Determine the symptoms most commonly associated with CTE

Is there evidence for the association between chronic traumatic encephalopathy in contact-sport athletes and the development of dementia symptoms?

In order to establish this link, we aim to:
- Determine the symptoms most commonly associated with CTE
- Establish criteria to distinguish these symptoms from other neurodegenerative disorders
- Compare the clinical presentation of CTE to the accepted clinical diagnostic criteria of dementia

The research question was identified through the PCID framework, where the population refers to contact-sport athletes, the intervention is the presence of CTE, the outcome is the presence of dementia symptoms, and no comparison group was utilized.

Introduction

Chronic Traumatic Encephalopathy (CTE) is a condition often found in contact-sport athletes that results from the cumulative effects of repetitive traumatic brain injuries (McKee, 2005). It was first described in boxers by Marland in 1928 as “Punch-Drunk Syndrome.” (Parker, 1934) and is presently known as Chronic Traumatic Encephalopathy, as this syndrome is present among other contact-sport athletes.

CTE is associated with many of the clinical signs and symptoms of dementia; however, it is neuropathologically distinct from other neurodegenerative diseases. Post-mortem studies of the brains of contact-sport athletes have consistently identified a number of distinct, organic changes in the brain that are characteristic of CTE. The most commonly observed brain pathology is the presence of clusters of hyperphosphorylated Tau protein called neurofibrillary tangles that are diffusely scattered throughout the brain. Fibrils in and stabilize microtubules in other disorganized form, helping to maintain the structure and function of neurites (Olmea et al., 2008). Repeated blows to the brain cause Tau to dissociate from microtubules, initiating a cascade of mechanisms that result in its hyperphosphorylation and abnormal folding (McKee et al., 2012). This results in the formation of the characteristic neurofibrillary tangles found in CTE. These structures often accompany other neurodegenerative diseases, but the pathology of CTE is unique in that neurofibrillary tangles are present without neuritic plaques (McKee et al., 2012). Neuritic plaques are peptide deposits composed of beta-amyloid protein, generally in conjunction with neurofibrillary tangles in other forms of dementia (McKee et al., 2012). It is this occurrence that makes CTE unique.

While CTE can be diagnosed histologically, its clinical presentation is not distinct. The symptoms of CTE are often identical to the symptoms of dementia that are outlined in the DSM-IV-TR. Dementia is defined by the American Psychiatric Association as the development of multiple cognitive deficits that include memory impairment and at least one of the following: language formulation or comprehension difficulties, motor disturbances, inability to recognize familiar people or objects, or a disturbance in the use of language, addition, people suffering from dementia experience confusion and disorientation within their environment. This is often accompanied by a progressive decline in activities of daily living. This combined disturbance—paranoia; delusions; or delirium. Individuals with dementia often have little or no awareness of their memory deficits, or other cognitive/behavioral abnormalities.

Individuals with CTE may present with any number of combinations of these symptoms. Although characteristic neuropathological signs of CTE can be found in the brain, the same cannot be said for its clinical presentation. Formal clinical diagnostic criteria for CTE have not yet been established because it cannot be distinguished from other neurodegenerative diseases based on behavior; diagnosis relies on histological confirmation. At the moment, a diagnosis of CTE is only considered when a patient has a known history of repetitive traumatic brain injury. The goal of this literature review was to examine the link between CTE and symptoms of dementia, and to determine if establishing clinical diagnostic criteria was possible.

Methods

A literature review was conducted using the following criteria.

Mesh Terms
- Athlete/Contact Sports
- Dementia
- Concussion/Traumatic Brain Injury (TBI)
- Neuropathological

Databases
- PsycINFO, PubMed, Scopus

Selection Criteria
- Articles examine pre-mortem symptomatology of CTE
- Articles investigate CTE and dementia in contact sports
- The case population must have suffered repeated TBI

Exclusion Criteria
- Articles must control for other neurodegenerative diseases
- Articles must control for major traumatic brain injury

Total Articles Reviewed
125

Selected Articles
8

Results

<table>
<thead>
<tr>
<th>Loss of Emotional Control</th>
<th>Memory Deficits</th>
<th>Task Monitoring Deficits</th>
<th>Motor/Neuromotor Features</th>
<th>Confusion/Distraction</th>
<th>General Somatic Pain</th>
<th>Insomnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTE</td>
<td>52%</td>
<td>52%</td>
<td>47%</td>
<td>57%</td>
<td>42%</td>
<td>12%</td>
</tr>
<tr>
<td>Control</td>
<td>4%</td>
<td>6%</td>
<td>4%</td>
<td>1%</td>
<td>5%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Figure 1. Observed clinical symptoms of CTE cases across each study.

