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Nonsteroidal anti-inflammatory drugs in Alzheimer's disease

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Article abstract—We reviewed the records of 210 patients in the Johns Hopkins Alzheimer's Disease Research Center to evaluate the role of nonsteroidal anti-inflammatory drugs (NSAIDs) on clinical features and progression of the disease. We compared patients taking NSAIDs or aspirin on a daily basis (N = 32) to non-NSAID patients (N = 177) on clinical, cognitive, and psychiatric measures. The NSAID group had a significantly shorter duration of illness at study entry. Even after controlling for this difference, the NSAID group performed better on the Mini-Mental State Examination, Boston Naming Test, and the delayed condition of the Benton Visual Retention Test. Furthermore, analysis of longitudinal changes over 1 year revealed less decline among NSAID patients than among non-NSAID patients on measures of verbal fluency, spatial recognition, and orientation. These findings support other recent studies suggesting that NSAIDs may serve a protective role in Alzheimer's disease.

Neuropathologic study of brain tissue from Alzheimer's disease (AD) patients has identified reactive microglia densely embedded around the amyloid core in senile plaques.[1] Postmortem analyses of AD brains also reveal the presence of several immunoprotective proteins that are normally absent or expressed at very low levels in normal brain.[2] These indicators of immune-mediated autodestructive processes in AD suggest a potential therapeutic role for anti-inflammatory medications. To test this hypothesis, Rogers et al[3] compared neuropsychologic performance before and after a 6-month trial of indomethacin (a widely used nonsteroidal anti-inflammatory drug) or placebo in 28 AD patients. Performance on cognitive tests declined substantially (8.4% decrease from baseline) in the untreated group. In contrast, the indomethacin group showed a slight improvement (1.3% increase over baseline).

Further support for an inverse relationship between anti-inflammatory medications and AD is the low prevalence of AD among patients with rheumatoid arthritis.[4-6] Case-control studies have suggested that anti-inflammatory medications, prescribed for rheumatoid arthritis and other conditions, act as a protective factor for AD.[4,7] Most recently, Breitner et al[8] studied twin pairs who were discordant for AD (ie, disease onset separated by more than 3 years). In women, unaffected or delayed-onset co-twins were more likely than AD probands to have had prior treatment with steroids, adrenocorticotrophic hormone, or extended use of nonsteroidal anti-inflammatory drugs (NSAIDs).

The present study is a further investigation of the relationship between anti-inflammatory medication use and neuropsychologic characteristics in a large sample of patients with probable or possible AD. We identified patients taking NSAIDs during the 12 months prior to study entry and compared them to those who were not.

Methods. We examined the records of 210 consecutive patients in the Johns Hopkins Alzheimer's Disease Research Center (ADRC). This cohort consists of patients diagnosed with probable or possible AD[9] who entered the ADRC in the period 1984 to 1987 (one patient died before his first visit). The initial evaluation for entry into the ADRC included a medical history review, neurologic, psychiatric, and neuropsychologic examinations, brain CT, and appropriate laboratory studies. The medical history included a survey of current medications and those taken over the previous 12 months, regardless of duration. Medications were categorized as NSAIDs, beta blockers, diuretics, digitalis, hypoglycemics, anticonvulsants, benzodiazepines, other sedatives and hypnotics, neuroleptics, antidepressants, "antidementia" drugs (eg, ergoloid mesylates, lecithin), multivitamins, miscellaneous prescription drugs (eg, platelet aggregates), and miscellaneous over-the-counter medications (eg, antacids). The coding of over-the-counter anti-inflam-

matory medications, such as aspirin or ibuprofen, depended on the reported frequency of their use. When used on a daily basis, they were coded as "NSAIDs"; when used on an as-needed basis, they were coded as "miscellaneous over-the-counter medications." The medication questionnaire was completed by a physician, based on an interview with the patient's caregiver (in most cases, the patient's spouse).

