# Evidence for neuroinflammation in Alzheimer's disease

**Anna Walters** *MBChB, MRCPsych,* **Emma Phillips** *MBChB, BSc Neuroscience, MRCPsych,* **Rui Zheng,** *MSc, MRCPsych,* **Maya Biju** *MBBS, MRCPsych* **Tarun Kuruvilla** *MRCPsych*

**New understanding in neuroscience has established that alongside the amyloid plaques, neurofibrillary tangles and atrophy, the neuroinflammation triggered by the CNS's innate immune response plays a central role in the pathogenesis of Alzheimer's disease (AD). In this review, the authors look at the roles that the cells of the immune response play in the pathogenesis of AD, the influence of genetics, the developing role for neuroimaging to detect inflammation and progress towards potential therapeutic strategies.**

Alzheimer's disease is the most common cause of dementia worldwide. It is currently estimated to affect 500 000 people in the UK and accounts for about two thirds of all causes of dementia.[1] It is characterised by progressive global cognitive impairment causing amnesia, apraxia, agnosia and aphasia.

There has been much research carried out into the pathogenesis of AD and great progress in its understanding has been made over the last quarter of a century. Cognitive decline is thought to be caused by accumulation of extracellular amyloid plaques and intraclular neurofibrillary tangles in the cortex, which affect neuronal function and eventually lead to neuronal death.

The current model is the 'amyloid cascade hypothesis',[2] in which amyloid plaques develop when amyloid precursor protein (APP) is abnormally cleaved by beta secretase and gamma secretase leading to formation of amyloid beta (Aβ). Aβ is not cleared from the CNS in the presence of AD and aggregates, forming plaques. These accumulate around neurones causing abnormalities in synaptic functioning, disruption in mitochondrial functioning and decreased levels of neurotransmitters such as acetylcholine.

Neurofibrillary tangles (NFTs) are intracellular inclusions of hyperphosphorylated tau protein and are also a pathological hallmark of AD. It is thought that NFTs may form in response to the increased stress on the CNS from the neurodegenerative process and accumulation of amyloid and plaque formation. This pathway is not, however, clear as it also has been shown that the formation of NFTs may precede plaque formation and they are not always distributed in the same regions. NFTs contribute to neuronal death and, unlike the plaques, the number of NFTs present correlates positively with the level of cognitive impairment.[2]

It has now been established that alongside the amyloid plaques, NFTs and atrophy, the neuroinflammation triggered by the CNS's innate immune response plays a central role in the pathogenesis of AD, along with other dementias and neurodegenerative disorders.

## The central nervous system's innate immune response

Microglia and astrocytes are two major cell components of the CNS's innate immune system and have a central role in the neuroinflammation process in AD. In health, microglia have a phagocytic role, clearing damaged neurones and any invading pathogens whilst promoting tissue repair.[3] They migrate to the site of injury where they initiate the innate immune response.[4] Astrocytes are also specialised glial cells, their role is in removal of debris and toxins from the cerebrospinal fluid (CSF) and release of neuroprotective factors. In AD there is a proliferation of both microglia and astrocytes in an activated form and post-mortem studies have found activated microglia and astrocytes clustered around the vicinity of amyloid plaques and NFTs.[5] When these cells are in activated form they release proinflammatory cytokines, chemokines and interleukins and cause a state of neuroinflammation and damage to the tissues.

