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Delayed Onset of Alzheimer's Disease With Nonsteroidal Anti-Inflammatory and Histamine H2 Blocking Drugs

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BREITNER, J. C. S., K. A. WELSH, M. J. HELMS, P. C. GASKELL, B. A. GAU, A. D. ROSES, M. A. PERICAK-VANCE AND A. M. SAUNDERS. *Delayed onset of Alzheimer's disease with nonsteroidal anti-inflammatory and histamine H2 blocking drugs.* NEUROBIOL AGING **16**(4) 523-530, 1995. – Factors that modify onset of Alzheimer's disease (AD) may be revealed by comparing environmental exposures in affected and unaffected members of discordant twin pairs or sibships. Among siblings at high risk of AD, sustained use of nonsteroidal anti-inflammatory drugs (NSAIDs) was associated with delayed onset and reduced risk of AD. After adjustment for use of NSAIDs, there was minimal effect on onset with reported history of any of three common illnesses (arthritis, diabetes, or acid-peptic disease). However, independent of exposure to NSAIDs, onset was unexpectedly delayed in those reporting extended use of histamine H2 blocking drugs. Randomized clinical trials will be needed to affirm the utility of these drugs for prevention, but the present findings may have implications for pathogenesis: because NSAIDs block the calcium-dependent postsynaptic cascade that induces excitotoxic cell death in NMDA-reactive neurons, and because histamine potentiates such events, excitotoxicity may deserve additional investigation in AD.

Alzheimer's disease Onset Nonsteroidal anti-inflammatory drugs Histamine H2 blocking drugs
Inflammation Cyclooxygenase Histamine Excitotoxicity NMDA glutamate receptors

ALZHEIMER'S disease (AD) is a progressive neuro-cognitive disorder which, without preventive intervention, will affect 10% of the developed world (17,22). The symptoms of AD appear typically between ages 65 and 90 (9). A later onset implies briefer and less severe symptoms, if any, before death (3). The identification of factors that alter onset is, therefore, important. The comparison of environmental exposures among affected and unaffected individuals may reveal such factors. Because several different genotypes, including variants at the polymorphic locus for apolipoprotein E (APOE), predispose to different onset ages for AD (11,12,15,32,35,36), it is wise to control for genetic influences when searching for environmental factors that modify onset (4). Consideration of genetic predisposition seems especially important for demonstration of factors that reduce risk by delaying the expression of AD, since protective influences will be of little consequence in those with no predisposition to disease. Thus, comparisons of exposure histories within discordant twin pairs (5) or others sharing similar disease risk are ideal for the demonstration of protective factors in an unaffected comparison group (8).

In an exploratory study of 50 twin pairs, we recently showed that prior use of glucocorticoids was associated with delay or absence of AD symptoms (6). A possible inverse association of AD with nonsteroidal anti-inflammatory drugs (NSAIDs) in the same study was inconclusive, owing to small numbers exposed. We sought to investigate the hypothesis that anti-inflammatory treatments, either steroids or NSAIDs, are associated with delayed onset of AD. Because additional twin samples with AD were not available to investigate these findings. Furthermore, we studied a sample of siblings who (like dizygous twins) share 50% of their genetic make-up. These brothers and sisters came from 45 pedigrees containing many cases of AD and assembled for genetic linkage studies (32).

METHOD

Subjects and Approach

We identified sibships meeting either of two conditions that could yield information regarding environmental modification of onset: (a) presence of 2 or more cases of AD with onsets that differed in age by 3 or more years; or (b) at least one affected individual and one or more unaffected sibs who had survived 3 or more years beyond the onset age of the index case. After excluding two sibships who had been identified and diagnosed

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by others, we approached 205 individuals whose diagnoses and ages at onset of AD, if any, had been previously established by consideration of all relevant data, including extensive longitudinal observation, laboratory testing, and autopsy confirmation when available (32). Arthritis, peptic ulcer disease, and other nonneurological conditions were not considered when making these diagnoses.

Subjects or their collateral informants received a letter that introduced the research in general but did not reveal the content of the forthcoming interview. We then administered a 15- to 20-min telephone interview to the subjects and/or to collateral informants characterized by subjects' relatives as "most knowledgeable" about their medical histories. Collateral respondents for demented subjects included 37 spouses, 56 siblings or other close relatives, and 17 others. A second informant was interviewed in three instances to obtain complete exposure information. Sixty-three of the 66 living unaffected subjects provided autobiographical exposure data. To control bias resulting from reliance on autobiographical data for nondemented subjects versus collateral responses for demented subjects, we also obtained collateral information for 59 (75%) unaffected individuals, including the 13 who were deceased (Table 1). Collateral informants for the latter were 3 spouses, 9 close relatives, and 1 other. Twenty-two spouses, 21 close relatives, and 3 others provided collateral information for 46 living unaffected subjects.