Thirty-two patients were identified who were taking NSAIDs at the time of entry into the ADRC. The two most common NSAIDs were aspirin, used by 12 patients, and ibuprofen, used by seven patients. Other NSAIDs, used by three or fewer patients each, were naproxen, combined aspirin/magnesium hydroxide/aluminum hydroxide, meclofenamate sodium, sulindac, naproxen sodium, fenoprofen calcium, piroxicam, and gold shots. Three patients were taking two or more NSAIDs concurrently. The remaining 177 patients comprised the non-NSAID group.

All subjects received a battery of neuropsychologic tests to assess mental status, various language functions, spatial cognition, learning and memory, mood, and the ability to carry out activities of daily living. The battery, described by Brandt et al,[10] consisted of the Mini-Mental State Examination[11] (MMSE), a Category Fluency Test, Boston Naming Test[12] (30-item short form), Responsive Naming Test,[13] Token Test,[14] Block Design subtest of the Wechsler Adult Intelligence Scale–Revised (WAIS-R),[15] Benton Visual Retention Test[16] (immediate and delayed), Gollin Incomplete Figures Test,[17] Delayed Recognition Span Test,[18] the Psychogeriatric Dependency Rating Scales[19] (PGDRS), and the Hamilton Depression Rating Scale.[20] Other variables of interest included age at onset (determined by history), duration of symptoms (years ill), years of education, and a rating of extrapyramidal symptoms.[21]

Results. We compared the relevant patient characteristics and mean scores on the neuropsychologic measures from visit 1 (table 1). Although there were substantially fewer patients taking NSAIDs than not, the assumption of homogeneity of variance was not violated. Therefore, t tests could be used to compare the groups on each measure. The groups did not differ significantly in age at disease onset or years of education. A MANOVA was performed to determine if there was an overall group difference in performance on the 10 cognitive tests from the battery described above. This analysis included data from only 128 of the 209 patients, because some tests (such as the Benton Visual Retention Test and the Block Design subtest of the WAIS-R) were not administered to patients who scored below 8 on the MMSE. The group difference was not significant (F[10, 117] = 0.72, p = 0.71), which may not be surprising because preexisting group differences would be attenuated or eliminated by excluding from the analysis the most severely impaired patients. Because of this limitation, we employed univariate analyses to explore group differences. Significant group differences in favor of the NSAID group were found for scores on the MMSE, Category Fluency Test, Boston Naming Test, and 10-second delayed recall of the Benton Visual Retention Test. In each case where a difference was found, the NSAID group performed better than did the non-NSAID group.

The groups also differed in disease duration (p = 0.003). The non-NSAID group had been ill longer at

Table 1. Baseline (visit 1) clinical and cognitive scores for probable/possible AD patients

	NSAID	Non-NSAID	p
N	32	177	
Onset age	67.59	65.72	NS
Years ill	3.13	4.21	0.003
Years of education	12.53	12.72	NS
Mini-Mental State Examination	17.53	14.10	0.002
Category Fluency Test	19.59	14.74	0.05
Boston Naming Test	18.00	13.84	0.01
Block Design	8.54	6.06	NS
Responsive Naming Test	10.31	8.72	NS
Token Test	136.56	129.13	NS
Benton Visual Retention Test			
Immediate	6.15	4.58	NS
Delayed	1.07	0.58	0.01
Gollin Incomplete Figures Test*	2.97	3.12	NS
Delayed Recognition Span Test	4.51	3.85	NS
Psychogeriatric Dependency Rating Scale			
Orientation*	1.46	1.76	NS
Behavior*	3.58	4.11	NS
Physical*	3.83	5.11	NS
Hamilton Depression Scale*	4.92	5.26	NS
Extrapyramidal Rating Scale*	0.61	0.57	NS

NSAID Nonsteroidal anti-inflammatory drug.
  NS Not significant.
    * Low scores indicate better performance on these measures.

