REVIEW

CNS Neuroscience & Therapeutics

The Role of Inflammation in the Pathogenesis of Delirium and Dementia in Older Adults: A Review

Mark J. Simone[1,2] & Zaldy S. Tan[2,3]

1 Division of Gerontology, Mount Auburn Hospital, Cambridge, MA, USA
2 Harvard Medical School, Boston, MA, USA
3 GRECC, VA Boston Healthcare System, Division of Aging, Brigham and Women's Hospital, Boston, MA, USA

Keywords
Alzheimer's disease; Delirium; Dementia; Inflammation.

Correspondence
Mark J. Simone, M.D., Division of Gerontology, Mount Auburn Hospital, 300 Mount Auburn Street, Suite 517, Cambridge, MA 02138, USA.
Tel.: 617-868-0847;
Fax: 617-491-6048;
E-mail: msimone@mah.harvard.edu

doi: 10.1111/j.1755-5949.2010.00173.x

SUMMARY

Aims: To review recent evidence that suggests inflammation plays a similar role in the pathogenesis of delirium and dementia. **Methods:** We performed a literature search of original research and review articles in PubMed using the keywords: delirium, dementia, and inflammation. We summarized the evidence linking inflammation to the pathogenesis of delirium and dementia. **Discussion:** Delirium and dementia share similarities in clinical and pathogenic features, leading to the speculation that instead of being distinct clinical entities, the two age-related conditions may be linked by a common pathogenic mechanism. Inflammatory markers have been shown to be elevated in both delirium and dementia, thereby implicating inflammation as a possible mediating factor in their genesis. There is evidence in both basic science and clinical research literature that elevated cytokines play a crucial role in the development of cognitive dysfunction observed in both dementia and delirium. **Conclusion:** Mounting evidence supports the role of inflammation in the development of both dementia and delirium. Further studies are needed to elucidate the mechanisms underlying these relationships.

Introduction

The human immune system is a complex system of adaptive and innate responses that provides protection from external and internal threats. The cells of the immune system (e.g., neutrophils and macrophages) communicate via cytokines, which are hormone-like proteins produced by a variety of immune cells. Cytokines are important mediators of the immune response, which initiate, perpetuate, or downregulate the response. Cytokines include interleukins (IL), tumor necrosis factors (TNF), and transforming growth factors (TGF-β 1–3). Certain cytokines are considered proinflammatory (IL-1, IL-6, and TNF-α), and others are anti-inflammatory (IL-4, IL-10, and IL-13) (Table 1).

Inflammation and Cognition

Systemic inflammation is present in many conditions that are known to precipitate cognitive changes in older adults, including infections, cancer, and surgery. Delirium and dementia are examples of acute and chronic declines in cognition, respectively, likewise associated with acute and chronic inflammatory states. Aging alone can cause an increase in peripheral cytokines, including IL-6 [1,2] and TNF-α [3]. However, the preponderance of both basic science and epidemiological evidence that inflammation plays a role in the pathogenesis of the two age-related diseases delirium and dementia begs the questions whether they are simply comorbid conditions, or whether inflammation plays a more central role in linking the two conditions. A recent study examining the relationship of acute and chronic inflammation on cognitive decline in patients with Alzheimer's disease showed that acute systemic inflammatory events were associated with an increase in serum levels of TNF-α and a 2-fold increase in rate of cognitive decline over a 6-month period [4]. Subjects with higher baseline levels of TNF-α were more likely to have delirium and were associated with a 4-fold increased rate of cognitive decline over a 6-month period compared to those with low TNF-α levels.

Table 1 Inflammatory markers and studies that show their link to delirium and dementia

Marker	Pro/anti-inflammatory	Role in delirium and dementia
IL-1	Proinflammatory	Increases neuronal tau phosphorylation [45] and activates astrocytes [46]; polymorphism linked to increased risk of AD [47,49,50]; levels elevated in AD [66,72]
IL-6	Proinflammatory	Levels elevated in delirium [26–29,30]; polymorphism linked to increased risk of AD [47]; levels linked to gray matter volume and memory function [51]; levels elevated in non-AD dementia [73]
IL-8	Proinflammatory	Levels elevated in delirium [26,27]
IL-RA	Anti-inflammatory	Levels decreased in delirium [32]
TNF-α	Proinflammatory	Polymorphism linked to increased risk of AD [47–48]; levels elevated in AD [67,70,72]; elevated levels linked to cognitive decline [4]
IGF-1	Anti-inflammatory	Levels decreased in delirium [32,35,36]
IFN-γ	Proinflammatory	Levels decreased in delirium [32,35,36]
CRP	Proinflammatory	Higher levels linked to poor cognitive performance/increased risk of cognitive decline [68]

Cognitive Disorders: Dementia and Delirium

Delirium is a condition characterized by an *acute* change in attention and cognition [5]. With a lack of reliable biomarkers, the diagnosis of delirium remains primarily clinical, and as such, screening tools like the confusion assessment method (CAM) have been developed [6], which allows recognition of delirium by the presence of four diagnostic criteria: (1) acute onset and fluctuating course, (2) inattention, and either (3) a change in level of consciousness, or (4) disorganized thinking.

