-T patients and age-matched controls. The sections were digitally photographed with an Olympus DP70 microscope camera and ectopic Purkinje cells were quantified. Using Scion Image software we measured the length of each section's Purkinje cell layer and calculated the presence of ectopic Purkinje cells in terms of linear density along

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the Purkinje cell layer. In our initial control (n=5) and A-T (n=5) groups we observed, respectively, an incidence of 0 and 12.7 ectopic Purkinje cells per meter of Purkinje cell layer length. These results, when considered in conjunction with the development and cytoarchitecture of the cerebellar cortex, provide important data pertinent to the timing of Purkinje cell loss in the progression of A-T.

6. NPAS3 immunohistochemistry in the developing human brain

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Schizophrenia is a severe mental disorder with a polygenic basis, which hinders our ability to characterize the underlying biology. The neuronal PAS3 (NPAS3) gene has been shown to be disrupted by a 9q/14q translocation in a family with schizophrenia, which may provide a clue to the pathogenesis of non-familial cases. NPAS3-deficient mice show behavioral and neurochemical abnormalities, but little is known about the distribution of the NPAS3 gene product in the developing human brain.

Immunohistochemical staining of human fetal and pediatric brains showed the anticipated pattern of nuclear staining in interneurons, but also revealed staining of non-neuronal elements, including Bergmann glia. Tissue microarrays were used to screen multiple brain regions. We are currently extending our study to adult autopsy cases to see whether altered staining patterns are seen in patients with neuropsychiatric illness.

7. Syrinx formation in non-Chiari fetal dysraphism

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The intrinsic spinal cord pathology of 13 predominantly mid-gestation cases of non-Chiari dysraphism was reviewed (gestational age 16 to 35 weeks). These cases fell into three groups: Omphalocele exstrophy imperforate anus (OEIS) (8 cases), Meckel-Gruber syndrome (3 cases), and a set of conjoined twins with fused sacral spinal cords. Among the OEIS patients, all displayed terminal myelocystocele while 4 of 7 had syrinx formation. Among cases of Meckel-Gruber patients, 2 of 3 showed syrinx as did both conjoined twins. In all cases the syrinx consisted of median or paramedian cavities only partially lined or unlined by ependyma and connecting to the central canal of the cord. In OEIS and the conjoined twins, the syrinx ascended from the lumbar cord to the thoracic spinal cord. In Meckel-Gruber, one syrinx spanned the length of the spinal cord and another was localized to the cervical cord. Two cases (one OEIS and one Meckel Gruber) displayed evidence of hemorrhage or cord infarct with additional diverticulum like cavities dissecting laterally into the cord. The similarity of the syrinx morphology to that seen in Chiari malformations suggests the dysraphic state is the primary contributor to syrinx pathology in the fetal and neonatal spinal cord.

8. Syrinx formation in fetal Chiari malformation

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We reviewed 25 cases of second trimester fetal Chiari malformations (gestational age 17.5 to 24 weeks). We demonstrate syrinx formation in 44% of cases. In all cases the syrinx was a of median or paramedian cavity only partially lined or unlined by ependyma and connecting to the central canal. Four morphologies were noted: 1. the syrinx was a simple extension of hydromyelia (n=2) 2. The syrinx was a collapsed midline or paramedian cavity with features suggestive of a dysraphic origin (n=7). 3. The syrinx dissected laterally and irregularly into the substance of the cord (n=1). 4. It represented cavitation in rostral degeneration from the myelomeningocele (n=1). There was no correlation between syrinx formation and the presence or absence of talipes, or with the size of the defect. Vernicomyelia was common (6 out of 25 cases) and no cases of vernicomyelia were observed without syrinx formation. There were 3 cases of paramedian syringes arising with dorsal ventral duplication of the central canal and one case associated with regression of a laterally duplicated central canal. Syrinx formation is often described as a late phenomenon in Chiari malformation, but it is present in the second trimester. To our knowledge, this is the first series of fetal Chiari malformation to document the prevalence of such spinal cord anomalies.