## The blood–brain barrier

The blood–brain barrier (BBB) regulates transport of cells and molecules between the tissue of the brain and the blood. It was thought that this allowed the brain to be an 'immune privileged' organ, protected from any systemic inflammatory response. We now know, however, that this is not the case. Inflammatory processes occur in the CNS in response to peripheral injury, as can be seen when a systemic infection
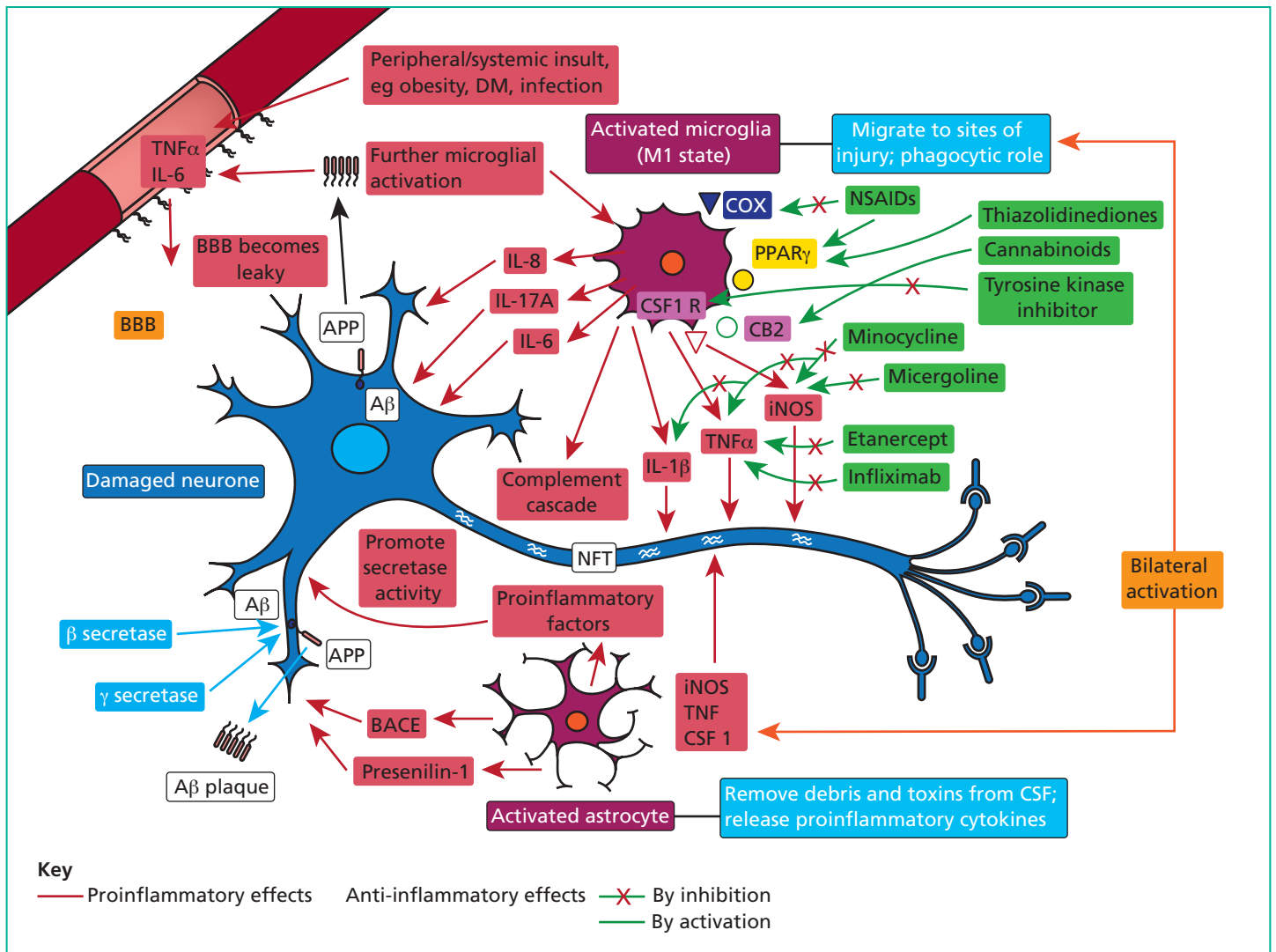
**Figure 1.** Diagram of the pro and anti inflammatory factors affecting neurones in Alzheimer's disease and the site of action of anti-inflammatory drugs

causes a clinical deterioration in a dementia.[6,7] This may in part be due to a disruption to the BBB caused by the AD process.[8] Whereas in health the BBB transports Aβ to the blood stream efficiently and prevents Aβ from the serum entering the CNS, in AD this mechanism is disrupted. Aβ42 modifies the tight junctions between the endothelial cells of the BBB, making them leaky and more easily allowing Aβ to accumulate. This leads to further toxicity to the BBB. Further loosening of the tight junctions is caused by proinflammatory cytokines, for example tumour necrosis factor alpha (TNFα), interleukin 1 beta (IL-1β), IL-17A, which are released in excess by microglia in AD.[9] This allows cells from the periphery, eg T cells and macrophages, to more easily enter the CNS. These cells also alter the microglia and astrocytes and potentiate the inflammation, causing further release of inflammatory cytokines and chemokines.