The structured telephone interview (available on request) addressed exposures by asking 9 primary questions of all respondents. Although our purpose was to ask about prior use of glucocorticoids, nonaspirin NSAIDs, and aspirin, we asked about several other exposures to mask the study hypothesis and to investigate the specificity of effects with anti-inflammatory compounds. We introduced the interview as a survey of "several prior medical conditions and treatments" and asked about the occurrence or treatment of three common medical conditions: arthritis (the most common indication for use of NSAIDs); adult-onset diabetes mellitus; and peptic ulcer disease. We chose these illnesses in preference to other common ailments, e.g., cardiovascular diseases, because the latter may be associated with altered risk of AD (2,22,39). Up to 54 additional questions were asked, when indicated, about physicians' diagnoses for the three illness variables, age at first appearance of symptoms, duration of symptoms, age at first use of medicines, duration of treatment, respondent's understanding of indication for treatment and, dosage for prescription drugs. The primary questions on drug treatments included a listing, read to respondents, of commonly prescribed or widely available drugs in a particular category (e.g., 14 prescription NSAIDs in common use before 1992, 4 brand names for ibuprofen, and generic or store brand ibuprofen). Available treatment responses for diabetes were insulin injections, oral agents, diet or none. Other potential "control" exposures included narcotic analgesics and acetaminophen (paracetamol) or, for acid-peptic disease, histamine H2 blocking drugs. If age at first use was not recalled, we asked respondents to estimate whether treatment began >10 years ago, 5 to 9 years ago, 3 to 4 years ago, 1 to 2 years ago, or <1 year ago. Similarly, when dates of use were not recalled, we asked about duration categories of 1 to 11 months, 1 to 2 years, 3 to 4 years, or >5 years. In scoring frequency of dosage we defined "daily use" as at least one dose on 4 or more days a week for >1 month. "Regular use" of steroids or narcotics meant repeated dosage on a schedule for >3 months. A "don't know" category was available for each question. Interviewers were unaware whether respondents were providing answers for early affected or late-affected sibs with AD but generally knew whether the subject was demented. Interviews were reviewed and edited by a physician (JCSB) who was unaware of the subject's condition, or whether the answers were provided by self-report or a collateral informant.

Analysis

We used survival analytic methods to assess alteration in risk of AD among sibs with particular illnesses or treatments. This approach categorizes subjects by their reported exposures before onset of AD (if any) and relies on subjects' censoring age (current age or age at death) or age at onset. The data were used to estimate and compare the age-specific hazard (incidence) of AD among groups with various reported exposures. Analyses were conducted using the semi-parametric proportional hazards model of Cox (13), fitted with the PHREG procedure in the SAS statistical package (33). The procedure uses Newton-Raphson iteration to maximize the likelihood of the specified model. Risk variables for exposure were coded as dichotomous dummy variables, using values of 0 for no exposure and 1 for exposure. The dependent variable was age of onset in affected individuals and either current age or age at death among those unaffected. Strata were formed consisting of all individuals within a given sibship and likelihood maximized under the assumption of a common hazard over all sibships. Significance of a risk association was evaluated with the Wald chi-square statistic, testing the null hypothesis that the fitted coefficient was equal to 0. The hazard ratio was then calculated as the natural anti-logarithm of the estimated coefficient.

RESULTS

Delay or Prevention of Onset With NSAIDs

Daily use of NSAIDs for 1 month or more was reported most commonly with various forms of ibuprofen (39% of those

TABLE 1

CHARACTERISTICS OF AFFECTED AND UNAFFECTED SIBS

Status	Number	No. Deceased	Censoring Age or Onset*
Affected	107	63	69.1 (9.4 years)
Unaffected, with			
collat. informants only	16	13	74.0 (9.0 years)
collateral + self	43	0	
self-report only	20	0	74.1 (11.3 years)
Total unaffected	79	13	74.0 (9.5 years)
Grand total	186	76	71.2 (9.8 years)

*Mean (SD); Censoring age is age at death, or current age if living.