the time of entry (4.2 years) than had the NSAID group (3.1 years). We therefore performed ANCOVAs, with years ill as the covariate, to compare the groups on the measures that differed initially. Results of those analyses indicated that the NSAID group still performed better than did the non-NSAID group on the MMSE (F[2, 206] = 6.09, p = 0.01), the Boston Naming Test (F[2, 206] = 4.3, p = 0.04), and the delayed condition of the Benton Visual Retention Test (F[2, 151] = 5.26, p = 0.02). Although the groups did not differ significantly on the remaining neuropsychologic measures, the differences between the residualized means on 11 of the 12 remaining cognitive and behavioral tests were in the expected direction, which far exceeds chance expectation (p = 0.003, binomial test).

To determine whether there was any influence of NSAIDs on the rate of progression of AD, we calculated change scores from visit 1 to visit 3 (1 year later) for each neuropsychologic measure. The patients' group assignments from visit 1 were maintained for this analysis, even if their medication status had changed in the ensuing year. Because the NSAID group had higher MMSE scores than did non-NSAID patients at visit 1, however, it was possible that the two groups would have different rates of cognitive change associated with their different starting points rather than with medication status per se. Specifically, one could argue on rational grounds that higher initial scores allow more "room" to decline over time and therefore may be associated with *greater* change scores; others (eg, Morris et al[22]), however, have found empirically that higher initial MMSE scores are asso-

Table 2. Clinical and cognitive 1-year change scores (visit 1 to visit 3) for probable/possible AD patients

	NSAID	Non-NSAID	p
Mini-Mental State Examination	3.93	4.76	NS
Category Fluency Test	3.67	6.31	0.038
Boston Naming Test	3.74	4.29	NS
Block Design	1.94	3.39	NS
Responsive Naming Test	1.13	1.68	NS
Token Test	16.94	10.28	NS
Benton Visual Retention Test			
Immediate	2.00	2.68	NS
Delayed	0.50	0.44	NS
Gollin Incomplete Figures Test*	-0.12	-0.12	NS
Delayed Recognition Span Test	-0.13	1.25	0.0002
Psychogeriatric Dependency Rating Scale			
Orientation*	-0.29	-1.49	0.004
Behavior*	3.50	3.65	NS
Physical*	-3.14	-5.08	NS
Hamilton Depression Scale*	2.09	2.52	NS
Extrapyramidal Rating Scale*	-0.26	-0.40	NS

NSAID Nonsteroidal anti-inflammatory drug.
NS Not significant.
* Low scores indicate better performance on these measures; therefore, positive change scores indicate improvement.

ciated with *slower* rates of decline. In this cohort, initial MMSE scores were positively correlated with 1-year change scores on the MMSE ($r = 0.15$, $p < 0.05$) and the Category Fluency Test ($r = 0.26$, $p < 0.001$). Those with greater initial MMSE scores also had increased behavioral problems as measured by the PGDRS ($r = 0.26$, $p < 0.004$) but less decline in physical problems on that scale ($r = -0.23$, $p = 0.01$). The mean raw change scores on the clinical and cognitive measures for each group are provided in table 2. Despite the fact that NSAID patients had higher MMSE scores than did non-NSAID patients at visit 1, and that those with higher initial MMSE scores showed greater decline after 1 year on the measures listed above in the cohort as a whole, the patients taking NSAIDs actually declined *less* than those who were not taking NSAIDs on the Category Fluency Test, Delayed Recognition Span Test, and Orientation subscale of the PGDRS. The other differences between groups were not statistically significant.