## The role of microglia

In AD, along with other dementias such as Parkinson's, frontotemporal dementia and Lewy body dementia, there is a proliferation of microglia.[10] Microglia are now thought to exist in a number of different phenotypes, in the same way as peripheral macrophages.[4] The proinflammatory M1 state occurs when microglia are activated, for example, after an acute insult, and leads to them releasing proinflammatory cytokines: TNFα, IL-1, IL-6, IL-18. This activation may occur in response to the amyloid plaques. A second state, the M2 state, is noninflammatory and is associated with secretion of anti-inflammatory cytokines: IL-4; IL-10; IL-13 and TNF-β.[11] It is now thought that in AD, a state of chronic inflammation, the microglia are 'primed'. In this state they show enhanced sensitivity to inflammatory stimuli and are more easily tipped into an M1, proinflammatory state. Microglia, and to a lesser extent astrocytes, are

also the main cells that contribute to the production of complement proteins in the brain. The complement cascade of proteolytic proteins has a major role to play in the clearance of pathogens and activated complement has been found in association with amyloid plaques.[12]

### The role of astrocytes

Astrocytes also proliferate and are activated in AD. This happens in response to excess Aβ and leads to upregulation of proinflammatory factors.[13] These proinflammatory factors in turn promote activity of secretases that enhance the production of Aβ from APP. Reactive astrocytes express beta amyloid cleaving enzyme, BACE, which has a role in the generation of Aβ, and presenilin-1, which forms gamma secretase that cleaves APP to form Aβ. As there are so many astrocytes in the CNS they may have a large role to play in the formation of Aβ,[10] but conversely astrocytes also form a protective barrier between neurones and Aβ and promote Aβ degradation.

### Genetic studies

Recent genome-wide association studies have given further weight to the role of the immune system in AD. Several genes have been identified as risk factors for late-onset, sporadic AD, among them TREM2, CD33, CR1 and CLU.[14,10] These genes have been linked with components of the immune response and neuroinflammation. TREM2 codes for the triggering receptor expressed on myeloid cells. Variants of this gene have been found in Alzheimer's disease and there are increased levels of TREM2 in the brains of aging mice. TREM2 knock-down mice show increases in proinflammatory cytokines, neuronal loss and cognitive impairment.[15] The CD33 gene is expressed in microglial cells and may limit the immune activation in response to 'self' molecules. Long-term CD33 inhibition has been linked to production of cytokines. Its expression is increased in AD and has been linked to reduced Aβ phagocytosis.[16] CLU and CR1 are genes that code for proteins that regulate the complement system.

### Neuroinflammation and the immune response: damaging or beneficial?

Although microglia potentiate the neuroinflammatory response it is likely that, in the early stages at least, they also have a beneficial role. In early plaque development microglia have a role in Aβ phagocytosis and clearance. They produce proteolytic enzymes that degrade Aβ.[9,4] The initial acute inflammatory response therefore aids clearance of Aβ and sustains tissue homeostasis. Astrocytes also seem to have a dual role in the pathology of AD. However, despite the fact that microglia are activated in AD, amyloid plaques continue to form. In a normal immune system reaction, the activation of the microglia, phagocytosis and production of cytokines would clear the pathogen or the damaged tissue and then healing could begin. In AD, Aβ continues to be produced, leading to ongoing inflammation. This may trigger a vicious cycle whereby further production of Aβ leads to ongoing activation and altered function of microglia.[17,18]

