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REVIEW

Management of chronic traumatic encephalopathy

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ABSTRACT

Introduction: Chronic Traumatic Encephalopathy (CTE) is a neuropathological disease defined by perivascular hyperphosphorylated tau protein depositions in a patchy distribution at the depths of cortical sulci in the brain. Presently, in living individuals, it cannot be precisely diagnosed or differentiated from other neurodegenerative diseases nor are there treatments for the underlying disease process. There are non-pharmacologic and pharmacologic treatments for the symptoms of CTE that improve the quality of daily life. That is the primary focus of this review article that used Pub Med and other standard databases but drew heavily from the author's personal experience managing patients at risk for CTE.

Areas covered: The history and pathology of CTE, aiding the clinician diagnosing CTE as unlikely, possible, or probable in the living, and symptom treatment are the major areas discussed.

Expert opinion: Diagnosing CTE during life with sensitive and specific biomarkers is the next critical step and only then will its incidence and prevalence, risk factors, and clinical features due to tauopathy versus axonopathy or other features be known.

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1. Introduction

The number of publications in PubMed with Chronic Traumatic Encephalopathy (CTE) as keywords has grown over 100-fold in the last 10 years. Because there is currently no therapy for the neurodegenerative disease process, many regards this disease as hopeless. This discounts the therapies and medications that can improve symptoms and improve the quality of daily life which forms the focus of this paper.

1.1. History

Dr. Harrison Martland, in a 1928 *Journal of the American Medical Association* article about boxers entitled 'Punch Drunk,' is credited with the first description of the clinical syndrome of CTE [1]. A coroner, he described the clinical pattern of cognitive, mood, motor, and behavioral features he observed in boxers that he termed Punch Drunk as follows:

> For some time fight fans and promoters have recognized a peculiar condition occurring among prize fighters which, in ring parlance, they speak of as "punch drunk." Fighters in whom the early symptoms are well recognized are said by the fans to be "cuckoo," "goofy," "cutting paper dolls," or "slug nutty."

The early symptoms of punch drunk usually appear in the extremities. There may be only an occasional and very slight flopping of one foot or leg in walking, noticeable only at intervals; or slight unsteadiness of gait or uncertainty in equilibrium. These may not seriously interfere with fighting. In fact, many who have only these early symptoms fight extremely well, and the slight staggering may be noticed only as they walk to their corners.

In some cases, periods of slight mental confusion may occur as well as distinct slowing of muscular action. The early symptoms of punch drunk are well known to fight fans, and the gallery gods often shout 'Cuckoo' at a fighter. I know of one fight that was stopped by the referee because he thought one of the fighters intoxicated.

Many cases remain mild in nature and do not progress beyond this point. In others, a very distinct dragging of the leg may develop, and with this there is a general slowing down in muscular movements, a peculiar mental attitude characterized by hesitancy in speech, tremors of the hands, and nodding movements of the head, necessitating withdrawal from the ring.

Later on, in severe cases, there may develop a peculiar tilting of the head, a marked dragging of one or both legs, a staggering, propulsive gait with the facial characteristics of the Parkinsonian syndrome, or a backward swaying of the body, tremors, vertigo, and deafness. Finally, marked mental deterioration may set in necessitating a commitment to an asylum.

He recognized the dose of repetitive head impacts as a major risk factor for developing what we now term CTE. Believing he saw symptoms of CTE in up to half of all veteran fighters, he recognized that those with the greatest number of fights, longest careers, were sluggers taking many blows to land one, or who sparred extensively was at greatest risk.

1.2. Terminology

It would be over a decade after Martland's publication before the term Chronic Traumatic Encephalopathy was used by Bowman and Blau in 1940 to describe a case of a 28-year-old professional

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Article highlights

- While CTE has been known for over 100 years it is only recently that it has been shown to be far more prevalent than suspected.
- While with certainty CTE can only be diagnosed by neuropathological criteria post-mortem, this paper provides a roadmap for the clinician to more accurately suspect CTE in the living as being unlikely, possible, or probable.
- While there are now more than 100 papers published annually, none to date have addressed its management.
- This paper provides direction to manage the clinical symptoms of CTE with pharmacologic and non-pharmacologic therapies that can improve the quality of daily life.
- While early detection of CTE prior to the onset of symptoms is not presently possible, using repetitive head impact exposure and clinical symptoms a high index of suspicion of CTE can occur and therapies instituted.

boxer in a book chapter 'Psychotic States Following Head and Brain Injury in Adults and Children' [2].