Unlike delirium, dementia is a *chronic* and progressive neurodegenerative disease characterized by deficits in multiple cognitive domains, neuropsychiatric symptoms, and functional decline. It is important to note that dementia is a chronic condition associated with chronic inflammation, whereas delirium is an acute condition associated with high systemic stress such as hospitalization, infection, or trauma.

Systemic Inflammation and the Brain

Despite the protection of the blood–brain barrier, it is now recognized that the brain is in communication with the immune system, thereby allowing systemic, peripheral inflammatory reactions to influence brain function, making the brain susceptible to the consequences of systemic inflammation [7,8]. It appears that peripheral cytokines can influence cognition directly through neurodegeneration, or indirectly, with effects on neurotransmission, sleep, and nutritional intake [8,9]. It should be noted that the exact mechanisms by which systemic inflammation affects the brain are still being worked out.

One proposed mechanism by which peripheral cytokines influence the brain is through cellular communication across the blood–brain barrier. Studies show that systemic inflammation activates vascular endothelial cells and perivascular cells located at the blood–brain barrier, which propagates the inflammatory cascade and directly or indirectly injures neurons [10]. When postmortem human brains were analyzed for evidence of this activation, brains with preexisting brain lesions from dementia also showed low activation of vascular endothelial cells, even in the absence of systemic inflammation, possibly explaining the vulnerability of patients with dementia to developing delirium. Clinical observational studies have shown increased permeability of the blood–brain barrier in patients with periventricular white-matter hyperintensities, a condition linked to cognitive impairment, vascular dementia, and other cardiovascular diseases [11,12].

A second mechanism by which cytokines may influence the brain is through stimulation of peripheral sensory neural afferents, such as the Vagus nerve, which leads to central cytokine production [8,9]. A third mechanism by which cytokines influence the brain is through altered neurotransmission, and in support of this, it has been shown that both central and peripheral cytokines alter noradrenergic, dopaminergic, and serotonergic metabolism in the brain [8].

Inflammation and Delirium

Pathogenesis of Delirium

Although the definitive pathogenesis of delirium remains unclear, several mechanisms have been proposed, including (1) neurotransmitter imbalance, with acetylcholine deficiency and dopamine excess; (2) reduced cerebral blood flow and metabolism; (3) dysregulation of stress response and the sleep–wake cycle; and (4) inflammation. The discussion in this paper will focus on the role of inflammation, but all of the listed pathogenic mechanisms may be interrelated and likely, two or more of these are at play in inducing delirium [13].

Inflammatory Markers in Delirium

Dysregulation of cytokines is believed to be the key inciter of neurodegeneration and subsequent cognitive impairment in delirium that results from activation of the systemic inflammatory cascade [8,9]. Therapeutic and investigational uses of interleukins in human and rat models induce symptoms of delirium [14,15], alter acetylcholine levels and activity [16,17], and mediate exotoxic neurodegeneration [18]. Risk factors for cytokine dysregulation include age as well as acute illness, infection, and trauma. Aging alters CNS and peripheral levels of certain cytokines even in the absence of disease or inflammation [1–3]. Further, studies in mice indicate that aging brains are predisposed to exacerbated neuroinflammatory cytokine responses as a result of changes in glial reactivity [19]. It is also becoming clear that the impact of peripheral inflammatory signals on the brain depends on existing levels of inflammation, as occurs in dementia or other direct brain lesions [9]. Administration of therapeutic levels of systemic cytokines in oncology patients can result in neuropsychiatric side effects, including impaired thought processing [20]. Peripheral cytokines (along with prostaglandins) are also thought to be responsible for the central behavioral changes seen with the syndrome of "sickness behavior," which refers to a constellation of symptoms associated with illness and delirium, such as lethargy, decreased learning, reduced mobility, reduced social activity, and increased sleep [8,9]. Sickness behavior is seen in conditions associated with systemic inflammation, such as infection or acute flares of chronic disease.