9. New missense A204G mutation in the Polymerase Gamma1 locus in Alpers-Huttenlocher disease

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This 17-month-old infant born at 38 weeks gestational age had a normal pregnancy and delivery. Soon during the neonatal period, partial seizures became increasingly frequent. Seizures were treated by polytherapy and became drug-resistant. He sustained two episodes of status epilepticus, the last having required induction of pentothal anesthesia. This was followed by a permanent alteration of consciousness and dysphagia. Some episodes of facial and shoulder myoclonic seizures were then recorded, followed by more sustained myoclonic jerks located to the left upper arm. An EEG done a few weeks before death showed abundant interictal spikes in the right posterior cerebral hemisphere. A PET scan done two weeks later revealed a hypermetabolic seizure focus in the left posterior frontal region. Although normal two months before death, a second MRI done one month before death revealed a diffusely distributed cortical atrophy associated with an abnormal T2-weighted signal in the white matter. Both skin and liver biopsies were within normal limits. A karyotype was normal. Search for mutations in the SCN1a locus was negative. However, the POLG1 locus revealed a novel missense p.A204G mutation. These findings will be discussed in the light of a literature review of phenotypic-genotypic correlations in the context of previously reported POLG mutations in the Alpers-Huttenlocher syndrome.

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10. Neocortical synaptogenesis in 11 human fetuses with holoprosencephaly

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Synaptophysin is a useful marker in fetal brain of the development of synaptic vesicles because it is a normal protein of the vesicular wall; it provides a precise temporal and spatial pattern of synaptogenesis. It is not specific for the type of neurotransmitter or synapse. We studied 11 postmortem human fetal brains, 19-38 weeks gestation, with alobar or semilobar holoprosencephaly, using synaptophysin immunoreactivity and other markers of neuronal maturation, with age-matched controls. Results showed abnormal patterns corresponding to the mediolateral gradient of genetic expression in the horizontal axis of the neural tube that we previously demonstrated in this malformation. The most aberrant patterns were at or near the midline; the least altered were lateral in the prosencephalon. Synaptophysin reactivity in the cortical plate was patchy, particularly in areas of severely abnormal nodular architecture. Reactivity did not correspond to the nodules of cortical neurons and was more intense than in the cortical plate of controls. In lateral regions of the same brains, reactivity was not patchy and was less intense than expected. Normal reactivity for age was seen only in areas of well organized cortex with preserved radial glial fibres demonstrated by vimentin. The most abnormal zones also showed displaced, disoriented neurons with abnormal cytological maturation sequences, shown with NeuN, NSE and calretinin. Comparisons were made with the subiculum of controls at midgestation, which normally exhibits nodular architecture. Altered synaptogenesis in holoprosencephalic brains might explain some clinical manifestations, such as epilepsy, as well as abnormal EEG patterns that reflect wide fields of cortical synaptic activity. Midfacial hypoplasias indicate involvement of mesencephalic neural crest tissue in this malformation, but do not predict severity of the cerebral dysgenesis by MRI or gross neuropathology and, in this study, also failed to predict either severity of abnormal microscopic architecture or abnormal synaptophysin distribution within the fetal cortical plate.

11. Fetal telencephalic flexure in maldevelopment of Sylvian fissure in holoprosencephaly, lissencephaly and schizencephaly

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The early fetal telencephalic hemisphere bends ventrally as the telencephalic flexure, beginning at nine weeks gestation, to form the operculum and Sylvian fissure. Consequences in the mature cerebral hemisphere are: 1) the posterior pole of the primitive telencephalon becomes not the occipital, but the temporal, lobe; 2) the dorsal (frontal) and ventral (temporal) lips of the Sylvian fissure are both derived from the ventral margin of the primitive telencephalon; 3) the occipital lobe derives from the dorsal part of the telencephalon; 4) the insula derives from the ventral part of the telencephalon; 5) the telencephalic flexure contributes to "rotation" of the hippocampus from a dorsal to a ventral position. The four fissures of the forebrain are formed by external mechanical forces; sulci are formed by internal mechanical forces. Abnormal development of the telencephalic flexure occurs in various cerebral malformations. In alobar and semilobar holoprosencephaly the telencephalic fissure fails to develop: the hippocampus remains dorsal and the visual cortex is rostral to the posterior pole. In lissencephaly the telencephalic flexure often, but not always, develops abnormally. In schizencephaly, the dorsal and ventral lips of the Sylvian fissure are both abnormal because both are ventral derivatives of the early telencephalon, hence are influenced by genes expressed along a ventrodorsal gradient of the vertical axis of the neural tube or, in some cases, may be due to non-genetic mechanical distorsion during formation of the operculum. Perisylvian epileptic syndromes may be associated with maldevelopment of the telencephalic flexure.

