

From Medscape Medical News

Inflammation Linked to Increased Cognitive Decline in Alzheimer's Disease



Susan Jeffrey

September 11, 2009 — A new study finds a link between systemic inflammation and increased cognitive decline in patients with established Alzheimer's disease (AD).

In this study, both acute and chronic inflammation, which were in turn associated with increased serum levels of proinflammatory cytokine tumor necrosis factor α (TNF- α), were associated with an increase in the rate of cognitive decline in patients with mild to severe AD.

"The role of TNF- α within the brain is controversial, with evidence supportive of both deleterious and protective effects," the authors, led by Clive Holmes, MRCPsych, PhD, from the University of Southampton, United Kingdom, conclude. "However, if systemic inflammation has different [central nervous system] consequences depending on the existing relative activation state of the central innate immune system, dampening down systemic TNF- α may prove to be beneficial in AD."

Their report is published in the September 8 issue of *Neurology*.

Inflammation and Cognitive Decline

Previous studies have shown an association between low-grade systemic inflammation and increased cognitive decline, as well as reduced hippocampal volume in people without dementia, the authors note. Some, but not all, studies have suggested that increased inflammation can increase the risk of developing AD, but few studies have looked at the effect of systemic inflammation in people with established AD.

Acute systemic inflammation from infections or tissue injury and more chronic inflammatory conditions such as atherosclerosis, periodontitis, or diabetes involve the systemic production of C-reactive protein and TNF- α , the authors point out. Previous preclinical research has shown that acute systemic inflammation contributes to neurodegeneration by the activation of primed microglial cells.

In this study, the authors hypothesized that acute systemic inflammatory events such as infections and tissue injury that were sufficient to increase systemic TNF- α would be associated with cognitive decline in AD patients.

A total of 300 community-dwelling patients with mild to severe AD were assessed at baseline and then every other month for 6 months. Testing included cognitive assessment and having blood samples taken and analyzed for systemic inflammatory markers including TNF- α , and caregivers were interviewed to determine whether the patient had developed any incident systemic inflammatory events.

During follow-up, 110 patients had acute inflammatory events that were associated with increases in serum TNF- α . Compared with participants without these events, they had a 2-fold increase in the rate of cognitive decline during this period.

Those who had high levels of TNF- α at baseline had a 4-fold increase in the rate of cognitive decline, independent of age, delirium, or concomitant cholinesterase use, the authors write, suggesting a relationship between serum TNF- α

and rates of both cognitive decline and long-term cognitive impairment. Patients with low levels of serum TNF- α throughout the study had no cognitive decline during the study period, they add.

The effect of having both an acute and chronic infection was particularly marked, the authors note; those participants with high baseline levels of TNF- α who then experienced an incident infection or injury had a 10-fold increase in the rate of cognitive decline over those who had low baseline TNF- α levels and no inflammatory events during the course of the study.

"One might guess that people with a more rapid rate of cognitive decline are more susceptible to infections or injury, but we found no evidence to suggest that people with more severe dementia were more likely to have infections or injuries at the beginning of the study," Dr. Holmes said in a statement from the American Academy of Neurology. "More research needs to be done to understand the role of TNF- α in the brain, but it's possible that finding a way to reduce those levels could be beneficial for people with Alzheimer's disease."

TNF- α and Etanercept

In a separate review article published in the September 1 issue of *CNS Drugs*, Edward Tobinick, MD, from the Institute for Neurological Research in Los Angeles, California, examined the role of TNF- α modulation as a potential treatment for Alzheimer's disease, and in particular, the use of perispinal administration of etanercept (*Enbrel*, Amgen), a potent anti-TNF fusion protein.

In a previously published 6-month open-label pilot study including 15 AD patients, Dr. Tobinick and colleagues reported sustained clinical improvement in these patients with this strategy. Since then, several other case studies from his group have documented rapid improvement after perispinal etanercept administration in AD and primary progressive aphasia, Dr. Tobinick writes in the new review article.

"Recent studies documenting rapid and sustained clinical improvement in AD and related forms of dementia following perispinal etanercept suggest the existence of rapidly reversible TNF-mediated pathophysiological mechanisms in AD, hypothesized to be related to the synaptic effects of TNF," he concludes. "Accumulating and emerging evidence supports the further study of perispinal etanercept for the treatment of AD in randomized clinical trials."

The study by Holmes et al was supported by the Alzheimer's Society. Dr. Holmes has disclosed that he has received research support from the Alzheimer's Society, the UK Department of Health, and the Medical Research Council. Disclosures for coauthors appear in the article. In the CNS Drugs paper, no outside funds were received in connection with the preparation of the manuscript. Dr. Tobinick owns stock in Amgen, the manufacturer of etanercept, and has multiple issued and pending US and international patent applications describing the use of perispinal etanercept for neurological disorders, including but not limited to AD and other forms of dementia.

Neurology. 2009;73:768–774; *CNS Drugs*. 2009;23:713–725. [Abstract](#) [Abstract](#)

Authors and Disclosures

Journalist

Susan Jeffrey

Susan Jeffrey is the news editor for Medscape Neurology & Neurosurgery. Susan has been writing principally for physician audiences for nearly 20 years. Most recently, she was news editor for thekidney.org and also wrote for theheart.org; both of these Web sites have been acquired by WebMD. Prior to that, she spent 10 years covering neurology topics for a Canadian newspaper for physicians. She can be contacted at SJeffrey@webmd.net.