Cytokine dysregulation can lead to neuronal injury through a variety of mechanisms, including (1) altered neurotransmission, (2) apoptosis, and (3) activation of microglia and astrocytes which leads to production of free radicals, complement factors, glutamate, and nitric oxide [8]. Also, the consequences of "sickness behavior" induced by cytokine dysregulation, including altered sleep, anorexia, and impaired nutrition may further impair cognition. Activation of the inflammatory cascade alters peripheral and/or central cytokines, leading to a central neurodegenerative inflammatory process that becomes clinically apparent as cognitive impairment when the cognitive reserve is breached.

Clinical Studies of Inflammation and Delirium

To further understand the role that inflammation plays in delirium, researchers have studied and measured levels of inflammatory markers in acutely ill patients. Precipitants of delirium, such as extracerebral infection, general surgery, head trauma, and cerebral ischemia, induce systemic or local acute phase responses, often in association with delirium. After cardiac surgery, for example, elevated levels of chemokines in a case-control trial were associated with delirium, although methods of measurement did not allow analyses of the roles of individual cytokines [21].

Inflammatory markers can be easily measured; however, interpretation may be difficult due to clustering of markers into groups that rise and fall with a specific time course, and due to confounding by other risk factors for delirium [22]. C-reactive protein (CRP), although an acute-phase reactant, is not useful as a surrogate of inflammation in delirium since it is nonspecific, and monitoring levels of CRP is not clinically useful in the management of delirium. Although there are conflicting results of studies of CRP in delirium, a small study showed that levels of CRP in serum collected at or soon after admission were highly predictive of delirium and recovery from it in acutely ill older adults [23]. Delirium in post-hip surgery patients and sepsis are also associated with elevated levels of CRP [24,25].

Detection of a sensitive and specific marker for delirium could aid in establishing the diagnosis. There is substantial evidence linking elevated levels of interleukins IL-6 and IL-8 to delirium. A study of elderly patients acutely admitted to the hospital found that patients who developed delirium were significantly more likely to have detectable levels of the peripheral cytokines IL-6 and Il-8, even after adjusting for infection, age, and baseline cognitive impairment [26]. Peripheral IL-6 and IL-8 levels were similarly elevated in patients who developed delirium in a prospective study of elderly patients admitted for acute surgical repair of hip fracture [27]. Interestingly, IL-6 was specifically associated with the hyperactive form of delirium, whereas IL-8 was highest in the days preceding the onset of delirium. Elevated IL-6 in association with delirium was similarly found in a study of elderly patients after abdominal surgery [28], however not in sepsis-associated delirium in a study of adults of all ages [24]. Interestingly, elevated levels of IL-6 were also detected in both the chronic and acute forms of schizophrenia, a psychotic disorder which shares some similar clinical features with delirium and which perhaps inflammation may also play a role in the pathogenesis of [29]. CSF levels of interleukins during delirium in a young population with SLE also showed an association with IL-6, but not other markers of inflammation [30].

Not all clinical studies on inflammation and delirium have found similar results however. A prospective case-control study of CRP, IL-6, and IGF-1 in patients before and after surgery for hip fracture did not find any relation between preoperative levels of these markers of inflammation and subsequent development of delirium [31]. A

recent observational prospective study of hospitalized elderly patients in an elderly acute care unit did not find elevated levels if IL-6 with delirium [32]. The researchers did, however, find that lower levels of the neuroprotective cytokines IGF-1 and IL-1RA were associated with delirium, and that high IFN-γ and low IGF-1 had significant effects on delirium severity. Interestingly, IL-1RA blocks the actions of other proinflammatory cytokines, and other studies have found that IL-RA levels are increased by haloperidol [33], an antipsychotic medication sometimes used to treat delirium and investigated as a possible prophylactic for delirium in elderly hip-surgery patients [34]. Low levels of IGF-1 in patients admitted to the hospital in a different small study were similarly found to be predictive of subsequent delirium [35]. Another study found similar associations between levels of IGF-1 and IFN-γ and delirium in acutely ill older patients, but not IL-6 or IL-RA [36]. Thus, a reliable biological marker for delirium remains elusive and is an area of intense investigation.

Inflammation and Alzheimer's Disease

Pathogenesis of Alzheimer's Disease

Alzheimer's disease (AD) is the most common form of dementia, and much of the evidence regarding the role of inflammation in dementia pertains to this subtype. The brain pathology of AD is characterized by the presence of β-amyloid neuritic plaques, intraneuronal tau neurofibrillary tangles, neuronal death and generalized cortical atrophy [37].

