Program Profile

The VA/DoD Chronic Effects of Neurotrauma Consortium: An Overview at Year 1

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This federally funded program identifies gaps in research and provides support services for scientific, clinical, and translational research projects focused on the long-term effects of mild traumatic brain injury in veterans and active-duty service members.

The Chronic Effects of Neurotrauma Consortium (CENC) is a federally funded research project devised to address the long-term effects of mild traumatic brain injury (mTBI) in military service members (SMs) and veterans. Announced by President Barack Obama on August 20, 2013, the CENC is one of 2 major initiatives developed in response to injuries incurred by U.S. service personnel during Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) as part of the National Research Action Plan. The CENC is jointly funded by the DoD and the VA, with a budget of $62.175 million over 5 years.

The consortium funds basic science, clinical, and translational research efforts with a closely integrated supportive infrastructure, including administrative services, regulatory guidance, study design, biostatistical consultation, data management, common data element application, and interdisciplinary communication. In addition, the consortium facilitates and integrates the activities of a diverse group of skilled specialty research teams, allowing them to fully focus their efforts on understanding and clarifying the relationship between combat-related mTBI and chronic neurotrauma effects, including neurodegeneration.

BACKGROUND

Nearly 20% of the more than 2.6 million U.S. SMs deployed since 2003 to OEF and OIF have sustained at least 1 TBI, predominantly mTBI. Almost 8% of all OEF/OIF veterans demonstrate persistent post-TBI symptoms more than 6 months postinjury. Acute mTBI effects are typically transient, with headache, cognitive, behavioral, balance, and sleep symptoms most often seen, but symptoms may persist and even lead to lifelong disability. In these individuals, additional chronic effects, such as neuroendocrinologic abnormalities, seizures and seizurelike disorders, fatigue, vision and hearing abnormalities, and numerous other somatic symptoms are more common over time. The long-term effects from single or repeated mTBIs on the persistence of these symptoms, on combat and trauma-related comorbidities, and on long-term brain functioning are unknown.

Increasing evidence supports the link between both concussions and combat-related trauma with chronic traumatic encephalopathy (CTE), which results in progressive cognitive and behavioral decline in subpopulations 5 to 50 years out from repeated or cumulative mTBI exposures. The possibility of a link between mTBI,

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persistent symptoms, and early dementia has widespread implications for SMs and veterans; however, these chronic and late-life effects of mTBI are poorly understood.

Traumatic brain injuries of mixed severity have been linked to a higher incidence of Alzheimer disease (AD) and other dementias and an earlier onset of AD, although negative findings have also been reported. Chronic traumatic encephalopathy has been reported to occur in retired boxers at higher rates and at younger ages compared with dementia in the general population. More recently, brain autopsies of athletes from a variety of sports with confirmed CTE have demonstrated elevated tau proteins, tau-immunoreactive neurofibrillary tangles, and neuropil threads, suggesting that pathologic processes similar to those occurring in AD may be involved. Longitudinal research bridging SMs, veterans, and athletes with neurotrauma has been fragmented and incompletely focused on the strategic needs (eg, troop readiness) and vision of the DoD and VA.

Critical gaps exist in the literature with few prospective, well-controlled, longitudinal studies on late-life outcomes and neurodegeneration after mTBI, as well as in related basic science research. These research gaps are particularly prominent in the potentially unique injuries and difficulties seen in combat-exposed populations. The existing research, although suggestive, is not rigorous or robust enough to allow for a clear understanding of the relationships, risks, and potential effective interventions for mTBI, chronic symptoms, and neurodegeneration.

The CENC was developed to create a road map of existing knowledge gaps, to recruit the top relevant subject matter experts in the country, to develop and establish a cohesive set of rigorously designed studies to address these knowledge voids, and to leverage core consortium resources both efficiently and effectively.

Given these gaps in scientific research and knowledge, the DoD and VA jointly issued a request for proposals to fund a project to address these concerns. After a competitive application process, an integrated proposal, led by researchers at Virginia Commonwealth University (VCU) was announced as the recipient of the Presidential award.

CONSORTIUM STRUCTURE

The CENC, serving as the comprehensive research network for DoD and VA, focuses on (1) identifying and characterizing the anatomic, molecular, and physiologic mechanisms of chronic injury from mTBI and potential neurodegeneration; (2) investigating the relationship of comorbidities (psychological, neurologic, sensory, motor, pain, cognitive, and neuroendocrine) of trauma and combat exposure to TBI with neurodegeneration; and (3) assessing the efficacy of existing and novel treatment and rehabilitation strategies for chronic effects and neurodegeneration following TBI.

The consortium is a collaboration among more than 30 universities, nonprofit research organizations, VAMCs, and military medical centers made up of a leadership core, 5 research infrastructure cores, 8 active studies, a data safety monitoring committee, a consumer advisory board, a scientific advisory board, and an independent granting mechanism to foster additional research in chronic effects after mTBI.