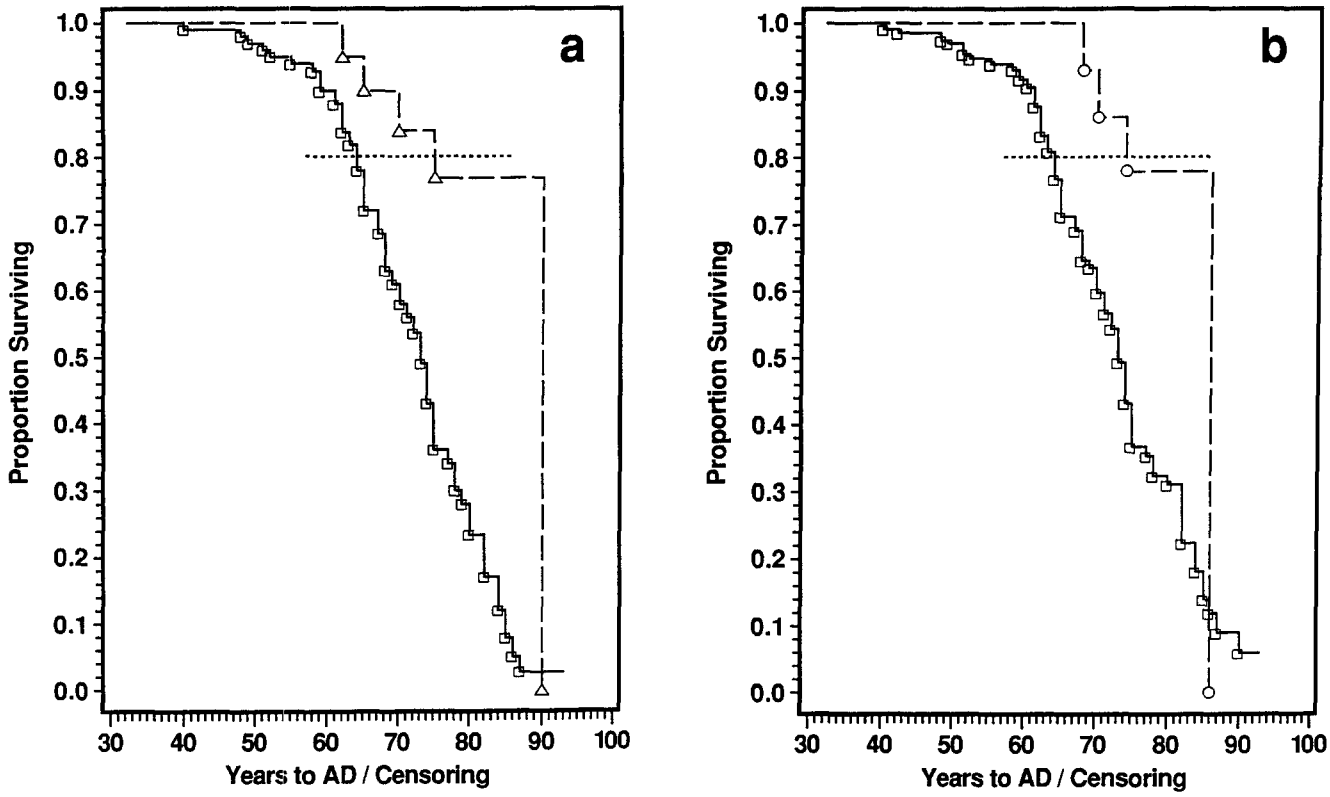

FIG. 1. Disease-free survival in subjects categorized by exposure to NSAIDs or histamine H2 blocking drugs. (a) Effect with NSAIDs. Survival curves plot the estimated probability of remaining free of disease as a function of age. The squares and triangles at the bottom of each riser in the step-plot indicate appearance of one or more new cases among the unexposed and exposed groups, respectively. The method intrinsically adjusts for attrition in the numbers at risk as older ages are considered. The cumulative survival estimates are obtained by chain multiplying the individual survival fractions (number surviving free of disease divided by number at risk) at the appearance of each new case through the age in question. The cumulative incidence before age 90 in the exposed group is 1 minus the survival fraction of 0.75 or 0.25. The comparable figure for unexposed subjects is 0.97. The difference in lifetime risk between the two groups is highly significant (see text). (b) Effect with histamine H2 blocking drugs (subjects with collateral informants). The step plot is generated as in 1a. There is a 10-year difference between the exposed (circles) and unexposed (squares) groups' ages at which cumulative incidence of 20% is realized. The difference in the two curves is highly significant (log rank $\chi^2 = 9.413$, $df = 1$, $p = 0.0022$).