Inflammation and Alzheimer's Disease

As in delirium, several lines of scientific evidence have implicated inflammation in the pathogenesis of AD [38]. However, unlike delirium, where there is an acute cognitive deficit associated with an acute insult and associated inflammatory response, the cognitive decline of AD typically develops over years, and the associated inflammation is more likely to be a lower level but chronic response. Many neuroinflammatory mediators, including cytokines, chemokines, prostaglandins, and free radicals, are upregulated in areas of the brain affected by AD pathology. Postmortem studies of the brain in AD demonstrate the presence of acute-phase reactants (including CRP, proinflammatory cytokines, and activated complement cascade proteins) in the senile plaques and neurofibrillary tangles [39,40]. The concentration of inflammatory markers is intense, with levels higher than that seen in infarcted hearts, atherosclerotic plaques, or replaced joints [41]. The implications of this finding are unclear, but proinflammatory cytokines are known to alter the expression and processing of β-amyloid precursor protein [42,43], and fibrillar β-amyloid in turn promotes the production of proinflammatory cytokines by microglial and monocytic cell lines [44]. IL-1 also increases neuronal tau phosphorylation [45] and activates astrocytes [46]. On a parallel note, polymorphisms of some inflammatory genes, including IL-1, IL-6, and TNF-α have been associated with an increased risk of developing AD [47–50], thereby indirectly incriminating inflammatory responses in the development of the disease. Peripheral IL-6 levels in healthy subjects aged 30–54 years have been shown to be inversely related to hippocampal gray matter volume and memory function, suggesting a role of systemic inflammation in both neurodegeneration and cognitive decline [51].

Chronic inflammation is also thought to play a role in the pathogenesis of vascular dementia, a form of cognitive impairment characterized by large vessel disease with strategic single and multiple strokes and small vessel disease with progressive damage to the deep white matter [52]. Binswanger disease is a subtype of vascular dementia characterized by progressive small vessel damage. Pathologically, the brains of patients with Binswanger disease show gliosis of the white matter with inflammatory cells around blood vessels, where markers of inflammation including cyclooxygenase-2 are also present [53]. Microglia activation, reactive astrocytes, and fibrinogen are found in areas of demyelination [54].

Clinical Studies on Inflammation and Dementia

The concept that anti-inflammatory agents might play a role in AD risk modification arose from the findings of activated microglia and acute phase reactants associated with amyloid plaques and neurofibrillary tangles in AD brains. Several clinical investigations looking at the potential role of inflammation in AD have supported a possible link between inflammation and dementia. Six of seven case-control studies showed that a diagnosis of arthritis reduced the risk for AD, perhaps due to the chronic use of anti-inflammatory drugs [55]. Nonsteroidal antiinflammatory drugs (NSAIDs) may influence the neuroinflammatory response through several mechanisms: (1) by inhibiting cyclooxygenase-1 and cyclooxygenase-2, (2) by activating the peroxisome proliferator g (PPARg) nuclear transcription factor, and (3) by reducing cellular responses to glutamate [56].

A number of observational population-based studies have likewise linked anti-inflammatory interventions to a lowered risk of developing AD. In the Rotterdam Study, the intake of NSAIDs for more than 24 months was associated with a relative risk for AD of 0.2 (95% CI

0.05–0.83) while the use of NSAIDS for shorter periods of 1 to 23 months was associated with a non-significant risk reduction (95% CI 0.62–1.11) [56]. Similar AD risk reductions were seen in chronic NSAID users in the Baltimore Longitudinal Study on Aging [57], Cache County Study [58], and Canadian Study on Health and Aging [59]. An inherent challenge in epidemiological studies that attempt to relate AD risk with NSAID use is the possibility of confounding by other, as yet unidentified variables that distinguish subjects with arthritis and other indications for chronic use of anti-inflammatory medications, and possible risk of increased complications from NSAID use. In addition, a randomized placebo-controlled clinical trial of rofecoxib or naproxen vs. placebo failed to demonstrate a beneficial effect of nonsteroidal anti-inflammatory drugs (NSAIDs) on the progression of AD [60]. Observational studies that have evaluated the relations of markers of systemic inflammation to AD risk have been inconclusive; circulating cytokines have been reported to be elevated [61,62], decreased [63], or unaltered [64,65] in AD patients compared to cognitively-intact controls. Cross-sectional studies that explored the association between circulating inflammatory cytokines and AD showed that both IL-1 [66] and TNF-α [67] blood levels were elevated in patients with AD. High plasma levels of CRP and IL-6 have been associated with poorer cognitive performance at baseline and with a greater risk of cognitive decline over a 2-year follow-up period in some studies [68], although the Women's Health Study found no evidence of a link between high sensitivity CRP and decrements in cognitive function [69]. One possible explanation for the conflicting findings of studies on the relation of serum cytokines and AD may be that circulating levels of cytokines reflect systemic inflammation, but may not adequately mirror intracerebral inflammatory responses. For example, prior studies have reported higher CSF levels of TNF-α relative to serum levels in AD patients [70]. Of note, brain perivascular macrophages and microglia that participate in intraparenchymal inflammation are derived from circulating macrophages [71]. Thus, measurement of the spontaneous production of cytokines (such as IL-1 and TNF-α) by peripheral blood mononuclear cells (PBMC) may better reflect their potential to contribute to intracerebral inflammation compared to assessment of serum cytokine levels. At the Framingham Study, we observed that higher levels of PBMC production of the inflammatory cytokines IL-1 or TNF-α were associated with an increased risk of developing AD. In addition, we found that the presence of unfavorable levels of several PBMC cytokines was associated with an approximately 2-fold increase in risk of AD compared to those with favorable levels [72]. More recently, another prospective study found that serum IL-6, hsCRP, SAA, and PGF-2α levels are not associated with the risk of AD, but high serum IL-6 levels may be associated with increased risk of non-AD dementia [73].

