

Chronic Traumatic Encephalopathy and its Variant “Dementia Pugilistica”: A Review

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Abstract

Dementia Pugilistica (DP) is the initial term used to characterize a progressive cognitive deterioration, as result of multiple concussions, occurring in boxers, who have ended their professional carrier. As a similar deterioration is also observed in American football players, and other contact sport athletes, and in military veterans a more general term is used called chronic traumatic encephalopathy (CTE). It is not known whether the clinical and neuropathological characteristics are completely the same in CTE of athletes and military veterans compared to DP, described in boxers.

Different clinical stages of these diseases have been proposed starting with mild psychiatric symptoms and progressing to a severe dementia status and eventual associated motor symptoms.

As DP and CTE are classified as neurodegenerative diseases mainly characterized by hyperphosphorylated tau pathology, also a grading system of the neuropathological lesions has been introduced, starting with discrete foci in the frontal cerebral cortex and with a progressive generalization during the further evolution. Also, other neurodegenerative diseases can be found associated to DP and CTE.

Currently, some of the greatest challenges are that DP and CTE cannot be diagnosed with certainty during life and that the incidence and the prevalence of these disorders remain uncertain. Also, the post-mortem lesions can sometimes not be distinguished from those in the Alzheimer’s disease.

Keywords: *Dementia Pugilistica; Chronic Traumatic Encephalopathy; Tau Pathology; Alzheimer’s Disease; Lewy Body Disease; Frontotemporal Lobar Degeneration; Motor Neuron Disease*

Introduction

The term “Dementia Pugilistica” (DP) has been introduced in 1973 by Corsellis, referring to a severe post-concussion syndrome in boxers [1]. Previously several terms have been used such as punch-drunk syndrome, chronic boxer’s encephalopathy, boxer’s dementia, and traumatic boxer’s encephalopathy [2]. Chronic brain injury associated with boxing occurs in approximately 20% of professional boxers [3].

Chronic traumatic encephalopathy (CTE) is now used as a more general term because there are reports of a similar syndrome in American football players, and in other contact sport athletes, military veterans or others with histories of repetitive brain traumas [4-7].

People sustaining a traumatic brain injury are 4 times more likely to develop dementia at a later stage than people without a history of brain trauma [8]. DP and CTE can only be diagnosed with certainty by a post-mortem examination of brain tissue [9].

CTE can also been observed years after just a single moderate to severe traumatic brain injury. However, little consensus currently exists on the specific features of the post-traumatic brain injury syndromes that might permit their confident clinical and/or pathological diagnosis [10].

As it is not certain whether the clinical aspects and the evolution of the post-mortem lesions are completely the same DP and CTE will be retained in this review as separate entities, depending of the title of the citation.

Concussion grading scales

The most used grading systems are those proposed by Cantu [11] and by the American Academy of Neurology (ANN) [12]. In both classifications grade 1 is defined when there is no loss of consciousness but post-traumatic amnesia or confusion that clear up in less than 15 to 30 minutes. Grade 2 is characterized by loss of consciousness of less than 1 minute in the Cantu classification but not in the ANN system. However, in both grading systems post-concussion symptoms persist mainly between 15 and 30 minutes, but lasting no longer than 24 hours. In the grade 3 of the Cantu classification there is a loss of consciousness for more than 1 minute with post-traumatic amnesia lasting more than 24 hours and post-concussion signs or symptoms persisting for more than 7 days. The ANN guidelines differ only by the duration of the loss of consciousness, which can be either brief (seconds) or prolonged (minutes).

However, these grading systems are criticized, mainly because it is observed that boxers knocked unconscious for brief periods of time often recovered more quickly than those who did not lose consciousness at all [13,14].

Clinical features

DP and CTE are slowly progressing diseases starting predominantly with mood disturbances such as unable to tolerate loud noise, depression and hopelessness or confusion. The symptoms progress over decades, leading to cognitive deficits and dementia [15]. DP has some common clinical features with Alzheimer’s disease (AD) [16,17].

The combined history of head injury and alcohol and/or drug abuse is a significant predictor of any CTE-like changes. Age (> 40 years) is also a significant predictor [18].

