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Management of Neuropsychiatric Symptoms for Chronic Traumatic Encephalopathy

Review Article

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Abstract

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease associated with repeated head injury. The common presenting neuropsychiatric manifestations and diagnostic strategies for early diagnosis and subsequent treatment will be reviewed. This article discusses methods for injury prevention, risk assessment, and methods for supportive symptom management including lifestyle modifications, physical, occupational, and neurorehabilitation, and pharmaceutical management. Lastly, we propose the use of assessment tools validated for other neurodegenerative disorders in CTE to establish a baseline, track outcomes, and measure improvement in this population.

Keywords: Chronic Traumatic Encephalopathy; Neurodegeneration; Neuropsychiatric Disease; Treatments.

Introduction

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease linked to repeated head injury and is associated with neurological and psychological deficits including abnormalities in cognition, mood, behavior, and movement [1–3]. CTE was initially observed in professional boxers but has since been reported in athletes in other contact sports (such as soccer, football, and rugby) and people prone to repeat mild head trauma such as veterans experiencing blast injury, physical abuse victims, and epilepsy patients [4–11]. In recent years, growing media attention has raised awareness for chronic traumatic encephalopathy and the potential consequences of repeat head injuries [12–18]. However, there is still much that is unknown about accurately identifying and diagnosing CTE, effectively treating the disease, and monitoring patient outcomes to manage the disease and help patients.

Clinical Issues

The clinical manifestations and progression of CTE can differ between patients. Many signs and symptoms overlap with other diseases. Patients may experience a wide breadth of neurological and psychiatric deficits so it is important that primary care, neurologist, psychologists, and psychiatrists work together to identify and manage patients who may have CTE. Some commonly reported clinical manifestations of CTE include depression, anxiety, paranoia, impulsivity, aggression, inattention, difficulty concentrating, memory problems, language impairments, headache, dysarthria, and motor abnormalities [1,2,6,19–26]. The symptoms, however, are non–specific and are present in various other neurodegenerative diseases. The differential diagnosis for these symptoms may include CTE, Alzheimer's Disease (AD), frontal temporal dementia, vascular dementia, Parkinsonian disorders, neurosyphilis, vitamin B12 deficiency, or corticobasal degeneration [21,25–30]. For instance, a study found that neuropsychiatric symptoms were comparable in the CTE and AD groups both at the time of dementia diagnosis and in the very late stages of the disease [25]. CTE can also present with motor symptoms that resemble Parkinson's disease [26]. Given how closely these symptoms overlap with neurodegenerative illnesses, it might be challenging to identify a distinct clinical profile for CTE.

Neuropsychological Issues

Neuropsychological deficits are likely to increase in severity and duration after repeated injury, suggesting cumulative neuropsychological damage [31,32]. Establishing a baseline neurocognitive profile can be a crucial clinical tool and will serve as a clinical reference marker to follow changes in players' neuropsychiatric presentations. Furthermore, the identification of risk factors, changes in gameplay rules, and removal from play regulations could allow sports medicine doctors and other physicians involved with the care of patients prone to repeated head injury to reduce the development of CTE later in life [33–35]. As innovative imaging modalities and biomarkers are discovered, early in vivo diagnostic strategies should be explored combining clinical manifestations, neurological and psychiatric examination, and diagnostic tools. Novel treatment strategies in clinical trials offer promise for more targeted therapeutics for CTE that may improve patient outcomes in the future. Throughout the life of these patients, before and after disease onset, a multidisciplinary approach, including sports medicine physicians, primary care, neurology, psychiatry, psychology, and physical/occupational therapy, should be adopted to enhance patient care.

Diagnostics

Currently, a definitive diagnosis of CTE can only be made after an autopsy is performed, demonstrating specific pathological features. Aggregation of p–tau within neurons, astrocytes, and cell processes around small vessels at the level of the cortical sulci in an irregular pattern is pathognomonic of CTE. These findings along with other supporting neuropathological features can help differentiate CTE from other tauopathies [6,36]. Other pathological changes that have been observed include neuroinflammation, microgliosis, astrogliosis, astrocytic tangles, TD–43, hyperphosphorylated tau protein–associated neurofibrillary tangles, neutrophil neurites, neuronal loss, diffuse brain atrophy, ventricular enlargement, cavum septum pellucidum, and substantia nigra depigmentation [6,20,37–41]. CTE pathology normally originates in the cerebral cortex and then progresses to affect numerous regions of the brain, most commonly the medial temporal lobe, hypothalamus, thalamus, and mammillary bodies [6,42]. Despite needing autopsy data for a definitive diagnosis, a presumptive diagnosis can be made for clinical or research purposes using different sets of proposed diagnostic criteria [43–47]. However, a consensus as to what criteria should be adopted across clinical practice has not been determined. As more research reveals imaging strategies and biomarkers that may be useful in identifying CTE in vivo, studies should aim to determine the best strategy to combine clinical presentation, biomarkers, and imaging to allow for early diagnosis in patients.

