Fibrinogen Is Associated With an Increased Risk of Alzheimer Disease and Vascular Dementia

Marieke van Oijen, MD; Jacqueline C. Witteman, PhD; Albert Hofman, MD, PhD; Peter J. Koudstaal, MD, PhD; Monique M.B. Breteler, MD, PhD

Background and Purpose—Vascular and inflammatory factors may play an important role in the pathogenesis of dementia. Studies reported an association between plasma levels of inflammation markers and the risk of dementia. Both fibrinogen and C-reactive protein are considered inflammatory markers. Fibrinogen also has important hemostatic properties. We investigated the association of fibrinogen and C-reactive protein with dementia.

Methods—The study was based on the prospective population-based Rotterdam Study. Fibrinogen was measured in a random sample of 2835 persons. High-sensitivity C-reactive protein was measured in the total cohort of 6713 persons. We identified 395 incident dementia cases during follow-up (mean, 5.7 years). We estimated the associations of fibrinogen and C-reactive protein with dementia using Cox proportional hazard models.

Results—Persons with higher levels of fibrinogen had an increased risk of dementia. The hazard ratio for dementia per SD increase of fibrinogen was 1.26 (95% CI, 1.11 to 1.44), adjusted for age and gender, and 1.30 (95% CI, 1.13 to 1.50) after additional adjustment for cardiovascular factors and stroke. For Alzheimer disease, the adjusted hazard ratio was 1.25 (95% CI, 1.04 to 1.49), and for vascular dementia it was 1.76 (95% CI, 1.34 to 2.30). High levels of C-reactive protein were not associated with an increased risk of dementia.

Conclusions—High fibrinogen levels were associated with an increased risk of both Alzheimer disease and vascular dementia, but levels of C-reactive protein were not. This suggests that the increased risk of dementia associated with fibrinogen is because of the hemostatic rather than the inflammatory properties of fibrinogen. (Stroke. 2005;36:000-000.)

Key Words: fibrinogen ■ C-reactive protein ■ dementia ■ Alzheimer disease ■ risk

Vascular factors are believed to play an important role in the pathogenesis of dementia, both Alzheimer disease and vascular dementia.1,2 Both inflammatory and hemostatic factors have been implicated in the development of vascular disease. There is evidence for a role of inflammation in dementia. Signs of inflammation, such as activated microglia and inflammatory mediators including C-reactive protein and complement factors,3 are present in the brain of demented persons. It is thought that this inflammatory response contributes to neuronal death. Also, a beneficial effect of nonsteroidal antiinflammatory drugs has been suggested.4 However, it is less clear how this inflammatory process affects or is affected by peripheral inflammatory disease or markers of disease. Previous studies suggested that peripheral markers of inflammation are elevated in the plasma of patients years before the clinical syndrome of dementia developed.5,6

Both fibrinogen and C-reactive protein are acute-phase proteins. High levels serve as nonspecific markers for inflammatory disease. Fibrinogen also has important hemostatic properties because it affects platelet aggregation and endothelial function. Fibrinogen is a major determinant of plasma viscosity and induces red cell aggregation. High levels of fibrinogen in plasma might reduce blood flow, predispose to thrombosis, and enhance atherogenesis.7

High levels of fibrinogen and C-reactive protein are associated with an increased risk of cardiovascular disease and stroke.8,9,10 Whether increased levels reflect active involvement in the pathogenesis of atherosclerosis or merely reflect the presence of nonspecific inflammatory disease is not clear. Because dementia is associated with both vascular and inflammatory factors, we hypothesized a relation between both fibrinogen and C-reactive protein and dementia. We investigated this association in the Rotterdam Study, a prospective population-based cohort study among men and women aged 55 years and over.

Methods

Study Population and Design

The Rotterdam Study is a population-based prospective cohort study that was designed to investigate the incidence and causes of
cardiovascular, neurope degenerative, locomotor, and ophthalmologic diseases in the elderly. From 1990 to 1993, all 10 275 residents aged ≥55 years of Ommoord, a district of the city of Rotterdam, were invited to participate, and 7983 (78%) men and women agreed. The Medical Ethics Committee of the Erasmus Medical Center approved the study, and written informed consent was obtained from all of the participants. At the baseline clinical examination, 7047 persons were screened for dementia and had blood samples drawn. Prevalent dementia was diagnosed in 334 persons, resulting in a cohort of 6713 persons at risk for dementia. Follow-up examinations were conducted in 1993 to 1994 and in 1997 to 1999. In addition, through linkage with records of general practitioners, the total cohort was continuously monitored for morbidity and mortality. This resulted in a virtually complete follow-up until January 1, 2000.

