ORIGINAL CONTRIBUTION

Platelet Activation in Alzheimer Disease

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Background: In light of recent reports of diminished platelet serotonin concentration and increased plasma serotonin levels in patients with Alzheimer disease (AD), we hypothesized that a state of heightened platelet activation might be present in AD.

Objective: To compare baseline activation of unstimulated platelets in patients with AD with that in control subjects.

Patients and Methods: Flow cytometry was used to measure platelet activation in 91 patients with probable AD and 40 age-matched control subjects. Groups were compared for percentage of circulating platelet aggregates, expression of CD62p, formation of leukocyte-platelet complexes, and presence of circulating platelet microparticles, controlling for effects of demographic, clinical, physiological, and logistical factors.

Results: Multiple analysis of covariance on ranked data revealed a 39.5% increase in percentage of platelet aggregates (P=.0001), a 59.3% increase in expression of CD62p (P=.001), and a 53.3% increase in leukocyte-platelet complexes (P=.0001) in the group with AD but no differences in the number of platelet microparticles, overall platelet count, plasma fibrinogen level, or plasma platelet factor 3. Activation was weakly correlated with sex, but was independent of age, severity of disease, duration of disease, depression, agitation, and family history of dementia.

Conclusions: Platelets of patients with AD exhibit greater unstimulated activation than those of controls. Potential causes of such activation include possible stimulation of platelets by damaged cerebral endothelial cells or platelet activation induced by membrane abnormalities previously reported to be present in platelets of patients with AD. In light of recent evidence that platelets are the principal source of both amyloid precursor protein and β-amyloid peptide in human blood, it is possible that AD platelet activation may reflect or even contribute to the pathogenesis of the disease.

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ALTHOUGH principally a disease of the brain, Alzheimer disease (AD) has also been associated with peripheral manifestations.[1] Platelets have received particular attention in this regard, with reported abnormalities including increased membrane fluidity,[2,3] increased α_2-adrenoreceptor binding,[4] increased monoamine oxidase activity,[5,6] reduced cytochrome *c* oxidase activity,[7] increased protein kinase C activity,[8] and reduced phospholipase C activity.[9] Platelets have also recently been shown to be the principal source of both amyloid precursor protein and β-amyloid peptide in human blood.[10,11]

Additionally, alterations in platelet serotonin levels and uptake have been reported in patients with AD.[12-15] Relevant to the present study, a report of decreased platelet serotonin and increased plasma serotonin concentrations in patients with AD[15] led us to consider, in keeping with a recent suggestion by Rosenberg et al,[16] that a state of increased platelet activation might be present in patients with AD. To test this possibility, we examined unstimulated platelets from patients with AD and age-matched controls using flow cytometry with fluorescent immunolabeling of platelet and leukocyte surface antigens. Four measures of platelet activation were examined: (1) percentage of circulating platelets formed into aggregates (PAg); (2) expression of CD62p (P-selectin), a protein that appears on platelet membrane surfaces when platelets are activated[17]; (3) percentage of circulating platelets bound to leukocytes (WBC-PLT), a process that occurs when platelets are activated[17]; and (4) plasma concentration of platelet microparticles (PMPs, microvesicles formed from small seg-

PATIENTS AND METHODS

Consecutive sampling was used to select 91 patients meeting the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria[19] for probable AD. Patients were selected from individuals evaluated at the University of Miami Memory Disorders Clinic, Miami, Fla, for complaints of progressive cognitive decline. All patients underwent extensive cognitive, neurological, psychiatric, and laboratory investigations, including magnetic resonance imaging of the brain, to establish the diagnosis. Forty control subjects were selected from related (n=5) or unrelated (n=35) caregivers of patients. All subjects gave their informed consent to participate in the study. All control subjects were interviewed by a board-certified neurologist and psychiatrist and were judged to be cognitively intact for their age and free of neurological and psychiatric disease. Twenty-five of the 40 control subjects underwent additional extensive testing identical to that of the patients except that magnetic resonance imaging of the brain was not performed.

