eISSN 1303-1775 • pISSN 1303-1783

Neuroanatomy (2010) 9: 5–7

Review Article

The neuroanatomical relationship of Dementia Pugilistica and Alzheimer's Disease

Published online 17 October, 2010 © http://www.neuroanatomy.org

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Received 17 June 2009; accepted 11 October 2010

ABSTRACT

Dementia Pugilistica is a neurodegenerative disorder commonly attributed to the sport of boxing. More commonly referred to as 'punch drunk syndrome', it is most often caused by repetitive trauma to the brain. Symptoms of Dementia Pugilistica include a wide-range of motor disturbances and cognitive difficulties. The most prevalent and identifiable pathological characteristic of Dementia Pugilistica is amyloid plaque deposition and subsequent neurofibrillary tangle formation, which are indistinguishable to those seen in Alzheimer's disease. Although Dementia Pugilistica and Alzheimer's disease do not share similar etiologies, there is considerable overlap in the developmental processes and progression and potentially treatment. © **Neuroanatomy. 2010; 9: 5–7.**

Key words [Dementia Pugilistica] [Alzheimer's disease] [amyloid plaque] [neurofibrillary tangles] [punch drunk syndrome]

Dementia Pugilistica

Dementia Pugilistica, more commonly known as 'Punch Drunk Syndrome', is a degenerative brain disorder resulting from head trauma. Dementia Pugilistica (DP) is typically associated with the sport of boxing; although symptoms of DP may appear immediately after a single traumatic brain injury, they are typically described following the cessation of exposure to chronic brain injury. Although DP has been described primarily in boxers, it may be caused in any manner in which the head is exposed to repetitive trauma [1]. Cases of DP in boxers show a positive correlation between the number of matches and the severity of symptoms; more bouts leads to more trauma, and results in more severe symptoms [2-4]. DP may be categorized as a late-onset disease with many boxers not exhibiting symptoms until years after retirement [2,5,6].

Symptoms of DP may include; gait ataxia, slurred speech, impaired hearing, tremors, disequilibrium, neurobehavioral disturbances, and progressive cognitive decline [2,5]. Further, most cases of DP present with early onset cognitive deficits [2]. Behavioral signs exhibited by patients include; premorbid personality traits, aggression, hypertension, suspiciousness, paranoia, childishness, hypersexuality, depression, and restlessness [1,2,5-8]. The progression of DP leads to more prominent behavioral symptoms such as; difficulty with impulse control, irritability, inappropriateness, and explosive outbursts of aggression [2,5,6]. Studies also indicate that patients with DP display difficulties with: memory, information processing, attention, concentration, sequencing abilities, judgment, reasoning, future planning, organization, and slowed finger tapping speed [2,5-7]. Boxers with DP can also exhibit symptoms resembling other degenerative disorders, including: Parkinsonism, Dementia, Alzheimer's disease, Wernicke-Korsakoff syndrome, and Kluver-Bucy syndrome [2,5-7].

Neuroimaging and post-mortem examination are used to provide anatomical and physiological evidence for potential causes of the clinical signs exhibited by patients diagnosed with DP. Neuropathological examination of the brain's of DP patients have revealed neurofibrillary tangles, neuritic plaques, cerebral infarcts, fenestrated septum pellucidae, atrophic and gliotic mammillary bodies, pale substantia nigrae and locus ceruleae, thalamic gliosis, loss of Purkinje cells in the cerebellum, cerebral and cerebellar atrophy and lesions, and fornix degeneration and degradation [2,5-7,9,10]. Damage to the superior cerebellar peduncle and red nucleus is believed to contribute to slurring dysarthria and tremors [2]. Substantia nigral degeneration and neuronal loss in the lentiform nucleus is believed to contribute to Parkinsonian symptoms associated with DP [2]. Cortical atrophy, specifically in the temporal lobe, is likely responsible for patients exhibiting hypersexual behavior such as exhibited in Kluver-Bucy syndrome [2]. Damage to the septum pellucidum may be the cause for feelings of depression in boxers with DP. Damage to the mamillary

bodies and the fornices suggest a cause for inappropriate emotions and abrupt mood changes, and is consistent with the symptoms of Wernicke-Korsakoff syndrome [5]. Enlargement of the subarachnoid space and ventricular enlargement may be a result of a combination of cerebral atrophy and the movement of cerebrospinal fluid during repeated trauma.

