THE ROLE OF ANTI-INFLAMMATORY DRUGS IN THE PREVENTION AND TREATMENT OF ALZHEIMER’S DISEASE

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ABSTRACT

Risk factor intervention is a useful strategy for prevention of poorly understood diseases. Fifteen studies have examined the relation of glucocorticoid and nonsteroid antiinflammatory treatments and onset or progression of Alzheimer’s disease (AD). Fourteen of these studies suggest that such treatments (especially nonsteroidal agents) prevent or ameliorate symptoms of AD. Abundant circumstantial evidence implicates inflammation in the pathogenesis of AD. Inhibition of cyclooxygenases, the central action of nonsteroidal antiinflammatory drugs (but not a prominent effect of steroids), limits inflammation, but it may also alter neural metabolic pathways, resulting in cell death from excitotoxicity or oxidative stress. Randomized controlled trials are needed to determine whether steroids, nonsteroidal antiinflammatory drugs, or both can prevent or treat the symptoms of AD.

ALZHEIMER’S DISEASE: TREATMENT APPROACHES

Treatments of complex diseases may be categorized as empirical versus rational. Empirical treatments, those discovered serendipitously with no prior
suggestion of therapeutic benefit, include many of the important treatments in medicine (e.g. digitalis, aspirin, quinine). By contrast, rational treatments rely on prior knowledge of disease cause or pathogenesis and address these directly (e.g. vitamin replacement in nutrition deficiency disorders, L-DOPA in Parkinson’s disease). Recent years have witnessed the growth of a third, intermediate approach: intervening on factors discovered in epidemiologic studies to increase or decrease the risk of disease or its rate of progression (e.g. dietary restrictions in heart disease and diabetes). Now, the enormous power of high-resolution molecular science often rapidly provides a rational basis for treatment strategies that originated as empirical observations or epidemiologically based interventions.

Unfortunately, no known empirical treatments exist for Alzheimer’s disease (AD). Rational treatments will require knowledge of the causes or mechanisms of AD, which remain under intense investigation. Although the neuropathologic hallmarks of AD (β–amyloid plaques, neurofibrillary tangles, and cortical deficiency in acetylcholine) are well known, these features do not necessarily reflect the underlying cause of the disease or its symptoms. In fact, attempts to enhance cholinergic activity (e.g. with tacrine) have met with only modest success (1). Likewise, the utility of rational treatments that inhibit amyloidogenesis (2) or phosphorylation of tau protein into neurofibrillary tangles (3) will require the demonstration that such inhibition alters the development or progression of AD symptoms.

Until recently, the intermediate AD treatment strategy of risk-factor intervention seemed equally dismal in prospect. The most potent risk factors discovered to date (other than age itself) are genes (4, 5), several of which have now been identified (see AD Roses, this volume). Obviously, little can be done currently to alter these genes. The remaining (environmental) factors that are suggested to modify risk of AD have been recently reviewed by Henderson (6), Breteler et al (7), and Fratiglioni (8). These include head injury (9–13), hypothyroidism (14, 15), and past history of depression (7, 16, 17). Evidence has also mounted that AD risk is increased in those with lower premorbid intelligence (18), low educational achievement (19–22) or complexity of lifetime occupation (22), and lower intracranial volume (23). The convergence of the last four findings may support the concept that “cerebral reserve” influences risk of AD, such that those with less synaptic density or neuronal development may be susceptible to the effects of the neurodegenerative AD process a few years sooner than their counterparts (24, 25). Notwithstanding the scientific interest of all these risk factors, a quick glance at the list reveals that none will be easily amenable to modification. Most are intrinsically undesirable and are therefore probably avoided already to the extent possible.
ANTI-INFLAMMATORY TREATMENTS AND ALZHEIMER’S DISEASE: THE EPIDEMIOLOGIC EVIDENCE

This review deals with a potential new treatment strategy that rests on the association of AD with prior occurrence of several medical conditions or treatments. Numerous reports now suggest that patients who take anti-inflammatory drugs or suffer from inflammatory diseases like arthritis have reduced risk of developing AD (26–29). Especially provocative is the study of McGeer et al (30), which reviewed 7490 hospital discharges of elderly patients seeking concomitant diagnoses of rheumatoid arthritis and AD. The rate of such occurrence was 0.39%, or six to twelve times lower than would have been predicted (assuming independence of the two diagnoses) by the product of the rates for the individual diseases. Interpreting this finding, McGeer proposed that sustained use of nonsteroidal anti-inflammatory drugs (NSAIDs—a mainstay of treatment in rheumatoid arthritis), corticosteroids, methotrexate, or other anti-inflammatory agents might mitigate against the neurodegenerative process of AD. Subsequently, Lucca et al (31) showed that subjects entering AD clinical trials reported little prior use of NSAIDs when compared with population samples of the same age. It is possible, of course, that the AD cases in both studies may have under-reported symptoms that would lead to the diagnosis of a specific disorder such as rheumatoid arthritis (32), or to the prescription of anti-inflammatory treatments. There are related results, however, that show a low incidence of AD in Japanese leprosy patients who are on continuous dapsone (which has anti-inflammatory activity) or its derivative (33). Chui et al (34) have also shown that prevalence of amyloid plaques is reduced in the brains of leprosy patients (treatment history unknown). Finally, Rich et al (35) found that AD research clinic patients who endorsed ongoing use of NSAIDs at entry had experienced later onset of symptoms, showed reduced severity of symptoms after adjustment for age and duration of disease, and—most interestingly—displayed slower progression of symptoms upon longitudinal evaluation of a wide variety of neuropsychologic measures.