Upon presentation to the psychiatric division of Bellevue Hospital, he exhibited childish behavior, depress, explosivity, poor short-term memory, and lack of insight. Initially diagnosed as traumatic encephalopathy, when he remained unimproved over 18 months, they changed their diagnosis to reflect this persistence and the term CTE was born.

Reporting on 69 cases of chronic neurological disease in boxers, MacDonald Critchley a British neurologist was the first to publish using the term chronic traumatic encephalopathy in a peer-reviewed journal [3]. He, like Martland, observed that boxers with this syndrome were usually 'sluggers' rather than 'scientific boxers,' were usually second – or third-rate boxers, and were boxers known for being able to 'take' a punch and absorb punishment. He found this syndrome more common in professional rather than amateur boxers and, while in all weight classes, more so in smaller men who fought bigger and heavier opponents.

Critchley described what he called the 'groggy state' as midway between normal performance and a knockout. He characterized it as 'mental confusion with subsequent amnesia, together with an impairment in the speed and accuracy of the motor skill represented by the act of boxing.'

1.3. Pathology

It was a team of British researchers led by Dr. J. A. Nicholas Corsellis at Rumswell Hospital in Essex England, who first described the neuropathology of CTE in 15 deceased boxers [4]. This research included interviews with the families and associates of the boxers. Four types of brain damage, which they correlated with behavioral changes, were identified.

The first was a tearing of the septum pellucidum between the lateral ventricles which he felt caused emotional lability and rage reactions.

Secondwas scarring of the undersurface of the cerebellum that resulted in slurred speech, broad-based gait, and a slowing of motor movement.

Third was decreased pigment of the substantia nigra that resulted in a Parkinson Syndrome of tremor and rigidity of the limbs.

And finally, the occurrence of neurofibrillary tangles, especially in the medial temporal lobe, without the senile plaques of Alzheimer's Disease that he felt was responsible for the mental/cognitive decline.

In 2009, Dr. Ann McKee and her team reviewed 45 cases in the world literature and described additional cases of CTE [5]. Since then, many additional cases have been reported and NIH consensus criteria for the neuropathological diagnosis of CTE have been published. The characteristic pathology of CTE includes identifying aggregates of hyperphosphorylated tau protein in a perivascular distribution at the base of sulci [6,7].

One result of the increase in postmortem cases and the standardization of pathological criteria is the recognition that CTE is not limited to boxing or football. Neuropathological changes of CTE have been seen in athletes who have participated in professional wrestling, hockey, bull riding, and rugby. Moreover, many military veterans who have been exposed to blast injury and found to have CTE have also played contact sports when they were younger, providing two sources of exposure to head trauma. CTE also has been found in individuals exposed to repetitive traumatic brain injury (RTBI) but were not athletes.

2. Symptoms of CTE

CTE pathology typically is associated with symptoms in one of four clinical domains: (a) cognitive; (b) behavioral; (c) mood; and (d) motor [8,9]. Based on 202 published cases of male athletes with histories of RTBI that met criteria for neuropathologically confirmed CTE, the core diagnostic symptoms defined as being present in 70% or more of neuropathologically confirmed CTE cases without comorbid disease include: cognitive (impairment of memory, attention, executive dysfunction), behavior (physical or verbal violence, explosivity, loss of control and short fuse) and mood (depression and helplessness). No motor symptoms reached core levels.

The clinical features in CTE, similar to other neurodegenerative disorders, are heterogeneous. Two distinct clinical presentations have been described by Stern et al. [9]. The first, occurring at a much earlier age (mean age of onset 34.5 standard deviation (SD) = 11.6), consists of behavior and mood symptoms. The second, occurring at a much later age of onset (mean age at onset 58.5, SD = 17.7), consists of cognitive impairment. Over time, the cognitive group almost always progressed to dementia while the behavior mood did not. Montenigro et al. also identified a 'mixed' subtype in which cognitive, behavior and mood symptoms were equally predominant [8].

At this time the only precisely accurate means of diagnosing CTE is by post-mortem autopsy using the NIH consensus criteria [7]. Thus, while clinicians cannot with certainty diagnose CTE in the living to help the clinician determine if CTE is unlikely, possible, or probable, Montinegro et al. have proposed new clinical research diagnostic criteria for CTE that he calls Traumatic Encephalopathy Syndrome (TES) [8]. TES is based on the clinical features reported in neuropathologically confirmed cases of CTE without comorbid disease and a systematic review of the previous literature [5,6,9] while overcoming the limitations identified in previous criteria [10–15].

