Optical Coherence Tomography: A Potential Tool for Detecting Early Signs of Chronic Traumatic Encephalopathy?

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INTRODUCTION

Concussive injuries are produced by acceleration and deceleration forces on the brain. These rapid linear or rotational forces cause the brain to elongate and deform, stretching individual cells and blood vessels, and altering membrane permeability.[1] The increased permeability, uncontrolled influx of calcium ions, swelling of mitochondria, disruption of microtubules, and alterations in axonal transport cause axonal swelling and lead to diffuse axonal injury that may continue to persist weeks after the initial concussive event.[2]

There is evidence to suggest that a history of trauma to the central nervous system, as in mild traumatic brain injury, is a risk factor for neurodegenerative conditions and late-life dementia, including Alzheimer's disease (AD).[3] A history of repetitive head trauma in particular has been found to cause chronic traumatic encephalopathy (CTE). Neuropathological evidence of CTE have been found post-mortem in former athletes who played in various contact sports, including American football, professional wrestling, boxing, hockey, and soccer, as well as in non-athletes. It is theorized that individuals subject to similar, high risk conditions are also susceptible to CTE, including falls, motor vehicle accidents, assaults, epileptic seizures, and military combat.[1-4]

SYMPTOMS OF CHRONIC TRAUMATIC ENCEPHALOPATHY

One of the key features of CTE is that the disease continues to progress decades after the initial traumatic event. The age of onset of CTE is younger than that of AD and the disease process is slower. Like many other neurodegenerative diseases, CTE leads to disordered cognition, disturbances in mood and behavior, and changes in motor functioning. The symptoms of CTE are insidious and can be categorized into three stages of progression *(Table 1)*.[5] The first stage is characterized by affective disturbances and psychotic symptoms. The second stage involves social instability, erratic behavior, memory loss, and initial symptoms of Parkinson disease. Stage three is defined by general cognitive dysfunction progressing to dementia, full-blown Parkinsonism, as well as speech and gait abnormalities.

NEUROPATHOLOGY OF CHRONIC TRAUMATIC ENCEPHALOPATHY

CTE is grossly characterized by a reduction in overall brain weight due to generalized atrophy, enlarged ventricles, cavum septum pellucidum with fenestrations, and pallor of the substantia nigra.[2,3] The brain of a patient with AD, however, is virtually indistinguishable from an age-matched normal as there is only a modest degree of cerebral cortical atrophy, which tends to spare the primary motor, sensory, and visual areas.[7]

On the microscopic level, CTE is described as having neurofibrillary tangles (NFTs) containing phosphorylated tau protein and astrocytic tangles throughout the cerebral cortex in a dense, superficial distribution, with focal epicenters at the depths of sulci and around small vessels.[3] The patchy, irregular location of the cortical NFTs and astrocytic tangles suggests that the distribution is related to direct mechanical injury from blows to the side or top of the head given their multifocal dorsolateral frontal and parietal, inferior frontal and occipital, and lateral temporal distributions.[2] Neuronal loss and gliosis commonly accompanies NFTs, especially in the hippocampus, the entorhinal cortex, and amygdala.[2]

In comparison, AD is characterized by the accumulation of senile β-amyloid plaques throughout the cerebral cortex and NFTs containing phosphorylated tau protein in medial temporal lobe structures as well as in many forebrain and midbrain areas.[7,8] Unlike CTE, β-amyloid plaques are a cardinal feature in AD and the distribution of NFTs is uniform, less dense, and are found in deeper cortical layers *(Figure 1)*.[2,4] Other pathological changes in AD include microvascular amyloid deposition, granulovascular degeneration, loss of neurons with white matter, synapse loss, inflammation, oxidative damage, and gliosis that also occur in the hippocampus, the entorhinal cortex, and amygdala.[8]

	MOOD	BEHAVIORAL	COGNITIVE	MOTOR
Stage 1	• Fatigue • Insomnia • Irritability • Apathy • Loss of Interest • Depression/Anxiety • Labile Emotions	• Personality Changes • Paranoid Delusions • Psychosis		
Stage 2	• Mood Swings • Euphoria • Mania • Flat Affect	• Aggression • Rage • Physical and Verbal Violence • Explosivity • Loss of Control Inappropriate Speech • Disinhibited Behavior • Socially Inappropriate • Social Isolation	• Memory Impairment • Impaired Attentions • Lack of Insight • Dysgraphia • Perseveration • Executive Dysfunction • Visuospatial Difficulties	• Ataxia, • Dysarthria • Weakness • Spasticity
Stage 3			• Language Difficulties • Alogia • Cognitive Impairment • Reduced Intelligence • Dementia	• Rigidity • Tremor • Masked Facies • Gait • Parkinsonism
	YOUNGER CLINICAL PRESENTATION		OLDER CLINICAL PRESENTATION	

Table 1. Symptomology of Chronic Traumatic Encephalopathy *Two forms of presentation: 1) younger onset with initial behavioral and mood disturbances but with minimal cognitive and motor features; and 2) older onset with greater cognitive impairment and motor disturbances.*[5]