Because of its potential impact on platelet activation, the use of medications was extensively examined for all subjects. The use of medications was ascertained by structured interview with caregivers of patients. Interviews were performed by 2 separate interviewers in sessions conducted approximately 2 hours apart on the same day. When discrepancies between interviews were noted (this occurred in <5% of cases), the caregiver was interviewed again to resolve differences. The use of medications was numerically encoded by delineating 42 categories of medication (including prescription and nonprescription drugs) and was incorporated into the statistical analyses by inserting each of the 42 categories separately and also by incorporating them as meaningful groups (eg, all anti-inflammatory agents, all antihypertensive agents, or all anti-agitation agents). The use of medications for 6 of the categories is shown in **Table 1** for both patients and controls. Less frequent use of nonsteroidal anti-inflammatory drugs (NSAIDs) by patients with AD was noted, in keeping with recent reports[20] comparing the use of NSAIDs by patients with AD and matched controls.

Blood drawing for all subjects occurred either while fasting at 9:30 AM (n=94) or not fasting at 1 PM (n=37). Coincident sampling of patients and controls was used throughout the study (2-3 patients and 1 control subject each week) to ensure that patients and controls were matched for both time and date of blood drawing. A blood sample was taken from a vein in the antecubital fossa using a 21-gauge needle. After drawing an initial 7 mL for analysis of serum chemistries, an additional 9 mL was drawn directly into silicone-coated glass tubes (Vacutainer tubes, Becton, Dickinson & Co, Franklin Lakes, NJ) containing citrate anticoagulant. Chemical and cytometric analyses were conducted within 1 to 3 hours after blood drawing to ensure reliability (±10%) of the results.[21]

SAMPLE PREPARATION

Platelet marker CD41 (GPIIb/IIIa) and activation marker CD62p (P-selectin, GMP-140, PADGEM) were labeled by adding 5 µL of fluorescein isothiocyanate–labeled α-CD41 (Cat No. 0649, clone P2, Coulter Corp, Miami, Fla) and 5 µL of phycoerythrin labeled α-CD62p (Cat No. 348107, Becton, Dickinson & Co)) to a solution of 100 µL of phosphate-buffered saline solution and 50 µL of citrated whole blood. Leukocytes were labeled in another tube in which α-CD62p was replaced with α-CD45. Samples were incubated for 10 minutes, fixed by adding 160 µL of 4% p-formaldehyde in phosphate-buffered saline solution, incubated for an additional 10 minutes, diluted with 1.0 mL of phosphate-buffered saline solution, and then left to stand for 2 hours or long enough to visually observe that hemolysis was complete.

FLOW CYTOMETRY

A flow cytometer (Profile II flow cytometer, Coulter Corp), calibrated daily for particle size, particle fluorescent intensity, and laser beam alignment using standard microbeads, was used for cytometric measures. Parameters were adjusted so that the coefficient of variation was less than 2%. The sample flow rate was set at 20 µL/min with sheath pressure of 4 psi, with a laser output of 15 mW, and with samples measured in 60-second intervals. A preset threshold of CD41 fluorescein isothiocyanate fluorescence was used to trigger event counting, with events mapped onto a 2-dimensional histogram with x- and y-axes representing, respectively, the log side scatter and the log forward scatter of the laser light. Particles of 10-µm size or larger formed a well-defined cluster taken to comprise a combination of platelet aggregates and leukocyte-platelet complexes. The 2 classes of particles were differentiated via a second histogram in which the x- and y-axes corresponded to CD41 and CD45 fluorescence intensity, respectively. The PAg was calculated as

Continued on next page

ments of platelet membrane sometimes extruded during platelet activation).[18] Between-group comparisons were made for each of these measures of platelet activation and an additional within-group analysis confined solely to the patient group with AD was undertaken to examine the question of whether platelet activation could be associated with a particular set of clinical features that might define a distinct subgroup of patients with AD.

