CHRONIC TRAUMATIC ENCEPHALOPATHY

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Chapter 13 was published in Memory Loss, Alzheimer's Disease, and Dementia: A Practical Guide for Clinicians, by Budson AE & Solomon PR, Copyright Elsevier (2016).

CHAPTER 13: Chronic Traumatic Encephalopathy

QUICK START: CHRONIC TRAUMATIC ENCEPHALOPATHY	
Definition & etiology	• Chronic traumatic encephalopathy is a progressive neurodegenerative disease associated with repetitive brain trauma.
Cognitive and behavioral symptoms, in order of prevalence at presentation	• Memory impairment • Executive dysfunction • Attention & concentration difficulties • Sadness/depression • Hopelessness • Explosivity • Language impairment • Visuospatial difficulties • "Out of control" • Physically violent • Verbally violent • Impulse control problems • Suicidal ideation/attempts
Summary of diagnostic criteria	**General Criteria for Traumatic Encephalopathy Syndrome:** *All five criteria must be met* 1) History of multiple impacts to the head. 2) No other neurological disorder present that likely accounts for all clinical features 3) Clinical features must be present for a minimum of 12 months 4) At least 1 Core Clinical Features must be present and considered a change from baseline 5) At least 2 Supportive Features must be present **Core Clinical Features of Traumatic Encephalopathy Syndrome:** *At least 1 must be met:* 1) *Cognitive*. Difficulties in cognition substantiated by impairment on standardized tests 2) *Behavioral*. Emotionally explosive, physically and/or verbally violent 3) *Mood*. Feeling overly sad, depressed, and/or hopeless **Supportive Features of Traumatic Encephalopathy Syndrome**: *At least 2 must be present:* (1) *Impulsivity*, (2) *Anxiety*, (3) *Apathy,* (4) *Paranoia*, (5) *Suicidality*, (6) *Headache*, (7) *Motor Signs,* including dysarthria & features of parkinsonism, (8) *Documented Decline*, for a minimum of one year, (9) *Delayed Onset*, at least 2 years **Traumatic encephalopathy syndrome diagnostic subtypes:** (1) Behavioral/Mood Variant, (2) Cognitive Variant, (3) Mixed Variant, (4) Dementia.
Imaging findings	• Cavum septum pellucidum is commonly seen on MRI or CT. Atrophy and hypofunction is typically observed in medial temporal and in frontal lobes.
Treatment	• Treatment is supportive. Cholinesterase inhibitors, memantine, and SSRIs can be tried.
Top differential diagnoses	• Alzheimer's disease, dementia with Lewy bodies, frontotemporal dementia, vascular dementia, progressive supranuclear palsy, corticobasal degeneration, and normal pressure hydrocephalus.

A 63-year-old man presented with progressive memory, concentration, mood and behavior problems over several years. He was a veteran of the army for six years in his twenties, and reported being “knocked out” or “dazed” more than a dozen times while in combat. In the army he also boxed competitively for several years and frequently had his “bell rung,” although he reported only being knocked unconscious five times. After the army he married and owned a successful small business. For the past 4-5 years his wife noted that he became increasingly withdrawn and moody. After making several poor financial decisions he closed down his business. In the last 3 years he began very uncharacteristic behaviors including yelling and “flying off the handle” over minor issues. His primary care physician referred him to a psychiatrist who prescribed fluoxetine, which improved his mood and anger. Two years ago his mood and anger worsened, and increasing doses of fluoxetine and other selective serotonin reuptake inhibitors (SSRIs) could not control the symptoms; after an episode of physical aggression toward his wife risperidone was prescribed. In the past year he had clear-cut impairment of his concentration, memory, and function. His wife notes that he now has “no short-term memory” and that he “does nothing” all day long. Neurological examination revealed mild bilateral 3-4 Hz tremor present at rest and with action. He scored 15 on the MoCA, making errors on the visuospatial / executive, attention, delayed recall, and orientation sections. Head CT revealed atrophy (most notably in hippocampi and frontal lobes, bilaterally) and a cavum septum pellucidum.