Such findings from clinical samples are subject to several sources of bias and confounding (36, 37) that can lead to spurious associations or misleading conclusions as to cause and effect. Some control over these difficulties is available in carefully designed epidemiologic studies of populations or samples that are selected for attributes other than the disease or treatment in question. With one notable exception (38), such studies now suggest an inverse association between AD and prior use of NSAIDs or other anti-inflammatory drugs. Graves et al (39) described a case-control study in which an odds ratio (o.r.) of 0.73 [95% confidence interval (c.i.) of 0.38–1.38] suggested that AD risk may be reduced in those reporting prior use of glucocorticoids (an
o.r. of less than 1 indicates inverse association between two variables). The EURODEM collaborative meta-analysis of 11 case-control studies of AD (15) calculated an o.r. for osteoarthritis and AD of 0.7 (95% c.i. of 0.5–1.0). Broe et al (27) found an o.r. for arthritis and AD of 0.56 (95% c.i. of 0.36–0.87) in an analysis of 400 matched pairs of Australian AD cases and controls. Henderson et al (40) found a significant inverse association of AD and heavy analgesic use in the same subjects (o.r. 0.7) and noted a significant interaction with age: The effect was apparent only in AD cases with onset after age 70 (o.r. 0.52, P = 0.03, P for interaction with age = 0.05). More recently, two studies have compared prevalent AD cases ascertained systematically from defined populations with normal subjects from the same source. The Canadian Study of Health and Aging found an o.r. of 0.55 (95% c.i. of 0.37–0.82) for AD and concurrent or prior use of NSAIDs (21). The Rotterdam population study of AD (41) found an o.r. of 0.38 (95% c.i. of 0.15–0.95) associated with concurrent NSAID use. Many of these studies also showed relative specificity of the reported effects with arthritis or antiinflammatory drug use, as contrasted with other common diseases or treatments.

Because there are probably several forms of AD with distinct distributions of onsets associated with different predisposing genes (5), the above-described case-control work is vulnerable to a variety of difficulties that can result when comparisons are made between cases and controls of unmatched genotype. For the most part, these difficulties will introduce noise in the analyses and thus reduce statistical power to detect real effects. Even when subjects are matched for (known) genetic risk factors, results may differ widely depending on the age of the sample (42). Thus, two recent studies have attempted to achieve some control on genes, and to examine further the interaction with age first noted above in the Australian case-control study. In a study of 50 twin pairs who were discordant for onset of AD, Breitner et al (43) found an o.r. of 0.25 (95% c.i. of 0.06–0.95) for AD and prior treatment with ACTH or cortico-steroids. Similar (but inconclusive) effects were observed in the small number of twin pairs who differed with respect to sustained prior use of NSAIDs. Combining the two drug classes post hoc into a single variable of anti-inflammatory treatments yielded an o.r. of 0.24 (95% c.i. of 0.07–0.74). The effect was stronger in monozygous than in dizygous pairs (o.r. in the former 0.09, 95% c.i. of 0.00–0.67), and in pairs over age 70 (o.r. 0.13, 95% c.i. of 0.01–0.97).

The same investigators have followed up these findings with a detailed study of siblings (similar in effect to dizygous twin pairs) from families at very high risk of AD (37). Survival analytic methods were used to demonstrate specifically that the onset of AD is delayed with sustained prior exposure to NSAIDs. When subjects reported more than 1 year of sustained NSAID use, the hazard ratio (analogous to o.r. in time-dependent analyses) with AD onset was 0.075 (95% c.i. of 0.02–0.26). In the same study, the effect with glucocor-
ticoids was similar to that reported previously but was inconclusive because of the small numbers of subjects who reported prior use of these drugs. As with the preceding twin study, results from Breitner’s sibling study suggested that the inverse relation with AD was attributable to the anti-inflammatory treatments and not to the presence of arthritis or other underlying clinical indication for their use. Again, the effect was stronger in older subjects (age >70). When subjects were categorized by their genotype at APOE, the polymorphic locus for apolipoprotein E (the major known genetic risk factor for AD), there was a trend suggesting that NSAIDs were effective mainly in subjects who lacked the pathogenic ε4 allele. The sibling study also showed an unexpected finding: a similar inverse relation between AD and sustained prior use of histamine H2 blockers. The latter drugs had never been previously investigated as a potential risk (or protective) factor for AD, and the interpretation of this finding therefore requires confirmation in independent studies.