RESULTS

Demographic and clinical characteristics of patient and control groups are shown in Table 1. Groups were matched for age (P=.12) and sex (Fisher exact test, P=.68). Since coincident sampling was used, there were no significant differences between patients and controls with regard to time or date of blood drawing (P=.48 and P=.78, respectively). The use of medications was infrequent for most classes of drugs and was generally comparable between patients and controls. Exceptions were the significantly greater use of NSAIDs by controls and the use of neuroleptics by 21 (23.1%) of the patients and none of the controls. Trends toward lower education level, less frequent use of cigarettes, and more frequent family history of dementia (first-degree relatives affected) in the group with AD were noted, in accord with some prior

100 × (No. of Platelet Aggregates/Total No. of CD41+ Particles).

The WBC-PLT was calculated as

100 × (No. of Leukocyte-Platelet Complexes/Total No. of CD41+ Particles).

In addition to PAg and WBC-PLT, mean CD62p fluorescence (CD62p-FL) was determined by dividing the total CD62p fluorescence for all CD41+ particles by the total number of CD41+ particles. The value of CD62p-FL thus obtained was taken to reflect the expression of CD62p surface antigen on the external plasma membrane, resulting from fusion of platelet α-granules with the plasma membrane during platelet activation. Finally, flow cytometry was additionally used to quantify the presence of PMPs according to the method previously described by Horstman et al.[22]

Other measures obtained from patients and controls included platelet count, plasma fibrinogen levels, and platelet factor 3 activity of platelet-rich, platelet-poor, and platelet-free plasma, determined as previously described.[23]

CONTROL MEASURES

To control for factors other than the presence of AD that might have influenced platelet activation, a number of additional variables served as covariates in the between-groups analysis, including demographic factors (age and sex), clinical factors (use of medications, cigarette smoking, alcohol use, and history of diabetes, heart disease, and renal disease), physiological factors (blood pressure and cholesterol level), and logistical factors (time and date of blood drawing).

In addition, measurement was made within the group with AD of a number of clinical variables that could be used to determine whether an identifiable subgroup of patients with AD was particularly susceptible to platelet activation. These additional measures included (1) estimated age at onset of disease (derived by structured interview by 2 independent examiners; the mean of the 2 estimates was used for analyses); (2) duration of illness (computed as the result of subtracting age at disease onset from patient age); (3) severity of disease, assessed with 3 measures: Mini-Mental State Examination ,[24] Assessment of Cognitive Abilities in Dementia,[25,26] and Blessed Dementia Scale[27]; (4) presence of family history of dementia, determined by structured interview with identification of presence of dementia in first-degree relatives[28]; (5) presence of depression, quantified with the Cornell Depression Scale[29]; and (6) presence of agitation, quantified with the Cohen-Mansfield Agitation Inventory.[30]

STATISTICAL ANALYSES

Multiple analyses of covariance were used to compare patients with AD with controls for each of the 4 activation measures. Examination of the distributions for both patients and controls for each of the platelet activation measures revealed significant deviations from normality in each case; hence, a multivariate extension of the nonparametric Wilcoxon rank-sum test was used to compare groups.[31] Wilcoxon scores were obtained by ranking raw scores for each of the platelet activation measures using the combined data for patients and controls. Wilcoxon scores were then compared between groups using analysis of covariance. For each of the 4 activation measures, models were derived by incorporating age, sex, and time and date of blood drawing as covariates and then simplifying the models via backward elimination by removing variables with $P>.10$. For each of the 4 models, the effect on the between-groups comparisons was then determined for each of the remaining control measures: use of medications, cigarette smoking, use of alcohol, blood pressure, serum cholesterol levels, and history of diabetes, heart disease, and renal disease.

To determine whether a relationship among the activation measures was present, Spearman correlation coefficients relating the 4 measures were obtained. To determine whether the activation measures independently discriminated between patients and controls, a forward stepwise discriminant analysis was performed on ranked data with the activation measures contributing most to the discriminating power of the model as measured by Wilks λ being selected for entry. A significance level of .15 was chosen as the entry and removal criterion for inclusion in the model.