Table 1. Five criteria for TES.

History of multiple impacts, 2 moderate or severe TBI's, 4 concussions, or 6 years of sub-concussive trauma (e.g. contact sports, military service, domestic abuse).
Regarding other neurological disease that can account for all signs and symptoms; exclude if post-concussion syndrome or single TBI, but include if PTSD, mood/anxiety disorder, substance abuse, other neurodegenerative disease.
Clinical S/S must be present a minimum of 12 months.
Presence of at least one core clinical feature: Cognitive (defined as 1.5 standard deviation below normal on standardized cognitive neuropsychological test), Behavioral (described as explosive, short fuse, out of control, physical or verbally violent or intermittent explosive disorder), Mood (feeling overly sad, depressed, hopeless or diagnosis of major or persistence depressive disorder).
Two or more supportive features must be present: documented decline of at least 12 months, delayed onset, impulsivity, anxiety, apathy, paranoia, suicidality, headache, motor features.

The five criteria that must be met for the diagnosis of TES are summarized in Table 1. For the clinicians, meeting the criteria for TES does not mean the diagnosis of CTE is necessarily highly likely, but not meeting the criteria makes the presence of CTE remote. While the validity and accuracy of TES are still a work in progress, we believe it is useful for the clinician in terms of thinking how likely CTE is to be present.

3. Clinical assessment for CTE

The strongest predictor of CTE likelihood given the presence of cognitive, behavior or mood symptoms is the total amount of brain trauma sustained at the subconcussive and concussive level. The neurologic history must include a detailed assessment of exposure to repetitive head trauma and concussions.

Each concussion should be assessed for a number of symptoms, severity of symptoms, and duration of symptoms as can first be remembered. While the number of concussions is relevant, the proximity of concussions – especially within weeks or months and severity as determined by duration of signs and symptoms – is felt to be even more important.

An attempt to understand the amount of subconcussive trauma by recording seasons of play of all contact or collision sports participated in is detailed. In our experience at Boston University with hundreds of cases of CTE, it is total brain trauma at the concussive and subconcussive level that best correlates with risk for CTE. In approximately 20% of CTE cases, we find no history of concussion but many years of RTBI from subconcussive hits.

Because it will provide a direction for management, we find it useful to use a CTE symptom/signs checklist (Table 2) that is divided into cognitive, behavioral, mood, motor, and vestibular/ocular domains. Use of such a checklist arranged this way affords easy insight into which domains are most involved and thus where therapy most needs to be directed. A score for number and severity of symptoms/signs is given for each domain every time a patient is seen. This affords a quick window as to where therapy needs to be focused and whether improvement is being achieved.

Because CTE is a clinical diagnosis, we try to obtain as much objective data as we can to support it [16,17]. As described below, three investigations can be useful. However, we would like to state at the outset that one can have CTE even if all of these biomarkers are negative.

Persistent elevation of total tau (t-tau) in the spinal fluid, although not specific for CTE, is indicative of some type of ongoing brain injury, suggesting that symptoms are not due solely to post-concussive syndrome or depression. In the right clinical context elevation of CSF t-tau can suggest CTE.

Structural brain imaging can look for cavum and regional patterns of brain atrophy. Although individuals may have a cavum present from birth as a normal variant, the presence of a cavum septum pellucidum and, even more specifically, a cavum vergae, may be a sign of prior head trauma. One possible mechanism is that when the brain is rapidly accelerated or decelerated, the fluid in the ventricles tends to resist the sudden motion due to inertia, and the resultant pressure can cause a small tear or fenestration to occur in one of the leaflets of the septum. Fluid then leaks in between septal leaflets, creating the cavum. MRI and CT scans can generally detect the cavum and sometimes the fenestrations as well. It should be noted that there is no direct relationship between the development of a cavum and CTE, other than that they are both related to head trauma.

Finding regional brain atrophy on the imaging study suggests that there is some neurodegenerative or other brain disease present, which may or may not be CTE. Although one would not necessarily see any brain atrophy in patients with underlying mild stages of CTE pathology (stages I and II), moderate and severe CTE (stages III and IV) involve the hippocampus as well as multiple cortical regions. One would expect to see hippocampal atrophy as well as patchy cortical atrophy, typically in the frontal lobes, in moderate and severe stages of CTE.

Functional brain imaging studies, such as fluorodeoxyglucose (FDG) positron emission tomography (PET) and technetium-99 single photon emission computed tomography (SPECT) scans can detect the patchy hypometabolism in the frontal lobes and elsewhere in the brain of an individual with CTE years before any actual atrophy has developed. For this reason, these functional imaging studies can be particularly useful to detect early disease in living patients.