endorsing such use of any NSAID), naproxen (16%), sulindac or indomethacin (8% for each), and piroxicam (5%). Figure 1A shows survival curves (21) for the subjects categorized by prior daily exposure to any nonaspirin NSAID(s) for >1 month. To avoid the possible effects of disproportionate reporting of exposures in autobiographical data, the figure shows results with information from collateral informants only. Similar results were obtained, however, when autobiographical data were included (Table 2). Presumably because of the nature of the sample (which includes several sibships in which all subjects eventually developed AD) the lifetime risk of AD in the unexposed group is extreme. By comparison, the age-specific risk among subjects exposed to NSAIDs is substantially lower (log rank $\chi^2 = 11.97$, $df = 1$, $p = 0.0005$). The horizontal line at 20% cumulative incidence of AD (as an example) is intersected 11 years later in exposed subjects.

We investigated these differences and the association of AD with the remaining exposures using proportional hazards models after the sample was stratified by sibship. The number of strata varied as the number of sibships with relevant exposure information; for example, the analyses with NSAIDs (collateral informants) considered 36 sibships containing from 2 to 8 (mean, median and mode all = 4) members. Table 2 reports hazard ratios (h.r.) that compare the estimated incidence of disease over time in exposed and unexposed sibs. The h.r. is similar to the more familiar odds ratio but is preferable for conditions like AD, because it deals with onset of AD as a time-dependent process (7). An h.r. of less than 1 implies reduced risk of AD with exposure. Thus, the h.r. of 0.228 with NSAIDs indicates that the 20 NSAID users experienced about 1/4 the age-adjusted risk of the 111 nonusers. The criterion for exposure to NSAIDs in the prior twin study had been daily use for at least 1 year. The h.r. here with use of NSAIDs for >1 year ($n = 17$, median duration of exposure 5 years, mean = 9.18, SD = 8.78 years) was 0.075 ($p = 0.0001$), implying that long-term users of these drugs showed less than 1/10 the risk of nonusers for developing AD.

To avoid the possibility that unaffected comparands bore no predisposition to disease, we also undertook an analysis with affected individuals only. The h.r. in this analysis was predictably displaced toward the null value of 1.0, because of truncation in subjects (ignoring those with greatest delay of onset resulting in death before disease expression). Although in the predicted direction, results of this analysis and that of AD with glucocorticoids were statistically inconclusive because of small numbers of exposed subjects affected (only 3 affected subjects had been exposed to NSAIDs in the 31 sibships with multiple

TABLE 2

HAZARD RATIOS FOR RISK OF AD WITH EXPOSURE TO ANTI-INFLAMMATORY OR ANALGESIC DRUGS

Exposure	Source of Data*	Proportion Exposed	Hazard Ratio (95% c.i.)†	p value‡
Glucocorticoids	COL only	6/130	0.542 (0.114–2.570)	0.4405
	COL + AU	9/151	0.569 (0.123–2.633)	0.4703
NSAIDs	COL only	20/131	0.228 (0.068–0.722)	0.0175
	COL + AU	25/151	0.192 (0.058–0.639)	0.0071
(1–12 month)	COL + AU	4/129	0.188 (0.024–1.491)	0.1450
(>1 year)	COL + AU	17/142	0.075 (0.022–0.261)	0.0001
(affected only)	COL only	5/58	0.272 (0.031–2.367)	0.2381
(age ≤ 70)	COL + AU	7/56	0.583 (0.179–1.899)	0.3708
(age > 70)	COL + AU	18/76	0.215 (0.051–0.909)	0.0366
(no ϵ4 allele)	COL + AU	14/48	0.139 (0.018–1.057)	0.0566
(≥1 ϵ4 allele)	COL + AU	11/84	0.556 (0.200–1.547)	0.2611
(women)	COL + AU	17/96	0.181 (0.056–0.580)	0.0040
(men)	COL + AU	8/55	0.415 (0.098–1.757)	0.2320
(AD since 1980)	COL + AU	25/124	0.254 (0.074–0.872)	0.0295
(ignoring exposures for unaffected in last 5 years)	COL + AU	21/151	0.229 (0.068–0.771)	0.0174
Aspirin	COL only	31/136	0.349 (0.130–0.938)	0.0368
	COL + AU	40/157	0.343 (0.139–0.844)	0.0199
(1–12 month)	COL + AU	4/121	0.625 (0.086–4.558)	0.6410
(>1 year)	COL + AU	35/152	0.369 (0.171–0.796)	0.0123
Acetaminophen	COL only	10/131	0.157 (0.020–1.222)	0.0770
	COL + AU	17/152	0.104 (0.014–0.787)	0.0283

*AU = autobiographical; COL = collateral informant(s); †from Cox proportional hazards models; ‡probability of observed data under null hypothesis (h.r. = 1.0).