### Potential triggers for the activation of a proinflammatory state

It has long been recognised clinically that an episode of delirium or a severe systemic insult can trigger the onset of dementia. Changes to the BBB in AD allow cells that have proliferated in a state of chronic inflammation or immune response in the periphery to cross into the CNS. TNFα and IL-6 are produced peripherally and are in excess in the serum in AD. They then cross the BBB and activate the central innate immune response. 'Sickness behaviour', which is associated with raised TNFα, is thought to be explained by this mechanism.[6] It is characterised by the neuropsychiatric symptoms of apathy, anxiety and low mood, which are common in AD, even in the absence of a delirium.[7]

Systemic inflammatory events are also associated with raised levels of TNFα in the serum and have been found to be associated with a more rapid rate of cognitive decline over a six-month period.[6] This supports the link between the peripheral immune system and the CNS. Conditions that lead to prolonged proinflammatory states peripherally are also associated with increased risk for AD, for example type 2 diabetes and midlife obesity. Traumatic brain injury, which causes chronic activation of microglia is also a risk factor for AD.[4]

### The role of imaging in detecting neuroinflammation

Functional neuroimaging is currently an important tool in the diagnosis of AD. Currently, 2-deoxy-2[F-18]fluoro-D-glucose positron emission tomography (FDG-PET) scans looking at glucose metabolism are used to distinguish frontal lobe dementia from AD, and amyloid PET scans to help diagnose AD in the early stages are becoming more widely available. PET scans that are able to detect activated microglia not only help to show the patterns of microglia in different neurodegenerative diseases and provide evidence for their involvement, but may be developed into a useful diagnostic tool. The first tracer to

demonstrate activated microglia on a PET scan that became available in humans was 11C-PK11195. This is a specific ligand for the peripheral benzodiazepine receptor (PBR) binding site translocator protein (TSPO) which is expressed on activated microglia.[19] PET imaging using this ligand is able to show the distribution of activated microglia in experimental and human brain disease. Increased 11C-PK11195 binding has been found in AD compared with healthy controls, particularly in the entorhinal, temporoparietal and cingulate cortices, in the same distribution as amyloid plaques. Cortical 11C-PK11195 binding also correlated with cognition scores.[20,21] 11C-PK11195 binding can also be seen in other dementias. For example, in frontotemporal dementia binding is particularly seen in the frontal, medial temporal and subcortical regions.[22] In Parkinson's disease binding is seen in the substantia nigra and putamen. In Parkinson's disease dementia binding is also seen more in the association cortex compared with those without dementia. This supports the evidence that microglial activation is a common pathway in a number of dementias and neurodegenerative diseases, and not limited to the formation of amyloid plaques. Currently, second generation TSPO ligands with higher specificity for activated microglia are being developed and evaluated.

## Therapeutic strategies for targeting neuroinflammation

As the evidence and theory have developed behind the role of neuroinflammation as a cause for AD, so too have the targets for therapeutic intervention. This initially began when epidemiological studies found that those who used nonsteroidal anti-inflammatory drugs (NSAIDs) on a long-term basis for rheumatoid arthritis had half the risk of developing Alzheimer's disease compared with the general population.[23,24,25] Since then other agents have been studied including TNFα inhibitors and anti-TNFα antibodies, peroxisome proliferator-activated receptor gamma (PPARγ) agonists, cannabinoids, minocycline and nicergoline and tyrosine kinase inhibitors. Table 1 shows a summary of trial results so far.

The mechanism by which NSAIDs exert their effect is thought to be via cyclo-oxygenase 1 and 2 (COX-1 and COX-2) inhibition, and activation of PPARγ. In AD, PPARγ levels in the CNS are found to be raised and when activated in microglia it supresses the expression of proinflammatory factors. COX is a regulatory enzyme that produces a variety of proinflammatory mediators.[26] However, when this relationship was investigated further in randomised controlled trials there were mixed results across a range of different NSAIDs. Two trials looking at indomethacin *vs* placebo showed positive effects on cognitive ability after six months and a positive trend with no statistical significance after one year.[27,28] Celecoxib and naproxen versus placebo was reviewed by the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) Research Group in healthy individuals with a family history of AD and they found no benefits in terms of onset of AD or cognitive decline.[29] However, Breitner *et al* (2011)[30] then followed the ADAPT group of patients up for a further two years and found that asymptomatic individuals prescribed naproxen had a lower incidence of AD. But there was no beneficial effect of prescribing NSAIDs in those with clinically established symptoms of dementia.