Additional analysis, confined to data from the patient group with AD only, was directed toward a search for clinical factors that might have delineated subgroups with AD that differed with respect to platelet activation. For this analysis, stepwise multiple regression modeling was used, again using rankings of platelet activation measures as the dependent variables, and using patient age, age at onset of disease, sex, education, duration of disease, family history of dementia, and scores on the Mini-Mental State Examination, Assessment of Cognitive Abilities in Dementia, Blessed Dementia Scale, Cornell Depression Scale, and Cohen-Mansfield Agitation Inventory as independent variables in the analysis. Because of the multiple comparisons involved in this analysis, α was set at .05 to indicate a statistical trend and at .01 to establish statistical significance.

reports[32-34] regarding comparative frequencies for these variables in patients with AD and controls.

Comparisons between patients and controls for the 4 measures of platelet activation are indicated in **Table 2** and depicted in the **Figure**. Mean levels of PAg were increased by 39.5%, mean CD62p-FL was increased by 59.3%, and mean WBC-PLT was increased by 53.3% in patients with AD compared with controls. Distributions for each of the measures, as reflected by values of skewness, kurtosis, and coefficients of variation, were comparable between groups. No group differences were found in PMPs ($P=.77$), total platelet count ($P=.75$), fibrinogen levels ($P=.85$), or in platelet factor 3 activity of platelet-rich plasma ($P=.53$), platelet-poor plasma ($P=.27$), or platelet-free plasma ($P=.94$).

Of the variables incorporated as covariates in the models, sex entered significantly for PAg ($P=.002$) and WBC-PLT ($P=.02$), with men exhibiting greater activation than women, and date of blood drawing entered significantly for CD62p-FL ($P=.0001$). In no case, however, did any of the covariates (including sex, date or time of blood drawing, use of medications, cigarette smoking, use of alcohol, blood pressure, cholesterol level, and history of diabetes, heart disease, or renal disease) change the significance of the between-group comparisons of the primary platelet activation measures. Because of the

Table 1. Comparison of Clinical Variables in Patients With AD vs Control Subjects*

Variables	Control Subjects (n=40)	Patients With AD (n=91)	P†
Mean (±SD) age, y	72.7±8.7	75.0±7.6	.12
Mean (±SD) education, y	13.5±5.8	11.5±4.7	.02
Sex, F/M	24/16 (F=60.0%)	58/33 (F=63.7%)	.68
Mean (±SD)			
Age at onset of disease, y	. . .	70.4±8.3	
Duration of disease, y	. . .	4.6±3.2	
Cigarettes, pack-year	18.0±28.9	9.0±22.0	.06
No. (%) using			
Aspirin, Y/N	8/32 (20.0)	13/78 (14.3)	.44
NSAIDs, Y/N	10/30 (25.0)	4/87 (4.4)	.001
Dipyridamole, Y/N	1/39 (2.5)	2/89 (2.2)	.99
Neuroleptics, Y/N	0/40 (0.0)	21/70 (23.1)	<.001
SSRIs, Y/N	1/39 (2.5)	7/84 (7.7)	.43
Calcium channel blockers, Y/N	7/33 (17.5)	16/75 (17.6)	.99
Mean (±SD) plasma fibrinogen level, mg/dL	412.7±91.8	415.6±76.1	.85
	Control Subjects (n=25)	**Patients With AD (n=91)**	
Mean (±SD)			
MMSE score	27.1±3.4	13.9±7.5	<.001
Serum cholesterol level, mg/dL	220.0±37.7	230.9±46.2	.31
Platelet count, $\times 10^9$/L	224.6±59.8	229.0±58.3	.75
Family history of dementia, Y/N	3/22 (Y=12.0%)	39/52 (Y=42.9%)	.004

*AD indicates Alzheimer disease; ellipses, not applicable; NSAIDs, nonsteroidal anti-inflammatory drugs; Y/N, yes or no; SSRIs, selective serotonin reuptake inhibitors; and MMSE, Mini-Mental State Examination.
†F statistic or Fisher exact test.

marked difference between groups with respect to use of NSAIDs and neuroleptics, additional analyses were conducted for the subset of 87 patients and 30 controls who did not use NSAIDs and for the subset of 70 patients and 40 controls who did not use neuroleptics. Differences between groups remained significant in both cases for levels of PAg (*P*=.0001 and *P*=.0001), CD62p-FL (*P*=.005 and *P*=.004), and WBC-PLT (*P*=.003 and *P*=.01).