Results with data from collateral informants (COL) and also, for comparison, with addition of autobiographical data from unaffected subjects lacking collaterals (AU). To improve statistical power, the latter method was used for stratified analyses of main effects or for analyses of interactions. Genotype at APOE was determined using the polymerase chain reaction and restriction fragmentation isotyping, as previously described (34). The sample was stratified by sibship, except for male versus female, young versus old, and APOE genotype comparisons. Owing to small numbers available, simple odds ratios instead of hazard ratios are given for dose-response effects with NSAIDs and aspirin. The variable numbers in the denominators for proportion exposed reflect results of stratification or of variable numbers of subjects with missing data.

cases; only 6 subjects had used regular doses of glucocorticoids, according to their collateral informants).

Studies of Specificity: Additional Effect With Histamine H2 Blockers

We examined the specificity of the effect with NSAIDs by assessing the relation of AD to the three medical conditions and other treatments assessed concurrently. Although adequate power was available to detect an association of AD with any of the three illnesses, only arthritis was associated with a significant alteration in AD risk (Table 3). Because many arthritic subjects would likely have used NSAIDs, we set up an orthogonal comparison of arthritis without use of NSAIDs, as contrasted with NSAIDs used for other indications (no arthritis), and both arthritis and NSAIDs. As was the case in our prior twin study, the association of arthritis with AD was substantially vitiated when subjects reported no use of anti-inflammatory treatments (here, NSAIDs). By contrast, the effect with NSAIDs appeared to be strong among the 4 subjects who lacked arthritis as an indication for use.

We also examined several of the treatments in interaction with NSAIDs. For example, we posited that many subjects using nonaspirin NSAIDs would also have used aspirin for similar indications. An orthogonal comparison of the effect with aspirin and NSAIDs, as above, suggested that aspirin alone produces a weak but similar effect to NSAIDs. Subjects who used acetaminophen (paracetamol) daily reported ingestion of much higher doses than those who took aspirin daily, mostly for prevention of heart disease. Without concomitant use of NSAIDs, daily acetaminophen, which has a weak anti-inflammatory action (29), showed an effect similar to low dose aspirin, but this was statistically inconclusive. The weaker effect with use of both acetaminophen and NSAIDs versus that with NSAIDs alone probably reflects the substantially lower doses of NSAIDs that were reported by those who reported use of both types of drug daily.

Although most of the interview items gave predicted results, there was a strong and unexpected reduction in risk of AD among those reporting prior use of histamine H2 receptor blocking drugs that are commonly prescribed for acid-peptic disease (proportion exposed 29/180, proportion with collateral informants 21/156, see Fig. 1B.). As with aspirin and NSAIDs, the effect with H2 blockers showed an increase in strength with duration of treatment (median in those with >1 year of exposure 5 years, Mean = 7.60, SD = 7.21 years). Because NSAIDs

