Canadian Association of Neuropathologists

L'Association Canadienne des Neuropathologistes

ABSTRACTS

October 16th-19th, 2013
Ottawa, Ontario
Abstracts and unknown cases presented at the 53rd annual meeting

Can. J. Neurol. Sci. 2014; 41: 119-127

The Canadian Association of Neuropathologists (CANP) held their 53rd Annual Meeting at the Westin Hotel in Ottawa from October 16th to 19th, 2013. Dr. Ian Mackenzie presided. Drs. John Woulfe and Jean Michaud handled local arrangements. The banquet was held at the Domus Café in the Byward Market district.

The academic program of 23 scientific presentations and 16 unknown case submissions was assembled by CANP Secretary/ Treasurer Dr. Peter Gould into sessions on Neurodegeneration, Inflammation, Tumours, Pediatrics, Nerve and Muscle and other topics. Session chairs were Drs. John Woulfe, Gerard Jansen, Sid Croul, Jean Michaud, and Jeff Joseph.

Following a successful introduction in 2011, several unknown cases were submitted for scanning and viewing online, as coordinated by Dr. Rob Hammond.

The Jerzy Olszewski Guest Lecture was delivered by Dr. Michael G. Schlossmacher from the University of Ottawa, on the subject of "Parkinson's-linked LRRK2: At the crossroads of genetics, environmental triggers and inflammation."

Dr. Blake Gilks presented the Quality Assurance session, on the subject of "External proficiency testing for immunomarkers."

The 2013 symposium, chaired by Dr. Mackenzie, was devoted to Disorders of Peripheral Nerve and Muscle. Dr. Michael A. Rudnicki from the Ottawa Health Research Institute discussed "Molecular regulation of muscle stem cell function." Dr. Michael W. Lawlor from the Medical College of Wisconsin discussed "Diagnostic and genetic considerations in the congenital myopathies." Dr. Duygu Selcen from the Mayo Clinic reviewed "Myofibrillar myopathies."

The Gordon Mathieson Invited Member Lecturer for 2013 was Dr. Juan Bilbao from the University of Toronto, who described "Fifty Shades of Pathology in one thousand sural nerves."

The Resident Awards Committee was made up of Drs. Claire Coiré, Alex Easton and Stephan Saikali. The Mary Tom Award for the best clinical paper was given to Dr. Veronica Hirsch-Reinshagen (supervisor Dr. Mackenzie) for her presentation "Clinicopathological correlations in FTD/ALS with C9ORF72 mutation." The Morrison H. Finlayson Award for best basic science paper was given to Alexandra Rogers (supervisor Dr. Chan) for her presentation: "CIC in Neurodevelopment and Oligodendrogliomagenesis."

Scientific Papers

1. Hereditary Ataxia: The Neuropathological Experience

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Over a 20-year-period, 125 autopsy cases were diagnosed as spinocerebellar ataxia type 1 (SCA-1) in 13; SCA-2 in 10; SCA-3 in 11; SCA-4 in 1; SCA-6 in 6; SCA-7 in 1; SCA-17 in 1; Friedreich's ataxia (FRDA) in 45; FRDA carriers in 2; autosomal recessive spastic ataxia of Charlevoix and Saguenay in 1. The mutation remained unknown in 12 dominant and 4 recessive ataxias. The material also included 19 cases of multiple system atrophy (MSA) and non-MSA sporadic ataxia. An ataxic phenotype was present in diseases that are not normally classified as hereditary ataxia (number of cases in parentheses): Baltic myoclonus (1); Niemann-Pick disease type C (1); familial spastic paraparesis (2); polyglucosan body disease (2); and pallidonigroluysian disease (1). The collection conforms to the clinical experience: FRDA is the most common form of hereditary ataxia, and the mutation remains unknown in 10-20 percent of SCA. A detailed study of cerebellar cortex, dentate nucleus (DN), and inferior olivary nucleus by immunohistochemistry of calbindin-D28k, neuron-specific enolase, glutamic acid decarboxylase, and vesicular glutamate transporters 1 and 2 allowed the conclusion that the critical

ataxia-causing lesion is almost invariably located in the DN. Atrophy of DN was also present in SCA-6, previously thought to be a "pure" cerebellar cortical degeneration. Grumose degeneration of DN was most prominent in FRDA and SCA-3. Pontine atrophy was present in SCA-2 and SCA-7 while variable in SCA-1 and SCA-3.