The stepwise discriminant function analysis, performed to determine whether the activation measures independently discriminated between patients and controls, revealed that PAg provided the most discriminating power and that none of the other activation measures added significantly to the model. Spearman correlation coefficients (**Table 3**) revealed significant correlations among PAg, CD62p-FL, and WBC-PLT, the 3 measures that discriminated between patients with AD and control subjects in the initial regression analyses.

In the analysis confined to the group with AD, conducted to look for clinical correlates of platelet activation, a trend was observed for the relationship between PAg and male sex (*P*=.04). No significant correlations were found for other variables, including other platelet activation measures and other clinical variables (age of patient, age at onset of disease, duration of disease, severity of disease, family history of dementia, or scores on the Blessed Dementia Scale, Cornell Depression Scale, or Cohen-Mansfield Agitation Inventory).

Table 2. Platelet Activation in Patients With AD vs Control Subjects*

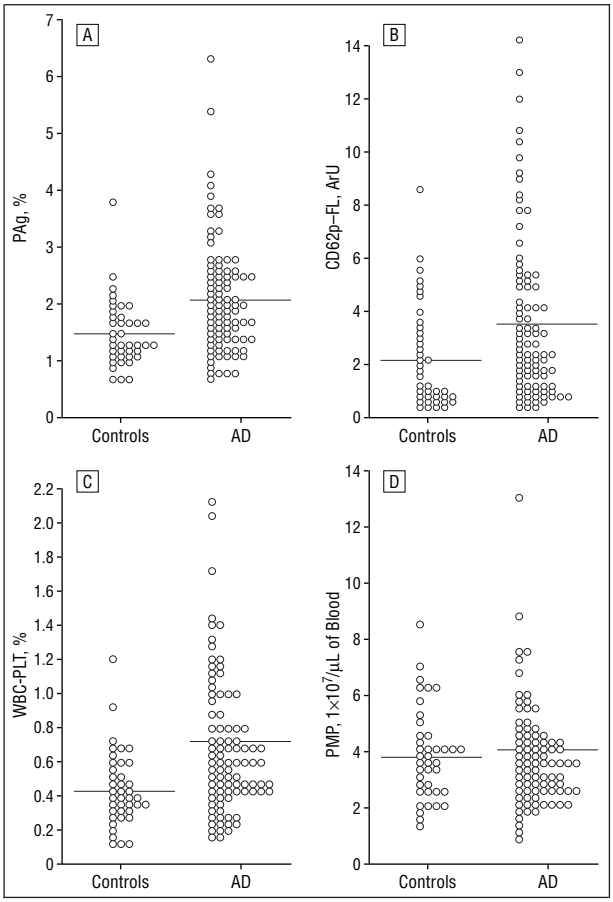
Platelet Activation	Platelet Activation, %, Median (Range)		P†
	Control Subjects (n=40)	Patients With AD (n=91)	
PAg	1.32 (0.67-2.53)	2.02 (0.73-6.29)	<.001
CD62p-FL	1.89 (0.35-10.43)	2.76 (0.39-14.28)	.001
WBC-PLT	0.44 (0.12-1.06)	0.61 (0.17-2.13)	.001
PMP	3.5 (1.6-8.4)	3.5 (0.8-12.9)	.77

*Data presented are for unadjusted raw data. AD indicates Alzheimer disease; PA, platelet aggregate; CD62p-FL, CD62p fluorescence; WBC-PLT, leukocyte-platelet complexes; and PMP, platelet microparticles.
†P values reflect significance of between-group comparisons of ranked data, covarying for any of age, sex, or time or date of blood drawing that remained in the model after application of the backward elimination procedure (see the "Statistical Analysis" subsection in the "Methods" section).