12. FUS mutations in familial ALS

I.R. Mackenzie, A. Eisen, H. Stewart, M. DeJesus-Hernandez, R. Rademakers

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Approximately 10% of amyotrophic lateral sclerosis (ALS) has a positive family history (FALS). Recently, mutations in the gene encoding the fused in sarcoma (FUS) protein have been identified as the cause of FALS type 6. FUS is a ubiquitously expressed DNA/RNA binding protein involved in various aspects of RNA metabolism. Translocation of the 5' portion results in fusion oncogenes that cause a variety of human cancers. Most of the mutations identified in FALS have been missense mutations in the final exon 15. We describe a mother and daughter who presented simultaneously (aged 61 and 38 respectively) with symmetric proximal pelvic and pectoral weakness, suggestive of a myopathy. Only later did they develop features of classical Charcot ALS. Screening for SOD-1 mutations was negative. They each died after a 3-year course and autopsy was performed only on the mother. Neuropathological examination confirmed severe loss of lower motor neurons with only minimal evidence of upper motor neuron degeneration. Ubiquitin-immunoreactive skeins and Lewy body-like inclusions were not evident and there was no TDP-43 pathology. However, immunohistochemistry for FUS demonstrated neuronal and glial inclusions in the spinal cord, brainstem motor nuclei and a number of extramotor regions. Sequencing of the FUS gene identified a c.1561C>T (p.R521C) mutation in both the mother and daughter. It remains to be confirmed if this particular clinical-pathological phenotype is typical of ALS with FUS mutations.

13. Frontotemporal dementia with FUS pathology

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Frontotemporal dementia (FTD) is a clinical syndrome with heterogeneous molecular basis. Although the neuropathology in most FTD is characterized by abnormal cellular aggregates of either tau or TDP-43 protein, there remains a significant proportion negative for both. Mutations in the fused in sarcoma gene (FUS) have recently been identified as a cause of familial amyotrophic lateral sclerosis (ALS). Because of the recognized clinical, genetic and pathological overlap between ALS and FTD,

we investigated the possible role of FUS in tau/TDP-negative FTD. In all cases, FUS immunohistochemistry (IHC) demonstrated normal physiological staining of neuronal nuclei and cytoplasm. No FUS pathology was identified in control cases of FTD with TDP or tau pathology. However, in cases with ubiquitin-positive, tau/TDP-negative pathology (atypical FTLD-U), FUS IHC labeled all the ubiquitinated neuronal cytoplasmic and intranuclear inclusions and also demonstrated previously unrecognized glial inclusions. Immunoblot analysis confirmed increased amounts of insoluble FUS in post-mortem aFTLD-U brain tissue. All cases were sporadic and no abnormalities of the FUS gene were identified. Abundant FUS pathology was also demonstrated in another subtype of tau/TDP-negative FTD, neuronal intermediate filament inclusion disease. In these cases, FUS-positive inclusions were more numerous than those labeling for intermediate filaments (IF) and all neurons with IF inclusions also contained FUS aggregates. These findings suggest that FUS is the pathological protein in a significant subgroup of FTD and reinforce the overlap between FTD and ALS.

14. FUS pathology in Basophilic Inclusion Body disease (BIBD)

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Universities of Toronto, Zurich, Kansai, Okayama, and British Columbia

BIBD is a form of frontemporal lobar degeneration (FTLD), presenting as either behavioural disturbances (FTLD-bv) or amyotrophic lateral sclerosis (ALS), and characterized by basophilic (BI) neuronal cytoplasmic inclusion (NCI). Their basophilia relates to RNA stress granules. BI are non-argyrophilic, tau negative, but a subset shows ubiquitin immunoreactivity (IR). The absence of TDP-43 pathology led us to explore the related protein, Fused-in-sarcoma (FUS), recently identified in subjects with TDP-43 negative ALS.

We collected 6 subjects, (M:F 4:2), average age at onset 45.5 (range 29-57), disease duration 7.83 years (range 5-12), presentation 3 FTD-bv, 3 motor syndromes (2 ALS, 1 PSP). All had severe atrophy of the striatum and substantia nigra, and cortical atrophy congruent with the clinical presentation. BI were intensely labelled by FUS antibodies, which additionally disclosed many other NCI. Affected areas showed decreased nuclear FUS IR in both NCI bearing and free neurons. FUS-IR intranuclear inclusions (INI), always associated with NCI, were relatively common in one case only. Glial cytoplasmic inclusions were abundant in subcortical tissues.