4. Disease management

Presently, the treatment and management of CTE vary from case to case and remains to be validated with prospective treatment trials. That said, we currently manage patients suspected of having CTE first with therapies and then, if necessary, with pharmacology as well. This section will describe the indications for the different therapies and pharmacology in detail. Before we go into detail, though, some general concepts that apply to all CTE patients being treated for suspected CTE warrant discussion.

4.1. Exercise

Today physical exercise is being used to treat memory disorders, stroke, post-concussion syndrome, and more serious brain injuries [18–21]. The precise mechanisms of how exercise improves outcomes are not presently clear. Two recent small studies suggest in one case that aerobic exercise rehabilitation may act by restoring normal CBF regulation [20]. Another

Table 2. Chronic traumatic encephalopathy: signs/symptoms checklist.

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TODAY'S CHRONIC TRAUMATIC ENCEPHALOPATHY SIGNS/SYMPTOMS CHECKLIST

Please rate your symptom severity based on how you feel today. Circle one number for each.

	None	Mild		Moderate		Severe	
Impaired Memory	0	1	2	3	4	5	6
Impaired Attention	0	1	2	3	4	5	6
Executive dysfunction	0	1	2	3	4	5	6
Dysgraphia	0	1	2	3	4	5	6
Physical violence	0	1	2	3	4	5	6
Verbal violence	0	1	2	3	4	5	6
Explosivity	0	1	2	3	4	5	6
Loss of control	0	1	2	3	4	5	6
Short fuse	0	1	2	3	4	5	6
Impulsivity	0	1	2	3	4	5	6
Paranoid delusions	0	1	2	3	4	5	6
Depression	0	1	2	3	4	5	6
Hopelessness	0	1	2	3	4	5	6
Suicidality	0	1	2	3	4	5	6

	None	Mild		Moderate		Severe	
Anxiety	0	1	2	3	4	5	6
Fearfulness	0	1	2	3	4	5	6
Irritability	0	1	2	3	4	5	6
Apathy	0	1	2	3	4	5	6
Ataxia	0	1	2	3	4	5	6
Dysarthria	0	1	2	3	4	5	6
Parkinsonism	0	1	2	3	4	5	6
Tremor	0	1	2	3	4	5	6
Masked facies	0	1	2	3	4	5	6
Rigidity	0	1	2	3	4	5	6
Balance Issues	0	1	2	3	4	5	6
Blurred Vision	0	1	2	3	4	5	6
Double Vision	0	1	2	3	4	5	6
Dizziness	0	1	2	3	4	5	6

Date _____ Time _____ Signature of Patient or Patient's Legal Representative _____

Print Name of Patient's Legal Representative (If applicable) _____ Relationship to Patient _____

For Office Use Only:

C _____/4 B _____/7 M_____/7 M _____/6 V _____/4

C _____/24 B _____/42 M_____/42 M _____/42 V _____/24

Total Symptom Load _____/28 Total Symptom Score_____/168

Date: _____ Time: _____ Signature: _____

study suggests aerobic exercise can increase neurogenesis and neuroplasticity [22]. We recommend that our patients engage in aerobic exercise at least 30 min daily, five days each week [23].

Presently we are exploring a research protocol using the Vasper equipment. It involves a recumbent bike with cooling cuffs applied to upper arms and legs. With moderate exertion lactic acid is built up due to the restricted blood flow. This high build up of lactic acid causes an increase in endogenous growth hormone production at night during sleep. It is thought that this increase in growth hormone is what is responsible for the cognitive, somatic, and sleep symptom improvement [24]. In a small pilot study, although both control and experimental groups experienced significant clinical symptoms checklist improvement at six weeks, the improvements were statistically more stable in the experimental groups.

Thus, while the mechanisms are as yet speculative, it appears that exercise, especially aerobic exercise, is beneficial to patients suspected of having CTE and formal exercise prescription is appropriate.

4.2. Diet

A healthy diet is also a general therapy felt useful for those with neurodegenerative as well as other disorders. The Mediterranean Diet has been the one most widely supported. It shifts away from but does not eliminate animal fats and promotes monounsaturated fats high in omega 3 as found in plants and fish. Olive oil replaces butter as the primary fat. It also stresses a high consumption of fruits and vegetables.