INFLAMMATION AND ALZHEIMER’S DISEASE: BASIC SCIENCE FINDINGS

The value of observational data such as those suggesting an inverse association between AD and anti-inflammatory treatments is increased when work in the basic sciences can provide rational mechanisms to account for the observations. Numerous recent experiments now provide a considerable body of evidence for the involvement of immune and chronic inflammatory mechanisms in AD. Excellent reviews have recently been offered by Aisen & Davis (44) and by McGeer et al (45, 46). There is evidence of elevated activity in AD of cytokines such as interleukin-1β (IL-1β) (47), IL-6 (48, 49), and tumor necrosis factor (50). These cytokines are mediators of the so-called acute-phase reactants to cellular injury such as fibrinogen, C-reactive protein, and α1-antichymotrypsin. Preliminary data suggest that the last two are elevated in cerebrospinal fluid of AD patients (44), and α1-antichymotrypsin is a component of the amyloid plaques that are a hallmark of AD (48, 51, 52). Some isoforms, but not others, of the amyloid precursor protein, which gives rise to the Aβ fragment that accumulates as amyloid in these same plaques, contain protease inhibiting domains (53), and it has been suggested that the amyloid precursor protein is itself an acute-phase reactant (its expression is dramatically influenced by cytokines such as IL-1 and IL-6) (54, 55). Amyloid synthesis and deposition are dramatically increased at or near sites of neural injury (56).

Activated microglia are found within or near all AD lesions (57). These phagocytic cells produce complement proteins (58). They attach to their targets using surface receptors for immunoglobulins (57, 59) and complement components (59, 60). They generate oxygen-free radicals (61–63), nitric oxide
(62, 63), and other potential toxins (64). They produce IL-1β, IL-6, and tumor necrosis factor. Finally, there is strong evidence for synthesis of numerous brain-derived components of the classical complement pathway in AD (65) (see also 45), and a critical distinction has been proposed between those amyloid plaques that contain dystrophic neurites (presumed evidence of nearby nerve process destruction) and the complement Membrane Attack Complex of components C5b–C9 (45, 66, 67), versus so-called diffuse amyloid plaques, which lack these features.

THE STATE OF THE ART, INTERPRETATION, AND CURRENT POTENTIAL FOR TREATMENT

These findings lend credence to the role of inflammation in AD, and they therefore support a role of anti-inflammatory treatments in the palliation or prevention of AD symptoms. They do not, however, prove that inflammatory mechanisms cause the neurodegenerative process of AD, as opposed to mopping up after some other sort of primary neural injury. The posited inflammatory mechanisms do not, for example, explain why the various isoforms of apolipoprotein E should have a dramatic effect on risk of AD. Furthermore, they do not explain why anti-inflammatory treatments should have differential effects on early onset versus late-onset cases, or on those with the ε4 allele atAPOE versus those without this allele. Finally, to the extent that H2 blockers actually do stem the occurrence of the AD process, a purely inflammatory theory of AD pathogenesis offers no direct explanation for this phenomenon.

Breitner et al (37) have proposed an alternate explanation for the epidemiologic observations with anti-inflammatory treatments and H2 blockers (with further support for the latter now available in preliminary evidence from additional, JCS Breitner, unpublished experiments). This formulation relies upon the demonstrated activity (68) of all NSAIDs as inhibitors of cyclooxygenase(s) (COX), which oxidize arachidonic acid (typically cleaved from cell membranes by phospholipase A2) to prostaglandins (69–71). It is noteworthy here that glucocorticoids, which are otherwise far more potent anti-inflammatory agents, do not inhibit activity of COX [although the enzyme’s synthesis may be reduced in some cell types when steroids are present (72)]. Thus, a finding that NSAIDs ameliorated or prevented the process of AD whereas steroids did not would suggest that inhibition of COX, and not suppression of acute-phase response and other aspects of inflammation, is the key to the activity of anti-inflammatory interventions in AD.