The FUS pathology links BIBD to atypical FTLD-U, with which it shares the striatal focus of the atrophy, and differs by the visibility of NCI on H&E and the absence or scarcity of vermiform INI. The consistent motorneuron involvement suggests that the intimate relationship between ALS and FTLD-U can occur on the basis of either TDP-43 or FUS misdistribution.

15. FUS-immunoreactive neuronal intranuclear inclusions in neurodegenerative disease.

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Neuronal intranuclear inclusions (NIIs) are a histopathological hallmark of several neurodegenerative disorders, particularly those caused by unstable triplet repeat expansions. For the polyglutamine (polyQ) diseases, the role played by NIIs in neurodegeneration has remained enigmatic. Defining the molecular composition of NIIs represents an important step in understanding the pathophysiology of these disorders. Recently, a nuclear protein, "fused-in-sarcoma" (FUS) was identified as the pathological protein in two forms of sporadic TAU- and TDP-43-negative frontotemporal lobar degeneration (FTLD-IF and FTLD-UPS). In these conditions, pathological FUS is present in both neuronal cytoplasmic inclusions and NII. Previous studies have also demonstrated FUS to be a component in the NIIs in Huntingtin's disease (HD). The objective of the present study was to determine the range of neurodegenerative disorders characterized by FUS-positive NII. In addition to FTLD-IF and FTLD-UPS, immunostaining for FUS revealed intense reactivity of NIIs in all polyQ diseases studied including HD and spinocerebellar ataxias 1 and 3 as well as in neuronal intranuclear inclusion body disease. In contrast, there was no FUS staining of NIIs in inherited forms of FTLD-TDP caused by GRN and VCP mutations, in FXTAS (an RNA-mediated disease) or in muscle cells in oculopharyngeal muscular dystrophy (a polyA disease). The results of this study contribute to our understanding of nuclear mechanisms of disease in neurodegeneration and suggest that FUS accumulation in NIIs may be a unifying pathogenetic theme among several neurodegenerative disorders.

16. Glioblastoma multiforme with extensive rhabdoid phenotype

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A 66-year-old woman presented with left sided weakness and occipital headache two weeks prior to admission. CT scan of the head showed 6.4 cm X 3.4 cm parietal occipital intra-axial ring-enhancing lesions. Histology showed mixed malignant glioma with numerous rhabdoid cells. The glial areas were GFAP-positive, fairly well demarcated from the rhabdoid-appearing tumor. Cells with perinuclear halos, consistent with an oligodendroglial or ependymal phenotype were also present. Immunohistochemistry showed that many of the cells were positive for EMA. Rare cells were positive for keratin, CAM5.2, or smooth muscle actin. The tumour was negative for desmin. BAF47 (INI-1) protein immunohistochemistry showed retention of nuclear immunoreactivity in non-rhabdoid tumour areas, with loss of nuclear staining in rhabdoid areas. Molecular studies showed a loss of one copy of the BCR gene, high-level amplification of EGFR (7p12) sequences; loss of PTEN (10q23) sequences, and loss of 22q11.2 and 22q13 sequences. The tumour progressed despite radiotherapy and she developed left sided

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weakness as a result and died 9 months later. The expression of a rhabdoid phenotype in a malignant glioma ("rhabdoid glioblastoma") is a rare occurrence, this being the second case reported in the literature to date.

17. Epithelioid versus rhabdoid gliomas are distinguished by monosomy 22 and immunohistochemical expression of INI-1 but not claudin 6