Measurement of Fibrinogen and C-Reactive Protein

Platelet poor plasma was frozen in liquid nitrogen and stored at −80°C until determination. Fibrinogen measurements were done at baseline in a random sample and were available for 2835 of the persons at risk. Fibrinogen levels were derived from the clotting curve of the prothrombin time assay using Thromborel S as a reagent on an automated coagulation laboratory (ACL 300, Instrumentation Laboratory). The coefficient of variation was 5%. High-sensitivity C-reactive protein (HsCRP) was measured for the total cohort in baseline serum samples kept frozen at −20°C, using a near-infrared particle immunoassay method (Immage, Beckman Coulter). The range of measurement was 0.2 to 1440 mg/L with a variation coefficient of 3.1%. In a random sample of the study (n = 29), we compared HsCRP measurements from baseline blood stored at −20°C and −80°C. The correlation between the measurements was high (Spearman correlation 0.99; P < 0.001). HsCRP levels were somewhat lower in blood stored at −20°C (mean difference, −0.5097; 95% CI, −1.637 to 0.618). Because the lowering of HsCRP levels was proportional, we do not expect it to affect the estimate.

Diagnosis of Dementia

The diagnosis of dementia was made following a 3-step protocol. Two brief tests of cognition (Mini-Mental State Examination10 and Geriatric Mental State schedule11 organic level) were used to screen all of the subjects. Screen-positives (Mini-Mental State Examination score <26 or Geriatric Mental State organic level >0) underwent the Cambridge examination for mental disorders of the elderly (Cambex).12 Subjects who were suspected of having dementia were, if necessary, examined by a neuropsychologist. In addition, the total cohort was continuously monitored for incident dementia through computerized linkage between the study database and digitalized medical records from general practitioners and the Regional Institute for Outpatient Mental Health Care. The diagnoses of dementia and Alzheimer disease were made in accordance with internationally accepted criteria for dementia (Diagnostic and Statistical Manual of Mental Disorders, Third Edition- Revised,).13 Alzheimer disease (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association,14 and vascular dementia (National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l’Enseignement en Neurosciences)15 by a panel of a neurologist, neuropsychologist, and researcher physician.

Covariates

At baseline, trained investigators interviewed all of the participants at home, collecting information on current health status and medical history. Additionally, at the research center, clinical measures were obtained. The body mass index was calculated [weight (kg)/length (m)^2]. Blood pressure was measured at the right brachial artery using a random-zero sphygmomanometer with the participant in sitting position. Nonfasting blood samples were drawn and immediately frozen. Total cholesterol, high-density lipoprotein cholesterol, and glucose were measured within 2 weeks. Immediately after blood sampling, white blood cell count was assessed in citrate plasma using a Coulter Counter T540 (Coulter Electronics). The quality of assessments was continuously monitored by Instruchemi. Genotyping for apoE was performed on coded DNA specimens without knowledge of the diagnosis. Persons were categorized on the basis of the presence or absence of an apoE e4 allele. Furthermore, ultrasonography of both carotid arteries was performed. As an indicator of atherosclerosis of the carotid arteries, we used intimamedia thickness (IMT) and presence of carotid plaques. Common carotid IMT was determined as the average of the maximum IMT of near- and far-wall measurements, and the average of left and right common carotid IMT was computed.16 Carotid plaques were determined at 6 different locations: common carotid artery, carotid bifurcation, and internal carotid artery at both the left and right side.16 To assess the presence of atherosclerosis of the lower extremities, we obtained the ankle-to-brachial index by computing the ratio of the systolic blood pressure at the ankle to the systolic blood pressure at the arm. We defined diabetes mellitus as a random or postload glucose level ≥11.1 mmol/L or the use of blood glucose-lowering medication.