2. Striatal blood-brain barrier permeability in PD: re-evaluating the spread of Lewy pathology

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Breakdown of the blood-brain barrier (BBB) has been implicated in the pathogenesis of neurodegenerative diseases including Alzheimer's disease and amyotrophic lateral sclerosis. The status of the BBB in Parkinson's disease (PD) has not been well-studied. We examined the integrity of the BBB in the striatum of five PD patients (age) and five normal controls (age). This was done by quantifying perivascular haemosiderin deposits with Perls' Prussian blue staining and examining extravasated serum proteins by immunohistochemistry. PD striata demonstrated evidence of loss of BBB integrity with increased perivascular haemosiderin deposits (4.1±1.1 per mm^2) compared with normal controls (0.78±0.22 deposits per mm^2).

This demonstration of striatal BBB permeability provoked a re-appraisal of the pattern of spread of Lewy pathology proposed by Braak. The existing pathological staging scheme for PD is incomplete and is founded on a postulated topographical pattern of spread that is inconsistent with known neuroanatomical connectivity patterns. We propose instead a spatiotemporally dichotomous process initiated in axon terminals, in both the periphery, and the CNS, by a blood-borne systemic noxious agent. In this scenario, the temporal sequence of sites involved by Lewy pathology is dictated by the relative accessibility of their axon terminals to the blood-borne pathogen. The anatomical basis for this proposal will be reviewed.

3. Exploring the biological significance of molecular mimicry between EBV and alpha-synuclein

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The abnormal oligomerization of alpha-synuclein (a-syn) is central to the pathogenesis of Parkinson's disease (PD), the most common neurodegenerative movement disorder. Braak and colleagues have proposed a spatiotemporally dynamic pathogenetic process wherein a-syn aggregation is initiated in the periphery by a yet-to-be identified agent. Subsequent to this initiating event, a-syn aggregation "spreads" in an autonomous, prion-like fashion towards the CNS. We have demonstrated previously cross-reactivity of a commercially-available monoclonal antibody (CS.1-4) generated against the EBV latent membrane protein 1 (LMP-1) with a-syn. We have subsequently demonstrated that this cross-reactivity is due to linear homology among similar c-terminal epitopes on a-syn and EBV LMP-1. We have hypothesized that this example of molecular mimicry may be biologically relevant with respect to the initiation of a-syn aggregation. In order to address this, we have analyzed the effect of CS.1-4 on a-syn oligomerization, using the technique bimolecular fluorescence complementation, in which a signal is produced when labelled proteins interact. Briefly, we fused either the C- or N-terminal regions of full length human a-syn with complementary halves of yellow fluorescent protein respectively, thereby requiring antiparallel alignment to produce a signal. We demonstrate that the CS1-4 antibody, as well as certain anti-syn antibodies targeting the cross-reactive epitope, but not anti-syn antibodies targeting other epitopes, induce a-syn oligomerization in cultured HT4 mouse neuroblastoma cells transfected with the a-syn constructs. In addition, the oligomer-inducing immunoglobulins are internalized into cells where they co-localized with a-syn aggregates. These results may have implications for the safety and efficacy of the anti-a-syn vaccination trials which have been initiated.

4. pSTAT3 immunoreactivity in amyotrophic lateral sclerosis and other neurologic diseases

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Activation of signal transducer and activator of transcription (STAT)3 by phosphorylation is thought to mediate anti-inflammatory responses to CNS injury mostly by regulating reactive astrogliosis. Although several studies suggested that pSTAT3 might represent an inflammatory marker, our recent study found no correlation between pSTAT3 immunoreactivity and multiple sclerosis inflammatory activity. pSTAT3 immunoreactivity has been observed within macrophages/microglia in the spinal cord of patients with amyotrophic lateral sclerosis (ALS), and within reactive astrocytes in the SOD1 transgenic mouse model of ALS. In the present study, we examined pSTAT3 immunoreactivity in postmortem brains of ALS patients. The pSTAT3 protein expression by western blotting was enhanced in 3 brains of ALS compared to those of 3 controls. Microscopic examination of 4 other ALS brains revealed the cellular immunoreactivity for pSTAT3 preferentially in the motor cortex and its subcortical white matter (WM). Our semi-quantitative analysis showed that the frequency of pSTAT3 immunoreactivity in WM of the motor cortex was significantly greater than those in the motor cortex, temporal neocortex and its WM ($p < 0.01$, by t-test). This pSTAT3 immunoreactivity was nonspecific as it was also seen focally in the brains of other neurologic diseases including Alzheimer disease, multiple system atrophy, cerebral infarction, and surgical specimens of focal cortical dysplasia. These findings suggest that pSTAT3 may play a role in non-cell autonomous pathology of ALS, preferentially involving axonopathy, and other neurologic diseases.