4.3. Cognitive rehabilitation

Cognitive disturbances will manifest with difficulties with attention, concentration, recent memory and impairment of executive functions (e.g., planning, reasoning, organization, sequential activities, multi-tasking, insight, and judgment). When it has progressed to the level needing assistance with activities of daily living we refer to the impairment as dementia. In our experience, cognitive therapy has a greater chance to significantly improve the quality of daily life the earlier it is instituted.

While the precise mechanism of action is unknown in CTE, it is doubtful that it is causing large-scale neuroplasticity or synaptogenesis or attacking the root cause. Rather, it is likely finding/teaching ways and strategies that compensate for impaired function. It uses cognitive exercises with computer and workbooks or work or other real-life activities.

Our cognitive therapists focus on a tri-fold approach to cognitive retraining that simultaneously involves education, symptom management, and increasing cognitive endurance. Patients are taught that doubling the cognitive loads and working longer can be counterproductive. Instead, scheduled breaks in a quiet place for 10–15 min as needed will increase performance. Large projects should be broken into single steps, more time should be allotted for assignments and non-essential cognitive work may be excused.

If the patient is or recently has been working and return to work is desired, the skills needed to return to work should be determined. The initial return to work plan should start with an assessment of skills needed to return to the current job, a determination of accommodations needed to optimize success and then a gradual transition back into the work setting. Usually, this means starting with reduced hours (2–4) and days (2–4) each week. To limit distractions, work should be started from the home setting whenever possible. Hourly 5–10-min breaks, extra time to complete tasks, and speech recognition programs to reduce computer time are additional useful accommodations. Then, as work tolerance increases, hours and days of work can be slowly increased: one hour, per day per week, 1 day per week. Then, gradually responsibilities can be increased, deadline reduced toward establishing norms, and breaks reduced.

We also recommend the following memory strategies [23]

* Practice Active Attention
* Minimize Distractions in the Environment
* Take Breaks
* Repeat Information Spaced Out Over Time
* Make Connections
* Create Visual Images
* Put It in a Location
* Use the First Letter
* Use Chunking
* Cluster Information by Topic
* Invent Rhymes
* Get Emotional
* Test Yourself
* Write It Down
* Learn the Name Well
* On the tip of your tongue? Relax
* Don't Block the Name
* Review Names prior to a Social Event

4.4. Mood/behavior therapy

For patients with prominent mood (depression, hopelessness, and anxiety) and behavioral (explosivity, impulsivity, short fuse) symptoms, psychological therapy/counseling by a clinical psychologist, neuropsychologist, or psychiatrist is recommended. If there are cognitive issues as well, then cognitive behavioral therapy (CBT) may be useful. This form of therapy investigates the relationship between thoughts, feelings, and behaviors and how certain patterns of thought may lead to maladaptive behaviors. With insight and awareness of these patterns of thought, correction of the counter-productive behavior can be undertaken.

When anxiety is the predominant symptoms meditation and relaxation techniques including yoga have been useful for some patients as have aerobic exercise programs. There is currently rising interest in mindfulness-based strategies where the focus is learning attention control and creating an acute appreciation of thoughts, feelings, and bodily sensations. The objective is to strengthen one's belief in one's own ability to complete tasks and reach goals while at the same time diminishing one's feelings of helplessness in the face of residual symptoms. In one small series of TBI patients, this has been reported to improve self-efficacy and quality of life [25].

4.5. Mindfulness

One non-pharmacological therapy that can be used to improve attention is mindfulness. It turns out that one can actually practice paying active attention in the same way that one can practice playing the violin or other skills. Practicing mindfulness is not for everyone, but for some individuals, it is an empowering, drug-free way for them to improve their attention. For our younger patients, we generally recommend one of the many phone applications available for this purpose, and for our middle-aged and older patients, guided mindfulness meditation through audiobooks and in-person classes tend to work best.

4.6. Occupational – ocular therapy (OOT)

Patients who will benefit from OOT will usually demonstrate blurred or double vision with smooth pursuit or convergence eye movements, while horizontal more than vertical saccadic eye movements, vestibular ocular reflex (VOR), or visual motion sensitivity (VMS) testing may produce dizziness, nausea, lightheadedness, or headache. Patients most frequently spontaneously complain of double or blurred vision, eye strain/headaches with reading or loss of place or skipping lines, or computer use, or words appearing to move, jump, or swim off a page. They may also complain of difficulty taking notes or the need to tilt the head back or closing an eye.

The evaluation by a certified ocular therapist will involve an assessment of visual acuity and visual efficiency. The later includes ocular motor skills (Fixation, Pursuits, Saccades), binocular vision

coordination of eyes together including convergence insufficiency, and accommodation of near and far focusing ability (accommodative in sufficiency).