TABLE 3

HAZARD RATIOS FOR AD WITH NSAIDs IN INTERACTION WITH OTHER VARIABLES, AND EFFECT WITH HISTAMINE H2 RECEPTOR BLOCKERS

Exposure or Condition	Proportion Exposed	Hazard Ratio (95% c.i.)*	p value†
History of peptic ulcer disease (all)	26/184	0.667 (0.296–1.501)	0.3278
Adult onset diabetes (all)	17/185	0.505 (0.203–1.257)	0.1422
Arthritis (all)	62/168	0.454 (0.242–0.852)	0.0139
Arthritis, no NSAIDs	29/123	0.682 (0.382–1.218)	0.3517
NSAIDs, no arthritis	4/99	0 (model indeterminate)	na
Arthritis and NSAIDs	20/116	0.281 (0.113–0.701)	0.0065
Aspirin, no NSAIDs	22/123	0.523 (0.269–1.020)	0.0574
NSAIDs, no aspirin	13/115	0.221 (0.069–0.707)	0.0110
Aspirin and NSAIDs	8/109	0.147 (0.020–1.063)	0.0575
Acetaminophen, no NSAIDs	7/125	0.196 (0.027–1.412)	0.1059
NSAIDs, no acetaminophen	13/132	0.203 (0.064–0.647)	0.0070
Acetaminophen and NSAIDs	7/125	0.255 (0.035–1.842)	0.1757
Peptic ulcer disease, no NSAIDs	16/124	0.577 (0.232–1.431)	0.2353
NSAIDs, no peptic ulcer disease	21/130	0.202 (0.074–0.553)	0.0019
Peptic ulcer disease and NSAIDs	4/112	0.544 (0.075–3.925)	0.5344
Histamine H2 blockers (all)	29/180	0.149 (0.044–0.501)	0.0021
(1–12 month)	11/162	0.203 (0.057–0.716)	0.0209
(>1 year)	10/161	0.060 (0.012–0.298)	0.0009
Histamine H2 blockers, no NSAIDs	18/124	0.247 (0.078–0.784)	0.0177
NSAIDs, no histamine H2 blockers	19/125	0.302 (0.122–0.750)	0.0098
Histamine H2 blockers and NSAIDs	7/113	0 (model indeterminate)	na
Peptic ulcer disease, no H2 blockers	9/149	1.656 (0.542–5.063)	0.3760
H2 blockers, no peptic ulcer disease	15/155	0.224 (0.052–0.974)	0.0460
H2 blockers and peptic ulcer disease	14/154	0.090 (0.011–0.703)	0.0217
Histamine H2 blockers (women)	16/114	0.168 (0.041–0.685)	0.0129
(men)	13/66	0.255 (0.061–1.071)	0.0620
(age $\leq$ 70)	11/64	0.180 (0.043–0.743)	0.0177
(age > 70)	18/93	0.254 (0.061–1.062)	0.0604
(no ϵ4 allele)	14/61	0.411 (0.094–1.788)	0.2360
($\geq$1 ϵ4 allele)	15/96	0.195 (0.048–0.799)	0.0231
(AD since 1980)	29/150	0.294 (0.080–1.075)	0.0643
(affected only)	4/72	0.758 (0.125–4.606)	0.7637
Use of insulin, oral hypoglycemics	14/185	0.526 (0.191–1.447)	0.2135

Collateral data where available, otherwise autobiographical data, except collateral data only for final line in table.

*†As in Table 2, except orthogonal comparisons not stratified by sibship.

Dose-response effect for H2 blockers was examined by calculation of simple odds ratios, owing to insufficient data for meaningful modeling.

can induce gastric irritation, which may have been treated with H2 blockers, we conducted an orthogonal analysis of H2 blockers and NSAIDs. Similarly, we examined the interaction of H2 blockers with their common indication, peptic ulcer disease. The effect with H2 blockers was not explained by use of NSAIDs or by presence of peptic ulcer disease.

Further Analyses: Stratification by Age, Gender, and Genotype at APOE

We observed trends (Table 2) suggesting that the effect with NSAIDs is stronger in subjects with onset or censoring after age 70 (interaction $p = 0.24$), and in those who lack an ϵ4 allele at APOE (interaction $p = 0.14$). The modest difference in results with male and female subjects likely reflects the greater proportion of females at later ages. No differences were apparent in the effect with H2 blockers among contrasting strata of gender or age, but there was a moderate trend toward increasing effect among those with at least one ϵ4 allele (Table 3). Larger numbers of subjects will be required to test the robustness of the opposite directionality of drug–APOE interaction with H2 blockers and NSAIDs.

Apparently Additive Effects of the Two Types of Drug

Figure 2 demonstrates a progressive reduction in proportion affected by AD among subjects with increasing exposure to NSAIDs, H2 blockers, or both. The corresponding hazard ratios are given in Tables 2 and 3. No cases of AD occurred among the seven individuals who had taken both types of drug for a

