Progress Report

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Title of Project: Understanding Chronic Traumatic Encephalopathy

Summary:
There is considerable scientific and community interest in the consequences of repetitive traumatic brain injury (TBI) and global public concern that even mild head injury may lead to a progressive neurodegenerative disorder known as chronic traumatic encephalopathy (CTE) in later life. However, the scientific knowledge in this area is preliminary and there is an urgent need for accelerated research efforts in the interests of public health.

This research program aims to assess the presence of CTE in brain donors collected through the Sydney Brain Bank (SBB). All SBB donors are collected through longitudinal, prospective brain donor programs with an interest in ageing and neurodegeneration. The cohorts are extremely well-characterised due to their participation in on-going health and lifestyle assessments during life.

Hypothesis vs Findings:
CTE is thought to occur as a consequence of traumatic brain injury (TBI) and approximately 20% of Sydney Brain Bank cases have a history of significant head injury. In addition, 9% of cases held in the Sydney Brain Bank have a neurodegenerative disorder where the risk of falling is high and an increased frequency of CTE has previously been noted in these individuals (Ling et al 2015). We therefore hypothesised that CTE would be found in approximately 10-20% of our cohort.

Over 2800 tissue sections have been cut and stained from 633 cases for the purpose of this project. We used current published research diagnostic criteria (McKee et al 2016) to assess the presence of CTE neuropathological change in the Sydney Brain Bank cohort. The brain regions screened were the middle frontal gyrus, superior and middle temporal gyri and inferior parietal lobule as these regions are through to be affected earliest in CTE. All sections were stained with antibody AT8, which detects phosphorylated tau protein, which accumulates in the diagnostic lesions in CTE.

Prior to commencing analysis of all 633 cases, 20 cases with variable levels of CTE neuropathology were screened by a neuropathologist and 2 independent research neuropathologists to ensure consistency with diagnosis. Inter-rater and intra-rater agreement was 100% in these 20 cases.

CTE neuropathological change was identified by the presence of *phosphorylated tau aggregates in neurons, astrocytes and cell processes around small vessels in an irregular pattern at the base of*

the cortical sulci (McKee et al 2016). The presence of age-related tau astrogliopathy (ARTAG) was also noted, but the presence of ARTAG alone was not sufficient to reach a diagnosis of CTE (Kovacs et al 2017).

All 2859 sections will now be screened for the presence of CTE neuropathological change and ARTAG. The symmetry of pathology will also be examined in cases where both hemispheres of the brain were collected (160 cases). The relationship between CTE and head injury, age, gender, prior participation in contact sport and co-existing disease will also be analysed.

What these research outcomes will tell us:
This work represents one of the largest studies of CTE pathology in a clinically, well-characterised brain bank population. It will answer questions that are of great public concern, including whether head injury is associated with CTE, whether it is more common in males or females and if it is commonly associated with other neurodegenerative disorders.

References

Kovacs et al 2017 Multisite assessment of ageing-related tau astrogliopathy (ARTAG) Journal of Neuropathology and Experimental Neurology Vol 76 pp605-619

Ling et al 2015 Histological evidence of chronic traumatic encephalopathy in a large series of neurodegenerative diseases. Acta neuropathologica 130: 891-893

McKee et al 2016 The first consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy Acta Neuropathologica 131:75-86