The ocular therapist will assess deficits in visual processing and perceptual skills including peripheral awareness, bilateral integration, directionality, visual motor integration and visual processing speed/reaction time. For each deficiency, the ocular therapist will provide appropriate eye exercises such as pencil pushups, wall/dot pushups, alternate cover, Brock string, or eccentric circles.

General compensatory strategies are also employed such as larger print, holding the target further away, tints for computer screens or the written page, tint glasses when photophobia is present, and eyeglass prisms when appropriate. Prisms are usually prescribed by an optometrist.

4.7. Vestibular therapy or vestibular rehabilitative therapy (VRT)

Some patients with suspected CTE as a result of repetitive head injury and resultant inner ear injury will have chronic symptoms of dizziness, vertigo, one's vision spinning horizontally or less commonly vertically, and as a result a feeling of having difficulty with balance and coordination that can impair especially walking and driving. In the CTE checklist, it is balance issues and dizziness that will be the major complaints. These patients are referred to certified vestibular therapists which are usually a physical therapist or occupational therapist with additional training in VRT.

Therapy consists of visual perception/eye tracking, postural and gait exercises done initially with the therapist and then at home as well [26,27]. The aim of therapy is to retrain/desensitize the brain to compensate for the misinformation received from the malfunctioning inner ear. Because it involves overstimulation of the damaged inner ear, symptoms are often initially exacerbated before they are improved. Because some patients with chronic vertigo will have the condition benign paroxysmal positional vertigo (BPPV) the vestibular therapist must be trained to recognize this condition and treat it with the Epley Maneuver which can correct symptoms in minutes.

While VRT may often require many weeks or months for maximal improvement, most patients will have significant improvement in their dizziness/vertigo/balance symptoms.

Because so much of VRT involves eye tracking oculomotor skills, it is often that patients will have visual symptoms as well and the ocular therapist and VRT will both work together with the same patient.

4.8. Motor therapy

Physical therapy is used to treat the motor symptoms of patients at risk for not just ataxia, rigidity, and Parkinsonism features but cervicogenic head/neck pain, dizziness, decreased neck strength, range of motion, poor posture, and decreased exercise tolerance. In each patient cervical range of motion, strength, mobility, and proprioception as well as dynamic and static balance is assessed, and appropriate corrective exercises implemented to correct deficits including endurance.

There are other therapies such as transcranial magnetic stimulation and hyperbaric oxygen therapy for which there is theoretical but not as yet scientifically proven benefit and since they are not used by the authors they do not rise to the level of recommendation at this time.

4.9. Endocrine assessment

An assessment of pituitary gland function is undertaken with fasting blood testing for prolactin, TSH, ACTH, cortisol, testosterone, and growth hormone (IGF). If the pituitary gland has been injured by repetitive head trauma, hormonal deficits detected can easily be corrected by hormonal supplementation accompanied by resolution of symptoms.

5. Pharmacologic management of patients with possible CTE

We must first note that there are no FDA-approved treatments for CTE, and therefore all medications described here are being used in an 'off label' manner.

Before adding any medications, we always first work to remove or minimize any medications that could cause cognitive impairment. These include many medications in the following classes:

* Anticholinergic medications
* Antihistamines (including over-the-counter)
* Narcotic pain medications
* Muscle relaxants
* Benzodiazepines
* All sedatives/sleeping aids [e.g. zolpidem (Ambien) mirtazapine (Trazodone), quetiapine (Seroquel)] – except melatonin (which is fine)
* Anticonvulsants
* Neuroleptics
* Incontinence medications (those that are anticholinergic)

5.1. Therapy for memory impairment

For memory impairment, we recommend the use of the cholinesterase inhibitors at their usual doses. This class of medications was developed for individuals with Alzheimer's disease and includes donepezil (Aricept), rivastigmine (Exelon), and galantamine. The expected benefits include a small but noticeable improvement in memory that will be persistent even as the individual declines. In other words, because cholinesterase inhibitors are symptomatic memory boosters, the individual will always have slightly better memory function on the medication than off it, at any given level of memory function. Thus, if they show initial benefit with this class of medication, we generally recommend individuals with CTE to stay on them for the remainder of their lives. Their major side effects are directly related to their pro-cholinergic effect and include loss of appetite, nausea, frequent bowel movements, vivid dreams, increase salivation, rhinorrhea, muscle cramps, and rarely bradycardia. We recommend an electrocardiogram (ECG) be obtained after the individual is at their target dose to detect

asymptomatic bradycardia and clinically significant heart block [17].

