ADITUM

Journal of Neurosurgery and Neurology Research

Open Access Review Article

Chronic Traumatic Encephalopathy: An Update Review

Jacques De Reuck
Department of Neurology, University Hospital, Ghent (9000), Belgium.

Article Info

Received: April 23, 2021
Accepted: May 01, 2021
Published: May 21, 2021

***Corresponding author:** De Reuck J, Ryvissche park 16, 9052 Zwijnaarde. Belgium.

Citation: Jacques De Reuck. "Chronic Traumatic Encephalopathy: An Update Review". J Neurosurgery and Neurology Research, 2(3); DOI: http;//doi.org/03.2021/1.1016.

Abstract

Chronic traumatic encephalopathy is a progressive neurodegenerative disease occurring in retired sportspersons who have received several head blows with concussions during their games. Dementia pugilistica is considered as a subtype used for retired boxers. The clinical symptoms start with mood disorders and with a progressive evolution into dementia and Parkinsonism. The disease is due to a progressive accumulation of hyperphosphorilated tau in neurons as neurofibrillary tangles, abnormal neurites and inclusions in astrocytes around small vessels. There is a tendency of the lesions to occur in clusters at the sulcal depths of the cerebral cortex. Chronic traumatic encephalopathy has to be differentiated from Alzheimer's disease, in which head trauma can also increase the illness symptoms. Recently, new tracers in positron emission topography of the brain have been used for a better evaluation of chronic traumatic encephalopathy. There is actually no treatment that allows to cure or to slowdown the evolution of chronic traumatic encephalopathy. However, new treatment studies are recently conducted and in progress.

Keywords: Chronic traumatic encephalopathy; Dementia pugilistica; Traumatic brain injury; Alzheimer's disease; Positron emission tomography

Introduction

Chronic traumatic encephalopathy is a neurodegenerative disease characterized by the presence of abnormally phosphorylated tau protein in the depth of one or more cortical sulci [1].

Extensive exposure of boxers to repeated neurotraumata has led in 1928 to the term called "punch drunk syndrome". This terminology was replaced by the less derisive term " dementia pugilistica" (DP) in 1937 [2].

However, the observation of the occurrence a similar clinical presentation in American football players has now led to the more commonly used term of chronic traumatic encephalopathy (CTE). It is now understood that exposure to traumatic brain injury (TBI) from any sport increases the risk of developing a progressive neurodegenerative disease. There have been some efforts to distinguish DP from CTE or to classify it as a subtype of the latter [3].

The true prevalence of CTE among individuals with a history of head trauma remains unknown [4]. DP is estimated to occur in approximately 20% of retired boxers [5].

There is some evidence that a single moderate or severe TBI can also induce progressive neuropathological changes [6].

The diagnosis of CTE can only be made conclusively by post-mortem neuropathological examination [7].

Neuropathology

CTE is characterized by the build-up of hyperphosphorilated tau (p-tau) as neurofibrillary tangles, abnormal neurites and inclusions in astrocytes around small vessels with a tendency to occur in clusters at the sulcal depths of the cerebral cortex [7].

The tau epitope in CTE maps to the filamentous tau inclusions in Alzheimer's disease (AD). Also, the abnormal tau proteins isolated from the DP type of CTE brains are indistinguishable from the six abnormally phosphorylated brain tau isoforms in AD [8]. However more recently, a different conformation of beta-helix creating hydrophobic cavities with additional cores, that is not related and absent in the tau filaments from AD brains, has been observed [9].

A four pathological stage scheme, characterizing the severity of p-tau varying from mild (stage 1) to severe (stage 4) was proposed for CTE by McKee and colleagues in 2013. They found a predilection for p-tau pathology in the dorsolateral frontal cortex, the superior temporal cortex, the entorhinal cortex, the amygdala and the locus coeruleus. The lowest CTE stages involved only the frontal cortex and the locus coeruleus [10]. In the medial temporal lobes the different tau profiles across the CTE stages proffering CA3 tau pathology and dystrophic neuritis clusters were as the markers for the transition between early (II) and late (III/, IV) stages [11]. Also the substantia nigra can be involved in the late stages [12].

