IS INFLUENZA AN INFLAMMATORY DISEASE? NO -- SO IS POST--STROKE DEMENTIA!

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A full understanding of the aetiology and pathogenesis of dementia is still lacking. Alternative pathophysiological mechanisms have been explored. One of these is the question whether inflammation may play a causative or more of a bystander role in the development of dementia. Since the year 2000, a total of 32 published studies investigated inflammation and dementia in the same study of which 16 were published in the past 5 years. Interestingly, only 5 articles investigated specifically the role of inflammation in post-stroke dementia. Taken together, these publication data show overall lack of research efforts and lack of evidence in this particular field. This is despite the well-known fact that dementia affects approximately 30% of stroke survivors. The incidence is high immediately after stroke, but the risk remains elevated during long-term follow-up. The most recent literature concerning vascular dementia has focused mainly on the concept of mixed dementia, the most commonly used term to define the clinical and pathological combination of Alzheimer's disease and vascular dementia. There is strong evidence that, particularly in older patients, vascular dementia and Alzheimer's disease may coexist as a mixed form of cognitive impairment or the occurrence of stroke may unmask or potentiate the clinical phenomenology of Alzheimer's disease. Cerebral infarctions have been shown to independently contribute, beyond their additive effect, to the likelihood of dementia without interacting with Alzheimer's disease pathology. These observations suggest that what we call vascular or post-stroke dementia may represent a much more mixed group with etiological, pathophysiological and clinical heterogeneity as well as with shared pathological pathways.

Inflammation is a frequently reported peripheral or even brain marker of dementia. While most studies are cross-sectional in nature, which limits the ability to draw inferences on cause and effects between inflammation and cognitive decline, some reports also show a prospective association between specific markers of vascular inflammation (VCAM, CRP) and the development of dementia. This is not surprising since inflammation is an integral part of vascular damage, atherosclerosis and stroke. Several arguments support the view that inflammation is not a causative factor in the presentation of post-stroke dementia, but merely a symptom of the disease.

[1] AD pathology (soluble Aβ/amyloid plaques) is one of the main triggers of neuroinflammation. It has been repeatedly observed, that increased levels of pro inflammatory factors, such as cytokines and chemokines, and the activation of the complement cascade are known to occur in the brains of AD patients and to contribute to the local inflammatory response once triggered by senile plaque.

[2] Neuroinflammation is a required response after infections and tissue injury in the attempt to repair and restore damaged tissue. Since inflammation is a two-sided phenomenon, it may also enhance neurodegeneration in conditions such as the commonly observed unresolved inflammation running over extended periods of time, even in small intensity. However, the assumption that inflammation may cause post-stroke dementia would imply a predominance of neurodegeneration over neurorepair, which is not necessarily the case.

[3] Assuming inflammation being a major causative contributor to post-stroke dementia, steroidal and non-steroidal anti-inflammatory treatments and interventions would need to show relevant clinical evidence. However, even though knockout animal models of inflammatory proteins and anti-inflammatory treatment alleviate AD-like pathology in laboratory experiments, clinical trials were less successful, even contradictory, some reporting potentially hazardous adverse effects. Using targeted approaches such as Etanercept, an anti-TNF-α agent, in CSF administration, improvements of symptoms such as aphasia and verbal fluency in AD patients were observed. Since these improvements were symptomatic and lasted for the duration of treatment only, the clinical results indicate that inflammation itself is a symptom and by-product of the underlying disease. An oral inhibitor of receptor for advanced glycation end products (RAGE), PF-04494700 showed no consistent effect on plasma levels of Aβ, inflammatory biomarkers, or secondary cognitive outcomes.

Instead, a number of vascular factors play a crucial role in the pathogenesis of dementia more broadly, not only in vascular or post-stroke dementia, but also in Alzheimer's disease (AD). Animal and human studies indicate that risk factors for vascular cognitive impairment (VCI) and AD, such as hypertension, aging, dyslipidemia, and diabetes, have profound effects on cerebrovascular regulation, and disrupt endothelium-dependent vasodilatation, functional hyperemia, and autoregulation negatively impacting on function of neuroons, glia, perivascular and vascular cells (neurovascular unit). Additionally, other mechanisms including vascular oxidative stress, ageing and inflammation disrupt neurotrophic function. Similarly, alterations of the blood-brain barrier and extravasation of plasma protein trigger vascular inflammation, oxidative stress, perivascular deem and axonal demyelination. Finally, ischemia itself promotes Aβ accumulation by enhancing production and reducing clearance which indicates a mixture of pathological signs and features across both AD and vascular / post-stroke dementia.

A reliable proof of inflammation as cause for dementia is still missing. In fact, inflammation is only one facet of the neuropathological profile of dementia, along with plaque and tangle formation, vascular pathologies, neurochemical deficits, cellular injury, oxidative stress, mitochondrial changes, changes in genomic activity, synaptic dysfunction, disturbed protein metabolism, and disrupted metabolic homeostasis. Taken together that vascular and post-stroke dementia are an etiologically, pathophysiologically and clinically heterogenous and mixed condition of dementia, the above argument applies to most dementias including post-stroke dementia.

No infectious disease physician would claim that Influenza is caused by inflammation and would not consider anti-inflammatories as a causative rather than a symptomatic treatment instead of using antibiotics. In post-stroke dementia, inflammation is a symptom of the disease and anti-inflammatory treatments would merely be symptomatic rather than causative. Not fully understanding the cause of post-stroke dementia - other than the stroke as a major contributor to cell death itself - should not mislead us to fall into the trap of mixing up symptoms and cause of the illness. *Post-stroke dementia is not an inflammatory disease.*