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Epithelioid and rhabdoid gliomas are rare entities that share some overlapping morphological features, but remain poorly characterized at the immunohistochemical and genetic level. We report 11 examples: 8 epithelioid glioblastomas (E-GBMs) and 2 rhabdoid GBMs (R-GBMs). A unique low-grade epithelioid glioneuronal tumor arising in a classic pleomorphic xanthoastrocytoma is included to underscore that epithelioid morphology is not necessarily a sine qua non for high grade tumor. E-GBMs tended to be superficially-located, circumscribed, supratentorial tumors composed of monomorphic, discohesive sheets of small rounded cells that mimicked metastatic malignant melanoma. R-GBMs showed areas of tumor with classic rhabdoid features arising as a subpopulation of an otherwise classic GBM, fitting the definition of composite extrarenal rhabdoid tumors. Polyphenotypic immunohistochemical expression and focal loss of INI-1 protein in the rhabdoid areas of R-GBMs distinguished them from E-GBMs. Monosomy 22 was identified in R-GBMs, but not E-GBMs. Molecular analysis of one R-GBM showed loss of the BCR gene, located 600 kilobases from the INI-1 gene. Immunostaining for claudin-6, a key component of tight junctions which we have previously shown to be a positive cytoplasmic immunohistochemical marker for atypical teratoid/rhabdoid tumors (AT/RTs), was also conducted. None of the E-GBMs, R-GBMs, or the low grade epithelioid glioneuronal tumor showed claudin-6 expression. We conclude that INI-1 protein can be lost in CNS tumors with rhabdoid phenotype, but these tumors, as well as other CNS epithelioid phenocopies, retain claudin-6. Thus, in the CNS, claudin-6 expression may be a good discriminator of AT/RTs from other CNS rhabdoid/epithelioid neoplasms.

18. Incidental cerebral high-grade astrocytoma: an autopsy case report

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High-grade astrocytomas (HGAs) are malignant neoplasms with rapid growth. The cellular origin of HGAs remains enigmatic, although current concepts emphasize a possible origin from neural stem cells or their progeny predominately in the subventricular zone. We report a miniature HGA discovered as an incidental finding in the temporal cortex during a routine postmortem neuropathologic examination. An 82 year-old male with coronary artery disease presented with non-neurologic symptoms and died of cardiorespiratory failure. Cranial CT one day prior to his death showed no abnormality except mild cerebral atrophy. The autopsy study disclosed a focal pale lesion in the cortex of the middle temporal gyrus with blurring of the gray/white matter junction. Microscopic examination of this focus revealed a HGA (1.5 cm maximum diameter), with high cellularity and nuclear: cytoplasmic ratio, and scattered mitoses. Neither microvascular proliferation nor necrosis was identified. This HGA occupied full thickness of the cerebral cortex, with limited extension into the subcortical white matter. Adjacent cortex and white matter were histologically normal. The neoplastic cells exhibited minimal immunoreactivity for p53, but high amplification of EGFR. This asymptomatic HGA is likely to represent a "fledgling" primary glioblastoma. The evidence from this case supports the interpretation that such tumors can arise at various sites, including sites remote from the subventricular zone.

19. Whole-genome-profiling of paediatric diffuse intrinsic pontine glioma (DIPG) highlights PDGFR and PARP as potential therapeutic targets

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DIPG is one of the most devastating of paediatric malignancies and one for which no effective therapy exists. A major contributor to the failure of therapeutic trials is the assumption that biologic properties of childhood brainstem tumours are identical to adult high-grade gliomas. A better understanding of the biology of DIPG itself is needed in order to develop agents targeted more specifically to these children's disease. Here we address this lack of knowledge by performing the first high-resolution, DNA-microarray analysis of paediatric DIPG.

Nine DIPGs were prospectively collected at post-mortem following consent for research purposes. Two pre-treatment surgical samples were also retrieved from our pathology archives. All were hybridized to Affymetrix SNP-arrays (250k or 6.0). Array findings were validated using quantitative-PCR, FISH, immunohistochemistry and/or microsattelite analysis.

Analysis of DIPG copy number alterations showed recurrent changes distinct from those of paediatric supratentorial high-grade astrocytomas. 33% of DIPGs had gains in PDGFRA and PARP-1. All expressed PDGF-R-alpha. Pathway analysis revealed genes with loss of heterozygosity were enriched for DNA-repair pathways.

Our data provides the first, comprehensive, genomic analysis of paediatric DIPG. Our findings of recurrent PDGFR pathway involvement as well as defects in DNA-repair pathways coupled with gain of PARP-1 highlight two potential, biologically-based, therapies targeted specifically at this devastating disease.