The neuro-psychiatric phenotypes of DP and CTE can be classified in 4 stages. In stage 1 headache, attention/concentration deficits, depression and suicidality are the main signs. Stage 2 is characterized by depression, behavioral changes, memory loss, exclusivity and aggression. In stage 3 there is cognitive and executive dysfunction, depression, aggression, mild dementia signs and suicidal behavior. In stage 4 the symptoms further evolve to severe dementia with memory impairment, aggression, paranoia, depression and suicidal behavior [19].

Less commonly tremor, dysarthria, ataxia and parkinsonian signs occur in DP patients [20]. Occasionally motor neuron disease is observed in CTE [21].

On a genetic basis, there are no clear risk factor genes for CTE [22]. However, the possession of an APOE epsilon 4-allele may be associated with an increased severity of chronic neurologic deficits in high-exposure boxers [23]. A slight increase in MAPT H1 type and a tendency of fewer homozygous carriers with the protective TMEM 106B rs3173615 minor allele are described in those with CTE signs compared to those without [24].

Conventional magnetic resonance imaging (MRI) is normal in the majority of professional boxers. Only a minority of them displays non-specific white matter changes. However, in all of them a decrease of diffusion anisotropy is observed [25].

Former athletes with multiple concussions are at increased risk of elevated levels of total tau in cerebrospinal fluid. This increase is associated with reduced white matter integrity on MRI. The levels are however lower than those observed in AD [26].

In a group of living former US football players with cognitive and psychiatric symptoms a higher tau level is observed on positron emission tomography in the superior frontal and medial temporal regions and in the left parietal zone. There is no association between the levels of tau deposition and the scores on cognitive and neuropsychiatric testing. A high level of β -amyloid is only observed in a minority of former football players similar to that in AD, on positron emission tomography [27].

Neuropathological features

DP and CTE are classified as neurodegenerative tauopathies [28].

The gross neuropathological findings in DP and CTE consist of atrophy of the cerebral hemispheres, medial temporal lobe, thalamus, mamillary bodies, brainstem with thinning of the corpus callosum. These changes can also be observed on post-mortem 7.0-tesla MRI (Figure 1). Other some gross features include pallor of the substantia nigra and locus coeruleus and atrophy of the olfactory bulbs, and cerebellum. Ventricular dilatation with fenestration of the cavum septum pellucidum has been considered to be the most typical lesion [29]. This association was for the first time described in old demented boxers by Ferguson and Mawdsley in 1965 [30].

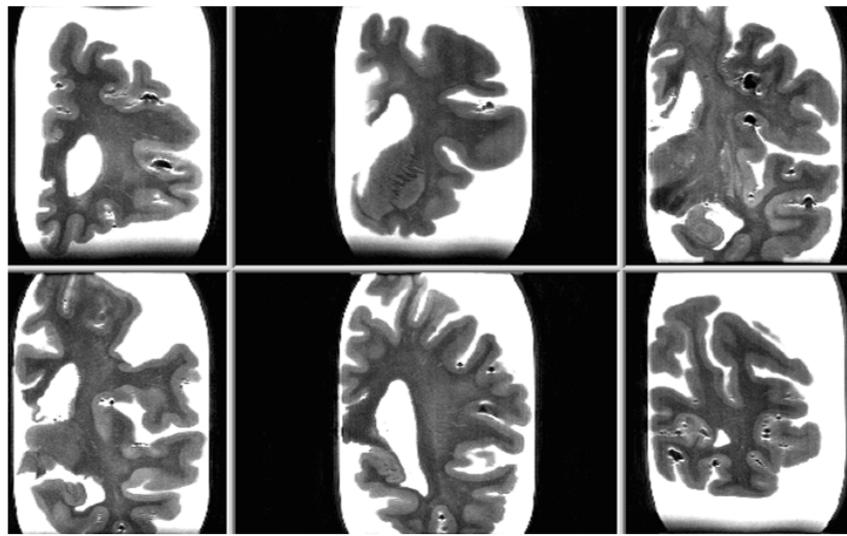


Figure 1: T2 sequence on magnetic resonance imaging of six coronal sections of a cerebral hemisphere in a post-mortem brain of a 54-year old man with a history of repeated brain concussions. Note the severe global cortical atrophy and the dilated ventricular system.