5. Clinicopathological correlations in FTD/ALS with C9ORF72 mutation

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Abnormal expansion of a hexanucleotide repeat in a noncoding region of the chromosome 9 open reading frame 72 gene (C9ORF72) is the most common genetic cause of familial and sporadic FTD and ALS. The neuropathology of these cases is characterized by TDP-43 immunoreactive intracellular inclusions. In addition, ubiquitin-positive, TDP-43-negative neuronal inclusions in certain areas are characteristic of cases with C9ORF72 mutation. This pathology results from unconventional translation of the abnormal GGGGCC repeat, resulting in three different dipeptide repeats (DPR).

This study evaluated clinicopathological correlations in 20 cases with the C9ORF72 mutation. DPR pathology was demonstrated by poly-GA IHC. Cases with clinical FTD had more severe degeneration of frontal cortex, while cases of ALS had more extensive loss of lower motor neurons. There was no correlation between the anatomical distribution of TDP-43 and DPR pathology. The severity of TDP-43 pathology correlated with the degree of degeneration in frontal cortex, hypoglossal nucleus, spinal ventral grey matter and striatum. In contrast, all cases showed a constant pattern of DPR pathology, with abundant inclusions in the neocortex, hippocampus and cerebellar cortex, but minimal involvement of the brainstem and spinal cord.

These findings suggest that, in cases of FTD/ALS due to C9ORF72 mutation, neurodegeneration is more closely related to TDP-43 pathology and that DPR inclusions may be of diagnostic importance but of uncertain pathogenic significance.

6. Neuropathologic Asymmetry in Diseases with Global Primary Brain Insults

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Neuropathologic asymmetry is seen with many global insults that span from malformations such as iniencephaly, to neurodegenerative diseases such as Parkinson's disease and corticobasal degeneration. Most cases of asymmetry are not due to a specific selective vulnerability of one hemisphere over the other, but are due to random (stochastic) processes. A notable exception is primary progressive aphasia which characteristically affects the left hemisphere, where speech is located. A rare instance of primary progressive aphasia in the right hemisphere in a left-hander with speech located in on the right, suggests a specific attack of speech circuitry, a true selective vulnerability of one hemisphere.

Stochastic processes contrast with deterministic processes in the study of causality and result in randomly and evenly distributed predominance between left and right hemispheres. Deterministic explanations do still apply at the cellular level: e.g. in hypoglycaemia, the onset of spreading depression, which heralds cell damage, can occur in one hemisphere many minutes before the other, giving one hemisphere say, a 20 minute insult and the other a 30 minute insult of isoelectricity, with a 10 minute asynchrony in onset of a flat EEG between hemispheres. In cancer, accumulating DNA mutations cause disease, but even gliomatosis cerebri is rarely perfectly symmetric. Indeed, cancer can be considered a stochastic process: all smokers will not get cancer, only an unlucky few who accumulate the right kinds of highly selective mutations affecting cell proliferation and survival. Illustrative examples can be found in many diseases for a stochastic element superimposed on a deterministic element that can explain asymmetry in neuropathology.

7. Surfen, a heparan sulphate antagonist, reduces T cell proliferation both in vivo and ex vivo: Applications for future therapeutic targets for the treatment of multiple sclerosis

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Heparan sulfate proteoglycans (HSPGs) are important components of the extracellular matrix and have roles in brain development and responses to injury. Connective tissue components are known to be major inhibitors of remyelination in a mouse model of demyelination and are found at the border of active demyelinating multiple sclerosis (MS) lesions; however, the role of HSPGS on the peripheral immune response is unknown. Here we report that the heparin sulfate antagonist surfen (20 mg/kg) reduced T cell proliferation in lymph nodes of anti-CD3 antibody-treated mice as measured by 3H-thymidine incorporation and raw cell counts. Furthermore, surfen (2.5, 5, and 10 μM) reduced T cell proliferation *in vitro* when applied directly to T cells stimulated with anti-CD3/CD28 coated beads. Ongoing work involves investigating potential mechanisms such as CD25/CD68 regulation and T cell receptor/CD28 signaling pathways. Future models of interest include experimental autoimmune encephalomyelitis and a mouse model of demyelination. Taken together, the immunomodulatory effects of surfen may help clarify the role of HSPGs in MS pathology and lead to the development of more targeted therapeutics.

8. Utility of routine molecular genetic testing in high grade primary brain tumors: 6 year OHSU experience and clinicopathologic correlation

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We retrospectively studied 222 high grade primary brain tumors, mostly gliomas, OHSU in-house cases or cases from affiliated hospitals that came in 2007- 2013 and received molecular genetic tests, clinical treatment and follow-up. The test panel included 1p19q and PTEN deletions, EGFR

amplification, IDH1/2 mutations and MGMT hypermethylation. Correlations between clinical data (e.g. demographics, radiologic presentation, extent of resection, clinical performance, therapy response, tumor progression, and survival), histopathologic indices (e.g. histological type, WHO grade, Ki67, p53, IDH1 immunohistochemistry) and already mentioned molecular markers were studied. From a clinical standpoint, 1p19q and MGMT remain by far the most important molecular markers for treatment response, progression free and overall survival. PTEN, EGFR and IDH are important for diagnostic purposes, but also have some impact on patient survival. Ki67 proliferative index and p53 status have less straightforward correlation with clinical outcome. IDH1/R132H immunohistochemistry is a good screening tool, but can be equivocal or falsely negative in less frequent IDH1 mutations. Overall, our findings support clinical usefulness of routine use of molecular markers for high grade primary brain tumors, but more consistency is needed in their application.