The association of a cavum septi pellucidi and dementia in old boxers was first described by Ferguson and Mawdsley in 1965. The significance and the epidemiology of the cavum septi pellucidi were however recently questioned [13].

White matter rarefaction, arteriosclerosis and tau with dementia in CTE were more frequently observed among older patients who had many years of their sports activities [14].

Clinical features

Cantu has proposed 3 grades of cerebral contusion. In grade 1 there is no loss of consciousness, less than 30 minutes post-traumatic amnesia and post-concussion symptoms for less than 24 hours. In grade 2 there is a loss of consciousness of less than 1 minute, post-traumatic amnesia of more than 30 minutes and post-concussion signs between day 1 and day 7. Grade 3 is characterized by a loss of consciousness of more than 1 minute or post-traumatic amnesia of more than 24 hours or post-concussion signs of more than 7 days [15].

The short-term sequels of acute brain injury include subdural haematoma and other catastrophic injuries, whereas mild TBI or concussion causes functional disturbances and axonal injury rather than gross structural brain damage. Following concussion, symptoms such as dizziness, nausea, reduced attention, amnesia and headache tend to develop acutely but usually resolve within a week or two. The developing brains in children and adolescents are more susceptible to concussion than the adult ones [16].

Many studies show a significant association between cumulative exposure to repetitive head trauma, judged by the length of the sportive career, and the risk for severity of CTE. There is also a significant relationship with the length of the sport activities and age of death [17].

TBI significantly increases the risk of developing AD and Parkinson's disease. Evidence for a possible role in TBI as a risk factor for sporadic amyotrophic sclerosis has been provided by studies of professional players of European football [18].

A minority of younger patients who do not experience the latency phase with symptoms of CTE may be clinically diagnosed as post-concussion syndrome [19].

In mild CTE behavioural or mood symptoms or both are present in 96%, cognitive symptoms in 85% and signs of dementia in 33%. In severe CTE pathology 89% had behavioural or mood disorders or both, 95% cognitive symptoms and 85% signs of dementia [20]. CTE manifests itself in four stages. In stage 1 the patients are asymptomatic or have mild memory and depressive symptoms. In stage 2 symptoms include behavioural outbursts and severe depression. Stage 3 is characterized by cognitive deficits including memory loss and executive dysfunction. In stage 4 advance language deficits, psychotic symptoms, profound cognitive deficits and motor features are observed [21].

Neuroimaging

Computed tomography of the brain does not allow the diagnosis of CTE [22]. Magnetic resonance imaging shows a significant increase of prevalence of cavum septum pellucidum and cavum vergae among boxers [23]. This is associated with lower regional brain volumes and cognitive performance in a cohort of exposed boxers to repetitive head trauma [24]. The extend of the cavum septum pelucidi is more pronounced in the posterior parts of the brain, probably due to the sudden increase of the intracranial pressure during the blows, that forces cerebrospinal fluid through small defects in the septal leaflets [25]. Brain diffusion constant increases and diffusion anisotropy significantly decreases in the corpus callosum and the internal capsule of boxers [26].

Positron emission tomography (PET) of the brain with fluorodeoxyglucose, tau and amyloid radiotracers, are powerful modalities in the diagnosis of TBI-related conditions and CTE [27]. Mildly elevated tau-PET binding is observed in a subset of amyloid-negative patients at risk for CTE, in a distribution consistent with the CTE pathology stages III-IV [28]. Former national football league players with cognitive and neuropsychiatric symptoms have higher tau levels measured by PET in brain regions that are affected by CTE than in controls [29]. A consistent increase of tau is mainly observed in the hippocampi, the amygdalae and the brainstem [30]. Also a close correlation is found between psychosis and tau binding capacity in the white matter [31].

