Increased Neuroinflammation in Chronic Traumatic Encephalopathy
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Background
Chronic traumatic encephalopathy (CTE) is a progressive neurodegenerative disease caused by repetitive mild traumatic brain injuries. Professional athletes in contact sports such as boxing and football and military veterans exposed to blasts are at risk for CTE. Pathologically CTE is a progressive tauopathy with accumulation of hyperphosphorylated tau in the form of neurofibrillary tangles, neurites, and tau-positive astrocytes. The clinical presentation of CTE is a combination of behavioral changes, cognitive impairments, and Parkinsonism. Although distinct from other neurodegenerative diseases, CTE has some similarities, including degeneration of the substantia nigra, and can co-exist with Parkinson’s disease, Lewy Body disease, and amyotrophic lateral sclerosis (ALS or motor neuron disease [MND]). In fact, CTE has been linked to ALS, and trauma may be a common cause in these cases of CTE with MND. Neuroinflammation has been indicated to play a role in the above neurodegenerative diseases, particularly ALS, and microglial cells are a major part of this pathological inflammation. Microglia are the macrophages of the brain, antigen presenting cells, and the first responders to infection and brain injury. Like macrophages, microglia change their morphology when activated. We here set out to look for microglia in the substantia nigra of CTE subjects with and without MND.

Objective
To determine whether the tau pathology and degeneration that occurs within the substantia nigra in CTE subjects is associated with increased microglia, a marker of neuroinflammation.

Methods
Subjects were chosen from two categories, those diagnosed with only CTE and those with CTE plus a motor neuron disease (MND). Of the subjects chosen, 5 were professional football players, 2 played college football, and one was a boxer. The controls had no known traumatic brain injury and were cognitively intact.

Table 1. Subject Demographic

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total</th>
<th>Age (Average)</th>
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</thead>
<tbody>
<tr>
<td>CTE</td>
<td>4</td>
<td>66 ± 15</td>
</tr>
<tr>
<td>(50-82)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTE + MND</td>
<td>4</td>
<td>50 ± 17</td>
</tr>
<tr>
<td>(33-67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>5</td>
<td>69 ± 10</td>
</tr>
<tr>
<td>(61-82)</td>
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</tbody>
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Stereology was used to count the number of activated and resting microglia based on cell morphology and Iba-1 staining. Astrocyte density (GFAP staining) was also determined using stereology.

Stereology
Optical Fractionator Program (Stereo Investigator, mbf Bioscience) was used to count microglia. 10 µm thick Iba-1 stained sections of the substantia nigra were used. The counting frames 100 µm X 100 µm (10,000 µm²) with an average of 200 sections analyzed.

Morphological Criteria

Resting Microglia – Iba-1 positive ramified cells without round nuclei.

Activated Microglia – Iba-1 positive cells with round nuclei and thick, extensive processes, bushy, or ameboid in shape.

Results
The increases in total microglia density (p=0.0203), resting microglia density (p=0.0378), and activated microglia density (p=0.0378, 1 tail) in CTE + MND compared to controls was statistically significant. Also, there was no correlation between total microglia density and astrocyte density in the substantia nigra.

Conclusions
Microglia are increased within the substantia nigra of CTE cases, and significantly increased in CTE with MND cases, suggesting increased levels of neuroinflammation compared to controls. This indicates neuroinflammation may play a role in the pathology of CTE. Ongoing studies involve looking at microglia and astrocyte densities in other areas of the brain commonly affected in CTE and CTE with motor neuron disease.

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References