Session 1: Traumatic and Neurodegenerative Neuropathology

Abstract 1

DNA damage and brain trauma: a clue to pathophysiology and biomarker development

LN Hazrati

The Hospital for Sick Children, Department of Pediatric Laboratory Medicine, University of Toronto, Toronto, Ontario, Canada

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Mild traumatic brain injury (mTBI) or concussion is a very common occurrence in contact sports, and can cause brain damage with long-term symptoms, including depression, aggression, memory loss, and an increased risk of neurodegeneration later in life. Recently, there has been increased attention towards concussion in sport both in research and media, however the nature and pathophysiology of mTBI-induced neurodegeneration remain unknown. The objective of this study is to identify early pathophysiological markers of TBI. This study used a collection of donated postmortem brains with a history of repetitive mTBI in contact sports and non-TBI control brains. Nanostring ncounter's immune panel was used to evaluate gene expression, and results showed that brains with a history of TBI tended to group with significantly older brains with no history of TBI in regards to their immune profile. Further analysis of this expression panel revealed that genes associated with senescence and secretory phenotype were upregulated in brains with a history of mTBI. Additionally, immunohistochemistry for γ-H2AX (a marker for double stranded DNA breaks) showed that brains with a history of repetitive TBI accumulated a spectrum of DNA damages not present in controls. This damage was widespread and involved mainly glial cells including oligodendrocytes, and astrocytes. The latter showed morphological changes reminiscent of senescence, including soma swelling and beading of processes. Further, these changes were accompanied by translocation of structural nuclear proteins. These changes preceded the appearance of abnormal protein deposition in the brain. Overall, these results suggest that DNA damage and cellular senescence are upstream events in the manifestation of post-mTBI symptoms and pathology, and represent promising opportunities for discovery of biomarkers for early TBI detection and follow-up of progression.

LEARNING OBJECTIVES

The presentation will enable the learner to:

1. Explore the relationship between trauma and DNA structural changes
2. Explore the relationship between trauma and senescence

Abstract 2

Is Alzheimer Disease a Disease?

JT Joseph

University of Calgary, Calgary, Alberta, Canada

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Problem: Alzheimer disease (AD) is defined as "an irreversible, progressive brain disorder that slowly destroys memory and thinking skills" (National Institute on Aging) and is pathologically characterized by abnormal deposition of neurofibrillary tangles and amyloid plaques. However, these abnormal protein aggregates also accumulate with aging, which complicates the distinction between aging and AD.

Results: This presentation will discuss the concepts of disease and then compare and contrast these with the definition of Alzheimer disease. It briefly discusses causality and examines how associations have to be conflated with causality in the pathological diagnoses of neurodegenerative diseases. It also indicates some inherent biases that pathologists have in identifying disease and the pathological changes resulting from diseases. The presentation will present examples from the Calgary Brain Bank of patients without known neurodegenerative disease who die at different ages, as well as different pathological presentations of neurofibrillary tangles and amyloid plaques. Several known causes of AD will be reviewed and contrasted with what is commonly considered "normal aging".

Discussion: This presentation argues that Alzheimer disease pathology represents a final common pattern of changes that results from several or possibly many different aetiologies. Recognizing that these changes have several different causes might better guide future research into late onset dementias.

LEARNING OBJECTIVES

This presentation will enable the learner to:

1. Consider observational biases used in the diagnoses of different dementias
2. Distinguish several aetiologies of Alzheimer-type Neuropathology
3. Contemplate how neuropathology has done a disservice in dementia research by focusing on accumulations of abnormal proteins

Abstract 3

Stereologic measures of beta-amyloid load in postmortem autosomal dominant Alzheimer disease brain validate PiB-PET as a useful biomarker

N Sinha, A Zhou, Y Li, N Joseph-Mathurin, C Xiong, JC Morris, R Bateman, TL Benzinger, NJ Cairns, Knight ADRC and DIAN

Washington University, St. Louis, MO, USA

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In vivo positron emission tomography (PET) using [C11]-labeled Pittsburgh Compound B ([C11]PiB) has previously been shown to detect amyloid-β (Aβ) in late-onset Alzheimer disease (LOAD) brain; however, the sensitivity of this technique for detecting β-amyloidosis in autosomal dominant Alzheimer disease (ADAD) has not been systematically investigated. To validate [C11]PiB PET as a useful biomarker of β-amyloidosis, we measured the cortical and regional standardized uptake value ratios (SUVRs) in 16 ADAD and 15 LOAD cases and compared them with histopathologic measures of β-amyloidosis in postmortem brain. The PiB-PET data were obtained between 40–70 min after bolus injection of ~15 mCi of [11C]PiB. MRI and PiB-

PET images were co-registered and SUVRs were generated for several brain regions. Using Aβ immunohistochemistry (10D5, Eli Lilly), the burden of Aβ plaques was quantified in 16 regions of interest using an area fraction fractionator probe (Stereo Investigator, MicroBrightfield, VT). There were regional variations in Aβ plaque burden with highest densities observed in the neocortical areas and the striatum. On spearman correlations, *in vivo* PiB-PET correlated with postmortem Aβ plaque burden in both LOAD and ADAD, with strongest correlations seen in neocortical areas. In summary, [C11]PiB-PET has utility as a biomarker in both ADAD and LOAD.