Prevention and Treatment

Guidelines have been published by the International Concussion in Sport Group, the American Academy of Neurology, the National Athletic Trainers Association and the 2013 Team Physician Consensus Statement Update [32]. Also a more recent 2017 Berlin Concussion in Sport Group Consensus Statement in collision sports has been published [33]. However most of these guidelines are based on those proposed by Cantu. He classified the guiding prevention principles for TBI as dependent from the grade of severity and the recurrence rate of the concussion. For grade 1 one week is needed for a first contusion, two weeks for the second one and termination of the sport season after the third one. For grade 2 one week is needed for a first contusion, one month for the second one and termination of season after the third one. For grade 3 one

month is needed for the first one, while for the second and the third contusion the season should be terminated [15].

Factors associated with delayed return to rugby play were young age, initial loss of consciousness, Cantu grade 3 and post-concussive syndrome of more than 5 days [34].

A protective effect of helmets in collusion sports reduces concussions by head contact [35]. The helmet-to-helmet impact is 30% less in high safety-rated ones compared to the lowest safety-rated ones in the American National Football League [36].

Data are insufficient to show that any intervention enhances recovery or diminishes long-term post-concussion sequels [37]. However some symptomatic treatments can be tried such as central cholinesterase inhibitors for cognitive disturbances and dementia, dopamine and associated drugs for Parkinsonism symptoms and antipsychotics for psychosis and behavioural disturbances [38]. Even acupuncture and music therapy are considered to be helpful to combat the early neuropsychiatric symptoms of CTE [39].

Discussion

During the recent years much advances have been made concerning the diagnostic mechanisms and the neuroimaging in CTE. Mainly the recent PET techniques with new tracers have contributed to a better understanding of TBI.

As CTE is characterized by accumulation of p-tau there is a growing interest in clinical trials with new tau-directed therapies. These treatments are hypothesised to have disease-modifying effects by reducing the concentrations of toxic forms of tau in the brain or by compensating for the loss of tau function [40]. Also a series of candidate treatments, including kinase inhibitors, antibody therapy and anti-inflammatory drugs are evaluated in preclinical animal models of CTE [41].

However there are some dough's that the pathogenesis of CTE is correlated solely to the repeated concussive injuries alone. The causes can be multivariate [42]. In particular it is known that TBI is promoting the severity of AD [43].

There are still major concerns about the traditional guidelines to be used for return to sport participation after concussion, who are inconsistently applied, in particular in boxing. Only a few athletic commissions require either formal consultation with a neurological specialist or formal neuropsychological testing prior to the return to the competition [44].

Conclusion

Although there are many advances during the recent years in the understanding of CTE, still some clear prevention and treatment modalities are missing.