Conclusion

Dementia and delirium are distinct clinical syndromes, yet linked by overlapping clinical features and shared pathogenic mechanisms. Dementia is recognized as one of the most common risk factors for delirium, and conversely, delirium can alter the course of dementia by contributing to a more rapid progression of cognitive deterioration, functional decline, and loss of independence [5,7,13]. Delirium can also be the initial presentation of dementia, leading one to question whether these are comorbid but distinct entities or whether a more intimate relationship exists [5,7]. This paper has explored the link between dementia and delirium, specifically focusing on the evidence that supports inflammation as a common pathogenic mechanism in both syndromes.

Although the results of studies published thus far have not consistently identified specific cytokines that are most likely to play a role in either condition, there is adequate evidence to justify future studies examining possible mediation of delirium and dementia by inflammatory cytokines. Rather than serum levels alone, investigators should consider using levels of PBMC-released cytokines, which may be more reflective of intracerebral inflammation than serum cytokine levels.

Only with further studies can we clarify whether inflammation is a true risk factor for delirium and dementia, elucidate the underlying pathophysiologic mechanisms for these associations, and identify potential therapeutic opportunities to intervene and mitigate the risk for subsequent cognitive decline.

Acknowledgments

Both authors contributed equally to the concept and design of this paper, the literature search, review of the material, drafting, revising, and final approval of the paper. The authors report no sources of funding for this project or additional individuals who have contributed to this paper. Dr. Tan is the recipient of a Geriatric Academic Career Award from the Health Resources and Services Administration. Dr. Simone reports receiving an honorarium for developing an online educational module for the Fenway Community Health Center.

Conflict of Interest

The authors have no conflict of interest.