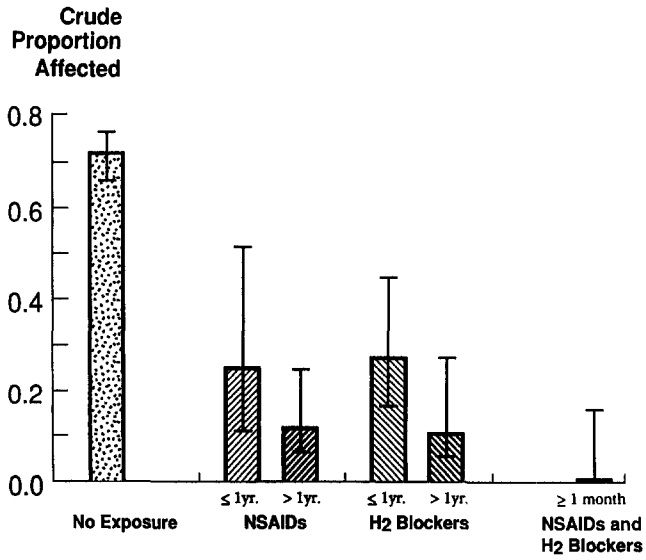

FIG. 2. Alteration in proportion affected by AD with exposure to NSAIDs, H2 blockers, or both. Crude proportions of subjects who had developed AD (means with standard errors shown). Subjects exposed to NSAIDs were evaluated without consideration of exposure to H2 blockers, and vice versa. Reduced proportions of subjects with 1 to 12 months exposure to NSAIDs or H2 blockers were affected with AD. With > 1 year of exposure, the proportions were reduced further. No subject exposed to both types of drugs (not necessarily concurrently) was affected.

month or more (although most had longer periods of exposure; compared with disease occurrence in unexposed subjects, Fisher's exact $p = 0.003$).

DISCUSSION

Comparison With Prior Work

These results corroborate prior observations suggesting that anti-inflammatory treatments are associated with delayed onset of AD (6). They argue specifically that better tolerated NSAIDs are at least as effective as steroids in this regard. They thus support the suggestion (27) that widespread use of NSAIDs by patients with rheumatoid arthritis accounts for reduced occurrence of AD among those with this condition (19). The present analysis in sibs suggests specifically that the reduction in risk with NSAIDs results from delay in the initial expression of AD symptoms. A similar finding with H2 blockers was unexpected, but appeared to be strong and showed a dose–response relationship.

Caveats

Several aspects of this study warrant caution. It employed subjects from families with intense aggregation of AD. Although these families had late-onset disease (not the rare, early onset familial AD that results from chromosome 14 or chromosome 21 mutations), different results might have occurred in more typical sporadic AD. Also, this study used retrospectively gathered data and is, therefore, potentially vulnerable to both confounding and bias. Confounding is spurious association of variables (e.g., a risk factor and a disease state) that results from their respective associations with a third variable (the confounder). Although confounded associations are sometimes misinterpreted as implying cause, the associations are nonetheless real and may therefore be informative. By contrast, bias from any of several sources can suggest associations that are altogether spurious. Bias occurs when a variable is represented out of proportion to its existence in the population of reference, and especially when the degree of such disproportionality differs in two groups being compared. We therefore discuss here the measures taken to control several types of bias.

Because sibs were ascertained from a single source with a response rate of 91%, *ascertainment bias* is not a likely problem. We attempted to curtail the problem of *differential exposure misclassification* due to inaccurate reporting by reading lists of the generic and brand names of anti-inflammatory drug exposures being studied and, when possible, making the inquiry in the context of questions about the disease indication for treatment. Such questionnaire data are of good quality for drugs that are socially acceptable and used chronically (18,23,31) and can be of equivalent quality to in-person interview data for such exposures over time when compared against a "gold standard" of pharmacy dispensing records (30). Retrospective self-report data on prescription NSAIDs, in particular, can show high concordance to pharmacy dispensing data when names of individual drugs and precise dates of use are not critical (42, West, S., personal communication, 1994).

After filling their prescriptions, patients may take "pain killing" drugs including NSAIDs sparingly in fear of dependence. Because such *noncompliance* can also result in exposure misclassification, subject reports arguably provide data on use of NSAIDs that equal or even exceed the quality of prescription or pharmacy dispensing data. The completeness and utility of medical and pharmacy records are further compromised by widespread availability of over-the-counter anti-inflammatory drugs, both ibuprofen and aspirin, and by the fact that often several physicians have prescribed these common drugs over the years to a given patient. For all these reasons, we found medical records to be of limited use in our prior twin study, and we decided not to rely on them here.

Another potential source of bias is *differential demand* for NSAIDs or H2 blockers among affected versus unaffected subjects. Because subjects with AD would likely have demanded or used fewer analgesic medications after the onset of dementia (and because such use could not, of course, delay the onset of AD), we ignored any reported use after disease onset. One analysis also discounted AD cases with onset before 1980, because such subjects would have had limited access before onset to either NSAIDs or H2 blockers which were widely prescribed only after the mid-1970s (Table 2). Likewise, because unaffected sibs survived an average of 5 years beyond the onset age of affected sibs (Table 1) and therefore had 5 more years for potential exposure, we explored results after ignoring reported use of NSAIDs or H2 blockers in the last 5 years of unaffected subjects' lives. Both of the latter 2 approaches resulted in negligible changes in the hazard ratios.