References

1. J Zuckerman SL, Brett BL, Jeckell A, Yengo-Kahn AM, Solomon GS (2018). Chronic traumatic encephalopathy and neurodegeneration in contact sports and American football. J Alzheimer Dis. 66 (1): 37-55.
2. Castellani RJ, Perry G (2017). Dementia pugilistic revisited. J Alzheimer Dis. 60 (4): 1209-1221.
3. Inserra CJ, DeVrieze BW (2021). Chronic traumatic encephalopathy. StatPearls (Internet).
4. Turk KW, Budson AZ (2019). Chronic traumatic encephalopathy. Continuum (Minneap Minn). 25 (1): 187-207.
5. Kokjohn TA, Maarouf CL, Daugs ID, Hunter JM, Whiteside CM, Malek-Ahmadi M (2013). Neurochemical profile of dementia pugilistica. J Neurotrauma. 30 (11): 981-97/
6. Smith DH, Johnson VE, Trojanowski JQ; Stewart W (2019). Chronic traumatic encephalopathy – confusion and controversies. Nat Rev Neurol.15 (3): 179-183.
7. Mckee AC, Abdolmohammadi B, Stein TD (2018). The neuropathology of chronic traumatic encephalopathy. Handb Clin Neurol.158: 297-307.
8. Schmidt ML, Zhukareva V, Newell KL, Lee VM, Trojanowski JQ (2001). Tau isoform profile and phosphorylation state in dementia pugilistica recapitulate Alzheimer's disease. Acta Neuropathol.101 (5): 518-524.
9. Falco B, Zivanov J, Zhang W, Murzin AG, Garringer HJ, Vidal R, et al (2019). Novel tau filament fold in chronic traumatic encephalopathy encloses hydrophobic molecules. Nature. 568 (7752): 420-423.
10. Alosco ML, Cherry JD, Russell Huber B, Tripodis Y, Baucom Z, Kowall NW, et al (2020). Characterizing tau deposition in chronic traumatic encephalopayhy: utility of the McKee CTE staging scheme. Acta Neuropathol.140 (4): 495-512.
11. Kelley CM, Perez SE, Mufson EJ (2019). Tau pathology in the medial temporal lobe of athletes with chronic traumatic encephalopathy: a chronic effect of neurotrauma consortium study. Acta Neuropathol Commun. 7 (1): 207.
12. Lepreux S, Auriacombe S, Vital C, Bubois B, Vital A (2015). Dementia pugilistica: a severe tribute to a career. Clin Neuropathol. 34 (4): 193-198.
13. Bodensteiner JB, Schaefer GB (1997). Dementia pugilistica and cavum septi pellucidi: born to box? Sports Med. 24 (6): 361-365.
14. Alosco ML, Stein TD, Tripodis Y, Chua AS, Kowall NW, Russell Huber B, et al (2019). Association of white matter rarefaction, arteriosclerosis, and tau with dementia in chronic traumatic encephalopathy. JAMA Neurol. 76 (11): 1289-1308.
15. Cantu RC (1992). Cerebral contusion in sport. Management and prevention. Sports Med. 14 (1): 84-74.
16. Ling H, Hardy J, Zetterberg H (2015). Neurological consequences of traumatic brain injuries in sports. Mol Cell Neurosci. 66(Pt B): 114-122.
17. McKee AC (2020). The neuropathology of chronic traumatic encephalopathy: the status of the literature. Semin Neurol. 40 (4): 359-369.

