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Inflammation and Alzheimer Disease

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ABSTRACT

Inflammatory mechanisms are active in patients with Alzheimer disease. Serum elevations of acute phase proteins such as α1-antichymotrypsin, along with deposition of inflammatory cytokines in the brain, suggest a "cerebral acute phase response" contributing to amyloid deposition and tissue destruction. Activated microglia possessing HLA-DR surface markers accumulate around amyloid plaques. The complement cascade leads to generation of the membrane attack complex, which may directly damage neuronal membranes. This growing body of evidence suggests that empirical trials of anti-inflammatory drugs are now appropriate to test the hypothesis that suppression of these mechanisms will slow the rate of progression of Alzheimer disease. Several drugs useful in the treatment of rheumatic diseases are candidates for study in Alzheimer disease, including glucocorticoids, antimalarial drugs, and colchicine. Pilot studies of the synthetic glucocorticoid prednisone indicate that treatment with a moderate dose is well tolerated in patients with Alzheimer disease, and suppresses serum levels of acute phase proteins. Based on this experience, a multicenter parallel-design placebo-controlled trial has been initiated with the Alzheimer's Disease Cooperative Study to determine whether treatment with prednisone can slow the rate of progression of Alzheimer disease.

Index Entries: Alzheimer disease; inflammation; acute phase response; complement cascade; microglia; therapeutics.

INTRODUCTION

Alzheimer disease (AD) is considered to be a neurodegenerative disorder rather than an inflammatory or autoimmune disease. However, in the past decade it has become evident that inflammatory/immune mechanisms are active in the AD brain. These mechanisms have the potential to contribute substantially to the deposition of cerebral amyloid and to neuronal death, raising the possibility that anti-inflammatory medications may slow the rate of progression of the disease (McGeer and Rogers, 1992; Aisen and Davis, 1994).

INFLAMMATORY MECHANISMS IN THE AD BRAIN

A consistent feature of most systemic inflammatory diseases is the acute phase response: elevations of normal serum proteins mediated by inflammatory cytokines, particularly interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor. In the AD brain, there is increased deposition of acute phase proteins such as α-1 antichymotrypsin (ACT) and α-2 macroglobulin, components of amyloid plaques (Abraham et al., 1988; Rozemuller et al., 1990). Upregulation of these proteins may be mediated by IL-1 and IL-6, also increased in AD brains (Abraham et al., 1990; Vandenabeele and Fiers, 1991); these cytokines can stimulate release of the amyloid precursor protein (APP) (Goldgaber et al., 1989; Altstiel and Sperber, 1991). Il-1 seems to play an important role in the maturation of senile plaques (Griffin et al., 1995).

Inflammatory cytokines may contribute to neuronal loss independent of amyloid plaque formation. Transgenic mice that overexpress IL-6 do not form amyloid plaques, but do show evidence of neurodegeneration (Campbell et al., 1993).

It is thus a reasonable hypothesis that suppression of inflammatory cytokines and the acute phase response may be beneficial in Alzheimer disease. A number of laboratories have reported increased levels of ACT in the serum of patients with AD compared to age-matched controls (Matsubara et al., 1990; Brugge et al., 1992; Hinds et al., 1994; Altstiel et al., 1995). The serum ACT level may be a peripheral marker of the cerebral acute phase response, in which case this measurement may be useful as a guide to anti-inflammatory therapy.

The classical complement pathway is activated in AD brains, with deposition of all of the tissue-bound products and generation of the membrane attack complex, as well as upregulation of complement regulatory proteins (Eikelenboom and Stam, 1982; McGeer et al., 1989). The membrane attack complex may directly contribute to neuronal cell death. In addition, anaphylatoxins released during complement activation may augment the inflammatory process. The complement protein C1q can bind to amyloid β-protein (Rogers, 1995), increasing aggregation and neurotoxicity.