9. Emergence of Primary CNS Lymphoma in a patient with Clinicopathologic Diagnosis of CLIPPERS – Case Report and Literature Review

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CLIPPERS (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids) is a recently described inflammatory disease centered in the pons with characteristic features including: (1) episodic brainstem symptoms responsive to corticosteroids and immunotherapy; (2) punctate and curvilinear gadolinium-enhancing lesions predominantly in the pons with variable involvement of other structures including the cerebellum, cerebral white matter, and spinal cord on magnetic resonance imaging (MRI); and (3) T-lymphocytic infiltrate with perivascular predominance in the brain biopsy specimens.

We report the case of a 74-year-old gentleman who initially presented in April 2012, complaining of diplopia, ataxic gait, weight loss and decreased appetite. Both neuroimaging and neuropathological features were consistent with CLIPPERS. He responded well to steroid therapy and was discharged home on prednisone (60 mg daily). In October 2012, he was readmitted with right-sided weakness, aphasia and urinary incontinence. Subsequent neuroimaging revealed new lesions in the left thalamus and internal capsule. The patient continued to decline clinically and passed away two weeks later. Neuropathological examination of the autopsied brain revealed a large B-cell lymphoma with extensive involvement of the left cerebral hemisphere and the brainstem, especially the pons. This case illustrates the need for close follow-up of patients suspected of CLIPPERS, and the importance of maintaining a high index of suspicion for primary CNS lymphoma (PCNSL), which often demonstrates an initial transient response to steroid therapy.

10. CIC in Neurodevelopment and Oligodendrogliomagenesis

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Oligodendrogliomas (ODG) are distinctive brain tumours composed of cells resembling oligodendrocyte precursors cells (OPCs). Genetic hallmarks of ODGs include 1p/19q chromosomal co-deletion and IDH1/2 mutation. Recently, the gene encoding Capicua (CIC), on chr19q13.2, was identified as mutated in most ODGs with concurrent 1p/19q loss and IDH1/2 mutation – a genetic signature rare in other cancers. Mutation of the retained 19q CIC allele is likely functionally important, but how it contributes to ODG biology is unknown. The aims of this study are to characterize the temporal and spatial expression of CIC in the normal mouse cerebrum, and to determine if CIC loss affects proliferation or differentiation of neural progenitors. To examine CIC expression, immunofluorescence staining was performed on forebrain tissue over a developmental time-course. CIC biologic functions were determined using a loss-of-function approach, introducing CIC shRNA or control shRNA into neural progenitors. Cells were examined for proliferation, and for cell identity using a panel of markers. Our data supports a role for CIC in regulating several processes in neural progenitors that are relevant to cancer including proliferation and, possibly, differentiation. CIC loss due to mutational inactivation may thus deregulate processes relevant to oligodendrogliomagenesis.

11. Validation of IDH1 R132H immunohistochemical staining using a glioma tissue microarray in laboratories across Canada

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Specific mutations in the isocitrate dehydrogenase gene IDH1 have been found in glial tumors, with mutations found in nearly all cases of secondary glioblastomas, which develop from lower-grade gliomas, but rarely in primary high-grade glioblastoma multiforme. Presence of IDH1 mutation in tumor is shown to correlate with longer survival. IDH1 R132H mutation IHC is becoming more and more widely used in brain tumor diagnosis; however, not every Pathology laboratory uses it routinely.

We have constructed a TMA with known 13 IDH1 R132H-positive and 17 IDH1 R132H-negative gliomas. The IDH1 R132H immunostaining (IHC) was performed using local protocols at six laboratories across Canada. This project was undertaken as part of the national Canadian Immuno-histochemistry Quality Control (CIQC) effort to provide External Quality Assurance (EQA) to ensure high quality immunostaining in clinical pathology laboratories across Canada. The established CIQC protocol for dissemination of IHC results is used.

We have conducted blinded validation of the TMA using IDH1 R132H IHC from different laboratories across Canada and achieved a 100% concordance in our calls.

The IHC protocol comparison showed that despite of protocol variability between laboratories, IDH1 R132H IHC is a reliable, accurate and reproducible technique for routine diagnostic practice.