PREVALENCE, DEFINITION, PATHOLOGY, AND PATHOPHYSIOLOGY

There is increasing evidence that head trauma may be associated with encephalopathy and dementia later in life. The exact pathogenesis of how head trauma at one point in life can cause dementia decades later is complex and is still being determined. We do know that, in addition to causing an encephalopathy that is maximal at the time of the head injury and generally improves (though not necessarily back to baseline), repetitive head injury has been associated with chronic traumatic encephalopathy, a progressive tauopathy with distinctive clinical and pathological features (McKee et al., 2013) (see Table 13.1).

Table 13.1. Pathologic and clinical stages of chronic traumatic encephalopathy

Stage	Pathology	Clinical symptoms & signs
I	Perivascular phospho-tau neurofibrillary tangles in focal epicenters at the depths of the sulci in frontal cortex	Headache, loss of attention & concentration
II	Stage I plus neurofibrillary tangles in superficial cortical layers adjacent to the focal epicenters and in the nucleus basalis of Meynert & locus coeruleus	Depression & mood swings, explosivity, loss of attention & concentration, headache, and short-term memory loss
III	Stage II plus mild cerebral atrophy, septal abnormalities, ventricular dilatation, concave third ventricle, depigmentation of locus ceoruleus & substantia nigra, dense phospho-tau pathology in the cortex, medial temporal lobe, diencephalon, brainstem, & spinal cord	Cognitive impairment with memory loss, executive dysfunction, loss of attention & concentration, depression, explosivity, and visuospatial abnormalities.
IV	Stage III plus further cerebral, medial temporal lobe, hypothalamic, thalamic, & mammillary body atrophy, septal abnormalities, ventricular dilation, and pallor of substantia nigra & locus coeruleus; phospho-tau in widespread regions including white matter, with prominent neuronal loss, gliosis of cortex, & hippocampal sclerosis.	Dementia with profound short-term memory loss, executive dysfunction, attention & concentration loss, explosivity, and aggression. Most also show paranoia, depression, impusivity, and visuospatial abnormalities. Many also have Parkinsonism, speech, and gait abnormalities.

From McKee et al, 2013

In one series McKee and colleagues analyzed the brains of 85 individuals with a history of repetitive mild traumatic brain injury and found evidence of chronic traumatic encephalopathy in 68 (80%) of them, including 64 athletes, 21 military veterans (most of whom were also athletes), and one individual with self-injurious head-banging behavior. The athletes included those who played football, hockey, boxing, and wrestling (Box 13.1); the veterans included those who fought in World War II, Vietnam, Gulf War, Iraq, and Afghanistan (McKee et al., 2013). Because of the selection bias of cases referred to autopsy, the exact prevalence of chronic traumatic encephalopathy in athletes, veterans, and the general population is unknown. Three studies of American

professional football players, each with more than 1000 subjects, have found the risk of all types of neurodegenerative disease between 3 and 5 times greater than that of the general United States population (Lehman, 2013).

BOX 13.1 CONTACT SPORTS THAT HAVE BEEN ASSOCIATED WITH MULTIPLE CONCUSSIONS

- **Boxing**
- **Football**
- **Wrestling**
- **Rugby**
- **Soccer**
- **Hockey**
- Lacrosse
- Skiing
- Karate
- Horseback riding
- Parachuting

Note: sports in **bold** have been associated with chronic traumatic encephalopathy at autopsy. From McKee, A.C., Cantu, R.C., Nowinski, C.J., et al., 2009. Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. J. Neuropathol. Exp. Neurol. 68, 709–735; & McKee et al., 2013.

CRITERIA

Stern and colleagues have developed research criteria for traumatic encephalopathy syndrome (Montenigro et al., 2014). See Box 13.2 for an abbreviated version of these criteria and Box 13.3 for potential biomarkers that support the diagnosis of probable chronic traumatic encephalopathy.