Data Analysis

Fibrinogen was normally distributed, and we examined the association of fibrinogen and the risk of dementia and subtypes of dementia using Cox proportional hazard models. First, we entered fibrinogen as a linear term (per SD) in the model. Next, quintiles of fibrinogen were made, and the lowest quintile was used as the reference category. Because both dementia and fibrinogen are associated with age and cardiovascular and inflammatory factors, we adjusted for age (and gender) and, additionally, for cardiovascular risk factors including smoking, body mass index, presence of diabetes mellitus, systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, and measures of atherosclerosis. Other potential confounders that we considered were presence of an apoE e4 allele, stroke, and the inflammatory markers white blood cell count and HsCRP.

To examine the influence of atherosclerosis, we constructed a composite measure of atherosclerosis.17 A point was added to the atherosclerosis score if the following characteristics were present: (1) plaques in ≥3 locations of carotid arteries; (2) average wall thickness of common carotid arteries in the highest quintile of the distribution; and (3) evidence of peripheral arterial disease, defined as the ankle-brachial index <0.90. The atherosclerosis sum score was analyzed in 4 categories corresponding to score values of 0 to 3.

To assess whether the effect of inflammatory markers was different in people with and without previous stroke, we performed stratified analysis. We repeated the analyses excluding previous stroke and censoring incident stroke cases.

Because the distribution of HsCRP levels was skewed, we used log-transformed HsCRP in the analyses. Extreme high values may indicate the presence of an active inflammatory disease. Therefore, we excluded persons with HsCRP levels >3 times the SD of the log-transformed HsCRP, resulting in a total of 6247 measurements. We examined the association between log-transformed HsCRP and dementia entering C-reactive protein as a linear term (per SD) in the model. Then, quintiles were made, and the lowest quintile was used as the reference category. Adjustments were made for cardiovascular risk factors, presence of apoE e4, previous stroke, white blood cell count, and fibrinogen.

Results

In the total cohort (random sample), we identified 349 (192) patients with incident dementia, of whom 230 (124) patients were diagnosed with Alzheimer disease, 26 (16) patients with Alzheimer disease and cerebrovascular disease, and 52 (31) patients with vascular dementia. Seventeen (7) patients developed dementia in Parkinson disease, and 24 (14) patients had dementia because of other causes, such as multisystem atrophy, frontotemporal dementia, and Lewy body dementia.
Table 1 shows that the cohort with fibrinogen measurements (n=2835) was a random cohort compared with the total cohort at risk (n=6713). Table 2 shows that increasing levels of fibrinogen were associated with an increased risk of dementia. The association could not be explained by cardiovascular or inflammatory factors. Table 3 shows that higher levels of fibrinogen were associated with an increased risk of vascular dementia and Alzheimer disease. Although the differences in study population might explain the different results, in our study, we did not find different in carriers and noncarriers of the apoE e4 allele.

Discussion

We found that higher levels of fibrinogen but not of HsCRP were associated with an increased risk of both vascular dementia and Alzheimer disease. This association was independent of cardiovascular risk factors and other inflammatory markers, such as white blood cell count. The occurrence of clinical stroke could not explain this association.

The strengths of the Rotterdam study are its prospective design, the population-based setting, and its large number of subjects. Because follow-up with respect to the diagnosis of dementia was virtually complete, selection bias is unlikely. Unfortunately, no data were available on other indicators of the coagulation and fibrinolytic system. It is difficult to differentiate between vascular dementia and Alzheimer disease, and some misclassification could have occurred classifying these subtypes.

An association between HsCRP level and the risk of dementia >20 years later has been reported in a nested case-control study in the Honolulu-Asia Aging Study, a study of Japanese-American men followed for several decades. A 3-fold significantly increased risk of dementia, both Alzheimer disease and vascular dementia, was found in men in the upper 3 quartiles of HsCRP compared with men in the lowest quartile. Although the differences in study population might explain the different results, in our study, we did not find differences in the association between men and women. Also, it is possible that midlife HsCRP is associated with risk of late-life dementia, as seems to be the case for more cardio-