<table>
<thead>
<tr>
<th>Scattered Neurofibrillary Tangles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of Neuritic Plaques and Lewy Bodies</td>
</tr>
<tr>
<td>Absent/Casum/Frenestrated Septum Peltinum</td>
</tr>
<tr>
<td>Demyelination or Glosis</td>
</tr>
<tr>
<td>Edema</td>
</tr>
<tr>
<td>Lack of Pigment in the Substantia Nigra</td>
</tr>
<tr>
<td>Neuronal Loss</td>
</tr>
<tr>
<td>Atrophy</td>
</tr>
<tr>
<td>Cerebral/Cortical Searing</td>
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<tr>
<td>Thinning of the Corpus Callosum</td>
</tr>
<tr>
<td>Thinning of the Hypothalamic Floor</td>
</tr>
<tr>
<td>Atrophy</td>
</tr>
<tr>
<td>Atherosclerosis</td>
</tr>
<tr>
<td>Neuronal Injury</td>
</tr>
</tbody>
</table>

Figure 2. Observed post-mortem neuropathological changes in CTE cases across each study.

Discussion

Most Common Clinical Symptoms of CTE

- Memory Deficits
- Task Monitoring Difficulties
- Motor/Neuromotor Features
- Confusion/Distraction
- General Somatic Pain
- Insomnia

Most Common Neuropathological Features of CTE

- Absent/Casum/Frenestrated Septum Peltinum
- Demyelination or Glosis
- Edema
- Lack of Pigment in the Substantia Nigra
- Neuronal Loss

The symptoms of CTE observed in these studies coincide with symptoms of dementia and neurodegeneration. The only symptom unique to CTE is amnesia, which may be a result of the recent musculoskeletal injuries experienced by contact-sport athletes. The presence of neurofibrillary tangles in the absence of neuritic plaques and Lewy bodies appears to be unique to CTE.

There are a number of methodological issues and biases that need to be addressed:

- Studies by Corrells et al., et al. (2015), Mokler et al., et al. (2010), Omalu, et al. and Parker are case series designs. There is a bias of selection in these studies. A case series data was obtained from family members of the deceased; also, the length of time between death and interviews with family members was not specified. Hindsight or wish biases may be present.
- Mokler et al., et al. (2012), Sayed, et al. and Seichepine, et al. were case-control studies. While they did all include a comparison group, the groups were not well matched. Individuals in these studies, the majority of whom were ex- or semi-professional athletes, were matched with comparisons from the general population. This matching fails to recognize the importance of lifestyle factors in the progression of disease.
- Selected studies lack detailed history of the nature of traumatic brain injury in each case, as well as other lifestyle factors (i.e. alcohol or substance abuse) that might have influenced the disease progression in each individual. This has the potential to introduce confounders to these studies.
- There is potential for non-differential misclassification biases in all studies that utilize only pre-mortem clinical data, because it is impossible to confirm CTE without neuropathological findings.
- All studies have inherent selection biases, and the individuals selected for the studies were either self- referred or referred by a family member. Certain individuals may have been more inclined to participate than others, and the individual differences between these people may be significant.
- All the studies are exploratory by nature and helped establish a foundation for further research by demonstrating consistency among clinical and neuropathological features of CTE. The associations implied by these studies are highly speculative, but provide enough grounds for more rigorous investigation.
- Our methodology had limitations. It is possible that we introduced an access of bias, having only selected studies that were available from the research databases that we had access to.
- We did, however, manage to avoid a recency effect by selecting articles that ranged from 1934-present. We also managed to eliminate the confounding effect of major traumatic brain injury by only selecting studies that included a control group of major traumatic brain injuries.
- This combined effort had no influence on the final results of this study. Our methodology would be to eliminate a very specific target population; that is, semi-professional and professional athletes. There is likely more similarity in lifestyle choices among athletes than there is among individuals in the general population.

Conclusion

The information gathered indicates a feasible link exists between CTE and dementia symptoms in contact-sport athletes. However, this study was suggestive in nature. Ultimately, the total population examined was small, and most studies had significant issues in their methodology. More research must be completed in this area.

We did identify the major symptoms of CTE. However, the diagnostic criteria is not unique to CTE and therefore is not of little clinical use. In conjunction with a history of ending lifestyle factors were eliminated by selecting a very specific target population; that is, semi-professional and professional athletes. There is likely more similarity in lifestyle choices among athletes than there is among individuals in the general population.

We were able to identify the most frequently observed neuropathological symptoms associated with CTE, which has practical implications for future studies. This could ensure that researchers are able to identify definite cases of CTE in post-mortem studies.

References


This review was a collaborative effort with equal credit being given to all authors.