Several sources of *recall bias* are also of concern here. Relatives commonly seek "reasons" for the development of AD in those afflicted. In the usual instance these factors (e.g., use of alcohol or aluminum cookware) are assumed to be directly (positively) associated with disease, but we found an inverse association of drug use with AD. We also attempted to control this sort of bias by not advising respondents in advance about the content of the interview, even though doing so might have improved accuracy of reporting on exposures. We relied on other measures to aid recall (see above), and we reasoned that the remaining "noise" from inaccurate recall would likely displace the observed hazard ratios toward the null value of unity. Recall bias was further controlled by separate analyses of subjects with collateral informants only (ignoring autobiographical informa-

tion) in the evaluation of main effects (Table 2). Comparison of results from collaterals alone versus analyses of both collateral and autobiographical data suggested only slight bias from differential recall. It is still possible that informants were less able to remember drug exposures from several years ago when the medicines were not currently being used (as they would likely not be in cases of AD). However, this last kind of bias is largely avoided in the comparison of early affected and later-affected AD cases, which still showed an inverse association of NSAID or H2 blocker use and AD. Finally, there is no apparent reason why this difficulty would apply to these compounds and not to other exposures such as presence of arthritis (without concomitant NSAIDs), diabetes, peptic ulcer disease, daily use of acetaminophen (without NSAIDs, although in the large doses taken there was a trend toward protection from AD), or use of insulin or oral hypoglycemics. A further control, regular use of narcotic analgesics, was of no value since only one subject reported this exposure.

Whatever their eventual value, our findings with H2 blockers represent a failure of one control variable intended to demonstrate the specificity of findings with NSAIDs or steroids. Our conclusions regarding effects of NSAIDs will be strengthened if their specificity can be further demonstrated. Additional tests of specificity are therefore planned in future studies, along with investigations to test the reproducibility of the findings with H2 blockers. Because we had not intended to investigate the latter specifically, we did not ask in detail here about acid-peptic disease (including gastroesophageal reflux disease, erosive esophagitis, and pathologic hyper-secretory conditions), several related treatments (sucralfate, omeprazole, misoprostol, metoclopramide), or even simple antacids (the latter had showed no effect in the prior twin study). These conditions and medicines, as well as several other common indications and their treatments, will be addressed in the same follow-up studies.

For now, we urge that this study should not be interpreted as justifying the widespread clinical use of NSAIDs or, especially, H2 blockers to prevent AD. The latter drugs have several side effects and the former increase risk of gastrointestinal ulceration and bleeding, particularly in the elderly (38). Balancing these known risks against the benefits of either H2 blockers or NSAIDs will require assessment of the latter in randomized controlled trials. We suggest that such trials are probably warranted for NSAIDs. With adequate samples, the trials could also consider their effects among different strata of age or APOE genotype.

Possible Implications for the Pathobiology of AD

Although this study's findings with NSAIDs and H2 blockers do not derive from a clinical trial, they seem strong, and their juxtaposition may provide new clues to pathogenetic mechanisms. The principal action of NSAIDs (41) is suppression of cyclooxygenase(s) (COX). One isoform of COX promotes inflammation through the synthesis of prostaglandins after being induced by interleukin 1β (IL-1β) and related cytokines (29). IL-1β is elevated in Alzheimer brain (16). Other markers of inflammatory change, including glial synthesis of several components of the classical complement pathway, have been demonstrated immunohistochemically in and around the amyloid plaque of AD (14,28).

It is not clear, however, that inhibition of COX-mediated prostaglandin synthesis in classical inflammation explains the effect of NSAIDs in AD. Our concurrent findings with H2 blockers may suggest a search for alternate explanations. In this connection, we offer the hypothesis that both types of drug curtail NMDA glutamatergic excitotoxicity. COX-dependent events are part of the calcium-dependent postsynaptic cascade that follows stimulation of NMDA receptors (25) and results in induction of immediate early genes including c-fos that may effect either long-term potentiation (26) or, with excessive stimulation, excitotoxic cell death (10,37). Vulnerability to the latter is increased in presence of the β-amyloid peptide of AD (24). The NMDA response cascade is also potentiated by histamine activation of H2 (40) or H3 (1) receptors (effect of H2 receptor blockers on the latter in the central nervous system being presently unknown). COX-mediated prostaglandin synthesis has also been implicated in postsynaptic transduction of histamine signals (20). Thus, our seemingly disparate findings with NSAIDs and H2 blockers may eventually be linked conceptually by several known aspects of the NMDA pathway. We suggest that the actions of cyclooxygenase, the NMDA pathway, and the factors that modulate them deserve further investigation in AD.

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