Imaging of Chronic Concussion

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KEYWORDS

• Concussion • Mild traumatic brain injury (mTBI) • Cerebral • Trauma
• Chronic traumatic encephalopathy (CTE)

KEY POINTS

- Cerebral concussion is a subset of traumatic brain injury resulting in transient impairment of neurologic function that usually resolves spontaneously, although in some cases, symptoms may be prolonged.
- Chronic traumatic encephalopathy is a recognized pathologic entity resulting from repetitive mild traumatic brain injury, clinically associated with progressive changes in memory, executive functioning, emotion and impulse control, and parkinsonism.
- CT and MR Imaging are the recommended imaging modalities to study patients with cerebral concussion. Although advanced neuroimaging techniques have shown significant potential to identify further injury and determine prognosis, their clinical utility is still under research.
- Conventional imaging findings in patients with cerebral concussion and chronic traumatic encephalopathy are absent or subtle in the majority of cases.
- The most common abnormalities include cerebral volume loss, enlargement of the cavum of the septum pellucidum, cerebral microhemorrhages, and white matter signal abnormalities, all of which have poor sensitivity and specificity.

GENERAL CONCEPTS

Cerebral concussion is a subset of traumatic brain injury (TBI) for which multiple definitions have been proposed. Some investigators use the terms, *concussion* and *mild TBI* (*mTBI*), interchangeably. The consensus statement from the 4th International Conference on Concussion in Sport, held in Zurich in November 2012, defined concussion as a brain injury and complex pathophysiologic process affecting the brain, induced by biomechanical forces. Common features in defining the nature of concussion include the following: (1) concussion may be caused either by a direct blow to the head, face, neck, or elsewhere on the body with an "impulsive" force transmitted to the head; (2) concussion typically results in the rapid onset of short-lived impairment of neurologic function that resolves spontaneously; in some cases, however, symptoms and signs may evolve over several minutes to hours; (3) concussion may result in neuropathological changes, but the acute clinical symptoms largely reflect a functional disturbance rather than a structural injury and, as such, no abnormality is seen on standard structural neuroimaging studies; and (4) concussion results in a graded set of clinical symptoms that may or may not involve loss of consciousness. Resolution of the clinical and cognitive symptoms typically follows a sequential course. In some cases, however, symptoms may be prolonged.[1]

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Chronic traumatic encephalopathy (CTE), also denominated "dementia pugilistica," "punch drunk," or "boxer's dementia," was originally described in boxers and more recently associated with repetitive concussions in other sports (eg, American football). CTE is associated with progressive changes in memory, executive functioning, emotion (in particular depression), and impulse control as well as parkinsonism, with evidence for a distinction between syndromes dominated by mood and behavior (earlier onset) versus cognitive impairment (later onset, determined retrospectively). CTE has been observed as early as the late teenage years. In professional athletes, symptoms of CTE are typically seen 8 years to 10 years after an individual retires from play.[2] After neuropathologist Omalu and colleagues' publication in 2005,[3] raising an alert about the potential neuropathologic sequelae of repeated mTBI in professional football players, a strong reaction in the sports and medical communities triggered intense research in this field.

PATHOLOGIC STUDIES IN CHRONIC TRAUMATIC ENCEPHALOPATHY

In 2015 McKee and colleagues[4] conducted a postmortem evaluation of the brain of from a cohort of 85 subjects with histories of repetitive mTBI, including athletes and military veterans, and found evidence of CTE in 68 subjects.[4] The investigators described 4 stages in the progression of CTE.

Stage I was characterized by perivascular hyperphosphorylated tau (p-tau) neurofibrillary tangles in focal epicenters at the depths of the sulci in the superior, superior lateral, or inferior frontal cortex and was clinically associated with headache and loss of attention and concentration.

In stage II CTE, neurofibrillary tangles were found in superficial cortical layers adjacent to the focal epicenters and in the nucleus basalis of Meynert and locus coeruleus. Individuals with stage II CTE experienced depression and mood swings, explosivity, loss of attention and concentration, headache, and short-term memory loss.

Stage III CTE showed macroscopic evidence of mild cerebral atrophy, septal abnormalities, ventricular dilation, a sharply concave contour of the third ventricle and depigmentation of the locus coeruleus and substantia nigra. There was dense p-tau pathology in medial temporal lobe structures (hippocampus, entorhinal cortex, and amygdala) and widespread regions of the frontal, septal, temporal, parietal and insular cortices, diencephalon, brainstem, and spinal cord. Most individuals with stage III CTE demonstrated cognitive impairment with memory loss, executive dysfunction, loss of attention and concentration, depression, explosivity, and visuospatial abnormalities.

Stage IV CTE was associated with further cerebral, medial temporal lobe, hypothalamic, thalamic and mammillary body atrophy, septal abnormalities, ventricular dilation, and pallor of the substantia nigra and locus coeruleus. Microscopically, p-tau pathology involved widespread regions of the neuraxis, including white matter, with prominent neuronal loss and gliosis of the cerebral cortex and hippocampal sclerosis. Subjects with stage IV CTE were uniformly demented with profound short-term memory loss, executive dysfunction, attention and concentration loss, explosivity, and aggression. Most also showed paranoia, depression, impulsivity, and visuospatial abnormalities. Advancing pathologic stage was associated with a significant decrease in brain weight and increased severity of cognitive abnormalities, supporting the validity of the pathologic staging scheme. In addition, pathologic stage correlated with duration of exposure to American football, survival after football, and age at death in those who played football.

In 2015, the neuropathologic criteria for diagnosis of CTE were refined by a panel of expert neuropathologists organized by the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Biomedical Imaging and Bioengineering. These criteria, presented in **Box 1**, have been used in subsequent pathology studies.[5]

In a review of more than 100 articles from both basic science and clinical medical literature, Giza and Hovda[6] described the pathophysiologic cascade after concussive brain injury. Experimental brain injury studies have shown acute abnormalities, including ionic fluxes, indiscriminate glutamate release, hyperglycolysis, lactate accumulation, and axonal injury. Later steps in this physiologic cascade involve increased intracellular calcium, mitochondrial dysfunction, impaired oxidative metabolism, decreased glycolysis, diminished cerebral blood flow, axonal disconnection, neurotransmitter disturbances, and delayed cell death. It is during this postinjury period, when cellular metabolism is already stretched to its limits, that the cell is more vulnerable to further insults.

EVIDENCE OF GLIAL DAMAGE

Kou and colleagues[7] described the glial damage in TBI. When TBI occurs, quiescent glia of multiple types become rapidly activated in a process termed, *reactive gliosis*. This process involves activated microglia initiating and sustaining astrocytic