References

1. Krabbe K, Pedersen M, Bruunsgaard H. Inflammatory mediators in the elderly. *Exp Gerontol* 2004;**39**:687–699.
2. Wei J, Xu H, Davies J, Hemmings G. Increase of plasma IL-6 concentration with age in healthy subjects. *Life Sci* 1992;**51**:1953–1956.
3. Paolisso G, Rizzo M, Mazziotti G, et al. Advancing age and insulin resistance: Role of plasma tumor necrosis factor-alpha. *Am J Physiol* 1998;**275**(2 Pt 1):E294–E299.
4. Holmes C, Cunningham C, Zotova E, et al. Systemic inflammation and disease progression in Alzheimer disease. *Neurology* 2009;**73**:768–774.
5. Inouye S. Delirium in older persons. *N Engl J Med* 2006;**354**:1157–1165.
6. Inouye S, van Dyck C, Alessi C, Balkin S, Siegal A, Horwitz R. Clarifying confusion: The confusion assessment method. A new method for detection of delirium. *Ann Intern Med* 1990;**113**:941–948.
7. Eikelenboom P, Hoogendijk WJ. Do delirium and Alzheimer's dementia share specific pathogenetic mechanisms? *Dement Geriatr Cogn Disord* 1999;**10**:319–324.
8. Wilson C, Finch C, Cohen H. Cytokines and cognition–the case for a head-to-toe inflammatory paradigm. *J Am Geriatr Soc* 2002;**50**:2041–2056.
9. Maclullich AM, Ferguson KJ, Miller T, de Rooij SE, Cunningham C. Unravelling the pathophysiology of delirium: A focus on the role of aberrant stress responses. *J Psychosom Res* 2008;**65**:229–238.
10. Uchikado H, Akiyama H, Kondo H, et al. Activation of vascular endothelial cells and perivascular cells by systemic inflammation-an immunohistochemical study of postmortem human brain tissues. *Acta Neuropathol* 2004;**107**:341–351.
11. Hanyu H, Asano T, Tanaka Y, Iwamoto T, Takasaki M, Abe K. Increased blood-brain barrier permeability in white matter lesions of Binswanger's disease evaluated by contrast-enhanced MRI. *Dement Geriatr Cogn Disord* 2002;**14**:1–6.
12. Starr JM, Wardla J, Ferguson K, MacLullich A, Deary IJ, Marshall I. Increased blood-brain permeability in type II diabetes demonstrated by gadolinium magnetic resonance imaging. *J Neruol Neurosurg Pschiatry* 2003;**74**:70–76.
13. Young J, Inouye S. Delirium in older people. *BMJ* 2007;**334**:842–846.
14. Renault PF, Hoofnagle JH, Park Y, et al. Psychiatric complications of long-term interferon alfa therapy. *Arch Intern Med* 1987;**147**:1577–1580.
15. van Steijn J, Nieboer P, Hospers G, de Vries E, Mulder N. Delirium after interleukin-2 and alpha-interferon therapy for renal cell carcinoma. *Anticancer Res* 2001;**21**: 3699–3700.
16. Li Y, Liu L, Kang J, et al. Neuronal-glial interactions mediated by interleukin-1 enhance neuronal acetylcholinesterase activity and mRNA expression. *J Neurosci* 2000;**20**:149–155.
17. Rada P, Mark G, Vitek M, et al. Interleukin-1 beta decreases acetylcholine measured by microdialysis in the hippocampus of freely moving rats. *Brain Res* 1991;**550**:287–290.
18. Huang T, O'Banion M. Interleukin-1 beta and tumor necrosis factor-alpha suppress dexamethasone induction of glutamine synthetase in primary mouse astrocytes. *J Neurochem* 1998;**71**:1436–1442.
19. Godbout J, Johnson R. Age and neuroinflammation: A lifetime of psychoneuroimmune consequences. *Immunol Allergy Clin North Am* 2009;**29**:321–337.
20. Licinio J, Kling M, Hauser P. Cytokines and brain function: Relevance to interferon-alpha-induced mood and cognitive changes. *Semin Oncol* 1998;**25**(Suppl 1): 30–38.
21. Rudolph JL, Ramlawi B, Kuchel GA, et al. Chemokines are associated with delirium after cardiac surgery. *J Gerontol A Biol Sci Med Sci* 2008;**63**:184–189.
22. Marcantonio ER, Rudolph JL, Culley D, Crosby G, Alsop D, Inouye SK. Serum biomarkers for delirium. *J Gerontol A Biol Sci Med Sci* 2006;**61**:1281–1286.
23. Macdonald A, Adamis D, Treloar A, Martin F. C-reactive protein levels predict the incidence of delirium and recovery from it. *Age Ageing* 2007;**36**:222–225.
24. Pfister D, Siegemund M, Dell-Kuster S, et al. Cerebral perfusion in sepsis-associated delirium. *Crit Care* 2008;**12**:R63.
25. Beloosesky Y, Hendel D, Weiss A, et al. Cytokines and C-reactive protein production in hip-fracture-operated elderly patients. *J Gerontol A Biol Sci Med Sci* 2007;**62**: 420–426.
26. de Rooij SE, van Munster BC, Korevaar JC, Levi M. Cytokines and acute phase response in delirium. *J Psychosom Res* 2007;**62**:521–525.
27. van Munster BC, Korevaar JC, Zwinderman AH, Levi M, Wiersinga WJ, De Rooij SE. Time-course of cytokines during delirium in elderly patients with hip fractures. *J Am Geriatr Soc* 2008;**56**:1704–1709.
28. Kudoh A, Takase H, Katagai H, Takazawa T. Postoperative interleukin-6 and cortisol concentrations in elderly patients with postoperative confusion. *Neuroimmunomodulation* 2005;**12**:60–66.
29. Naudin J, Mege JL, Azorin JM, Dassa D. Elevated circulating levels of IL-6 in schizophrenia. *Schizophr Res* 1996;**20**:269–273.
30. Katsumata Y, Harigai M, Kawaguchi Y, et al. Diagnostic reliability of cerebral spinal fluid tests for acute confusional state (delirium) in patients with systemic lupus erythematosus: Interleukin 6 (IL-6), IL-8, interferon-alpha, IgG index, and Q-albumin. *J Rheumatol* 2007;**34**:2010–2017.
31. Lemstra AW, Kalisvaart KJ, Vreeswijk R, van Gool WA, Eikelenboom P. Pre-operative inflammatory markers and