Table 2. The Association Between Fibrinogen and Risk of Dementia

<table>
<thead>
<tr>
<th>Fibrinogen, g/L</th>
<th>Model 1*</th>
<th>Model 2†</th>
<th>Model 3‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per SD increase fibrinogen</td>
<td>1.26 (1.11 to 1.44)</td>
<td>1.30 (1.13 to 1.50)</td>
<td>1.23 (1.03 to 1.46)</td>
</tr>
<tr>
<td>1st quintile</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>2nd quintile</td>
<td>1.42 (0.81 to 2.48)</td>
<td>1.50 (0.83 to 2.73)</td>
<td>1.44 (0.80 to 2.60)</td>
</tr>
<tr>
<td>3rd quintile</td>
<td>1.29 (0.74 to 2.22)</td>
<td>1.31 (0.72 to 2.37)</td>
<td>1.21 (0.67 to 2.16)</td>
</tr>
<tr>
<td>4th quintile</td>
<td>1.10 (0.63 to 1.92)</td>
<td>0.95 (0.51 to 1.76)</td>
<td>1.04 (0.58 to 1.87)</td>
</tr>
<tr>
<td>5th quintile</td>
<td>1.92 (1.15 to 3.21)</td>
<td>2.09 (1.19 to 3.68)</td>
<td>1.67 (0.95 to 2.91)</td>
</tr>
<tr>
<td>P trend</td>
<td>0.03</td>
<td>0.05</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*Hazard ratio (95% CI) for dementia (192 cases). †Adjusted for age and sex, current smoking, presence of apoE e4 allele, body mass index, presence of diabetes mellitus, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, atherosclerosis sum score, and previous stroke. ‡Adjusted for age, sex, C-reactive protein, and white blood cell count.
vascular risk factors, such as cholesterol and high-blood pressure. A case-cohort study within the Rotterdam study showed that high levels of inflammatory proteins α1-antichymotrypsin and interleukin 6 were associated with an increased risk of dementia. Elevated levels were present years before the onset of clinical disease.6 In this study, the findings regarding HsCRP in the present study do not show that high levels of inflammatory proteins are acute-phase proteins, and high levels serve as nonspecific markers for inflammatory disease. The correlation between these 2 markers is high (0.40 with a P<0.001). Because we found that fibrinogen was independently associated with the risk of dementia, whereas HsCRP was not, other properties of fibrinogen play a role. Fibrinogen is an inflammatory marker, as well as an important factor in the coagulation cascade. It is also a major determinant of plasma viscosity and affects endothelial function.7 Hyperfibrinogenemia may lead to reduced blood flow and enhanced thrombosis. These hemostatic properties can explain the association with dementia. We could not confirm a positive association between HsCRP and the risk of dementia.

Both fibrinogen and HsCRP are acute-phase proteins, and high levels serve as nonspecific markers for inflammatory disease. The correlation between these 2 markers is high (0.40 with a P<0.001). Because we found that fibrinogen was independently associated with the risk of dementia, whereas HsCRP was not, other properties of fibrinogen play a role. Fibrinogen is an inflammatory marker, as well as an important factor in the coagulation cascade. It is also a major determinant of plasma viscosity and affects endothelial function.7 Hyperfibrinogenemia may lead to reduced blood flow and enhanced thrombosis. These hemostatic properties can explain the association with dementia. We could not exclude that increased fibrinogen levels occur as an epiphenomenon of dementia-related processes and are not causally related. However, there is mounting evidence that vascular factors play a role in cognitive decline and dementia, both the vascular dementia and the Alzheimer disease subtype.

The role of plasma fibrinogen in the pathogenesis of dementia is not known. In a cross-sectional study, Stott et al18 showed raised levels of plasma fibrinogen in patients with ischemic stroke and vascular dementia. Other case-control studies did not find significant differences in the levels of fibrinogen between patients with vascular dementia or Alzheimer disease and controls.19,20 To our knowledge, the association of fibrinogen and vascular dementia and Alzheimer disease has not been studied in a large, prospective population-based setting.