Finally, the primary cellular component of brain inflammation in AD is probably the activated microglial cell, which has HLA-DR surface markers and may function as an antigen presenting cell, as well as a source of inflammatory mediators (McGeer et al., 1987; Haga et al., 1989; Wisniewski et al., 1991).

ANTI-INFLAMMATORY THERAPY FOR AD

Selection of candidate anti-inflammatory drugs for testing in AD should be based on clinical experience with rheumatic diseases that share these pathogenic mechanisms, as well as relevant animal experiments.

Glucocorticoids are the most important drugs for the suppression of inflammatory and autoimmune mechanisms. Prednisone, a synthetic glucocorticoid, is the most effective treatment for most of the inflammatory rheumatic diseases, including sytemic lupus erythematosus, a disease in which brain inflammation and complement activation cause major manifestations.

Pilot studies have demonstrated that low-to-moderate doses of prednisone are well tolerated in AD patients, and are effective in suppressing the acute phase response (Aisen et al., 1995); prednisone also suppresses complement activation in AD as reflected in plasma levels of the complement fragment C3a (Fagarasan and Aisen, unpublished data). A multicenter placebo-controlled therapeutic trial of prednisone in AD began enrollment in January 1995.

Nonsteroidal anti-inflammatory drugs (NSAIDs) have also been considered for use in AD. Epidemiologic studies suggest that use of NSAIDs may delay expression of AD (Breitner et al., 1994; Lucca et al., 1994; Rich et al., 1995), but the problem of recall bias confounds interpretation of this finding. One small pilot study suggested that treatment with indomethacin slowed the rate of progression of AD (Rogers et al, 1993). NSAIDs are not useful in the treatment of brain inflammation in diseases such as lupus, and they are generally ineffective in suppressing the acute phase response or slowing tissue destruction in rheumatoid arthritis, so they may not be optimal candidates for trials in AD.

In contrast to the NSAIDs, hydroxychloroquine has been proven to suppress the acute phase response and slow the rate of tissue destruction in rheumatoid arthritis (HERA Study Group, 1995). It has also been proven to be effective in the treatment of systemic lupus erythematosus (Mullins et al., 1956). The mechanism of the anti-inflammatory/immunosuppressive effect of this drug is not entirely clear, but among other actions, it suppresses mononuclear cell function (Salmeron and Lipsky, 1983; Sperber et al., 1993). Hydroxychloroquine is a lysosomotropic agent: it inhibits the activity of lysosomal acid proteases (DeDuve et al., 1974). Since lysosomal enzymes have been implicated in the pathogenesis of AD, this effect may be beneficial.

Colchicine is of particular interest because it is an antiamyloidogenic agent. Colchicine is dramatically effective in preventing and treating the secondary amyloidosis of Familial Mediterranean Fever (FMF) (Zemer et al., 1992; Zemer et al., 1986), and has been used in other human and experimental amyloidoses as well (Shirahama and Cohen, 1974; Kisilevsky et al., 1983). Though the primary protein component is different, the pathophysiology of FMF amyloid is similar to that of brain amyloid in AD: both are assumed to involve the generation of insoluble fragments from the altered processing of proteins upregulated in response to inflammatory cytokines. This similarity raises the hope that colchicine may be useful in AD. Colchicine may also favorably affect the processing of APP (Refolo et al., 1995), and suppress mononuclear cell function (Grinde and Seglen, 1981; Chang et al., 1987).

CONCLUSION

Therapeutic trials of anti-inflammatory drugs in AD are time-consuming and expensive. The efficacy of neurotransmitter augmentation regimens aiming for symptomatic benefit can be evaluated in short-term pilot studies, but testing an anti-inflammatory treatment that may slow disease progression requires a long study. Selection of agents for such studies must rely on experience in the treatment of other diseases that share pathogenic inflammatory mechanisms with AD. Animal and cell culture models of these mechanisms may also be useful in the development of anti-inflammatory strategies.

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