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Review article

Neuroinflammation in Lewy body dementia

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ABSTRACT

Neuroinflammation is increasingly recognized as a key factor in the pathogenesis of neurodegenerative conditions. However, it remains unclear whether it has a protective or damaging role. Studies of Alzheimer's disease and Parkinson's disease have provided much of the evidence for inflammatory pathology in neurodegeneration. Here we review the evidence for inflammation in dementia with Lewy bodies and Parkinson's disease dementia.

Neuroinflammation has been confirmed *in vivo* using PET imaging, with microglial activation seen in Parkinson's disease dementia and recently in dementia with Lewy bodies. In Parkinson's disease and Parkinson's disease dementia, microglial activation suggests a chronic inflammatory process, although there is also evidence of its association with cognitive ability and neuronal function.

Alpha-synuclein in various conformations has also been linked to activation of microglia, with a broad range of components of the innate and adaptive immune systems associated with this interaction.

Evidence of neuroinflammation in Lewy body dementia is further supported by pathological and biomarker studies. Genetic and epidemiological studies support a role for inflammation in Parkinson's disease, but have yet to provide the same for Lewy body dementia.

This review highlights the need to identify whether the nature and extent of microglial activation in Lewy body dementia can be linked to structural change, progression of domain specific cognitive symptoms and peripheral inflammation as a marker of central microglial pathology. Answers to these questions will enable the evaluation of immunotherapies as potential therapeutic options for prevention or treatment of dementia with Lewy bodies and Parkinson's disease dementia.

1. Introduction

Lewy body dementias (LBDs) include the closely related conditions of dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD). The clinical syndrome of DLB forms at least 4.2% of all dementia patients and is second only to Alzheimer's disease (AD) as a cause of degenerative dementia in older people [1]. Dementia also develops in over 80% of those with Parkinson's disease (PD) [2], a disorder where Lewy bodies play a prominent role, with PDD forming 3.6% of all dementia cases [3]. Autopsy studies of dementia cases have estimated the combined prevalence rate of LBDs to be even higher, at around 20% [4,5].

The etiology of LBDs is unclear, but a role for chronic neuroinflammation has been proposed, analogous to the emerging evidence for inflammation in the etiology of AD. The evidence to date for AD includes neuropathological studies with evidence of brain inflammation, Positron Emission Tomography (PET) imaging displaying microglial activation *in vivo*, genetic studies implicating polymorphisms in genes involved in the inflammatory response as risk factors, epidemiological studies indicating a protective effect of non-steroidal anti-inflammatory drugs (NSAIDs) and mouse models of AD in which NSAIDs reduced neuroinflammation and protein deposition [6–9].

In light of the gathering evidence for neuroinflammation in AD, we asked whether neuroinflammation is also involved in the etiology of LBDs. We review the literature for evidence of neuroinflammation in Parkinson's disease dementia and dementia with Lewy bodies, across multiple methodologies.

2. Literature search strategy

References were identified using searches of PubMed with key

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words. The following combinations were used in a search of titles and abstracts in June 2015 (the number of articles yielded is noted in brackets):

1. 'Lewy' and ('inflammation' OR 'neuroinflammation') (98 articles)
2. ('Parkinson's disease dementia' OR 'PDD' OR 'DLB' OR ('Dementia AND Parkinson*')) AND ('neuroinflammation' OR 'inflammation') (283 articles)
3. 'synuclein' AND 'microglia' (185 articles)
4. 'synuclein' AND ('inflammation' OR 'neuroinflammation') (210 articles)

The abstracts of these articles were screened and full texts of those potentially relevant articles to the review were obtained. In order to ensure that all relevant references were sourced, references were in turn reviewed for other relevant articles, supplemented by articles known to the authors.

3. Microglial function

Neuroinflammation describes the response to injury within the central nervous system (CNS) leading to the activation of microglia and astrocytes, release of cytokines and chemokines, invasion of circulating immune cells and complement activation. Microglia are the resident macrophages of the CNS, originating from progenitors in the embryonic yolk sac [10]. They provide the innate immune response to invading pathogens and also initiate the adaptive response through antigen presentation [11].

Microglia are resting or "inactivated" under physiological conditions with characteristic ramified morphology and distributed within brain regions, such that rami are close but not touching, implying each cell has its own distinctive territory. But even in this inactive state, they have been shown using two-photon microscopy to be continuously monitoring the extracellular spaces with their processes and protrusions in adult mice [12]. Activation leads to morphological change to a more rounded amoeboid shape, with targeted movement of processes towards sites of injury or stimuli to initiate phagocytosis [12] and leads to production of chemokines, that amplify the response by recruiting other microglia, plus cytokines, free radicals and proteases which destroy infectious organisms and infected neurons.