12. Chordoid Meningiomas: Incidence, Clinical and Pathological features and Prognosis. An 18 year study

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From 1995 to 2013, 1743 meningiomas were resected at St. Michael Hospital, Toronto. Following a database search and examination of the histopathology, we determined that 9 fulfilled criteria for chordoid meningioma. Thus chordoid meningiomas represent 0.51% of meningiomas. The Male: Female ratio was 3:6. Age ranged from 19 to 85 years, average 61.2 years. All chordoid meningiomas were supratentorial. Three tumors, two of which had undergone partial resection, recurred within one year. All 3 were treated with gross total resection and adjuvant radiotherapy. No deaths were recorded. Histological features of note were the absence of brain invasion and the rarity of lymphoplasmacytic infiltrates. Areas of necrosis were present in all tumors that eventually recurred and 2 non recurrent. In the initial resections of 2 recurrent and 1 non-recurrent tumors areas of atypical meningioma were identified. The proportion of sectional area displaying chordoid features ranged from 30 to 100% (mean 80%). Mitotic activity ranged from 0 to 7 per 10 high power fields, and showed no correlation with recurrence. To calculate the Ki67 index in an objective, automated manner hot spots were selected visually, and the index determined on ImageJ with the Immunoratio Plugin. The index ranged from 0.6 to 6.5% (mean 2.1%). There was no correlation with recurrence, but recurrent tumors had higher indices than their initial resections.

13. National Neuropathology Lecture Series

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Neuropathology is a specialty with rapidly evolving and expanding knowledge demands, and all Canadian Neuropathology residency programs face the challenge of delivering a comprehensive and current curriculum with limited number of faculty. The National Neuropathology Lecture Series aims to supplement the existing curriculum at Canadian post-graduate Neuropathology training programs, address common gaps among all training programs, promote 'sharing' of local subspecialty Neuropathology expertise between training sites, and augment the teaching of non-medical expert CanMEDS roles. It was launched in the fall of 2012 and is halfway through the two year pilot project in the utility of technology and inter-university collaboration in addressing the educational needs of a small specialty. An update at the halfway point of this pilot project will be provided, including results from the post-graduate Needs Assessment Survey, the available and planned curriculum for the lecture series, and usage data.

14. Pineal Parenchymal Tumours - A Toronto Based Review

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Pineal parenchymal tumours are relatively rare and series based on small numbers of patients from many different institutions. In an attempt to capture the experience from a large geographically limited population, we have surveyed the Adult hospitals in the Greater Toronto Area and identified twenty cases with surgical material in the archives from the past twenty years. These cases have been re-classified with current criteria. We have also constructed a database allowing correlation of presentation, Pathology, treatment and out come. The progress of this effort will be discussed.

15. Integration of Common Data Elements into Muscle Biopsy Reports

Jahannaz Dastgir[1], Anne Rutkowski[2], Rachel Alvarez[2], Stacy Cossette[2], Ke Yan[3], Ray Hoffmann[3], Caroline Sewry[4], Yukiko Hayashi[5], Hans-Hilmar Goebel[6], Carsten Bonnemann[1], Michael W. Lawlor[3]

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There is no current standard among pathologists for evaluating or reporting muscle biopsy findings. The National Institutes of Neurological Disorders and Stroke (NINDS) has recently launched a Common Data Element (CDE) project in an effort to standardize neuromuscular data collected in clinical reports to facilitate their use in research. For this study, the authors adapted the NINDS Muscle Biopsy CDE to generate a prospective muscle biopsy reporting form (CDE-R). Forty-nine (49) muscle biopsy reports from patients with a range of congenital muscle disorders were scored using this form. Analysis of the data highlighted: (1) inconsistent reporting of key clinical features from referring physicians, and (2) great variability in the reporting of a range of pertinent positive and negative pathological findings. We propose a format for muscle biopsy reporting that consists of the CDE-R checklist elements and a brief narrative comment that interprets the data in support of a final interpretation. Such a format would catalogue pathological findings in a standard manner and serve emerging patient needs with the expansion of genetic testing, research trials, and clinical trials in the field of muscle disease.

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16. Extrajunctional Myopathology in RAPSN Mutations

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Myopathology in patients' muscle tissues affected by mutations in the RAPSN gene as encountered in one of the Congenital Myasthenic Syndromes usually entails the neuromuscular junction by light and electron microscopy, but little is known of extrajunctional myopathology.

We report clinical, myopathological and genetic findings in a young girl with episodic severe respiratory distress and arrest since birth, generalized muscle hypotonia and proximal muscle weakness, bilateral ptosis, but no AchR or MuSK antibodies. Muscle biopsy revealed variation in fiber diameters in a myopathic fashion, type I fiber uniformity and scattered minicores by electron microscopy. Mutations in the RYR1 and SEPN1 genes having molecularly been excluded, she was found to be compound heterozygous for two mutations in the RAPSN gene one of which is novel.