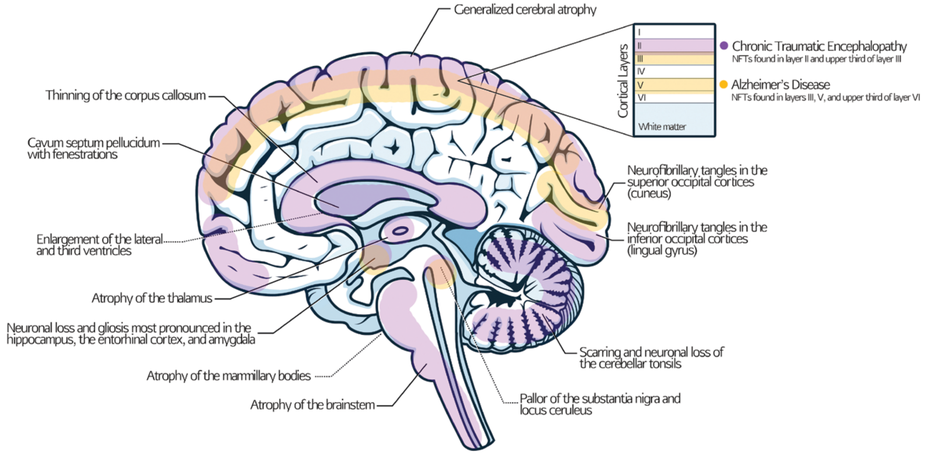

Figure 1. Gross Neuropathology of Chronic Traumatic Encephalopathy[2,4,6]

EFFECTS OF REPETITIVE HEAD TRAUMA ON THE RETINA AND OPTIC NERVE

Neuroinflammation is a consistent feature of any type of head trauma and diffuse axonal injury is the most prominent feature following traumatic brain injury.[9] Recently, studies using mouse models have shown retinal and optic nerve changes from single and repetitive traumatic brain injuries. Both single and repetitive traumatic injuries showed signs of thinning of the inner retina and decreased cellularity in the retinal ganglion cell (RGC) layer, suggestive of thinning of the retinal nerve fiber layer (RNFL) due to a decrease in optic nerve axons from local demyelination.[9,10]

Since the optic nerve is considered to be part of the white matter of the brain, it is logical to assume that diffuse axonal injury would negatively affect its structure and function after traumatic brain injury. However, studies have shown that the severity of the injury to the optic pathways does not always reflect the severity of axonal injury elsewhere in the brain.[10]

When compared to single traumatic brain injuries, repeated insults led to more profound and widespread damage to the RNFL due to the progressive nature of neuroinflammation in repeated head trauma.[10] Subsequent injuries have a cumulative damaging effect on the optic nerve, leading to widespread degeneration of the RGC layer.[10]

OPTICAL COHERENCE TOMOGRAPHY FOR EARLY DETECTION

To date, the only definitive means of diagnosing CTE is through post-mortem autopsy.[5] However, a number of biomarkers are believed to have the potential to identify CTE *in vivo*.[4] Examples of ongoing research include using diffusion tensor magnetic resonance imaging (DTI) to detect changes in white matter integrity following repeated head trauma,[4] measuring tau and phosphorylated tau in cerebral spinal fluid of concussed subjects,[4] and most recently, using [F-18]FDDNP positron emission tomography (PET) to detect neuropathological brain patterns consistent with CTE in retired professional American football players.[11]

Historically, optical coherence tomography (OCT) has been used to image cross-sections of the anterior and posterior segments of the eye. Recently, the OCT has also been used to detect early changes in the retina of patients with neurodegenerative diseases. For instance, studies have shown peripapillary RNFL thinning in patients with AD that is believed to reflect generalized axonal loss.[8] More recent studies using spectral domain OCT also reported macular changes in the ganglion cell complex (GCC). These changes in macular volume are thought to be reflective of neuronal loss of retinal ganglion cells in the ganglion cell layer (GCL) and in the inner plexiform layer (IPL) of the retina.[8] Based on these studies, it has been hypothesized that macular GCL/IPL thinning may be a more sensitive marker of early neurodegeneration in AD than evaluating the RNFL alone.[8]

The retinal changes from repetitive head trauma are very similar to the neurodegenerative effects on the retina in AD and as such, these changes are detectable using an OCT. Although more research in this area is still needed and a definitive diagnostic criteria needs to be established, it is quite possible that early signs of CTE can be detected by evaluating changes in the retina.

CONCLUSION

CTE is a neurodegenerative condition caused by repetitive concussive and sub-concussive head trauma that leads to progressive neurodegeneration with signs of RNFL thinning and ganglion cell loss in the retina. These changes may occur prior to the onset of symptoms and may be amenable to detection with an OCT. Of course, more research is needed to determine a standardized criteria for the diagnosis of CTE *in vivo*, either alone or as a mixed disease. However, from an optometric research perspective, it would be interesting to consider incorporating baseline OCT measurements in the work-up of young athletes at sports vision screenings as well as in the office for a patient with a history of a traumatic brain injury.

REFERENCES AVAILABLE UPON REQUEST