5.2. Pharmacologic therapy for apathy

Apathy is the most common neuropsychiatric symptom in Alzheimer's disease and other dementias, yet it is often ignored because it tends not to cause problems for caregivers. There are three main classes of medications that can be tried for apathy: levodopa formulations, dopamine agonists, and stimulants. Because stimulants will be discussed in detail in the therapy for attention section, below, we will simply note here that this class of medications can be extremely effective for treating apathy, particularly when accompanied by poor attention.

Carbidopa/levodopa (Sinemet) or one its newer formulations given in low dose, two to three times per day may show benefit in reducing apathy. At higher doses, its side effects are myriad, and may include (but are not limited to) confusion, hallucinations, dizziness, psychosis, nausea, and engaging in risky behavior. We generally try a low dose and move to other therapies if it is not successful.

Dopamine agonists include amantadine, memantine (Namenda), and pramipexole (Mirapex). These medications stimulate the dopamine receptor and may reduce apathy. In general, we start with memantine for patients who show apathy in the dementia stage of their disease, and try amantadine and/or pramipexole for those who are apathetic but do not have dementia. We use low doses, as side effects are common at higher doses and include (but are not limited to) confusion, hallucinations, dizziness, sleepiness (sometimes coming on suddenly impairing driving), and engaging in risky behavior.

Lastly, we will note that there are some activating antidepressants that can improve apathy; we will discuss these below under the therapy for depression and anxiety.

5.3. Pharmacologic therapy for impaired attention

Attention problems are common in head injuries of any type as well as CTE. Stimulants are the mainstay of therapy for attentional problems. The most common stimulants are methylphenidate (Ritalin, Concerta, Metadate, Methylin, Aptensio, Cotempla, Quillichew, Quillivant), Amphetamine (Adzenys, Dyanavel, Evekeo), and Dextroamphetamine (Dexedrine, ProCentra, Zenzedi). Stimulants boost up the monoaminergic systems, often stimulating both norepinephrine and dopamine receptors. We have used a variety of short- and long-acting stimulants at various doses in various settings, and one generally needs to tailor the use of stimulants to the patient and the setting more than with most other medications. If the individual is a student or working, it is reasonable to prescribe use during school or work hours and give a 'drug holiday' during evenings and weekends (with exceptions for difficult homework assignments). On the other hand, an individual with more marked attentional problems from CTE may need stimulants all-day, every day. Trial and error are often necessary. Common side effects include feeling nervous, jittery, anxious, anorexia, headache, palpitations, and dizziness, and serious reactions can include drug dependence and abuse, psychosis, mania, aggression, hypertension, myocardial infarction, stroke, seizures, arrhythmias, and sudden death. Consultation with a cardiologist is appropriate in the middle-aged or older individual.

5.4. Pharmacologic therapy for depression and anxiety

Patients with CTE show rates of depression and anxiety higher than that generally seen in other neurodegenerative diseases. An exhaustive discussion of pharmacotherapy for depression and anxiety is beyond the scope of this review. We will, however, share some general principles and the medications that we find most effective for these disorders.

Many antidepressants and anxiolytics can cause cognitive impairment. We try hard to stay away from these classes of medications. For example, we never prescribe a benzodiazepine for individuals who already have cognitive impairment at baseline.

For patients with depression and/or anxiety, we use low doses of sertraline (Zoloft) or escitalopram (Lexapro), both of which improve depression, anxiety, and also often agitation and aggression. There are many side effects of these selective-serotonin reuptake inhibitors (SSRIs), though few in the low doses that we generally use. Side effects may include apathy, headaches, gastrointestinal upset, periodic limb movements of sleep, suicidality, and sexual dysfunction, along with many others. Note that this class of medications has to be tapered down slowly.

For patients with depression and apathy, venlafaxine (Effexor) and bupropion (Wellbutrin, Forfivo) can be helpful in treating both symptoms. Headaches, nausea, insomnia, dizziness, anorexia, somnolence, mania, and suicidality are some of the possible side effects and reactions that can occur with these medications, which also should be tapered down slowly.

Exercise and mindfulness have been shown to be beneficial for both depression and anxiety, and we strongly promote both to treat these disorders.

