

YES, THERE IS A CAUSAL LINK BETWEEN DEMENTIA AND INFLAMMATION

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The long list of dementing illnesses caused by infectious agents such as spirochetes, prions, bacteria, viruses, fungi etc. represent a group where the inflammatory etiology is obvious and non-controversial

The question to be addressed is: Does a neurodegenerative disease such as the so-called Alzheimer Disease (AD) develop, during the cascade of events leading to dementia, an inflammation as a part of its disease process?

The Alzheimer Syndrome encompasses the sporadic AD of advanced age, the hereditary forms such as familial clustering, autosomal dominant and others, the Down Syndrome as well as mixed forms with vascular component or with Levy bodies, The clinical manifestations such as the age of onset and the speed of progression do vary considerably both between, as well as, within the groups. The common features are, clinically, the progressive nature of dementia and the pathognomonic plaques and tangles.

The symptoms of in AD are the result of synaptopathy, which begins with sporadic dysfunction, progresses to continuously increasing synaptic impairment and ends with a global failure. What is the causative factor of the synaptic damage? There is the deposition of Amyloid, which is the early harbinger of the incipient dementia, which increases as the disease progresses. The Tauopathy is linked to the neurofibrillary degeneration, but are they the cause of synaptopathy and ensuing dementia?

The research of the last two decades was a quantum jump in our insight of the goings on in the brain with AD, yet the answer to the main question: what is causing the dementia, remains still elusive. This question has been with us for over 100 years and it is interesting to look back at the hypotheses proposed by the pioneers of AD research in the first two decades of the 20th century. Simchowicz made one statement, which impressed me many years ago; it was not a publication, but a comment in the proceedings of a meeting. He was discussing the formation the plaques and stated, "The plaques represent the central nervous system equivalent to a granuloma". This statement indicates that he was regarding the inflammatory process as part of the sequence of events occurring in the brain affected by AD. Let us look at the glial response to determine if his heretical statement was correct by implying that the inflammation may be a causal link in the chain of events in a so called neurodegenerative disease.

The histopathology offers an important insight into the events, which occur as the pathological process progresses. The microglia, the mesenchymal component of the brain structure has to be especially appreciated for its diverse behavior, as it performs essential function during the pathological cascade. The unfortunate, oversimplified description microglia is that the cell at rest is the slender rod cell and after it phagocytized maximum amount of detritus it becomes the large, round granular cell. The living, functioning microglia in a tissue culture offers a totally different picture than the cell after fixation in a histological preparation. The time lapse reveals the active pulsating extension of the cells cytoplasm reaching far between the tightly packed neurons and astrocytes.

Microglial response to the plaques has been well documented. The cells congregate around the plaque like spokes of a wheel. These radiating cells show minimal, but distinct evidence of phagocytosis. The astrocytes surround the microglial spokes with some of their processes aiming at the center, while most process are engulfing the structure as if demarcating it from the surrounding tissue. Therefore we have a core (the offending substance), surrounded by phagocytes and demarcated not by fibroblasts, but astrocytes. Simchowicz was right, it is a granulomatous structure.

This is only part of the microglial activity in an AD brain. Some cells align themselves along the axon or surround the nerve cell body. While the astrocytes continue to engulf the cell body and the oligodendrocytes surround the axons, the microglia remains omnipresent.

These findings help us to appreciate the dynamics of the process, and affirm the role of inflammation, but the question, what is the prime trigger, which opens the floodgates, is still elusive.

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