COMMENT

The present study provides, to our knowledge, the first direct evidence of increased platelet activation in patients with AD. Three of the 4 indexes of platelet activation examined were elevated in patients with AD compared with controls. The elevations were substantial, with mean increases ranging from 39% to 59% over control mean values. There was, however, considerable overlap between groups for each of the measures, foiling hopes that the procedure might be used as a diagnostic test for AD.

The overlap in activation values may have been due in part to nondisease-related interindividual variation and random measurement error in both patient and control groups and may additionally have reflected preclinical AD in some of the control subjects. The possibility that the overlap was due to disease heterogeneity with only



Frequency distribution for platelet activation values (unadjusted raw data) for patients with Alzheimer disease (AD) (n=91) and for control subjects (n=40). Horizontal lines indicate mean values; WBC-PLT, leukocyte-platelet complexes; PAg, platelet aggregates; ArU, arbitrary units; and PMP, platelet microparticles.

certain subgroups manifesting increased activation was considered but a search for clinical variables that might have identified particular subgroups with AD especially prone to platelet activation yielded only a weak correlation for sex, with men exhibiting mildly greater platelet activation than women. Heterogeneity may become clearer as additional cases are examined, but in the present study it appeared that the platelet activation effect consisted of a shift toward activation in the group with AD as a whole for each of the 3 measures that showed between-group differences.

Methodological artifact is unlikely to have been responsible for the increased activation seen in the group with AD. A search for non-AD–related clinical variables deemed capable of elevating platelet activation values in the group with AD yielded only sex as a modest modifier, but its incorporation into the statistical models had no effect on the significance of the results. Surprisingly, the use of medications failed to alter platelet activation in either patients or controls for any of the medication categories looked at, including known anti-aggregatory agents, such as aspirin and NSAIDs. The lack of effect of medication may have been related to inaccuracies in caregiver's reports of use of medications (although care was taken to minimize this possibility), low or inconsistent dosing, or may have reflected an insensitivity of the type of activation observed in this study to the effects of the medications examined.

Table 3. Spearman Correlation Coefficients Between Activation Measures*

	Spearman Correlation Coefficients			
Measures	**PAg**	**CD62p-FL**	**WBC-PLT**	**PMP‡**
PAg	. . .	0.36†	0.65	0.04
CD62p-FL	. . .	. . .	0.45	0.15
WBC-PLT	. . .	. . .	. . .	0.13
PMP	. . .	. . .	. . .	. . .

**PAg indicates platelet aggregate; CD62p-FL, CD62p fluorescence; ellipses, not applicable; WBC-PLT, leukocyte-platelet complexes; and PMP, platelet microparticles.*
†P<.001.
‡P is not significant (corrected for multiple comparisons).

A marked effect on expression of CD62p was found for date of blood drawing, possibly corresponding in part to previous reports[35,36] of seasonal fluctuations in platelet membrane protein concentrations. However, patients and controls were matched with regard to date of blood sampling and incorporation of dates into the regression models did not change the significance of the results.

PATTERN OF PLATELET ACTIVATION

The pattern of AD platelet activation was scrutinized for clues pertaining to possible underlying mechanisms. Multiple components of the activation process appeared to be involved. The first, an increase in platelet aggregation, was suggested by the observed increase in levels of PAg in the patients with AD. Platelet aggregation has been reported to be associated with activation of protein kinase C and exposure of a platelet glycoprotein IIb/IIIa heterodimer complex that binds fibrinogen and von Willebrand factor in the aggregation process.[37] Relevant to these events, increased activity of platelet protein kinase C [8] and increased plasma concentration of von Willebrand factors[38] have been reported for patients with AD compared with controls. In contrast, plasma fibrinogen levels have been reported to be unchanged in patients with AD,[38] a finding that was corroborated in the present study. It is possible, as suggested by Mari et al,[38] that elevation of von Willebrand factor in patients with AD results from its secretion from endothelial cells damaged by amyloid angiopathy. Alternatively, in light of the present study, elevation of von Willebrand factor may result from its secretion from platelet α-granules during AD-induced platelet activation.

