Chronic Traumatic Encephalopathy

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First described by Martland as “punch drunk syndrome” in 1928 in former boxers, chronic traumatic encephalopathy (CTE) is not a new disease. Yet, for years, it largely resided in pathology textbooks, second-year medical school classrooms, and board exams. That changed in 2005 when it was described by Omalu in a former National Football League (NFL) player, and has since emerged as a pressing matter for the lay public, researchers, and clinicians. As investigators at Boston University, which has been a CTE epicenter for over a decade, we are humbled by the attention the work receives, are exceedingly aware of the limitations of what we know, and are hungry to offer patients more in terms of diagnosis and treatments. Leading the chorus that more original research is needed, we were initially a bit reluctant to offer another round of review papers when Dr. David Greer, the editor-in-chief of Seminars, asked us to guest edit this issue. However, we quickly realized that compiling a range of CTE-related reviews into a single source would provide the breadth and depth that individual reviews generally lack. We also saw the issue as an opportunity to provide extensive expert commentary on the research landscape and limitations, implications for public health, where the field should be moving and how clinicians may care for patients suspected of having CTE, even if they cannot be sure of a diagnosis.

Now that the issue is complete, we are confident that the contributors have made unique and valuable additions to the field. Bernick and Cantu begin the issue by reviewing the history of CTE from Martland and Corsellis’ initial descriptions of the clinical syndrome and neuropathology, respectively, to recent large case series from our team. McKee provides an evidence-based review of the neuropathology of CTE and addresses misrepresentations and confusions in the literature. Stein and Crary review the major comorbid pathologies that occur with CTE and examine the distinction between CTE and age-related pathology, including primary age-related tauopathy and age-related tau astrogliopathy. Mariani, Alosco, Mez, and Stern review the clinical presentation of CTE and expound on the role of diagnostic criteria and in vivo biomarkers. CTE may clinically resemble both Alzheimer’s disease (AD) and behavioral variant frontotemporal dementia. Lesman-Segev and Rabinovici compare the clinical aspects, genetics, fluid biomarkers, imaging, treatment, and pathology of these diseases, and offer inciteful cases to illustrate the similarities and differences.

Phelps, Mez, Stern, and Alosco propose a framework of risk factors that influence the neuropathological development of CTE, including both repetitive head impact (RHI) and nonhead trauma-related exposure. Fluid biomarkers are a hallmark of both research and clinical care for AD and for acute and subacute head trauma. Shahim, Gil, Blennow, and Zetterberg review the literature for potential CTE...
candidate biomarkers and pathways to advance the most promising candidates into clinical care. Although exposure to RHI is highly predictive of CTE pathology, not all individuals with a given level of RHI exposure develop CTE, suggesting other risk factors, including genetics, may also contribute. Abdolmohammadi, Evers, Dupre, and Mez explore concepts in genetic study design for CTE, implicated genes in CTE, and whether predictive genetic testing for CTE should be considered. Cherry and Goldstein review CTE pathobiology, first linking the biomechanical properties of RHI to initiation of CTE pathology, and second, describing abnormal tau hyperphosphorylation, accumulation, and spread. Finkel and Brand use a risk-based and decision-analytic approach to convincingly demonstrate that the links between RHI exposure, CTE pathology, and clinical symptoms are unlikely coincidental or artifactual, and that the costs of intervening are far smaller than the costs of failing to intervene. Lastly, Uretsky and Nowinsky provide the first review of CTE advocacy and consider the connections between CTE advocacy, research, and legislation over the last decade.

We deeply value the expertise and commitment of all of the authors to this issue of Seminars. We thank them wholeheartedly for imparting their knowledge and experience in these exceptional reviews. We also thank Dr. Greer for conceiving of this issue and for his thoughtful input into each review. We believe that readers will find these articles both insightful and practical.