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Increased Thromboxane Biosynthesis Is Associated With Poststroke Dementia

F. van Kooten, MD; G. Ciabattini, MD; P.J. Koudstaal, MD; D.E. Grobbee, MD; C. Klufft, PhD; C. Patrono, MD

Background and Purpose—It has been suggested that daily intake of aspirin is associated with a reduction of cognitive decline, both in normal and in demented subjects, but the mechanism is unclear. We have therefore studied the relationship between thromboxane (TX) A₂ biosynthesis, as reflected by the urinary excretion of 11-dehydro-TXB₂, and the presence of dementia in patients after acute stroke.

Methods—Patients from the Rotterdam Stroke Databank were screened for dementia between 3 and 9 months after stroke. Patients had a full neurological examination, neuropsychological screening, and, if indicated, extensive neuropsychological examination. Criteria used for the diagnosis of dementia were from the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition (Revised)*. Urine samples were taken at the time of screening. Urinary 11-dehydro-TXB₂ was measured by means of a previously validated radioimmunoassay.

Results—Dementia was diagnosed in 71 patients, and urine samples were available for 62. Median value (range) of 11-dehydro-TXB₂ was 399 (89 to 2105) pmol/mmol creatinine for demented patients versus 273 (80 to 1957) for 69 controls with stroke but without dementia ($P=0.013$). No difference was found between 44 patients with vascular dementia, 404 (89 to 2105) pmol/mmol creatinine, and 18 patients with Alzheimer's disease plus cerebrovascular disease, 399 (96 to 1467) pmol/mmol creatinine ($P=0.68$). In a stepwise logistic regression analysis, in which possible confounders such as use of antiplatelet medication, cardiovascular risk factors, and type of stroke were taken into account, increased urinary excretion of 11-dehydro-TXB₂ remained independently related to the presence of dementia (OR 1.12, 95% CI 1.03 to 1.22 per 100 pmol/mmol creatinine). The difference in metabolite excretion rates between demented and nondemented patients was most prominent within the subgroup of ischemic stroke patients who received aspirin ($P<0.01$).

Conclusions—Increased thromboxane biosynthesis in the chronic phase after stroke is associated with the presence of but not the type of poststroke dementia. It is particularly apparent in patients on aspirin, thereby suggesting the involvement of extraplatelet sources of TXA₂ production in this setting. (*Stroke*. 1999;30:1542-1547.)

Key Words: cyclooxygenase ■ dementia ■ platelets ■ stroke ■ thromboxanes

Dementia is one of the most important causes of disability in the elderly. The increased aging of the population calls for strategies that reduce both the occurrence and severity of dementia in order to lighten the burden on society in terms of health care, disability, and hospital and institutional care. It has been estimated that in 10% to 40% of all demented patients, vascular lesions or thromboembolic processes represent the identifiable cause of dementia.¹ Several studies²⁻⁷ have addressed the hypothesis that aspirin might have a beneficial effect on the occurrence and progression of dementia and on cognitive function in general. In one randomized trial, patients with multi-infarct dementia benefited from aspirin therapy, with improvement of cognitive performance scores and cerebral

perfusion values.² This study, however, was not placebo controlled. In another trial, subjects at high risk for cardiovascular disease showed better cognitive performance after 5 years of treatment with antithrombotic therapy (ie, aspirin, warfarin, or both) than those treated with placebo.⁵ The effect, however, was small, and the patients studied represented a subgroup from a trial that was designed for another purpose. In 2 nonrandomized, population-based studies, either no effect of aspirin on cognitive function was found at all^{6,7} or a small, not statistically significant, positive effect was reported.⁴ Finally, a positive effect on cognitive performance of NSAIDs or aspirin was reported in patients diagnosed with possible or probable Alzheimer's disease.³