A major goal for using imaging modalities to potentially help diagnose CTE would be to identify pathology consistent with the disease prior to autopsy. Magnetic resonance imaging (MRI) can detect cerebral atrophy, axonal injury, dilated perivascular spaces, ventricular enlargement, and cavum septum pellucidum [6,48–52]. MRI with FLAIR can be used to assess white matter hyperintensities and can represent a variety of neuropathology [53]. Diffuse Tensor Imaging (DTI) is another way of assessing white matter and has become a popular potential imaging modality to assist in the diagnosis of CTE. DTI can detect abnormalities in white matter that are indicative of axonal injury, which is present in CTE due to recurrent traumatic brain injury [54]. Abnormalities in regional cerebral blood flow and brain activity can be visualized using a functional MRI (fMRI) [49,52,55]. Although these imaging modalities can identify neuropathology that is consistent with autopsy findings in patients with confirmed CTE, these findings alone are not specific and do not provide a diagnosis [6,20]. Positron emission tomography (PET) scan offers promise as a potential diagnostic tool to find pathology specific to CTE and assist in earlier in vivo diagnosis. The PET scan with the 18F–FDDNP tracer labels tau and can thus be very helpful in visualizing tau aggregates that are important to post–mortem CTE diagnosis. Early work in small cohorts has shown that the distribution of tau aggregation, as shown by 18F–FDDNP PET, is consistent with autopsy findings and is distinct from other neurodegenerative disorders such as Alzheimer's disease. However, studies using larger sample sizes will be needed to validate these promising results [52,56,57]. Other probes which could be helpful include tracers for beta–amyloid, TDP–43, 18–FG D, and markers of neuroinflammation [49,52,53,57,58]. In addition to imaging modalities, serum and CSF biomarkers could help identify CTE as well as possible risk factors and prognostic information [6,52,59,60].

Treatments

Unfortunately, there is no cure or approved treatment for CTE. Therefore, it is important to minimize the risk of CTE by reducing repetitive head trauma and identifying risk factors. Events that increase the risk of head injury such as targeting in football or body checking in hockey should be minimized or eliminated from the game [33,34,61–63]. Following a blow to the head, players should be evaluated by a physician or a certified athletic trainer to rule out the possibility of a concussion [33,34]. If a concussion is sustained, or cannot be ruled out, players should be removed from practice or the game ~~for~~ at least for the day to prevent future injuries. Players should be monitored to determine when it is safe for them to return to play and should not do so until concussion symptoms resolve [33,34]. Players and coaches should be counseled on the importance of following these guidelines [33,34]. Although repeat head injuries are the primary risk factor for CTE, other risk factors such as genetics, comorbidities, lifestyle, and psychosocial factors may also modulate a person's risk of disease development [3,35,64–67]. The APOEε4 allele may be associated with worsened CTE pathology on autopsy and is suspected to worsen outcomes and recovery after TBI [35,68]. Comorbidities such as cardiovascular disease, sleep–disordered breathing, and substance abuse as well as lifestyle factors such as poor diet and exercise could also affect disease risk and should be managed with the help of primary care physicians [35,69].

Currently, only supportive care is available for the treatment of patients with CTE, and management is focused on addressing symptoms of the disease. Mental health disturbances may be addressed through mindfulness, cognitive behavioral therapy, other forms of mental health counseling, and medications such as antidepressants, anxietolytic, and ADHD medications [6]. Lifestyle modifications such as diet and exercise can be useful in enhancing mental and physical well–being [6,69,70]. Interestingly, a healthy diet has also been shown to slow the progression of symptoms and pathogenesis of CTE [71,72]. Vestibular rehabilitative therapy can be helpful in patients with ear damage and occupational–ocular therapy can be offered to patients with eye problems that resulted from recurrent head injuries [6]. Physical therapy may help address movement problems and occupational therapy could be used to help patients perform activities of daily living despite their disease. Due to the overlap in symptomology and pathology with other disorders, such as Alzheimer's disease and Parkinson's Disease, medications for these conditions may provide benefits for patients as an "off–label" use [6]. Preclinical studies have demonstrated promise for therapeutics, such as medications and immunotherapy, targeting processes that are important for the progression of CTE, such as neuroinflammation and tau hyperphosphorylation and accumulation [6]. Psychedelic medications are promising therapeutics in CTE for their ability to treat neuropsychiatric deficits and ability to promote neuroplasticity and suppress neuroinflammation and neurodegeneration [73–84].

Outcomes

As potential novel therapeutics are studied in preclinical trials, ways of assessing treatment success and patient outcomes are necessary. There is a scarcity of research investigating the assessment of interventions for patients being treated for CTE. As CTE shares clinical manifestations with other forms of dementia, assessment of interventions in those illnesses could prove useful in the setting of CTE. An emerging trial from Biogen offers promise for neurodegenerative cognitive decline.