In 2012, a Cochrane review of aspirin, NSAIDs and corticosteroids looked at 14 randomised controlled trials and found that there was no benefit in prescribing any of these medications in AD, and an increased number of side-effects. There was also a trend towards higher death rates in those treated with NSAIDs, somewhat higher for selective COX2 inhibitors.[31] These disappointing results may be because NSAIDs do not have a specific enough anti-inflammatory action and are actually inhibiting the beneficial phagocytic effects of microglia on Aβ.

TNFα is a proinflammatory cytokine released by microglia and has been implicated as having a central role in the neuroinflammation of AD.[32,33] Trials on TNFα inhibitors and anti-TNFα antibodies have been generally more positive than those looking at NSAIDs. Work done using mouse models showed that decreasing TNFα can decrease amyloid plaque load and tau phosphorylation.[10] TNFα inhibitors such as etanercept have been used in clinical trials in AD. Etanercept is a large molecule that does not cross the BBB. One small study looked at the effects on cognition of weekly perispinal injections of etanercept.[34] After six months with this treatment there was an improvement in all variables from baseline, including verbal learning, fluency and memory. However, this was a small study not compared with placebo. In 2014, a phase II trial compared the safety and tolerability of subcutaneous etanercept with placebo in AD. This study randomised 41 patients and was able to show that etanercept was well tolerated with few adverse events and a slower rate of cognitive decline.[35] The anti-TNFα antibody, infliximab, (currently used for Crohn's disease, ankylosing spondylitis and rheumatoid arthritis) has been shown to reduce the levels of TNFα, amyloid plaques and tau phosphorylation in mice models.[36] Thalidomide is also a TNFα inhibitor and was shown to attenuate neuroinflammation, Aβ deposition, tau phosphorylation and improve memory function.[37]

| Drug | Trial | Outcome measure | Outcome |
|---|---|---|---|
| Indomethacin *vs* placebo | Rogers, *et al* 1993[27] | Cognition | Positive (small scale trial) |
| Indomethacin *vs* placebo | De Jong, *et al* 2008[28] | Cognition | Positive trend but no statistical significance after 1 year |
| Celecoxib 200mg twice daily *vs* naproxen sodium 220mg twice daily *vs* placebo | Martin, *et al*: ADAPT 2008[29] | Cognition Onset of AD | No improvement in cognition with celecoxib or naproxen over placebo |
| Celecoxib 100mg twice daily *vs* naproxen 22mg twice daily *vs* placebo | Breitner, *et al*: ADAPT 2011[30] | Cognition Onset of AD CSF tau to Aβ42 ratio | Asymptomatic individuals prescribed naproxen experienced lower AD incidence No benefit of NSAIDs in later stages of AD |
| Aspirin, NSAIDs, corticosteroids | Jaturapatpom, *et al* Cochrane review 2012[31] | 14 randomised controlled trials | No benefit of prescribing in AD and increased side-effects |
| Perispinal etanercept, weekly (not placebo controlled) | Tobinik, *et al* 2007[34] | Activities of daily living Speech in primary progressive aphasia | Positive |
| Subcutaneous etanercept *vs* placebo (water) weekly Double blind randomised phase II trial | Holmes, *et al* 2014[35] | Safety and tolerability Cognition Activities of daily living Carers and clinical impression of change | Good safety and tolerability Lower rates of decline in etanercept group at 6 months |
| Infliximab (mouse models) | Shi, *et al* 2011[36] | TNFα levels, amyloid plaques and tau phosphorylation | Positive reduction in pathology |
| Rosiglitazone *vs* placebo *vs* donepezildouble blind randomised controlled trial | Gold, *et al* 2000[39] | Safety and tolerability Cognition | Negative for rosiglitazone *vs* placebo Good safety and tolerability |
| Minocycline (mouse models) | Parachikova, *et al* 2010[42] | Plaque formation and neuroimmune response | Positive |

