Session 1: Traumatic and Neurodegenerative Neuropathology

Abstract 1

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

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doi: 10.1017/cjn.2019.255

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?

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doi: 10.1017/cjn.2019.256

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

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doi: 10.1017/cjn.2019.257

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-