18. Vanittallie TB (2019). Traumatic brain injury (TBI) in collusion sports: possible mechanisms of transformation into chronic traumatic encephalopathy (CTE). Metabolism.
19. Zetterberg H, Blennow K (2018). Chronic traumatic encephalopathy: fluid biomarkers. Handb Clin Neurol. 158: 323-333.
20. Mez J, Daneshvar DH, Kiernan PT, Abdolmohammadi B, Alvarez VE, Huber BR, et al (2017). Clinicopathological evaluation of chronic traumatic encephalopathy in players of American football. JAMA 2318 (4): 360-370.
21. McKee AC, Stern RA, Nowinski CJ, Stein TD, Alvarez VE, Daneshvar DH, et al (2013). The spectrum of disease in chronic traumatic encephalopathy. Brain. 136:43–64.
22. Shetty T, Raince A, Manning E, John Tsiouris (2016). Imaging in chronic traumatic encephalopathy and traumatic brain injury. Sports Health. 8 (1): 26-36.
23. Lee JK, Wu J, Banks S, Bernick C, Massand MG, Modic MT, Ruggieri P, Jones SE (2017). Prevalence of traumatic findings on routine MRI in a large cohort of professional fighters. Am J Neuroradiol. 38 (7): 1303-1310.
24. Lee KJ, Wu J, Bullen J, Banks S, Bernick C, Modic MT, Ruggieri P, et al (2020). Association of cavum septum pellucidum and cavum vergae with cognition, mood, and brain volumes in professional fighters. JAMA Neurol. 77 (1): 35-42.
25. Aviv RI, Tomlinson G, Kendall B; Takkar C, Valentine A (2010). Cavum septi pellucidi in boxers. Can Assoc Radiol J. 61 (1): 29-32.
26. Zhang L, Heier LA, Zimmerman RD, Jordan B, Ulug AM (2006). Diffusion anisotropy changes in the brains of professional boxers. Am J Neuroradiol. 27 (9): 2000-2004.
27. Ayubcha C, Revheim ME, Newberg A, Moghbel M, Rojulporte TJ, Werner TJ, Alavi A (2021). A critical review of radiotracers in positron emission tomography imaging of traumatic brain injury: FDG, tau, and amyloid imaging in mild traumatic brain injury and chronic traumatic encephalopathy. Eur J Nucl Med Mol Imaging. 48 (2): 623-642.
28. Lesman-Segev OH, La Joie R, Stephens ML, Sonni I, Tsai R, Bourakova V, et al (2019). Tau PET and multimodal brain imaging in patients at risk for chronic traumatic encephalopathy. Neuroimage Clin. 24: 102025.
29. Stern RA, Adler CH, Chen K, Navitsky M, Luo Ji, Dodick DW, et al (2019). Tau positron-emission tomography in former national football league players. N Engl J Med. 380 (18): 1716-1725.
30. Lee BG, Leavitt MJ, Bernick CB, Leger GC, Rabinovici Gil, Banks SJ (2018). A systematic review of positron emission tomography of tau, amyloid beta and neuroinflammation in chronic traumatic encephalopathy: the evidence to date. J Neurotrauma. 35 (17): 2015-2024.
31. Takahata K, Kimura Y, Sahara N, Koga S, Shimada H, Ichise M, et al (2019). PET-detectable tau pathology correlates with long-term neuropsychiatric outcomes in patients with traumatic brain injury. Brain. 142 (10): 3265-3279.
32. Echemendia RJ, Giza CC, Kutcher JS (2015). Developing guidelines for return to play: consensus and evidence-based approaches. Brain Inj. 29 (2): 185-194.
33. Patricios JS, Ardern CL, Hislop MD, Aubry M, Bloomfield P; Broderick C, et al (2018). Implementation of the 2017 Berlin Concussion in Sports Group Concensus Statements in contact and collusion sports: a join position statement from 11 national and international sports organisations. Br J Sports Med. 52 (10): 635-641.
34. Chermann JF, Klouche S, Savigny A, Lefevre N, Herman S, Bohu Y (2014). Return to rugby after brain concussion: a prospective study in high level rugby players. Asian J Sports Med. 5 (4).
35. Emery CA, Black MA, Kolstad A, Martinez G, Nettel-Aguirre A, Engebretsen L, et al (2017). What strategies can be used to effectively reduce the risk of concussion in sport? A systematic review. Br J Sports Med. 51 (12): 978-984.
36. Colello RJ, Colello IA, Abdelhameid D, Cresswell KG, Merchant R, Beckett E (2018). Making football safer: assessing the current National Football League policy on the type of helmets allowed on the playing field. J Neurotrauma. 35 (11): 1213-1223.
37. Giza CC, Kutcher JS, Ashwal S, Barth J, Getchius TSD, Giola GA, et al (2013). Summary of evidence-based guideline update: evaluation and management of concussion in sports: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 80 (24): 2250-2257.
38. Cantu R, Budson A (2019). Management of chronic traumatic encephalopathy. Expert Rev Neurother. 2019; 19 (10): 1015-1023.
39. Lucke-World BP, Logsdon AF, Nguen L, Eltanahay A, Turner RC, Bonasso P, et al (2018). Supplements, nutrition, and alternative therapies for the treatment of traumatic brain injury. Nutr Neurosci. 21 (2): 79-91.
40. Boxer AL, Yu JT, Golbe LI, Litvan I, Lang AE, Hoglinger GU (2017). Advances in progressive supranuclear palsy: new diagnostic criteria, biomarkers and therapeutic approaches. Lancet Neurol. 16 (7): 552-563.
41. Breen PW, Krishnan V (2020). Recent preclinical insights into treatment of chronic traumatic encephalopathy. Front Neurosci. 14.
42. Solomon GS, Zuckerman SL (2015). Chronic traumatic encephalopathy in professional sports: retrospective and prospective views. Brain Inj. 29 (2): 164-170.
43. Jellinger K (2019). Traumatic brain injury and Alzheimer's disease neuropathology. Alzheimers Dementia. 15 (9): 1236-1237.
44. Seifert T, Bernik C, Jordan B, Alessi A, Davidson J, Cantu R, et al (2015). Determining brain fitness to fight: has the time come? Phys Sportsmed. 43(4): 395-402.