DEPARTMENT OF DEFENSE
BLAST INJURY RESEARCH PROGRAM COORDINATING OFFICE

Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy (CTE)?

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Literature Review Summary

The Biological Basis of Chronic Traumatic Encephalopathy Following Blast Injury

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State of the Science

- Initial consensus reached recently on the neuropathology of CTE
- Associations between CTE development and frequency or type of head injury exposure cannot be determined
- Existing animal models do not comprehensively reflect CTE neuropathology
- Ongoing biomarker development may enable identification and study of CTE neuropathology in living persons
- Treatment is not established; mitigation strategies focus on prevention

Purpose: Research Questions

- What is the current evidence describing the pathophysiological basis of CTE?
  - What biological processes following head injury are associated with the development of CTE?
  - What advances in neuroimaging or biomarkers of CTE may lead to the development of diagnostic tools or therapeutic strategies?
- What associations are known between the mechanism(s) of head injury (e.g., single or multiple exposures, impact or nonimpact injury) and the development of CTE?
  - Does the frequency of exposure to head injury correlate with the development of CTE?
  - Are there any known distinctions between how impact injury, nonimpact injury, and blast-induced injury are associated with the development of CTE?

Methods

- Literature sources: PubMed, the Defense Technical Information Center (DTIC), Google, and Google Scholar
- Search terms
- Clinical and animal model studies
- Reviews and primary research
- 2005 to 2015, inclusive
- Research questions

Methods: Search Terms

Condition		Pathology	Outcome Measure(s)	Study Population(s)
Alzheimer's disease	Motor neuron disease	Activated kinases	Assessment	Animal models
Auditory	Neurodegeneration	Apolipoprotein E (ApoE) genotype	Computational models	Athletes
Behavioral disorder	Neurodegenerative	Astrocytes	Diagnostic	Boxing
Blast event	Parkinsonism	Astroglial tangles	Diffraction spectrum imaging or DSI	Breacher
Blast exposure	Post-concussion syndrome or PCS	Axonopathy	Diffusion Tensor Imaging or DTI	Football
Chronic TBI	Post-traumatic stress disorder or PTSD	Beta-amyloid	Magnetic Resonance Imaging or MRI	International Space Program
Chronic traumatic encephalopathy or CTE	Potentially concussive event or PCE	Biomarker	Screening	Military
Cognition	Proteinopathies	Epigenetics	Positron Emission Tomography or PET	NASA
Cognitive deficits	Repetitive head injury	Glymphatics	Treatment	NCAA
Concussion	Suicide	Microglia		NFL
Headache/ migraine	Tauopathy	Neuroendocrine		Occupational blast
Head trauma	Traumatic brain injury or TBI	Neurofibrillary tangles		Post-mortem
Hearing	Traumatic encephalopathy	Neuropathology		Sports
Inflammation	Vascular injury	Neurosensory		Soccer
Late effects of TBI	Vertigo or dizziness	TDP-43		Veteran
Mild traumatic brain injury or mTBI	Eye, retina, optic nerve, retinal ganglion cells, photoreceptors			

Literature Review Findings

- Neuropathology
- Exposure to head injury
- Animal models
- Biomarkers
- Treatment and prevention
- Research needs

Neuropathology: Existing Consensus

Required criteria for diagnosis of CTE

- Abnormal perivascular accumulation of tau in neurons, astrocytes, and cell processes in an irregular pattern at the depths of the cortical sulci

Supportive criteria for a diagnosis of CTE

- Macroscopic abnormalities in the septum pellucidum (cavum, fenestration), disproportionate dilatation of the third ventricle or signs of previous brain injury
- Abnormal tau immunoreactive neuronal lesions affecting the neocortex predominantly in superficial layers 2 and 3 as opposed to layers 3 and 5 as in AD
- Abnormal tau (or silver-positive) neurofibrillary lesions in the hippocampus, especially in CA2 and CA4 regions, which differ from the preferential involvement of CA1 and subiculum in AD
- Abnormal tau immunoreactive neuronal and astrocytic lesions in subcortical nuclei, including the mammillary bodies and other hypothalamic nuclei, amygdala, nucleus accumbens, thalamus, midbrain tegmentum, and substantia nigra
- Tau immunoreactive in thorny astrocytes in subpial periventricular and perivascular locations