High levels of fibrinogen are associated with cerebrovascular disease, which may explain the association with dementia. Because adjustment and censoring for previous or incident stroke did not change the association, other mechanisms might be suggested. Possibly, small vessel disease (white matter lesions) or silent cerebral infarction mediates the association. Silent brain infarcts are common in an elderly population and are associated with the risk of dementia.21 In patients with symptomatic small vessel disease, fibrinogen has been correlated with the amount of leukoaraisis.22 Also, significantly higher levels of fibrinogen in plasma have been

| TABLE 3. Hazard Ratio (95% CI) for Alzheimer Disease (124 cases) and Vascular Dementia (31 cases) |
|---------------------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Fibrinogen, g/L | Model 1* | Model 2† | Model 3‡ | Model 1* | Model 2† | Model 3‡ |
| Per SD increase | 1.23 (1.04 to 1.46) | 1.25 (1.04 to 1.49) | 1.22 (0.98 to 1.52) | 1.59 (1.25 to 2.01) | 1.76 (1.34 to 2.30) | 1.41 (0.96 to 2.06) |
| 1st quintile | 1 (ref) | 1 (ref) | 1 (ref) | 1 (ref) | 1 (ref) | 1 (ref) |
| 2nd quintile | 1.46 (0.73 to 2.91) | 1.60 (0.77 to 3.35) | 1.55 (0.73 to 3.28) | 1.73 (0.16 to 19.14) | 1.39 (0.12 to 15.74) | 1.62 (0.15 to 17.90) |
| 3rd quintile | 1.38 (0.71 to 2.70) | 1.55 (0.75 to 3.20) | 1.31 (0.62 to 2.74) | 3.32 (0.39 to 28.71) | 2.48 (0.27 to 22.89) | 2.97 (0.34 to 25.75) |
| 4th quintile | 1.27 (0.65 to 2.49) | 1.16 (0.55 to 2.45) | 1.30 (0.63 to 2.71) | 3.82 (0.46 to 32.02) | 2.62 (0.28 to 24.34) | 2.81 (0.32 to 24.48) |
| 5th quintile | 1.75 (0.92 to 3.33) | 1.95 (0.96 to 4.00) | 1.67 (0.80 to 3.47) | 9.50 (1.24 to 73.13) | 8.68 (1.08 to 69.71) | 5.39 (0.66 to 44.27) |
| P trend | 0.17 | 0.20 | 0.32 | 0.001 | 0.002 | 0.04 |

*Adjusted for age and sex; †Adjusted for age, sex, current smoking, presence of apoe ε4 allele, body mass index, presence of diabetes mellitus, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, atherosclerosis sum score, and previous stroke; ‡Adjusted for age, sex, C-reactive protein, and white blood cell count.

| TABLE 4. The Association Between C-Reactive Protein and Risk of Dementia |
|--------------------------|--------------------------|--------------------------|--------------------------|
| CRP, mg/L | Model 1* | Model 2† | Model 3‡ |
| Per SD increase ln (CRP) | 0.95 (0.84 to 1.06) | 1.00 (0.88 to 1.14) | 0.91 (0.81 to 1.03) |
| 1st quintile | 1 (ref) | 1 (ref) | 1 (ref) |
| 2nd quintile | 0.79 (0.56 to 1.11) | 0.81 (0.55 to 1.20) | 0.71 (0.50 to 1.02) |
| 3rd quintile | 0.65 (046 to 0.93) | 0.72 (0.49 to 1.07) | 0.61 (0.42 to 0.88) |
| 4th quintile | 0.63 (0.44 to 0.89) | 0.68 (0.45 to 1.00) | 0.57 (0.40 to 0.83) |
| 5th quintile | 0.99 (0.72 to 1.37) | 1.17 (0.81 to 1.71) | 0.90 (0.64 to 1.26) |
| P trend | 0.64 | 0.74 | 0.36 |

CRP indicates C-reactive protein. Hazard ratio (95% CI) for dementia, n=6247 (measurements exceeding 3 times the SD have been excluded from the analyses). *Adjusted for age and sex; †Adjusted for age, sex, current smoking, presence of apoe ε4 allele, body mass index, presence of diabetes mellitus, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, atherosclerosis sum score, and previous stroke; ‡Adjusted for age, sex, fibrinogen, and white blood cell count.
found in patients with silent (lacunar) infarction. In the Austrian stroke prevention study, higher serum fibrinogen levels were independently associated with white matter intensities and lacunar lesions on MRI. Because we do not have imaging in this population, we were unable to assess this.

We found a strong association with vascular dementia (notwithstanding the small number of incident cases; n=31), which supports the hypothesis of a vascular mechanism. If fibrinogen plays a causal role in both vascular dementia and Alzheimer disease through vascular disease, then new perspectives regarding treatment emerge. Modifying components of coagulation and blood viscosity, such as fibrinogen, could be beneficial in prevention and control of dementia.

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