the risk of postoperative delirium in elderly patients. *Int J Geriatr Psychiatry* 2008;**23**:943–948.
32. Adamis D, Lunn M, Martin FC, et al. Cytokines and IGF-I in delirious and non-delirious acutely ill older medical inpatients. *Age Ageing* 2009;**38**:326–332; discussion 251.
33. Song C, Lin A, Kenis G, Bosmans E, Maes M. Immunosuppressive effects of clozapine and haloperidol: Enhanced production of the interleukin-1 receptor antagonist. *Schizophr Res* 2000;**42**:157–164.
34. Kalisvaart K, de Jonghe J, Bogaards M, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. *J Am Geriatr Soc* 2005;**53**:1658–1666.
35. Wilson K, Broadhurst C, Diver M, Jackson M, Mottram P. Plasma insulin growth factor-1 and incident delirium in older people. *Int J Geriatr Psychiatry* 2005;**20**:154–159.
36. Adamis D, Treloar A, Martin FC, Gregson N, Hamilton G, Macdonald AJ. APOE and cytokines as biological markers for recovery of prevalent delirium in elderly medical inpatients. *Int J Geriatr Psychiatry* 2007;**22**:688–694.
37. Rombouts S, Barkhof F, Witter M, Scheltens P. Unbiased whole-brain analysis of gray matter loss in Alzheimer's disease. *Neurosci Lett* 2000;**285**:231–233.
38. McGeer P, McGeer E. NSAIDs and Alzheimer disease: Epidemiological, animal model and clinical studies. *Neurobiol Aging* 2007;**28**:639–647.
39. Iwamoto N, Nishiyama E, Ohwada J, Arai H. Demonstration of CRP immunoreactivity in brains of Alzheimer's disease: Immunohistochemical study using formic acid pretreatment of tissue sections. *Neurosci Lett* 1994;**177**:23–26.
40. Duong T, Nikolaeva M, Acton P. C-reactive protein-like immunoreactivity in the neurofibrillary tangles of Alzheimer's disease. *Brain Res* 1997;**749**:152–156.
41. McGeer P, McGeer E. Inflammation and the degenerative diseases of aging. *Ann N Y Acad Sci* 2004;**1035**:104–116.
42. Forloni G, Demicheli F, Giorgi S, Bendotti C, Angeretti N. Expression of amyloid precursor protein mRNAs in endothelial, neuronal and glial cells: Modulation by interleukin-1. *Brain Res Mol Brain Res* 1992;**16**: 128–134.
43. Vasilakos J, Carroll R, Emmerling M, et al. Interleukin-1 beta dissociates beta-amyloid precursor protein and beta-amyloid peptide secretion. *FEBS Lett* 1994;**354**: 289–292.
44. Combs C, Karlo J, Kao S, Landreth G. beta-Amyloid stimulation of microglia and monocytes results in TNFalpha-dependent expression of inducible nitric oxide synthase and neuronal apoptosis. *J Neurosci* 2001;**21**: 1179–1188.
45. Li Y, Liu L, Barger S, Griffin W. Interleukin-1 mediates pathological effects of microglia on tau phosphorylation and on synaptophysin synthesis in cortical neurons through a p38-MAPK pathway. *J Neurosci* 2003;**23**: 1605–1611.
46. Griffin W. Inflammation and neurodegenerative diseases. *Am J Clin Nutr* 2006;**83**:470S–474S.
47. McGeer P, McGeer E. Polymorphisms in inflammatory genes and the risk of Alzheimer disease. *Arch Neurol* 2001;**58**:1790–1792.
48. Culpan D, MacGowan S, Ford J, et al. Tumour necrosis factor-alpha gene polymorphisms and Alzheimer's disease. *Neurosci Lett* 2003;**350**:61–65.
49. Wang W, Liao Y, Wu S, Tsai F, Lee C, Hua C. Association of interleukin-I beta and receptor antagonist gene polymorphisms with late onset Alzheimer's disease in Taiwan Chinese. *Eur J Neurol* 2005;**12**:609–613.
50. Yucesoy B, Peila R, White L, et al. Association of interleukin-1 gene polymorphisms with dementia in a community-based sample: The Honolulu-Asia Aging Study. *Neurobiol Aging* 2006;**27**:211–217.
51. Marsland A, Gianaros P, Abramowitch S, Manuck S, Hariri A. Interleukin-6 covaries inversely with hippocampal grey matter volume in middle-aged adults. *Biol Psychiatry* 2008;**64**:484–490.
52. Rosenberg G. Inflammation and white matter damage in vascular cognitive impairment. *Stroke* 2009;**40**(3 Suppl):S20–S23.
53. Tomimoto H, Akiguchi I, Wakita H, Lin J, Budka H. Cyclooxygenase-2 is induced in microglia during chronic cerebral ischemia in humans. *Acta Neuropathol* 2000;**99**:26–30.
54. Simpson J, Fernando M, Clark L, et al. White matter lesions in an unselected cohort of the elderly: Astrocytic, microglial and oligodendrocyte precursor cell responses. *Neuropathol Appl Neurobiol* 2007;**33**:410–419.
55. McGeer P, Schulzer M, McGeer E. Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease: A review of 17 epidemiologic studies. *Neurology* 1996;**47**:425–432.
56. in t' Veld B, Ruitenberg A, Hofman A, et al. Nonsteroidal antiinflammatory drugs and the risk of Alzheimer's disease. *N Engl J Med* 2001;**345**:1515–1521.
57. Stewart W, Kawas C, Corrada M, Metter E. Risk of Alzheimer's disease and duration of NSAID use. *Neurology* 1997;**48**:626–632.
58. Zandi P, Anthony J, Hayden K, Mehta K, Mayer L, Breitner J. Reduced incidence of AD with NSAID but not H2 receptor antagonists: The Cache County Study. *Neurology* 2002;**59**:880–886.
59. Lindsay J, Laurin D, Verreault R, et al. Risk factors for Alzheimer's disease: A prospective analysis from the Canadian Study of Health and Aging. *Am J Epidemiol* 2002;**156**:445–453.
60. Aisen P, Schafer K, Grundman M, et al. Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression: A randomized controlled trial. *JAMA* 2003;**289**:2819–2826.
61. Bagli M, Papassotiropoulos A, Hampel H, et al. Polymorphisms of the gene encoding the inflammatory