Neurofibrillary tangle (NFT) development in the cerebral cortex is the most prevalent pathological abnormality in patients with DP. NFTs involve damage to the protein structure of the neuron, which makes normal enzymatic activity and communication difficult, ultimately leading to cell degeneration and death [5]. NFTs may occur as a normal part of aging, but are located mainly in the hippocampus and temporal lobe and are uncommon in the neocortex of otherwise healthy individuals [9]. NFTs are present in the earliest stages of DP and are thought to be caused by repetitive brain trauma [9]. As DP progresses the number of NFTs increase, along with cognitive decline and memory loss. Alzheimer's disease is also a degenerative brain disorder involving NFT formation and progression of symptoms similar to that of DP. Findings in patients with DP reveal NFTs in all layers of the cerebral cortex with high densities concentrated in more superficial layers of the neocortex, specifically layers II and III [10]. NFTs associated with DP are found in a perivascular distribution, a feature not present in early Alzheimer's disease [3,9]. Perivascular distribution of NFTs in DP may be a result of the shearing force between blood vessels and surrounding tissue occurring during acceleration and shifting of the brain as a result of head trauma.

In DP, NFTs are found early-on at the base of the brain, in the brainstem, parietal lobe, frontal lobe, and temporal lobe, but are rare in the occipital lobe [4,9-11]. Later stages of DP reveal high densities of NFT formation occurring in the cingulate gyrus, Ammon's horn, amygdala, subiculum, and entorhinal cortex [5,9-11]. Late onset of NFT formation in the regions of the brain used primarily for memory consolidation may provide a mechanism for the progressive cognitive and memory decline associated with DP. Alzheimer's disease is characterized by NFT formation appearing early-on in the cingulate gyrus, entorhinal cortex, and hippocampal formation, and later progression leads to other areas of the neocortex, mainly the frontal lobe [9-11]. Boxers with DP typically display high densities of NFT distribution predominantly in the baso-lateral region of the brain, mainly in the inferior temporal neocortex, which is where the brain suffers the most during impact [3]. Impact testing shows areas of the brain most effected during trauma are consistent with early NFT formation in DP [9].

In later stages of DP amyloid plaques appear, whereas they are not present early-on [9-12]. Amyloid plaques are depositions of amyloid beta-protein that may result in tissue damage and lead to neuronal cell death [9-12]. NFT formation occurring in the absence of amyloid plaques suggests chronic traumatic brain injury as the cause of their formation in DP [9-12]. In Alzheimer's disease, NFT formation is thought to be induced by amyloid plaque deposition, whereas in DP, NFT formation precedes amyloid plaque deposition [4, 9-12]. However, NFTs observed in the brain's of patients with Alzheimer's disease and DP are morphologically and immunohistochemically indistinguishable [4,9-11]. Although the process by which NFT formation begins in Alzheimer's disease and DP is different, the NFT's among the two diseases are indistinguishable, and amyloid deposition in the later stages of DP may be the main cause for the progression of NFT formation, which would indicate that the later stages of DP are pathologically similar to Alzheimer's disease.

Cases exhibiting later stages of DP reveal cerebrovascular amyloid deposits with amyloid presence both in and around cortical blood vessels [4]. Common results of chronic traumatic head injury are multiple small brain hemorrhages and damage to the blood brain barrier [4, 13-16]. As mentioned previously, high densities of NFTs exist in a perivascular distribution in patients with DP. Following cessation of chronic traumatic head injury, DP symptoms continue to progress with continued NFT formation. It is possible that even though NFT formation is caused by repetitive head trauma early on, that later stages of DP could exhibit NFT formation similar to Alzheimer's disease. Amyloid deposition in cerebral blood vessels in DP may penetrate through the damaged blood brain barrier and initiate further NFT formation [4,6]. This suggests a possible mechanism for the presence of amyloid beta-protein associated with NFTs in later stages of DP. Amyloid deposition in cerebral vasculature and perivascular NFTs also account for significant reductions in cerebral blood flow in DP patients [2,7]. With the presence of amyloid deposition in the later stages of DP and given that NFT formation is occurring even though patients are no longer experiencing head trauma, the possibility of amyloid induced NFT formation suggests that the later stages of DP are pathologically similar to Alzheimer's disease.

Conclusion

An important aspect of the debilitating symptoms of DP is its progressive nature, which continues even after trauma ceases. It is suggested that NFT formation in DP is initiated by trauma, but even after the cessation of repetitive head trauma the disease continues to progress [9]. NFT formation in DP occurs in the same regions of the brain as Alzheimer's disease, but NFTs also appear in some regions of the brain that are more unique to DP [4,9-11]. NFTs appearing in DP and Alzheimer's disease are indistinguishable; the mechanism of NFT formation in the later stages of DP (after the cessation of head trauma) and Alzheimer's disease may also be similar; with amyloid deposition causing the initiation of NFT formation in both diseases. This suggests that the continued NFT formation experienced in the later stages of DP may be caused by amyloid deposition, suggesting that although DP and Alzheimer's disease do not share similar etiologies, there is considerable overlap in the developmental processes and progression and potentially treatment.

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