Exclusions to the diagnosis of primary CTE

- CA1 predominant neurofibrillary degeneration in the hippocampus in association with amyloid plaques, as seen in AD
- Cerebellar dentate cell loss, prominent coiled bodies in oligodendroglia, and tufted astrocytes as seen in progressive supranuclear palsy
- Severe involvement of striatum and pallidum with astrocytic plaques in cortical and subcortical structures as seen in cortical basal degeneration

Adapted from: Report from the First NIH Consensus Conference to Define the Neuropathological Criteria for the Diagnosis of Chronic Traumatic Encephalopathy: http://www.ninds.nih.gov/research/tbi/ReportFirstNIHConsensusConference.htm

Neuropathology

- Macroscopic
  - Reduction of brain weight
  - Enlargement of ventricles
  - Abnormalities in septum pellucidum (cavum, fenestration)
  - Depigmentation of the locus coeruleus and substantia nigra
- Microscopic
  - Tau: abnormal aggregation of hyperphosphorlyated tau protein in brain areas including superficial layers of the cerebral cortex, subcortical nuclei, and brainstem
  - TAR DNA-binding protein (TDP-43): abnormal aggregation in brain areas including brainstem, basal ganglia, diencephalon, medial temporal lobe, frontal, temporal, and insular cortices, and subcortical white matter
  - Beta-amyloid protein (Aβ)
  - Axonal injury
  - Neuroinflammation

Exposure to Head Injury

- Limitations of data describing frequency and/or type of head injury exposure
  - Inconsistent data collection
  - Exposure to injury characterized as exposure to sport or occupation
  - Retrospective, subjective
- Exposure frequency
  - Single vs. multiple mTBI: cognitive function
  - Concussion frequency: cognitive impairments, self-reported depression
- Exposure type
  - Neuropathologically confirmed CTE without concussion
  - Multiple concussions without CTE pathology
  - Blast injury

Animal Models

- Existing animal models do not comprehensively reflect CTE neuropathology
- Animal models of TBI may be informative
  - Blunt-force
  - Blast
- Neuropathological analysis
  - Tau
  - Axonal injury
- Neurobehavioral analysis
  - Cognitive assessment (spatial learning and memory)
  - Motor assessment (balance and sensorimotor coordination)

Biomarkers: Neuroimaging

- Positron emission tomography (PET)
  - Tau
  - Aβ
  - Metabolic activity
  - Neuroinflammation
- Diffusion tensor imaging (DTI)
  - White matter abnormalities; axonal injury?
- Magnetic resonance imaging (MRS)
  - N-acetyl aspartate (NAA): neuronal damage
  - Choline (Ch): membrane damage, diffuse axonal injury
  - Glutamine (Glx): excitotoxicity
  - NAA/Ch, NAA/Cr ratios
  - Creatine (Cr)
- Functional magnetic resonance imaging (fMRI)

Biomarkers: Biospecimens

- Cerebrospinal fluid (CSF)
  - Tau
  - Neurofilament light
  - Glial fibrillary acidic protein (GFAP)
- Blood plasma
  - Tau
  - S-100β
  - neuron-specific enolase

Treatment and Prevention

- Prevention of injury
  - Helmets/headgear
  - Return-to-activity guidelines
- Intervention development
  - Blockade of tau aggregation

Limitations

- Existing clinical data gathered postmortem
- Case duplication in the literature
- Selection bias
- Clinical symptom data are retrospective, subjective

Research Needs

- Population/epidemiological studies
- Standardized pathology protocols
- Clinical diagnostic criteria
- Biomarker development

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