On microscopic examination the neurofibrillary tau tangles are concentrated in the superficial layers of the neocortex in DP and CTE, whereas in AD they predominate in the deep layers. In DP brains they prevail in the frontal and temporal cortices mostly in the depth of the sulci with an irregular patchy perivascular distribution [31].

The spectrum of hyperphosphorylated tau pathology allows a progressive staging of the lesions from stages I to IV in CTE brains [5]. In stage I positive tau pathology is found in discrete foci in the cerebral cortex, most commonly in the superior or lateral frontal cortices, typically around small vessels at the depths of sulci. In stage II there are multiple foci of positive tau at the depths of the cerebral sulci and there is localized spread of the neurofibrillary pathology from these epicenters to the superficial layers of adjacent cortex. The medial temporal lobe is spared of neurofibrillary positive tau pathology. In stage III positive tau pathology is more widespread in the frontal, insular, temporal and parietal cortices with the greatest severity in the frontal and temporal lobes. Also, the amygdala, the hippocampus and the entorhinal cortex show substantial neurofibrillary pathology. In stage IV widespread severe positive tau pathology affects most regions of the cerebral cortex and the medial temporal lobes, sparing the calcarine cortex. There is also diffuse atrophy of the white matter and thinning of the corpus callosum. Most cases show septal abnormalities including a cavum septum, perforations, fenestrations or total absence of the posterior septum. The locus coeruleus and substantia nigra are pale [32].

Generally, tau abnormalities in the white matter are not as severe as in the adjacent gray substance. Tau-positive fibrillar astrocytic tangles are found in the white matter, but the major abnormality is that of dot-like or spindle-shaped tau-positive neuritis [7]. In contrast to AD the novel tau filament folds enclose hydrophobic molecules [33].

Astrogliosis in DP and CTE is more diffuse than in other degenerative taupathies [34]. There is a significant increase of active microglia with elevated inflammatory cytokines [35].

Other abnormalities frequently found in the cerebral and cerebellar white matter include small arterioles with thickened fibro-hyalinization of vessel-walls, perivascular haemosiderin containing macrophages, widening of the perivascular spaces, and white matter rarefaction [36].

Axonal signaling pathway-related proteins are down regulated in neurons and oligodendrocytes of CTE [37].

The role of β -amyloid peptides is controversial. In athletes and military veterans with CTE 44% had some amyloid deposition primarily in diffuse plaques and 10% met the criteria for AD [38]. The diffuse β -amyloid deposits are most frequently seen in the upper cortical layers [39]. Amyloid- β deposition in senile plaques is significantly associated with the presence of the APOE epsilon 4-allele, older age at symptom onset and older age at death in DP [40]. DP and CTE can be associated with mainly leptomeningeal frontal cerebral amyloid angiopathy [41].

One study mentions that iron is also involved in the pathogenesis of traumatic brain injury [42].

Motor neuron disease is associated with 12% of the DP and TBE cases, 11% of AD, 16% of Lewy body disease (LBD) and 6% of fronto-temporal lobar degeneration (FTLD) [5].

Discussion and Conclusion

In the literature the DP and CTE entities are mixed-up not allowing whether there are clinical and neuropathological differences. Also, the term of CTE is frequently used to cover post-traumatic encephalopathies in athletes as well as in boxers.

Currently, some of the greatest challenges are that DP and CTE cannot be diagnosed with certainty during life and that the incidence and prevalence of these disorders remains uncertain [15]. Also, the specificity of the lesions on computed tomography and MRI during life is questionable [43]. This is also confirmed in post-mortem brains with mild traumatic brain injury, examined with 7.0-tesla MRI [44].

Also it is uncertain whether some neurodegenerative features such as those of AD [39], of LBD [45], of amyotrophic lateral sclerosis and FTLD [46] are to be considered as features of the DP and CTE or are due to other associated neurodegenerative diseases.

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