Her father had delay in motor development, hypoventilation syndrome, a myopathic face, mild generalized muscle weakness and fiber type disproportion with minicores in his biopsied muscle. He carried one of the heterozygous RAPSN mutations. His father was said to have similar clinical features.

These findings expand the nosological spectrum of fiber type uniformity, minicores and of extrajunctional RAPSN myopathology which will be discussed together with the complex genetic aspects.

17. Intraepidermal small nerve fiber density in a patient with erythromelalgia

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Erythromelalgia is a rare familial or sporadic clinical syndrome characterized by intermittent redness, heat and burning pain involving more commonly the lower extremities. Very few reports of quantitative assessment of small nerve fiber density have been published. The patient is a 74-year-old lady who had symptoms for nearly 10 years and complained of numbness of her feet and of burning sensation developing during the day and worse at night. She presents a striking red-purple discoloration of both feet and a decreased perception of vibration distally. There is no known family history. The laboratory reveals a small M protein by electrophoresis and the urine gammopathy screen shows free kappa light chains. The nerve conduction studies are within normal limits for age. Two 3-mm punch biopsies were done on the lateral leg and thigh and frozen. Following an internationally standardized procedure, four 50 micron thick sections were stained with the protein gene product (PGP) 9.5. The intraepidermal nerve fiber density (IENFD)/ linear mm was assessed and compared with published international normative values. In the lower leg, the IENFD is 0.2 fibre/mm while the 0.05 quantile IENFD value for this patient age and sex is 2.2 fibers / mm. The value of the thigh biopsy is also low. There is no amyloid in either skin biopsy. These results are thus highly suggestive of a small fiber sensory neuropathy.

18. Histopathological spectrum of pediatric diffuse intrinsic pontine glioma (DIPG)

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DIPG is a devastating malignancy with poor prognosis and no effective therapy. In the majority of cases diagnosis is based on MRI findings with biopsy material rarely available. A potential contributor to the failure of DIPG clinical trials is the use of agents targeting the genetic alterations of adult glioblastoma. Our group has developed an autopsy-based protocol to investigate the biology of DIPG, allowing us to investigate the histologic and genetic features of this tumor. Here, we review 73 DIPGs (55 autopsy and 18 biopsy) describing the clinic-pathological and molecular features of this disease. Fourty-seven patients had glioblastoma, 14 anaplastic astrocytoma, 9 grade-II astrocytoma, and 3 had features of primitive neuroectodermal tumor. Approximately 1/3 of patients had leptomeningeal spread of their tumor. Further, diffuse invasion of the brainstem, spinal cord and thalamus was common with some cases showing spread as distant as the frontal lobes suggesting that focal radiation may be inadequate for these patients. Importantly we show that clinically classic DIPGs represent a diverse histologic spectrum, including multiple cases which would fit WHO grade II astrocytoma criteria which nevertheless behave clinically as high grade astrocytomas and harbor the histone K27M-H3.3 mutation. This suggests that the current WHO astrocytoma grading scheme may not apply to pediatric brainstem gliomas.

19. Precocious synaptogenesis in neocortex and cyclopean retina in a 13.5wk fetus with alobar holoprosencephaly and trisomy-13

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Genetic programming of cerebral development involves not only tissue morphogenesis but also timing of onset of each developmental process, which must be coordinated with other processes both spatially and temporally, for normal function. Precocious synaptogenesis in the neocortical plate in holoprosencephaly was previously demonstrated in 5 of 6 fetuses of 20-31 weeks gestation, compared with age-matched controls. We examined a 13.5 week fetus with trisomy-13, alobar holoprosencephaly, cyclopia and absent ears. Immuno-cytochemical demonstration of synapse formation was performed, using the synaptic vesicle protein synaptophysin. Reactivity in the cortical plate was patchy and precocious; in controls it is not expected until after 20 weeks gestation. Radial glial fibres, as demonstrated by vimentin, were beneath and

parallel to the cortical plate rather than perpendicular orientation, probably because of massive hydrocephalus with compression and distortion. A corpus striatum was not identified, but the poorly formed thalamus had synaptophysin reactivity around many neurons. The cyclopean eye had ocular features of maturational delay including a persistent hyaloid artery; ganglion cells were reduced in number and reactive for calretinin, but retinal synaptophysin reactivity was paradoxically precocious. Premature onset of neocortical synapse formation may promote epileptic circuitry formation sooner than it might have developed, leading to severe infantile epilepsies postnatally. The visual system is the last of the special sensory systems to mature, yet in this case showed early synapse formation. Absence of external ears is rare and results from faulty craniofacial induction by neural crest tissue.