LEARNING OBJECTIVES

This presentation will enable the learner to:

1. Discuss how PET-PiB beta-amyloid imaging is used as a potential biomarker of Alzheimer disease (AD)
2. Correlate postmortem neuropathologic evidence of beta-amyloidosis with PET-PiB data, and learn that PET-PiB is a potentially useful tool to detect beta-amyloidosis in presymptomatic and symptomatic individuals

Abstract 4

Microvascular pathology of Friedreich cardiomyopathy

A Koeppen[1,3], A Sossei[1], A Travis[1], E Kleinhenz[1], J Mazurkiewicz[2], P Feustel[2], J Qian[3]

[1]Veterans Affairs Medical Center; [2]Department of Neurosciences and Experimental Therapeutics; [3]Department of Pathology, Albany Medical College, Albany, NY, USA

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Nikolaus Friedreich (1877) was aware of heart disease in his patients but thought it was unrelated to the neurological disorder. In 1946, Dorothy Russell considered cardiomyopathy an integral part of Friedreich ataxia (FA). In addition to sparse inflammatory infiltration, sections show fibrosis and capillary hyperplasia. We examined the left ventricular walls of 41 homozygous FA patients aged 10–87 and 21 controls aged 2–69. An antibody to CD34 enabled quantitative capillary profile counts for a comparison with cardiomyocyte counts in the same field. Mean capillary counts in normals were $1926 \pm 341/mm^2$, and the median ratio of capillaries to cardiomyocytes was 1.0 (interquartile range [IQR]: 0.9-1.2). In FA, however, the number of cardiomyocytes/mm^2 was less, and the median ratio of capillaries to heart fibers was 2.0 (IQR 1.4-2.4). There was a significant correlation of the higher guanine-adenine-adenine trinucleotide length (shorter allele, GAA1) with the younger age of onset, shorter disease duration, and lower cardiomyocyte counts. The ratio of capillaries to heart fibers was higher in patients with long GAA1 repeat expansions (e.g., 3.31 in GAA1 of 1200). Double-label immunofluorescence for CD34 and S100A4 revealed co-expression in endothelial cells, supporting endothelial-to-mesenchymal transition in the pathogenesis of cardiac fibrosis (supported by Friedreich's Ataxia Research Alliance).

LEARNING OBJECTIVES

The presentation will enable the learner to:

1. Describe endothelial-to-mesenchymal transition in the pathogenesis of cardiac fibrosis in Friedreich cardiomyopathy

Session 2: Pediatric, Epilepsy and Miscellaneous Neuropathology

Abstract 5

Parasagittal intraparenchymal hemorrhage in complicated second stage labour: a report of three cases

K Grenier, M Basheer, P Shannon

Department of Pathology and Laboratory Medicine, Mount Sinaï Hospital, University of Toronto, Toronto, Ontario, Canada

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The increased use and mastery of ceasarian section for deliveries and the refinement of technologies for assisted delivery in the setting of dfficult second stage of labour have made intrapartum deaths more rare and modern obstetrical pracices are rarely accompanied by the classic forceps related intracranial injuries. We document a novel pattern of intracranial injury in three cases of neonatal death following prolonged labor, of which two out of three required vacuum and forceps.

All three showed similar bilateral parasagittal intraparenchymal haemorrhages and cerebral edema, in a pattern reminiscent of "gliding contusion, as well as subgaleal haemorrhage of varying amout. Two out of the three cases showed parietal bone fractures and one demonstrated extensive craniolcuniae. We briefly discuss the significance of these findings and implications for future cases.

LEARNING OBJECTIVES

This presentation will enable the learner to:

1. Explore the current theories leading to neonatal death in prolonged labor
2. Summarize the known pathological findings associated with vacuum and forceps
3. Discuss the significance of intraparenchymal hematoma in the setting of prolonged delivery

Abstract 6

Non-Perfused Brain and Retino-Dural Hemorrhage

RN Auer

University of Saskatchewan, Saskatoon, Canada

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10 cases of pneumonia causing cardiac arrest and non-perfused brain occurred at ages 40 days-30 months, in a medico-legal setting. In each deceased child, both the pneumonia and non-