Finally, because patients may have been taking aspirin in low doses for cardiac or stroke prophylaxis rather than the larger doses used for anti-inflammatory purposes, and because other studies involving anti-inflammatories did not include aspirin as an NSAID, we conducted additional analyses excluding patients taking aspirin or aspirin-containing medications. This reduced the NSAID group to 21 patients; the non-NSAID group remained unchanged at 177 patients. After covarying for years ill, analyses revealed that the NSAID group performed better than did the non-NSAID group on the MMSE (NSAID residualized mean = 17.32, non-NSAID mean = 14.16, $p = 0.017$) and the Boston Naming Test (NSAID residualized mean = 17.63, non-NSAID mean = 13.91, $p = 0.05$).

Discussion. The results of this study support a protective role for anti-inflammatory medications in the cognitive impairment of patients clinically diagnosed with AD. Even after correcting for disease duration, patients taking NSAIDs had higher scores on the MMSE, Boston Naming Test, and delayed condition of the Benton Visual Retention Test than did patients equated for education and age at disease onset who were not taking NSAIDs. There was also a trend toward better performance for NSAID than non-NSAID patients on the remaining neuropsychologic variables. The tests on which group differences emerged are particularly noteworthy because overall mental status, as measured by the MMSE, is often used to index severity of dementia, and confrontation naming, measured by the Boston Naming Test, is typically impaired early in the course of AD and declines very regularly and precipitously with disease progression.[23] Thus, anti-inflammatory medications appear to benefit neuropsychologic performance on the tasks that are most sensitive to early impairment and subsequent decline in AD. Performance differences on the MMSE and Boston Naming Test remained even when the sample size was reduced by removing patients whose only anti-inflammatory medication was aspirin.

The present results are also consistent with the findings of Rogers et al[3] of a significant divergence in MMSE scores between well-matched AD patient groups after 6 months of randomly assigned indomethacin or placebo. In that study, change scores on the Boston Naming Test over the 6-month interval were also in the predicted direction, although the group difference did not reach significance. In the current study, analyses of change scores calculated for a 1-year interval revealed less decline among the NSAID than non-NSAID patients on measures of verbal fluency, spatial recognition, and orientation. This result is particularly striking considering that, among the entire cohort, higher initial MMSE scores were associated with slightly greater deterioration on the MMSE, Category Fluency Test, and Behavior subscale of the PGDRS after 1 year. The reduced decline among the NSAID patients, who also had higher initial MMSE scores, suggests that NSAID use may supercede (ie, reverse) the steeper decline associated with higher initial mental status scores.

There are several mechanisms by which NSAIDs may enhance cognitive performance or inhibit its decline in AD. NSAIDs may confer a protective function in AD by their primary anti-inflammatory properties, free-radical quenching, or a combination of these factors.[24]

Rogers et al[25] found several immune-related antigens (eg, HLA-DR, a major histocompatibility complex class II surface glycoprotein) in AD brains in association with neuritic plaques. Others[2] have detected the C1-C4 components of classic complement proteins in senile plaques, dystrophic neurites, neuropil threads, and some neurofibrillary tangles by immunohistochemical staining. These findings provide evidence of a complement-mediated inflammatory response at the sites of greatest neuropathology in AD. These inflam-

matory changes may be involved in the development of AD pathology or may be a secondary response by the diseased brain. The cells apparently implicated in antigen expression are the reactive microglia associated with phagocytosis of immune complexes. Notably, reactive microglia are the predominant inflammatory cell population in the CNS, and are associated not only with senile plaques but with neurofibrillary tangles and dystrophic neurites as well.[2] Thus, chronic anti-inflammatory medication use could potentially slow or reverse cognitive deterioration in AD patients by inhibiting inflammatory responses.

Another potential mechanism involves free radicals, which have also been implicated in the pathogenesis of AD.[24] Salicylate, the prototypic NSAID, serves as a trap for hydroxyl radicals.[26] Thus, NSAIDs may reduce inflammation in AD through free-radical quenching.