20. Pre And Perinatal Infarcts Of The Brainstem: A Neuropathological Study Of 7 Cases

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Brainstem infarcts are rarely recognized although their clinical expression are well-known and fully described such as Pierre-Robin sequence, absence of swallowing, Möbius syndrome and respiratory distress, frequently associated with arthrogryposis. Indeed, these lesions are inconstantly identified because of their reduced volume, beneath the resolution of imaging. Postmortem examination allows precise identification of the structures involved and understanding of the etiopathogenic mechanisms of such lesions.

We studied 5 fetuses, from 22 to 33 wg, presenting with fetal akinesia, absence of swallowing and hydramnios, including 22wg- monozygotic twins and, 2 neonates, 1 with cord strangulation, showing respiratory distress and Möbius syndrome, died shortly after birth.

All cases displayed brainstem ischemic lesions located in the tegmentum, including a severe atrophy, gliosis and calcifications involving cranial nerves nuclei, constantly abducens, facial, vagal, spinal hypoglossal and ambiguus nuclei. In 3 cases, they were associated with bilateral mesencephalic cavities and, in 1 case, with bilateral thalamic atrophy. In addition, all cases, but 1, demonstrated lesions in anterior horns of spinal cord. All these lesions involved a border zone between 2 arterial territories supplied by paramedian penetrating and long circumferential arteries and suggest watershed infarcts due mostly to a severe hypotension.

These observations demonstrate that brainstem watershed infarcts may occur at various stages of the fetal life from the first trimester to late gestation depending on the cause and require a careful neuropathological study.

21. Utility of Brain Biopsy in Acquired Pediatric Encephalopathy of Suspected Inflammatory Etiology

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Introduction: In cases of acquired pediatric encephalopathy of suspected inflammatory etiology the differential diagnosis chiefly involves vasculitis and encephalitis. In children, CNS vasculitis usually is lymphocytic, non-necrotizing and affects small-vessels (ie, SVcPACNS). Currently, differentiating vasculitis from encephalitis is crucial given significant differences in medical treatment. Unfortunately, the histologic criteria for the diagnosis of SVcPACNS are somewhat imprecise. Our primary goal was to review the BCCH experience with cases of acquired pediatric encephalopathy of suspected inflammatory etiology undergoing biopsy.

Methods: A retrospective clinicopathologic review of cases of 'acquired pediatric encephalopathy of suspected inflammatory etiology' was undertaken. All cases leading to brain biopsy at BCCH from 2000-2013 were included. Histologic review was initially directed by criteria set forth by Elbers et al (2010) and Kennard et al (1981).

Results: 17 biopsies were identified from 16 patients. 13/17 biopsies exhibited inflammation characteristic either of vasculitis (10/17; predominately SVcPACNS) or encephalitis (3/17), while 4/17 biopsies displayed non-specific pathologic changes. The pattern of vascular inflammation seen in vasculitic and encephalitic cases was noted to overlap in some instances. The latter prompted us to propose revised histologic criteria for the diagnosis of pediatric SVcPACNS: 1) angiocentric predominant inflammation; 2) ± mild diffuse microglial activation; 3) absence of or only rare microglial nodules; 4) absence of neuronophagia.

Conclusion: Brain biopsy in the context of pediatric acquired encephalopathy of suspected inflammatory etiology has a good diagnostic yield. Revised criteria for the histologic diagnosis of pediatric SVcPACNS are suggested.

22. Neuropathology of Type 6 Pontocerebellar Hypoplasia

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The pontocerebellar hypoplasias are a diverse group of paediatric development diseases that are frequently associated with defects in tRNA synthetase genes. We report three siblings born to non-consanguineous parents, who were each hypotonic at birth, developed seizures, had repeated apneic spells, and died within two months of life. Neuroimaging showed all had profound cerebellar hypoplasia and simplified cortical gyration. Autopsies on the younger twin siblings, who died three weeks apart, revealed small and immature cerebella, at an approximate developmental age of less than 16 weeks. Multiple brain regions showed either hypoplastic changes or regressive changes, or

both. The pontine base and cerebellum had extensive regressive changes, while the inferior olivary nucleus in the medulla was markedly hypoplastic. Both twins were microencephalic and had coarse, simplified gyri; cortices were immature and deep white matter displayed extensive astrocytosis. Genetic testing of the twins via whole exome sequencing demonstrated two mutations in the mitochondrial arginyl-tRNA synthetase gene (RARS2), indicating the siblings had type-6 pontocerebellar hypoplasia (PCH-6). The pathological findings of normal earlier development and later hypoplasia and degeneration indicate that the effect of the mutations were less in early gestation but became profound during middle and late gestation development.