cytokine interleukin-6 determine the magnitude of the increase in soluble interleukin-6 receptor levels in Alzheimer's disease. Results of a pilot study. *Eur Arch Psychiatry Clin Neurosci* 2003;**253**:44–48.
62. Singh V, Guthikonda P. Circulating cytokines in Alzheimer's disease. *J Psychiatr Res* 1992;**31**:657–660.
63. Richartz E, Stransky E, Batra A, et al. Decline of immune responsiveness: A pathogenetic factor in Alzheimer's disease?. *J Psychiatr Res* 2005;**39**:535–543.
64. van Duijn C, Hofman A, Nagelkerken L. Serum levels of interleukin-6 are not elevated in patients with Alzheimer's disease. *Neurosci Lett* 1990;**108**:350–354.
65. Lanzrein A, Johnston C, Perry V, Jobst K, King E, Smith A. Longitudinal study of inflammatory factors in serum, cerebrospinal fluid, and brain tissue in Alzheimer disease: Interleukin-1beta, interleukin-6, interleukin-1 receptor antagonist, tumor necrosis factor-alpha, the soluble tumor necrosis factor receptors I and II, and alpha1-antichymotrypsin. *Alzheimer Dis Assoc Disord* 1998;**12**:215–227.
66. Licastro F, Pedrini S, Caputo L, et al. Increased plasma levels of interleukin-1, interleukin-6 and alpha-1-antichymotrypsin in patients with Alzheimer's disease: Peripheral inflammation or signals from the brain?. *J Neuroimmunol* 2000;**103**:97–102.
67. Bruunsgaard H, Andersen-Ranberg K, Jeune B, Pedersen A, Skinhøj P, Pedersen B. A high plasma concentration of TNF-alpha is associated with dementia in centenarians. *J Gerontol A Biol Sci Med Sci* 1999;**54**:M357–M364.
68. Yaffe K, Lindquist K, Penninx B, et al. Inflammatory markers and cognition in well-functioning African-American and white elders. *Neurology* 2003;**61**: 76–80.
69. Weuve J, Ridker P, Cook N, Buring J, Grodstein F. High-sensitivity C-reactive protein and cognitive function in older women. *Epidemiology* 2006;**17**:183–189.
70. Tarkowski E, Blennow K, Wallin A, Tarkowski A. Intracerebral production of tumor necrosis factor-alpha, a local neuroprotective agent, in Alzheimer disease and vascular dementia. *J Clin Immunol* 1999;**19**:223–230.
71. Stoll G, Jander S. The role of microglia and macrophages in the pathophysiology of the CNS. *Prog Neurobiol* 1999;**58**:233–247.
72. Tan Z, Beiser A, Vasan R, et al. Inflammatory markers and the risk of Alzheimer disease: The Framingham Study. *Neurology* 2007;**68**:1902–1908.
73. Sundelöf J, Kilander L, Helmersson J, et al. Systemic inflammation and the risk of Alzheimer's disease and dementia: A prospective population-based study. *J Alzheimers Dis* 2009;**18**:79–87.