BOX 13.2 CRITERIA FOR TRAUMATIC ENCEPHALOPATHY SYNDROME

General Criteria for Traumatic Encephalopathy Syndrome: *All five criteria must be met*

1) History of multiple impacts to the head based upon the type of injury (a) and source of exposure (b).
   a) Types of injuries:
      i). Mild traumatic brain injuries or concussions, minimum of 4
      ii). Moderate/severe traumatic brain injury
      iii). "Subconcussive" trauma
   b) Source of exposures:
      i). Involvement of "high exposure" contact sports for minimum of 6 years, including at least 2 at college level or higher
      ii). Military service
      iii). History of any other significant exposure to repetitive hits to the head
      iv). For moderate/severe traumatic brain injury, any activity resulting in the injury
2) No other neurological disorder present that likely accounts for all clinical features
3) Clinical features must be present for a minimum of 12 months
4) At least 1 Core Clinical Features must be present and considered a change from baseline
5) At least 2 Supportive Features must be present

Core Clinical Features of Traumatic Encephalopathy Syndrome: *At least 1 must be met*

1) *Cognitive*. Difficulties in cognition as reported by either self or informant, by history, or clinician's report of decline and substantiated by impairment on standardized tests
2) *Behavioral*. Emotionally explosive, physically and/or verbally violent
3) *Mood*. Feeling overly sad, depressed, and/or hopeless

Supportive Features of Traumatic Encephalopathy Syndrome: *At least 2 must be present*

1) *Impulsivity*. Impaired impulse control as demonstrated by new behaviors
2) *Anxiety*. History of anxious mood, agitation, excessive fears, or obsessive and/or compulsive behavior
3) *Apathy*. Loss of interest in usual activities, loss of motivation and emotions, and/or reduction of voluntary, goal-directed behaviors
4) *Paranoia*. Delusional beliefs of suspicion, persecution, and/or unwarranted jealousy
5) *Suicidality*. History of suicidal thoughts or attempts
6) *Headache*. Significant and chronic headache, with at least one episode per month for six months
7) *Motor Signs*. Dysarthria, dysgraphia, bradykinesia, tremor, rigidity, gait disturbance, falls, and/or other features of parkinsonism
8) *Documented Decline*. Progressive decline in function and/or a progression in symptoms and/or signs, for a minimum of one year
9) *Delayed Onset*. Delayed onset of clinical features after significant head impact exposure, usually at least 2 years and in many cases several years after the period of maximal exposure

Traumatic encephalopathy syndrome diagnostic subtypes:

(1) Behavioral/Mood Variant, (2) Cognitive Variant, (3) Mixed Variant, (4) Dementia.

Criteria for (4) Traumatic Encephalopathy Syndrome Dementia:

a) Progressive course of Cognitive Core Features, with or without Behavioral and/or Mood Core Features
b) Cognitive impairment (or cognitive impairment exacerbated by behavioral and/or mood) severe enough to interfere with the ability to function independently at work or in usual activities, including hobbies, and instrumental activities of daily living

Adapted from Montenigro et al., 2014. Please see Montenigro et al. for full research criteria.

BOX 13.3 POTENTIAL BIOMARKERS FOR THE DIAGNOSIS OF PROBABLE CHRONIC TRAUMATIC ENCEPHALOPATHY
1) *Cavum Septum Pellucidum*. Or cavum vergae, or fenestrations based on neuroimaging study 2) *Normal Beta Amyloid CSF Levels* 3) *Elevated CSF p*-tau/*tau Ratio* 4) *Negative Amyloid Imaging* 5) *Cortical atrophy* beyond expected for age as seen on MRI (or CT), and in particular, frontal, thalamic, hippocampal, and/or amygdalar atrophy 6) *Positive Tau Imaging (experimental)*. PET paired helical filament tau imaging suggestive of abnormal tau deposition 7) *Cortical Thinning (experimental)*. Based on MRI measurement
Adapted from Montenigro et al., 2014. Please see Montenigro et al. for full research criteria.

COMMON SIGNS, SYMPTOMS, AND STAGES

McKee et al. (2013) have defined four pathological stages of chronic traumatic encephalopathy and the common symptoms and signs associated with each (Table 13.1). There has also been the recognition that there are two common clinical presentations of chronic traumatic encephalopathy (Box 13.2; Stern et al., 2013; Montenigro et al., 2014):

- a Behavioral/Mood Variant whose initial features develop at a younger age with behavioral and/or mood disturbance, and
- a Cognitive Variant whose initial features develop at an older age and involved more cognitive impairment.

THINGS TO LOOK FOR IN THE HISTORY

There are two main things to look for in the history of a patient who may have chronic traumatic encephalopathy. The first is a history of repetitive head trauma of some type, such as contact sports, military service, domestic abuse, head banging, motor vehicle accidents, etc. The second is the constellation of behavioral, mood, cognitive, and sometimes motor features that are common with the disorder (see Boxes 13.1 & 13.2). See Box 13.4 for some of the features that are most common at presentation.