Additional components of platelet activation found to be enhanced in patients with AD were the expression of CD62p on the external plasma membrane surface and creation of leukocyte-platelet complexes. These 2 measures were colinear in the regression models, consistent with reports[17,39] that CD62p mediates leukocyte-platelet conjugation. Both CD62p-FL and WBC-PLT were, in turn, colinear with PAg, suggesting a shared mechanism underlying the increases in the 3 activation measures.

In contrast to its effects on PAg and expression of CD62p, AD did not appear to alter PMP formation. This is consistent with a similar finding reported by Lee et al,[21] who found no differences in circulating PMP between patients with AD and 31 controls without dementia. An additional finding in the present study was the absence of elevated platelet factor 3 activity in either platelet-rich or platelet-poor plasma of patients with AD, lending support to the premise that PMP is needed to promote platelet factor 3 activity by facilitating the prothrombinase reaction needed for hemocoagulation.[18] The dissociation between PMP and expression of CD62p found in the present study has been observed clinically in patients with isolated platelet factor 3 activity deficiency (Scott syndrome) and in vitro when activation is induced by adenosine diphosphate and epinephrine.[18] In the context of dementia syndromes, however, it places a signature on AD platelet activation that may help distinguish it from the activation pattern observed in certain other dementing illnesses. Thus, in the study by Lee et al,[21] circulating PMP was found to be increased both in patients with cerebrovascular dementia and in patients with mixed cerebrovascular and AD dementia, suggesting that measurement of circulating PMP might help distinguish pure AD from dementia of vascular origin.

RELATION TO OTHER AD ABNORMALITIES

It is possible that the increased platelet activation observed in the present study is related to other reported AD abnormalities. With respect to serotonin, reports of elevated plasma serotonin and reduced intraplatelet serotonin levels present a pattern ostensibly consistent with platelet activation, since intraplatelet serotonin reduction could be a result of serotonin extrusion from intracellular granules by activated platelets. Alternatively, and not mutually exclusively, plasma serotonin levels may be elevated in patients with AD because of a process independent of platelet activation (such as release from damaged endothelial cells in the cerebral microcirculation), rendering elevation of serotonin levels a potential cause rather than consequence of platelet activation. Similarly, changes in AD platelet membrane fluidity[2,3] might be related as a cause or effect of AD platelet activation.

RELATION TO AD PATHOPHYSIOLOGICAL FEATURES

In addition to potential relationships between platelet activation and serotonin and membrane fluidity changes, it is also possible that AD platelet activation relates directly to the cerebral component of AD pathophysiological features. Particularly inviting is the possibility that endothelial cell damage in the cerebral microcirculation induced by amyloid angiopathy might cause platelet activation by local stimulation or by secretion of a platelet-activating factor into the general circulation. The report[38] of increased circulating von Willebrand factor in patients with AD is consistent with this possibility since activated platelets have been reported to bind to injured endothelial cells through a mechanism involving von Willebrand factor.

An additional possibility, that platelet activation is not merely a result but may also relate to the cause of the AD pathological process, must also be considered. Thus, platelets store amyloid precursor protein (APP) in α-granules,[40] incorporate it in platelet and PMP membranes,[41] and secrete it on platelet activation[10,40,42] in quantities sufficient to make platelets a principal source of circulating APP.[10] Platelets have also been reported to secrete and be a principal source of circulating β-amyloid peptide,[11] plasma levels of which have been reported to be elevated in AD[43] and Down syndrome.[44] If, as has been suggested by a number of investigators,[45-48] cerebral APP and its metabolites derive in part from circulating sources, then the present study provides a possible mechanism whereby increased levels of APP and β-amyloid peptide secretion by activated AD platelets could conceivably contribute directly to the AD pathological process. Simultaneous measurement of platelet activation and plasma levels of APP and β-amyloid peptide may shed further light on this issue.

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