20. IDH1 immunohistochemistry in glial tumours

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Mutations in isocitrate dehydrogenase 1 (IDH1) have been recently identified as early events in the development of low grade astrocytomas and oligodendrogliomas. Cell culture experiments suggest that these mutations lead to inactivation of wild-type IDH1 with formation of catalytically inactive heterodimers and reduction of alpha-ketoglutarate levels, leading to induction of hypoxia-inducible factor subunit HIF-1 alpha. It is unknown whether IDH1 heterodimers accumulate in affected tumour cells, in which case they might be identifiable by immunohistochemistry in surgical neuropathology specimens.

A series of 14 low grade glial tumours (7 astrocytomas and 7 oligodendrogliomas) resected at CHA Hôpital de l'Enfant-Jésus between 2007 and 2009 were stained with a commercilaly available antibody against IDH1. This antibody detects IDH1 accumulation in prostatic adenocarcinoma, but did not show significant IDH1 accumulation in glial tumour cells.

21. Cytological, histological and ultrastructural findings of two variants of mixed pituitary adenoma-gangliocytoma

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Pituitary adenomas containing a ganglion cell component are rare. They are tumours of undetermined histogenesis, although three main theories have been proposed. The first suggests that heterotopic hypothalamic-type neurons within the pituitary produce hormones which stimulate adenomatous growth of the adenohypophysis. The second theory is that pituitary adenomas develop neuronal differentiation, while the last proposes that both the adenomatous and neuronal components arise from pituitary embryonal rests. Morphologically, mixed pituitary adenoma-gangliocytomas form a heterogeneous group. We report two cases that demonstrate both ends of the morphological spectrum. The first tumour contained only isolated ganglion cells, and otherwise resembled a classical growth hormone-producing pituitary adenoma. The second case, however, contained abundant neuropil with gangliocytic cells and intermediate cells admixed with rare adenomatous clusters expressing prolactin. In both cases, the diagnostic features were apparent on intra-operative smears. It is not yet known whether the prognosis of mixed pituitary adenoma-gangliocytomas differs from that of pituitary adenomas. However, it is important to recognize a gangliocytic component, since these tumours may not respond fully to hormone-targeted therapy. The cytological features aiding intra-operative diagnosis will be reviewed, together with the wide range of morphological and ultrastructural features of this unusual group of tumours.

22. Neuropathology of solvent abusers in Manitoba

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The neuropathology of solvent inhalation (especially toluene) has characteristic features, consisting of patchy myelin loss with white matter macrophages that contain granular inclusions. However, it has only been described in a small number of case reports. We conducted a retrospective study of medicolegal autopsies in the Province of Manitoba from 1985-2008 inclusive searching for the terms "solvent or glue or toluene or inhalation". We found 73 autopsy cases with documented history of solvent abuse. Among these were 6 fetuses and infants with history of maternal exposure, 15 children 12-17 years, and 52 adults 18-66 years. Clinical aspects also include seizures in 8 individuals and mixed alcohol abuse in 35. Circumstances of death included 22 acute intoxication, 15 hanging, 7 trauma, 7 sepsis / aspiration, 4 fire / burns, 3 hypothermia, and others. The brain material for review included paraffin blocks from 33 brains cut by a neuropathologist and 28 brains cut fresh by forensic pathologist (with 1-2 sections of brain). All samples were recut and stained with solochrome cyanin to demonstrate myelin and periodic acid Schiff (PAS) to highlight the characteristic inclusions. In addition, 6 cases of multiple sclerosis and 40 cases of alcohol or multiple drug abuse (excluding inhalation) were examined. All slides were examined in a blinded manner by the senior author. The characteristic macrophages in solvent abuse brains but not in alcohol / drug abuse or multiple sclerosis also exhibit birefringence on polarization. Patchy loss of myelin and the prevalence of inclusions were documented semiquantitatively. Six cases (age 15-53, median 22 years) had early or mild changes consisting of rare inclusion-containing cells but no obvious myelin change. Thirteen cases (age 23-49, median 40 years) had well-established leukoencephalopathy with multifocal perivascular myelin loss and inclusion-containing macrophages. Six also had brain atrophy. Electron microscopy in two cases showed trilaminar inclusions. Ataxia and tremor were commonly reported clinically and three individuals were non-ambulatory. Given the sociologic nature of solvent abuse actual exposure is impossible to ascertain, however it would appear that there is a duration dependent effect. Interaction with alcohol and possible other risk factors also need to be considered to explain why not all heavy users develop the disease.