BOX 13.4 SPECIFIC CLINICAL FEATURES BY INITIAL CLINICAL PRESENTATION
• Memory impairment (85%) • Executive dysfunction (79%) • Attention & concentration difficulties (73%) • Sadness/depression (64%) • Hopelessness (64%) • Explosivity (58%) • Language impairment (58%) • Visuospatial difficulties (55%) • "Out of control" (52%) • Physically violent (52%) • Verbally violent (49%) • Impulse control problems (46%) • Suicidal ideation/attempts (30%) • Motor symptoms (parkinsonism, tremor, gait abnormalities, falls) (30%)
From Stern et al. (2013). % indicates the percent of individuals with autopsy proven chronic traumatic encephalopathy who had each feature at presentation.

THINGS TO LOOK FOR ON THE PHYSICAL AND NEUROLOGICAL EXAMINATION

The physical and neurological exam in most patients with chronic traumatic encephalopathy will be normal. Some patients, however, show signs and symptoms of parkinsonism including tremor, abnormal gait, and falls.

PATTERN OF IMPAIRMENT ON COGNITIVE TESTS
Following the cognitive domains commonly affected (Box 13.4), tests that most often show abnormalities in patients with chronic traumatic encephalopathy include those for memory, executive function, and simple and complex attention, followed by those for language and visuospatial function.

STRUCTURAL AND FUNCTIONAL IMAGING STUDIES
There are two types of imaging abnormalities to look for in patients who may have chronic traumatic encephalopathy. The first are abnormally enlarged cavum septum pellucidum and/or cavum vergae; these are anterior and posterior, respectively, fluid filled spaces between the leaflets of the septum pellucidum. Although these spaces may be present in up to 15% of healthy individuals, the theory is that during head trauma fluid waves produce fenestrations or holes in the septum pellucidum, allowing fluid to enter between the leaflets, creating the cavum septum pellucidum and/or cavum vergae. The second type of abnormality to look for on imaging studies is atrophy (on MRI or CT scans), hypometabolism (on flurodeoxyglucose (FDG) PET scans), and/or hypoperfusion (on technetium-99 (^{99}Tc) SPECT scans) of the cortex, particularly in medial temporal and frontal lobes. Abnormalities in the frontal lobes are frequently patchy, mirroring the pathology.

DIFFERENTIAL DIAGNOSIS
Head trauma does not always cause chronic traumatic encephalopathy. McKee et al. (2013) found that of the 85 individuals studied with a history of repetitive mild traumatic brain injury, 17 (20%) did not show changes of chronic traumatic encephalopathy. Of the 68 individuals who did show such changes, chronic traumatic encephalopathy was the sole pathology in 43 (63%), Lewy body disease was also present in 11 (16%), motor neuron disease in 8 (12%), Alzheimer's disease in 7 (11%), and frontotemporal lobar degeneration in 4 (6%). Epidemiological studies have shown that head trauma is a risk factor for other causes of dementia—especially Alzheimer's disease—as well as amyotrophic lateral sclerosis and Parkinson's disease.

Thus, other disorders to think about when considering chronic traumatic encephalopathy include Alzheimer's disease, dementia with Lewy bodies, and frontotemporal dementia, as well as disorders that can cause executive dysfunction and/or parkinsonism, such as vascular dementia, progressive supranuclear palsy, corticobasal degeneration, and normal pressure hydrocephalus.

TREATMENTS
Treatment is supportive. There are no US Food and Drug Administration (FDA) approved medications to treat chronic traumatic encephalopathy. Cholinesterase inhibitors can be tried for those with memory problems. Selective serotonin reuptake inhibitors (SSRIs) can be tried to help with behavior and mood symptoms. Memantine (Namenda) can be tried to improve attention in patients who are in the moderate to severe stage of dementia. Treatment with atypical antipsychotic medications may be tried in those who are explosive and physically violent (see *Chapter 24: Pharmacological treatment of the behavioral and psychological symptoms of dementia*, for more information, including important warnings regarding the use of these medications).

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