Leadership Core

The principal investigator for CENC is David X. Cifu, MD, chairman and professor of the VCU Department of Physical Medicine and Rehabilitation in Richmond, Virginia. The consortium co-principal investigators are Ramon Diaz-Arrastia, MD, PhD, professor of neurology, Uniformed Services University of the Health Sciences (USUHS) and director of the clinical research at the Center for Neuroscience and Regenerative Medicine in Bethesda, Maryland, and Rick L. Williams, PhD, co-principal investigator for CENC and senior statistician at RTI International in Raleigh, North Carolina.

Research Cores

The CENC operates 5 research infrastructure cores. The Biorepository Core, led by Dr. Diaz-Arrastia at USUHS, manages the storage and processing of biologic (blood and saliva) samples collected through all CENC protocols. The Biostatistics Core, led by Dr. Williams; Nancy Temkin, PhD; and Heather Belanger, PhD at RTI, provides study design guidance and biostatistical analysis to facilitate knowledge translation and dissemination.

The Data and Study Management Core is led by Dr. Williams at RTI. It centrally and securely maintains all collected data; oversees the clinical monitoring of research sites; provides a consortium research manager for each study who interacts with the study leadership, study site leaders, and staff; expedites and guides clinical protocols through regulatory approval processes; coordinates patient accrual and study activities across sites; develops and monitors data acquisition compliance; and facilitates exportation of all data collection to the Federal Interagency Traumatic Brain Injury Research informatics system.

The Neuroimaging Core is led by Elisabeth Wilde, PhD, at Baylor College of Medicine and the Michael E.

DeBakey VAMC in Houston, Texas. This core facilitates sequence development and pulse programming; provides training and supervision of technologists and support personnel; ensures acquisition, transfer, and storage of imaging data; oversees quality assurance; performs conventional and advanced imaging analysis; and interprets neuroimaging data.

The Neuropathology Core is led by Dr. Dan Perl and colocated at USUHS and Edith Norse Rogers Memorial Veterans Hospital/VA Boston Healthcare System. Dr. Perl manages the collection of brain specimens from the participants, using an existing national network of dieners and neuropathologists, catalogs and stores tissues, and administers requests for use of these tissues.

ACTIVE RESEARCH STUDIES

The Longitudinal Cohort Study addresses a critical research gap by identifying and characterizing the late effects of mTBI and assessing the influence and interaction of the many potential risk factors for early dementia. The study uses a wide array of self-report, laboratory, biophysical, neuropsychologic, and imaging assessment tools to evaluate a cohort (n = 880) of U.S. OEF/OIF combatants who have had at least 1 mTBI and a control group of participants (n = 220) who have experienced combat but have not had a mTBI, and then re-assesses them annually (in person or via telephone), with the goal of following the cohort for as long as resources are available.

Collaborating sites for this study include Hunter Holmes McGuire VAMC in Richmond, Virginia; James A. Haley Veterans' Hospital in Tampa, Florida; Michael E. DeBakey VAMC in Houston, Texas; Audie L. Murphy Memorial Veterans Hospital in San Antonio, Texas; VA Boston Healthcare System; Minneapolis VA Health Care System in Minnesota; and Fort Belvoir in Virginia. Dr. Cifu and Dr. William Walker lead this study.

Epidemiology of mTBI and Neurosensory Outcomes

This project integrates and analyzes several VA, DoD, and Centers for Medicare and Medicaid Services health care system data sets to study the chronic effects of mTBI on neurodegenerative disease and other comorbidities. The primary aims of the project include evaluating the association between mTBI and short-term clinical outcomes, including factors associated with resilience and effects of treatment; investigating long-term clinical outcomes, including neurosensory disorders and mortality; and identifying factors associated with low- and high-distress trajectories of comorbid burden after mTBI. Dr. Kristine Yaffe, Dr. Mary Jo Pugh, and Dr. Michael McCrea, are the leads of this study.

Tau Modification and Aggregation in TBI

This study aims to develop an animal model of repetitive-mTBI, which will allow the tracking of progressive intraneuronal tau alterations that can be correlated with behavioral dysfunction, neuronal protein, and gene expression signatures that can be used to assess the effects of interventions. The observations made in the animal model will be compared with findings generated from tissue obtained at autopsy from deceased SMs and veterans who sustained repetitive-mTBI. Dr. Fiona Crawford and Dr. Elliott Mufson lead this study.

Otolith Dysfunction

This study is examining the effect of inner ear dysfunction on balance, gait, and quality of life (QOL). Recent evidence suggests that otolith organ dysfunction can occur in patients with mTBI or blast exposure. If the dizziness and imbalance symptoms that occur following head injury or blast exposure are related to injury to the otolith organs rather than to the horizontal semicircular canal, then new treatment approaches may be necessary to focus on otolith organ pathway recovery. Performance on balance tasks while standing and walking and questionnaires on the impact on QOL will be compared in 4 groups of individuals (n = 120) with and without head injury/blast exposure (otolith organ dysfunction, horizontal canal dysfunction, both otolith and horizontal canal dysfunction, and healthy individuals). Dr. Faith Akin leads this study.