**Table 1.** Trials of drugs with anti-inflammatory action in AD

A further target for therapeutic intervention is PPARγ. PPARγ agonists (thiazoladinediones or 'glitazones') are used in the treatment of diabetes, which is a risk factor for Alzheimer's disease. PPARγ is expressed on microglia and when activated has been shown to reduce neuroinflammation and neurotoxicity in animal models of AD.[38] This has been demonstrated in repeated trials with animal models, using ciglitazone and pioglitazone. These medications have been shown to improve cognitive function, suppress inflammation and reduce amyloid levels.[26] Results have been replicated to some extent in clinical trials. While several small trials have shown benefits in mild AD for pioglitazone and rosiglitazone, a large placebo controlled randomised trial showed no beneficial effect of rosiglitazone compared to placebo or donepezil. [39]

Several other medications are thought to have potential with regard to mediating the neuroinflammatory pathway in AD, among them cannabinoids. CB2 receptors are found on microglia in the CNS and inhibit their proinflammatory effects. There is evidence that in AD, CB2 receptors are overexpressed in microglia surrounding plaques. Activation of CB2 receptors has been shown to reduce the neuroinflammatory response to Aβ in mouse models of AD, potentially by activation of PPARγ. CB1 receptors diminish excitotoxicity in the postsynaptic neurones by enhancing vasodilation and inhibiting endothelin-1.[40] However, so far clinical trials have only looked at their potential benefits in agitation and challenging behaviour, not at effects on improving cognition.[41]

Minocycline and nicergoline have potential to reduce the neuroinflammatory response as they are thought to target TNFα, IL-1β and inducible nitric oxide species (iNOS), all proinflammatory factors released by microglia.[42] Colony stimulating factor 1 receptor (CSF1R) has a role in regulating microglia and their proliferation in neurodegenerative disorders. This has recently been shown to have potential as a therapeutic target. A tyrosine kinase inhibitor that inhibits CSF1R has been shown to improve memory and performance on behavioural tasks in mouse models, although did not reduce the number of amyloid plaques.[43] Many of these treatments need further evaluation in larger randomised placebo controlled studies, and so far results have either been in smaller trials or have been unconvincing. The results do however support the importance of the immune response and inflammation in the development of AD, and the work to develop successful therapies continues.

## Conclusions

Although we now have a much clearer idea of the role of the innate immune response and the potentially damaging neuroinflammation that can result, the causes and consequences are still not fully understood. Neuroinflammation in AD may both be in response to the amyloid plaques and NFTs or, in part, a cause of them. In AD there is a chronic proinflammatory state, which patients may be predisposed to by genetics, by risk factors such as obesity, lifestyle and diabetes, and which may be exacerbated by systemic infections and the subsequent peripheral immune response. This chronic inflammation leaves microglia in a primed state, where they are easily tipped into a releasing cytotoxic cytokines, which potentiate neuronal damage and death. This then leads to the cognitive decline and symptoms of AD.

Alongside this, microglia and astrocytes may also have a beneficial role. There is evidence that they help to clear amyloid plaques and can be neuroprotective, particularly in the early stages of the disease. It is thought that the pathology of AD is evident in the brain 20 to 30 years before clinical dementia develops and it may be that treatment needs to be targeted at this prodromal stage of the illness. So far treatments targeting aspects of the neuroinflammatory pathway have shown only limited success, and we await the outcomes of further phase III trials and the potential for a role of functional neuroimaging in earlier detection.

*Drs Walters, Phillips and Zheng are Higher Specialist Trainees in Old Age Psychiatry at 2gether NHS Foundation Trust; Dr Biju is a ST6 Advanced Trainee in Old Age Psychiatry at Oxford Health NHS Foundation Trust, and Dr Kuruvilla is a Consultant in Old Age Psychiatry at 2gether NHS Foundation Trust, Charlton Lane Centre, Cheltenham.*

## Declaration of interests

No conflicts of interest were declared.

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