Cognitive impairment is a significant affliction in the course of CTE that often involves impairment in memory, concentration, insight, and executive function among other deficits [21]. The Mini–Mental Status Exam (MMSE) is a questionnaire that is used to measure cognitive impairment. While the MMSE is often used as a screening tool for diseases like Alzheimer's, it has also been used as an instrument to monitor cognitive decline in neurodegenerative disorders [85–87]. As neurodegenerative disorders progress, executive function often declines concurrent with cognitive decline. This may be reflected in decreased ability to perform activities of daily living (ADL) [88]. Activities of daily living (ADLs) are tasks that most people can perform without assistance, and the loss of capability in this arena can create a dangerous environment for patients [89]. A number of established instruments including the Bristol Activities of Daily Living Scale (BADLS) and the Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS–ADL19) are useful methods of tracking ADLs in patients suspected of executive function decline [90,91].

Behavioral changes in CTE can include disinhibition, child–like behavior, and episodes of volatile emotions that can lead to violence [2]. While these behavioral changes are often self–reported, some instruments may be used to assess symptoms over time [92]. The Neuropsychiatric Inventory (NPI) is an instrument that assesses neuropsychiatric state by scoring the severity and frequency of symptoms such as disinhibition, anxiety, and aggression [93]. NPI has been used as an instrument to measure behavioral changes in the setting of neurodegenerative disorders as well as in treatment [94,95]. In some cases, advanced CTE could cause tremors, gait disturbance, and other Parkinson–like features [45]. The Unified Parkinson's Disease Rating Scale (UPDRS) and the Movement Disorder Society–Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS–UPDRS) are tools that are widely used to measure the condition of a patient's Parkinson's disease course [96,97]. As significant portions of these exams focus on the motor consequences of Parkinson's disease, they may also be useful in following the manifestations of CTE–induced Parkinson–like motor symptoms [98]. Mood changes in CTE can include depression, anxiety, and apathy, in addition to others. A number of assessments may be employed to assess mood symptoms in patients. Similar to behavioral changes, the NPI has been used as a tool for measuring mood symptoms in patients being treated for neurodegenerative disease [99,100]. The Patient Health Questionnaire 9 (PHQ–9) is an instrument that detects depressive symptoms and assesses the severity of depression in patients [101]. Studies have established the efficacy of the PHQ9 in neurodegenerative disorders [102, 102].

While some instruments can be used to cover more than one aspect of CTE progression, such as questions in the NPI addressing behavioral and mood symptoms, no single assessment tool completely addresses all three facets of cognitive, behavioral, and mood changes. As such, a mixture of assessment tools may be necessary to properly monitor symptoms in patients with CTE as well as the evaluation of their treatment.

Conclusion

Chronic Traumatic Encephalopathy is a complicated neurodegenerative disorder with a broad range of clinical manifestations and a long clinical course from the time of repeat head injury to the onset and progression of symptoms later in life [2,3,20]. Adopting a multidisciplinary approach while treating patients with CTE is important. Sports medicine doctors and other physicians/licensed health professionals caring for athletes participating in contact sports as well as other people at risk for repeat head injury should begin thinking about ways to limit head trauma and minimize the risk for CTE long before the onset of the disease [3,33–35,64–67,103]. In patients who go on to develop the disease, a variety of health care professionals may be helpful in managing the diverse symptoms and coordinating the supportive care needed by each individual patient. Primary care physicians, neurologists, psychologists, psychiatrists, physical therapists, and occupational therapists are among some health professionals who may provide valuable assistance in these patient care teams. We summarize our recommendations for management of chronic traumatic encephalopathy in Table 1. Continued efforts of researchers to understand the pathogenesis of CTE as well as to develop novel strategies to diagnose and treat the disease is necessary.

Table 1: Proposed management of Chronic Traumatic Encephalopathy.

Injury prevention and risk management	Minimizing or eliminating plays in sport that increase the risk for head injury
	Expert evaluation during games and removal from play if a concussion is suspected
	Gradual return to play following concussion
	Management of comorbidities and CTE risk factors like cardiovascular disease, sleep–disordered breathing, and substance abuse
Mental health care	Mindfulness
	Cognitive behavioral therapy
	Antidepressants, anxiolytics, and ADHD medications
Lifestyle modifications and rehabilitation	Diet, exercise
	Vestibular rehabilitative therapy and occupational–ocular therapy
	Physical therapy
	Off–label use of medications for other degenerative diseases when appropriate
Intervention and outcome assessment	Use of scales and questionnaires: MMSE, BADLS, NPI, MDS–UPDRS, PHQ9
Multidisciplinary care	Collaboration between and licensed health professionals in primary care, sports medicine, neurology, psychology, psychiatry, physical and occupational therapy.

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Conflict of Interests

Authors declare that there are no Conflict of interests.

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