ADAPT

The ADAPT study (Assessment and Long-term Outcome and Disability in Active Duty Military Prospectively Examined following Concussive TBI) is investigating the association of early clinical and imaging measures with late (5 year) clinical outcome after blast-related mTBI from combat. The study (n = 100) will use 5-year follow-up advanced magnetic resonance imaging (MRI) and clinical outcome measures of combat mTBI, as a continuation of previous longitudinal research efforts (n = 575). Two groups of subjects will be studied: subjects who sustained a mTBI from blast during deployment and subjects without history of blast exposure and no diagnosis of deployment mTBI. Dr. Christine MacDonald leads this study.

Diffusion Tensor Imaging Phantom Study

This study involves the development and testing of a novel phantom that

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would be used to enhance accuracy, consistency, and reliability in both isotropic and anisotropic measurements derived from diffusion imaging, as well as other MRI-based measurements, using universal fluid disk chambers in a single phantom. Currently, the acquisition of diffusion data in large studies and clinical trials lacks standardization, and important differences exist in how data are acquired on scanners of different manufacturers, using different hardware or software, or when different acquisition parameters are used. As a result, development of large pools of data and the creation of normative data are hampered by inhomogeneity in the data set, which is difficult to analyze. The study team will perform detailed testing of the phantom materials and phantoms themselves, as well as examine diffusion imaging on 1 to 2 human volunteers at each of the 4 sites. Intra- and interscanner differences will be measured, and based on these findings, a more standardized imaging protocol that will provide optimal uniformity of diffusion imaging will be designed. Dr. Elisabeth Wilde leads this study.

Novel White Matter Imaging to Improve mTBI Diagnosis

This study will use myelin-sensitive novel imaging techniques (McDespot [multi-component driven equilibrium single pulse observation of T1/T2]) to improve correspondence with diagnostic groups after trauma exposure and correlation with cognitive deficits in mTBI. The study will recruit individuals (n = 82) from 4 groups, comorbid mTBI and posttraumatic stress disorder (PTSD), only mTBI, only PTSD, and controls who will be prospectively comprehensively assessed clinically (clinical interview, physical exam, neuropsychological assessment) and with advanced imaging (including McDespot, diffusion tensor imaging, and other forms of imaging). Dr. Amy Jak leads this study.

Peer Review Program

The CENC has an integrated grant program to identify scientifically valid and strategically important research projects. To date, 2 rounds of proposal requests and project support have been completed. Scientific review is conducted under the CENC Peer Review Program. Scientifically meritorious studies are identified by independent peer review and then undergo a Programmatic Review by CENC leadership before being recommended for

funding to the Government Steering Committee (GSC). Studies that are recommended must address road map gaps, develop innovative approaches, or provide an avenue for new researchers and novel research approaches to contribute to the consortium mission to advance the science of brain injury treatment and prevention. The CENC grant program is administered by Dr. Steven L. West.

Consumer Advisory Board

The Consumer Advisory Board (CAB) advises and makes nonbinding recommendations to CENC. The responsibilities of the committee members include (1) providing information that helps CENC leadership better appreciate and understand the issues and needs of TBI survivors and their support networks so appropriate research can be designed and implemented; (2) evaluating existing research and making recommendations for additions and/or modifications to project procedures; (3) providing input for the road map for future research based on members' personal experiences and knowledge; and (4) providing linkages to targeted communities for direct feedback and to assist in forming collaborative partnerships.

The CAB is composed of survivors of TBI, family members of survivors of TBI, providers of TBI services, service organizations with specific ties to SMs and veterans, and clinical and corporate representatives of transportation services for the disabled, the independent living movement, and assistive technology. Persons who are heavily engaged in political activity or who actively endorse a specific device or product are not eligible for membership on the CAB. Membership is composed of persons nominated by CENC leadership and approved by the GSC. The CAB is co-chaired by Charles Gatlin, MS, and General (Ret.) Peter Chiarelli.

Scientific Advisory Board

The members of the Scientific Advisory Board (SAB) advise and make nonbinding recommendations to CENC. Responsibilities of the committee members include (1) providing information that may help the consortium leadership better understand the issues related to TBI; (2) evaluating existing research; (3) recommending additions and/or modifications to project procedures; and (4) assisting CENC by helping leverage relationships with other researchers. The SAB is composed of members of the research community on TBI who are not part of CENC. Persons who may be considered to have positions of authority, such as active or retired flag officers or chief executive officers, may be eligible for general SAB membership but are not be eligible for chair positions. Membership is composed of persons nominated by CENC leadership and approved by the GSC. Col. Jamie Grimes, MD, and Henry Lew, MD, PhD, co-chair the SAB.

FEDERAL OVERSIGHT

The GSC oversees CENC. Members of the GSC are DoD and VA appointed and represent both government agencies and nongovernment subject matter experts. The GSC approves all studies to be conducted, recommends new studies, and identifies existing and new requirements. The GSC is the overall main governing and management committee for the project and the committee through which the DoD and VA interact and collaborate with the CENC. The GSC determines all major scientific decisions, and clinical studies proposed by the CENC committee proceed to the implementation stage only with the approval of the GSC. ●

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