5.5. Pharmacologic therapy for pseudobulbar affect

Pseudobulbar affect is when an individual cries or laughs for little or no reason. Crying is much more common than laughing, and for that reason, it is often confused with depression. The simple way to differentiate them is to ask the individual who is crying frequently, 'Are you feeling sad?' The depressed individual will say, 'Yes,' whereas the individual with pseudobulbar affect will say, 'No, I'm not sad but I can't stop myself from crying.' For these individuals, we use dextromethorphan/quinidine (Nuedexta). Side effects can include sedation, falls, diarrhea, and gastrointestinal upset, among others.

5.6. Pharmacologic therapy for agitation

The first thing to say here is that we try not to use medications for agitation if we can help it. We start with educating the family (or other caregivers) with the four R's:

* Reassure the individual that everything is alright.
* Reconsider things from the individual's point of view.
* Redirect the individual to an activity that decreases the agitation.

* Relax; the caregiver needs to relax when caring for the agitated individual, lest they escalate the situation with their own tone of voice and body language.

Next, we work hard to determine the underlying cause of the agitation. If agitation is due to anxiety (or if we cannot determine the cause of the agitation), we use sertraline (Zoloft) or escitalopram (Lexapro) as described above. If nighttime agitation is from a sleep disturbance, we work to treat the sleep disturbance (such as sleep hygiene or cycle problems). Rarely, we will use a low dose of risperidone (Risperdal) during the day or quetiapine (Seroquel) at night to treat the agitation. These atypical neuroleptics have many side effects which include sedation, falls, myocardial infarction, strokes, and death. For this reason, we tend to avoid them and, when we do use them, we use low doses.

There is some emerging evidence for the use of dextromethorphan/quinidine (Nuedexta) for agitation in dementia, and pimavanserin (Nuplazid) for psychosis in Parkinson's disease dementia, so those medications could also be tried in CTE patients with dementia.

6. Conclusions

CTE is a neurodegenerative disease that has been recently recognized as being much more prevalent than previously thought. Clinicians, patients, and families need to be able to recognize this disorder as its symptoms can be disabling. Although there are no published studies to guide our management of CTE, many non-pharmacologic and pharmacologic therapies have been used successfully in related disorders. We recommend that the clinician consider these therapies when treating patients with suspected CTE.

7. Expert opinion

Today there are NIH consensus criteria for the neuropathological diagnosis of CTE based on perivascular hyperphosphorylated tau deposition in the depths of sulci that distinguishes this disease from other neurodegenerative diseases and normal aging. What is lacking, however, is a unique profile of clinical symptoms and signs, longitudinal studies, and the ability to diagnose CTE during life.

Because all post-mortem neuropathologically confirmed cases of CTE (not 'CTE-like' cases) have had a history of repetitive head impacts (RHI), we know that RHI exposure is a necessary but not a sufficient cause of CTE, as not everyone with such exposure will develop CTE. The genetic and environmental risk factors beyond RHI are presently not known. Even the relative importance of variables associated with RHI, such as age of first exposure, cumulative exposure, severity and type of head exposure, and time between head impacts are currently unknown, despite being studied for a decade by our group at Boston University.

The next critical step will be the ability to diagnose CTE during life. Only then will we be able to determine its incidence and prevalence, risk factors and what clinical features are due to tauopathy versus axonopathy or other features.

An important step in diagnosing CTE during life will be developing sensitive and specific objective biological tests, 'biomarkers' analogous to those used for Alzheimer's disease, that can be added to the clinical evaluation. While we have studied many neuroimaging (including MRI, DTI, SWI, fMRI, MRS), spinal fluid, blood, and plasma biomarkers, none to date are truly CTE specific. One promising approach is to combine studies of PET tracers. For example, tracers that bind to hyperphosphorylated tau (such as flortaucipir, T807, AV1451) may show pathology in both Alzheimer's and CTE, whereas tracers that bind to amyloid (such as florbetapir) would only be positive in individuals with Alzheimer's. Thus, individuals who show binding to tau tracers and not amyloid tracers may have CTE. Longitudinal studies that follow patients during life until their neuropathological diagnosis are needed and are presently underway. Multicenter research projects can help us to better determine (1) neuroimaging and fluid biomarkers for the in vivo detection of CTE, (2) the clinical presentation of CTE, (3) the progression of CTE, and (4) genetic and head impact exposure risk factors for CTE, all of which can help us to improve and validate diagnostic criteria for the clinical diagnosis of CTE.

One day CTE will be detected early in the disease course, prior to the onset of symptoms, so that we can commence clinical trials for prevention. But for the present, while such detection is not possible based on RHI exposure and clinical symptoms alone, a high index of suspicion for CTE is warranted, and many non-pharmacologic and pharmacologic therapies used successfully in related diseases can be implemented.

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Declaration of interest

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