By contrast, COX is an important mediator of signal transduction in the calcium-dependent postsynaptic cascade that follows glutamatergic stimulation of the pyramidal cells with n-methyl-D-aspartate (NMDA)-type receptors (73) to induce long-term potentiation (74) or, with excessive stimulation,
excitotoxic cell death (75, 76). The latter cells are found predominantly in layers III and V of cortex and in hippocampus, all sites of intense neural injury in AD and the sites at which intraneuronal apoE appears to accumulate in this disease (77). Their vulnerability to excitotoxicity is increased in the presence of Aβ (78), and the sensitivity of their response to glutamate is increased in the presence of histamine, through a mechanism that may be inhibited (or at least suppressed) by blockade of H2 receptors (79).

Although none of this evidence offers conclusive proof that anti-inflammatory treatments or suppression of COX activity can inhibit or impede the pathogenesis of AD, it provides strong impetus to the search for such proof. An important goal for current research in AD is therefore an answer to the question of whether steroids, NSAIDs, or both are effective in preventing or ameliorating the symptoms of the disease. Most of the available epidemiologic evidence suggests that NSAIDs are the antiinflammatory agents that may influence the expression of the AD process. The single exception is Breitner's twin study, but that investigation counted steroid exposure when subjects had received only a single intraarticular injection of hydrocortisone. It seems unlikely that such a single injection would modify risk of AD, but more plausible that recall of such an injection would have served as a proxy indicator for severe arthritis, which would presumably have led to demand for other treatments. These other treatments may not have been captured by the study's data-gathering instruments, which included only a single retrospective question on the use of NSAIDs. The follow-up sibling study, which pursued these exposures in considerable detail, showed a weaker effect with steroid treatments than with NSAIDs.

Should physicians start prescribing antiinflammatory NSAIDs or steroids for the prevention or palliation of AD symptoms? We believe such prescriptions are premature until more is learned about whether either or both of these treatments are efficacious. The side effects of glucocorticoids are too well known to bear restatement here. The adverse effects of NSAID use are typically more benign, but these drugs induce a fourfold increased risk of (potentially fatal) asymptomatic gastrointestinal ulceration and bleeding (80). Experiments are needed that can help adjudicate the competing hypotheses that inflammatory processes are a primary cause of AD versus the notion that neurodegeneration results from mechanisms that involve COX but do not incorporate classical inflammatory pathways. Because steroids and NSAIDs are commonly used by the same individuals at different times for treatment of severe inflammatory diseases, it will probably not be possible to distinguish their effects in observational (retrospective) studies of subjects taking steroids or NSAIDs for treatment of inflammatory diseases. We note, however, that steroids are commonly used for the treatment of respiratory ailments and blood dyscrasias, for which NSAIDs provide no benefit. Thus, sufficient numbers of
patients may be available in large epidemiologic studies to assess the effects of steroids without NSAIDs, and vice versa.

Whatever the benefit of such observational studies, the definitive proof of the effects (or lack thereof) from these two strategies can only come from randomized controlled trials. One such trial with NSAIDs has been published. Rogers et al (81) conducted a small randomized controlled trial of the prototypic NSAID indomethacin in patients with mild AD. Twenty-eight subjects completed the trial, half of whom had been treated with indomethacin for six months, the other half of whom had been treated with placebo. Differential noncompletion was a problem in this study; a substantial proportion of those on the active drug dropped out, mostly because of the well-known gastrointestinal side effects of indomethacin. Outcome was measured in terms of change on several common neuropsychologic measures. Although no individual test yielded statistically significant results, there were clear trends with all measures that suggested the progression of AD was slowed or blocked in the treated group. A post-hoc combination of all tests into a composite measure did yield a significant effect of the treatment. Although preliminary, these results have stimulated widespread interest in the potential of NSAIDs as a treatment for AD.

In contrast to the randomized trial of indomethacin, a recently completed preliminary trial of low-dose prednisone (36) demonstrated that this treatment is well tolerated, but it provided no suggestion of any palliative or ameliorative effect in AD. A larger treatment trial with prednisone is now being conducted by the Alzheimer’s Disease Collaborative Study Group, and larger studies with indomethacin are said also to be underway. The additional data from these experiments will certainly help to clarify whether the principal effect of anti-inflammatory treatments in AD is through suppression of acute-phase reactants and other hallmarks of classical inflammation or through the suppression of COX. Other, more ambitious trials will be needed to assess whether NSAIDs, steroids, or both can forestall the development of AD symptoms in individuals who are currently asymptomatic. For the moment, we would emphasize that (particularly in view of the above preliminary results) a failure of the prednisone trial to show therapeutic benefit should not be taken as the last word on the role of anti-inflammatory treatments in AD. Not only is this a treatment (as opposed to prevention) trial, but the possibility remains that NSAIDs may be effective where steroids are not. This last notion will require testing with a separate trial of NSAIDs, preferably employed to prevent incident AD rather than to treat existing disease.
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Literature Cited