Microglia appear to have an important part both in MPTP disease progression and idiopathic PD [13], suggesting a central role for these glia in nigro-striatal degeneration, irrespective of etiology. Microglia may be especially susceptible to mechanisms of aging. Their maintenance is proposed to be dependent on self-renewal rather than replenishment by peripheral blood precursors [14,15], which could be highly significant in age dependent neurodegenerative conditions such as LBD. Systemic infections or disease, which rise in number with age, could also lead to priming of microglia, such that their response is exaggerated and damaging to nearby neurons leading to cognitive decline [16]. It has also been proposed that an initial stimulus that triggers microglial activation could persist in neurodegenerative disorders leading to repeated cyclical chronic neuroinflammation causing neuronal dysfunction and cell death [17,18]. The specificity of these changes to Lewy body dementias is unclear.

4. Imaging evidence of neuroinflammation and neuronal dysfunction

Imaging studies have shown an association between neuroinflammation *in vivo* and cognitive dysfunction. Microglial activation as a marker of neuroinflammation has been identified in PD and PDD [19] (see Table 1) using [^{11}C]-*R*PK11195 (RPK11195), a PET ligand that binds to a translocator protein found on microglia in their activated state. Extensive microglial activation has similarly been identified in another α-synucleinopathy: multiple systems atrophy [20], as well as other degenerative conditions, including AD [21,22].

An association between microglial activation in the midbrain and dopaminergic loss in the dorsal putamen has been found in the early stages of PD (less than 2.5 years), both contralateral to the clinically affected side, with levels of activation correlating with severity of motor impairment measured by the Unified Parkinson's Disease Rating Scale (UPDRS) [23]. In the later stages of disease (disease duration range 0.5–21 years), there is extensive microglial activation, with the basal ganglia, cortex and pons all showing significantly increased levels. The substantia nigra was however spared. Follow-up scans in eight of these subjects (after 18–28 months) showed no significant change in microglial activation from baseline despite a clear deterioration in disability as measured using the UPDRS. Cognition was however not assessed longitudinally [24]. The authors also noted a clear overlap in the areas of microglial activation and the regions proposed by Braak et al. [25] in their study of PD pathology. In PDD subjects, there is increased cortical microglial activation compared to control subjects, however levels of activation were also increased in comparison to PD cases – in the left parietal lobe [26].

In DLB, increased microglial activation in the substantia nigra and putamen, plus several cortical regions was found in a pilot imaging study of six cases of less than one year's duration [27]. That microglial activation occurs in more widespread regions in early DLB, where there is greater cognitive dysfunction compared to early PD, strengthens the link between microglial activation and cognitive decline.

A relationship between microglial activation and cognitive function was indeed found in PDD, where cortical activation levels inversely correlated with MMSE in temporo-parietal, occipital, and frontal cortical regions [19,26]. Fan et al. [19] demonstrated a significant negative correlation between whole brain levels of microglial activation and glucose metabolism. Within the temporo-parietal cortex there was voxel by voxel significant inverse correlation between levels of microglial activation and glucose metabolism in the immediate vicinity suggesting local damage, but the areas of correlation were small. The authors however suggest distant microglial activation could be linked to cell dysfunction in the medial temporal lobe through pre-existing neuronal pathways. Neither study of PDD assessed whether areas of increased activation (such as in the hippocampus) were linked to dysfunction in specific cognitive domains (such as memory), which may have provided a stronger link between inflammation and cognitive dysfunction.

Small clusters of positive correlations were also found between RPK11195 binding and amyloid load (as determined by [^{11}C] Pittsburgh compound B (PIB), a marker of fibrillary amyloid load) in PDD subjects, but only in the parietal lobe and anterior cingulate, as opposed to AD subjects in whom there was a stronger correlation between amyloid load and microglial activation. There was however little amyloid deposition found in PDD cases overall [19]. Proteins other than amyloid, such as α-synuclein or tau, could be triggering microglial activation in PDD, however currently there are no α-synuclein PET ligands available to demonstrate this and tau ligands have only very recently become available.

Overall small scale studies with *in vivo* imaging have suggested that in PD, PDD and in a small preliminary report of DLB, there is early microglial activation. But, this does not appear to increase over time. Significantly microglial activation also correlates inversely with cognitive function and to an extent protein

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