The results of this and other recent studies suggest a prophylactic and therapeutic role for NSAIDs in slowing or decreasing the cognitive impairments associated with AD. In the present study, we did not control experimentally the duration and dosing of patients' medications. Patients in the NSAID group may have been taking the medication for as few as 2 days at the time of study entry. Patients who used NSAIDs on an as-needed basis may have taken more of the medication spread out over the year than patients whose use was limited to the 2 days preceding entry into the ADRC. Nevertheless, we would have assigned them to the non-NSAID group in this study. These assignment decisions place a conservative bias on the present results. Therefore, group differences observed here are likely an underestimate of the true magnitude of difference between the cognitive performance of patients who use NSAIDs regularly and those who do not.
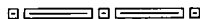
Methodologic limitations inherent in retrospective studies such as this one preclude us from addressing the specificity of the protective effect of NSAIDs. We coded patients' medication status into 14 drug categories and obtained demographic information, other patient characteristics, and performance scores on 10 cognitive measures and five clinical measures on multiple occasions. Given the overall sample size of 209 patients and the small and nonuniform number of patients taking each medication, the loss of statistical power associated with a true test of specificity would render such an analysis problematic. The results of this study, examining only the influence of NSAIDs on initial neuropsychologic performance and its relation to change after 1 year, are consistent with several lines of research suggesting a protective role for NSAIDs in the risk, severity, and progression of AD. Future studies should investigate this relationship prospectively and address the issue of specificity by comparing the effect of NSAIDs to that of other medications.

Acknowledgment

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Relationship between lifetime occupation and parietal flow:
Implications for a reserve against Alzheimer's disease pathology

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Article abstract—We previously reported an inverse relation between parietal cerebral blood flow and years of education in Alzheimer's disease (AD) patients matched for clinical severity. This suggested that the clinical manifestation of advancing AD pathology is delayed in patients with higher educational attainment. Other aspects of life experience may also provide a reserve against the clinical expression of AD. To test this hypothesis, we classified the primary lifetime occupations of 51 AD patients using the *Dictionary of Occupational Titles*, published by the US Department of Labor, and derived six factor scores describing intellectual, interpersonal, and physical job demands. Regional cerebral blood flow was measured using the xenon-133 inhalation method. After controlling for age, clinical dementia severity, and education, there was less relative perfusion in the parietal region in subjects whose occupations were associated with higher interpersonal skills and physical demands factor scores. We conclude that independent of education, aspects of occupational experience may provide a reserve that delays the clinical manifestation of AD.

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There have been reports of increased prevalence of dementia in individuals with lower educational attainment, suggesting that life experience may play a role in the clinical manifestation of dementia.[1,2] In a previous study,[3] we hypothesized that education may provide some form of a reserve that must be depleted below a threshold level before dementia is clinically manifested. In that sense, education would protect against the emergence of the clinical features of AD. This hypothesis predicted that, given comparable clinical severity of dementia, patients with more years of education would have more advanced AD pathology. To test this hypothesis, we used the reduced perfusion in the parietal area that occurs in AD[4-7] as an indirect index of AD pathology. Parietal perfusion and metabolic deficit is specific to AD,[8-11] correlates with disease severity,[6] and is homologous with areas of AD pathology.[12] We found that, given comparable clinical severity, years of education correlated inversely with parietal perfusion in AD, supporting our hypothesis.

The cognitive reserve hypothesis suggests that aspects of life experience supply a set of skills or repertoires that allow an individual to cope for a longer time with the progressing AD pathology before the effects of the disease become clinically apparent. If this is the case, the relatively brief period of life spent in school might not be as important as the bulk of later life experiences. To that end, we wondered whether a person's occupational experiences might also play a role in cognitive reserve.

To investigate this concept, we evaluated disease severity and regional cerebral blood flow (rCBF) indices from the same patients as in our previous study,[3] incorporating new information about dimensions of each patient's primary lifetime occupation. Our a priori hypothesis was that occupations that are more cognitively or interpersonally demanding might be associated with reserve. We predicted that after controlling for indices of disease severity, there would be an inverse correlation between measures of pa-