23. Tip of the iceberg: Subarachnoid hemorrhage, local subarachnoid venous thrombosis, widespread subclinical cerebral thrombosis, occult neoplasia, and terminal pulmonary embolism

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The cause of non-traumatic, non-aneurysmal SAH may remain obscure even after follow-up. Acute onset of headache in this 80-year-old man was due to SAH in the left cerebellopontine angle (CPA). Despite angiography, no cause was identified clinically. Hydrocephalus evolved, and a cardiac arrest occurred seventeen days after onset. Autopsy revealed SAH in the left CPA but no gross or microscopic evidence of aneurysm or vascular malformation. Instead, microscopy revealed organizing thrombosis of a subarachnoid vein in the left CPA; and multifocal cerebral arterial thrombosis and a few recent and older microinfarcts. Autopsy also revealed pulmonary thrombo-embolism, papillary thyroid carcinoma, multiple renal cell carcinomas in the kidneys, and a mucinous cystadenoma of the appendix. Cerebral venous thrombosis may present with SAH, and cancer is a recognized underlying cause of cerebral venous

thrombosis. In SAH of obscure cause, there may be an underlying coagulopathy. In autopsied cases, important procedures include detailed microscopic search for venous thrombosis at the site of the SAH; for more widespread cerebral vascular thrombosis; and, in the general autopsy, for pulmonary and other thromboembolism, and associates such as occult neoplasia.

Epithelioid and rhabdoid gliomas are rare entities that share some overlapping morphological features, but remain poorly.

24. Fatal cerebellar haemorrhage following Australian Brown Snake envenomation

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A 69-year-old female with a history of hypertension was bitten by an Australian Brown Snake on the western coast of Australia. Despite prompt medical intervention, she developed refractory hypertension and signs of systemic envenomation including coagulopathy. Her level of consciousness deteriorated and a brain CT showed an acute intraparenchymal cerebellar haemorrhage. She died 48 hours after being bitten.

Titles of Diagnostic Case Presentations

1. Oculopharyngeal muscular dystrophy

F. Al Sufiani, H. Desai, L.C. Ang

London Health Sciences Centre, University of Western Ontario, London; Windsor Health Center, Windsor, Ontario, Canada

2. Balo's concentric sclerosis

C. I. Coiré

Department of Pathology, Trillium Health Centre, Mississauga, ON, Canada

3. Immune reconstitutive inflammatory syndrome (IRIS)

J. Richardson, M.-C. Guiot

Department of Neuropathology, Montreal Neurological Institute and Hospital, Montreal, QC, Canada

4. Inflammatory pseudotumour of the right lateral ventricle

S. Al-Dandan, I.R.A. Mackenzie

Neuropathology Section, Department of Pathology and Laboratory Medicine, University of British Columbia

5. Necrotizing granulomatous meningitis following anti-TNF-alpha antibody treatment for rheumatoid arthritis

J. Wooff, R.J.B. Macaulay

Department of Pathology, QE 2 HSC and Dalhousie University, Halifax, Nova Scotia, Canada

6. Progressive multifocal leukoencephalopathy

B. Lach, B.S. Connolly, E. Stopa

Department of Pathology and Molecular Medicine, Hamilton Health Sciences Centre, MacMaster University, Hamilton, ON, Canada

7. Adult onset leukodystrophy with neuraxonal spheroids and pigmented glia

R.N. Auer

Calgary Laboratory Services, University of Calgary, Calgary, Alberta, Canada

8. Hypomyelination with atrophy of the basal ganglia and cerebellum

C. Dunham, D. McFadden, P Macleod

Calgary Laboratory Services, University of Calgary, Calgary, Alberta, Canada

9. Amyotrophic lateral sclerosis with basophilic inclusions (P62+ve, neurofilament +ve, no bunina bodies, TDP-43-ve and SOD1-ve)

J.M. Bilbao, L. Zinman, E. Rogaeva, B. Young, J. Robertson

Sunnybrook Hospital and the Tanz Centre for Research on Neurodegenerative Diseases, University of Toronto

10. Multiple system atrophy

A. Easton[1], J. Moeller[2]

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11. Gliofibroma, intermediate grade

J. M. Carter[1], L. Resch[2]

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12. Cerebral fibro-osseous pseudotumour

M. Alturkustani, F. Haji, J. Megyesi, I. Gulka, A. Parrent, R. Hammond

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13. Meningioma and related meningioangiomatosis

J.P. Rossiter

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