Glucocorticoids in Alzheimer’s Disease
The Story So Far

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Summary

The inflammatory hypothesis of Alzheimer’s disease states that specific inflammatory mechanisms, including the cytokine-driven acute-phase response, complement activation and microglial activation, contribute to neurodegeneration. If the hypothesis is correct, anti-inflammatory treatment aimed at suppression of these mechanisms could slow the rate of disease progression. Towards this goal, a multicentre trial of prednisone in Alzheimer’s disease is under way and pilot studies of other anti-inflammatory regimens are being conducted.

1. The Inflammatory Hypothesis of Alzheimer’s Disease

Specific inflammatory processes are active in the brain in Alzheimer’s disease (AD).[1,2] There is an acute-phase response, with increased expression of the inflammatory cytokines interleukin (IL)-1 and IL-6, and increased amounts of acute-phase proteins (which are components of amyloid plaques).[3-5] Complement proteins are upregulated and there is evidence that the complement cascade is activated, with the release of inflammatory anaphylatoxins.[6] The complement membrane-attack complex, which has the capacity to destroy cells via lysis of membranes, colocalises with cell membranes in the brains of patients with AD.[7] Activated microglial cells with human leucocyte antigen (HLA)-DR surface antigens accumulate around neuritic plaques.[8]

Studies in a number of in vitro and animal-model systems suggest that these inflammatory mechanisms contribute to neuronal loss in the AD brain. Inflammatory cytokines[9] and complement components[10,11] augment the toxicity of amyloid β protein (Aβ) in cell-culture systems. Activated microglia secrete neurotoxins[12] and augment amyloid toxicity in hippocampal slice cultures.[13] Inflammatory cytokines seem to participate in the maturation of neuritic plaques.[14] There is also evidence that the cytokines themselves may be neurotoxic: overexpression of IL-6 in the brains of transgenic mice leads to neurodegeneration.[15]

If the inflammatory response contributes to neurodegeneration in patients with AD, pharmacological suppression of these mechanisms may slow the rate of disease progression. A number of drugs may be considered candidates for this strategy, including glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine and antimalarials.

2. Glucocorticoids

Glucocorticoids, the most broadly effective and potent class of anti-inflammatory/immunosuppressive drugs in clinical use, are the appropriate choice to suppress the acute-phase response and complement activation in the brain.[2] The major concern with testing this class of drug is its potential toxicity in the population with AD. High-dosage corticosteroid regimens (e.g. prednisone ≥60 mg/day)
are typically used to suppress brain inflammation in disorders such as multiple sclerosis, lupus cerebritis and vasculitis; such regimens are associated with significant toxicity in the elderly, and patients with AD may be particularly susceptible to adverse effects on bone and behaviour.\cite{2,16}

The possibility that supraphysiological amounts of glucocorticoids are toxic to the hippocampus has been an important consideration. There is substantial evidence that glucocorticoids can cause or potentiate hippocampal injury in animals.\cite{17-19} However, animal studies indicate that the effects of glucocorticoids are complex and that, under some conditions, glucocorticoids have a protective effect.\cite{20} For example, it has been demonstrated that corticosterone may protect against stress-induced hippocampal atrophy in rats.\cite{21} Long term administration of high dose oral glucocorticoid therapy to aged macaque monkeys does not cause hippocampal neuronal loss (E. Peskind, personal communication).

In humans, the question of glucocorticoid-induced hippocampal toxicity is unresolved. In Cushing’s disease, the degree of cortisol excess may correlate with hippocampal atrophy.\cite{22} Indeed, AD may be associated with some degree of hypercortisolaemia,\cite{23,24} which leads to the hypothesis that an excess of glucocorticoids contributes to the hippocampal atrophy and dementia. Cognitive testing in healthy volunteers suggests that glucocorticoids may adversely affect declarative memory.\cite{25}

It seems likely that the effect of glucocorticoids on cognition is dependent on clinical circumstances, and on the dosage and duration of therapy. Patients with systemic lupus erythematosus who do not have overt neuropsychiatric disease show improved cognitive performance after treatment with prednisone.\cite{26} There have been no reports of adverse cognitive or behavioural effects with the low dosage (about 10 mg/day) prednisone regimens that are widely used to treat elderly patients with polymyalgia rheumatica and rheumatoid arthritis. If AD is an inflammatory disease, it is plausible that treatment with low to moderate dosages of glucocorticoids may yield benefits, without adverse effects on cognitive function.

Our group sought to determine whether prednisone treatment, at a dosage that may be tolerable during long term use in patients with AD, would suppress inflammatory markers in AD.\cite{16} There is no method of directly assessing brain tissue inflammatory activity. However, we chose 2 peripheral markers as surrogates in our dosage-selection studies: (i) serum $\alpha_1$-antichymotrypsin (ACT) level; and (ii) plasma level of the complement split product C3a.

While it remains to be determined whether suppression of these markers is a useful guide to the design of effective disease-modifying anti-inflammatory regimens, there is some evidence that peripheral levels of these peptides reflect CNS inflammatory activity in AD. A number of studies have shown that serum ACT level is elevated in patients with AD compared with age-matched controls,\cite{27-31} although a few researchers have reported no difference.\cite{32-34} The contradictory reports may, in part, be explained by heterogeneous patient groups; ACT levels are highest early in the course of AD, and decrease as cognition declines.\cite{30} Interestingly, there is also a negative correlation between plasma C3a level and disease duration among patients with AD.\cite{35}

In our pilot clinical studies of prednisone treatment in patients with AD,\cite{16} we found that an initial dosage of 10 mg/day had no effect on inflammatory markers. However, treatment with prednisone at an initial dosage of 20 mg/day (tapered to a maintenance dosage of 10 mg/day) suppressed peripheral levels of ACT\cite{16} and C3a\cite{35} in patients with AD. In the short term (7-week) pilot study,\cite{16} this latter regimen was not associated with significant adverse effects. In addition, there was no evidence of adverse effects on cognitive or behavioural assessment scores.

Based on these pilot studies, the Alzheimer’s Disease Cooperative Study group, a consortium of academic centres funded by the National Institute on Aging, has initiated the Multicenter Trial of Prednisone in Alzheimer’s Disease. In this double-