23. The histopathological spectrum of incipient polymicrogyria

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Human gyrification occurs in a highly stereotypical anatomical and temporal sequence, with even subtle changes leading to many human disorders. The absence of cortical convolutions in brains of many model organisms has however left the mechanisms of gyral formation largely obscure. Polymicrogyria (PMG), the formation of excessive small gyral-like structures, develops focally in response to early cortical injury and may thus provide insight into factors promoting human cortical fissurization. Although the neuropathology of long standing PMG is well documented, less is known about the cellular changes that occur prior to the folding process. Here we present the pathological findings of a cohort of cases with acute cortical injuries prior to, or during active polymicrogyria formation. Significant neurological abnormalities were identified in cortical regions at risk of PMG including disruptions in cortical layering, focal expansion of Cajal-Retzius cells populations, morphological changes in radial glial, and persistence of developmental transcription factors. These acute changes correlate and help unify the documented changes seen early in mouse models of polymicrogyria, and late in matured human PMG. Characterization of the spectrum of neuropathological changes of incipient PMG in humans may thus improve our understanding of the cellular mechanisms orchestrating both normal and abnormal cortical folding.

Titles of Diagnostic Case Presentations

1. Neuronal storage disorder consistent with Kuf's disease

A.S. Easton[1], S. Darvesh[2], P. Jarrett[3]

[1]Department of Pathology, [2]Department of Medicine (Neurology/Geriatric Medicine), Capital District Health Authority and Dalhousie University, Halifax, Nova Scotia; [3]Geriatic/ Internal Medicine, St Joseph's Hospital, Saint John, New Brunswick, Canada

2. Hereditary Diffuse Leukoencephalopathy with Axonal Spheroids/ Pigmentary Orthochromatic Leukodystrophy

Ana Nikolic[1], Eric Smith[2], Lothar Resch[1]

[1]Division of Neuropathology, University of Calgary, [2]Division of Neurology, University of Calgary, Calgary Alberta, Canada

3. ADCK3 Mutation with Cerebellar Atrophy with Widespread Cerebral Cortical Superficial Vacuolation Striato-pallidal Atrophy and Iron Deposition

Alaa Al-Khotani[1], Tony E Lang[2], Lili-Naz Hazrati[1]

[1]Department of Laboratory Medicine and Pathobiology, University of Toronto; [2]Department of Neurology, University Health Network, Toronto, Ontario, Canada

4. Ruptured infectious ('mycotic') aneurysm involving distal branch of middle cerebral artery, with focal collections of Gram-positive cocci in relation to calcified material

J.P. Rossiter[1], K.S. Cunningham[1], R.P. Pokrupa[2]

Department of Pathology and Molecular Medicine[1] and Division of Neurosurgery[2], Queen's University and Kingston General Hospital, Kingston, Ontario, Canada

5. Mass forming IgG4 related pachymeningitis

Simin Laiq, David G. Munoz

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6. Cerebral malaria - subtype (plasmodium falciparum) diagnosed by PCR

K.B. Urankar

Division of Neuropathology, University of California, San Francisco, California, USA.

7. Anaplastic Oligodendroglioma

A. Al-Khotani[1], S. Croul[2]

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8. Germ Cell Tumour with Colorectal Differentiation

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https://doi.org/10.1017/S0317167100016425 Published online by Cambridge University Press

9. Glioneuronal Tumour with Neuropil-Like Islands

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10. Tanycytic Ependymoma of the Filum Terminale with Pleomorphic Giant cells

Alaa Alkhotani, David G. Munoz

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11. Chronic multifocal encephalopathy with the morphological pattern of MELAS (Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, and Stroke-like episodes)

B. Danielson[1], D.G. Munoz[1,2]

[1]Department of Laboratory Medicine and Pathobiology, University of Toronto; [2]Division of Pathology, St Michael's Hospital, Toronto, Ontario, Canada.

12. Metastatic Merkel cell carcinoma differentiating to anaplastic ganglioneuroblastoma

B. Lach

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13. Leptomeningothelial carcinomatosis - signet ring cell carcinoma

K.B. Urankar

Division of Neuropathology, University of California, San Francisco, California, USA.

14. Intraneural synovial sarcoma

Arie Perry, Melike Pekmezci, Andrew Bollen

Division of Neuropathology, University of California San Francisco (UCSF), San Francisco, California, USA.

15. Neurogenic atrophy with abundant cylindrical spirals

B. Ellezam[1], C.-T. Nguyen[2], M. Vanasse[2]

Departments of [1]Pathology, [2]Neurology, CHU Ste-Justine, Université de Montréal, Montréal, Quebec, Canada.

16. Fetal midbrain watershed infarcts, remote with dentate-olivary dysplasia, severe, suspicious of Ohtahara syndrome

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https://doi.org/10.1017/S0317167100016425 Published online by Cambridge University Press