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These studies suggest a positive effect of aspirin treatment on cognitive performance, in both demented patients and otherwise healthy elderly subjects. The evidence, however, is scarce; the effect, if any, is modest; and the underlying mechanisms are largely unknown. Aspirin may be beneficial through its antiplatelet effect,⁸ by preventing recurrent cerebral infarcts, or through its anti-inflammatory properties. The dose requirement for the apparent beneficial effect of aspirin on cognitive performance would favor the antiplatelet effect as the most likely explanation. In a previous study, we reported an association between platelet activation, as reflected by thromboxane metabolite excretion, in the acute phase of stroke and stroke severity.⁹ There was also a nonsignificant trend for enhanced platelet activation in patients with the worst 3-month outcome as measured on the Rankin scale, a handicap scale that reflects the degree of independence of the patient, taking cognitive performance into account.

In this study, we have prospectively investigated the relationship between *in vivo* thromboxane biosynthesis during the chronic phase after stroke and the presence of poststroke dementia.

Subjects and Methods

Study Patients

Patients were recruited from the Rotterdam Stroke Databank, a prospective registry of patients with transient ischemic attack (TIA), ischemic stroke, or a primary intracerebral hemorrhage, admitted to the department of Neurology of the Dijkzigt University Hospital Rotterdam in the Netherlands. From March 1, 1993 until January 15, 1996, 825 consecutive patients were entered into this registry, of whom 300 met the entry criteria for the Dutch Vascular Factors in Dementia Study.¹⁰ Patients had to be 55 years or older, and they had to be admitted to our neurology ward with a TIA, cerebral infarction or intracerebral hemorrhage. Reasons for exclusion were, in short, as follows: 24% were too young, 15% died within 3 months after stroke, 6% did not give consent, 5% had had a TIA and no neurological signs on examination, 4% moved out of the region, 5% were untestable because of severe aphasia, 2% were not native Dutch speakers, and 3% were excluded for various other reasons. Of the remaining 300 patients, 71 were demented, and in 62 of these urinary samples were available for thromboxane metabolite measurements. Seventy-one control patients, including patients with TIA, ischemic stroke, and intracerebral hemorrhage, who were frequency matched for age and sex, were randomly taken from the 229 nondemented stroke and TIA patients. Urinary samples were available from 69 of the 71 control subjects. All patients were screened according to a strict protocol consisting of a full neurological examination, standardized blood tests, at least 1 and usually 2 CT scans of the brain, duplex scanning of the carotid arteries, and a cardiological analysis that included standard 12-lead ECG and, if indicated, 24-hour ECG monitoring and echocardiography. The nature and time course of the symptoms were recorded by means of a detailed checklist.¹¹ Patients with a cerebral infarction were further subdivided according to a clinical classification: Total anterior circulation stroke, partial anterior circulation stroke, lacunar stroke, and posterior circulation stroke.¹² Apart from the neurological history, the following vascular risk factors were recorded: smoking habits, hypercholesterolemia (history of hypercholesterolemia and/or fasting total cholesterol level >6.5 mmol/L),¹³ hypertension (history of hypertension and/or systolic blood pressure >160 mm Hg and/or diastolic blood pressure >90 mm Hg, treated or not), diabetes mellitus (history of diabetes mellitus type I or II and/or a random blood glucose of 8 mmol/L together with an HbA_{1c} level of 6.30% or more, treated or not),¹⁴ atrial fibrillation (history of atrial fibrillation and/or atrial fibrillation

on ECG), and a history of intermittent claudication, angina pectoris, prior myocardial infarction, retinal infarction, or stroke. We recorded the medication, especially antiplatelet and anticoagulant treatment, taken by the patients at the time of urinary sampling, which was between 3 and 9 months after the onset of stroke. As customary in the Netherlands, the vast majority of patients in our study were treated with a dose of 30 mg of aspirin daily. Only patients with a cardiac indication for aspirin (n=16) were treated with a higher dose, varying between 80 and 100 mg daily. Nine patients used NSAIDs on a regular but not daily basis. Eight of these 9 were also using aspirin, and only 1 used NSAIDs and no aspirin. In the analysis, this patient was grouped in the nonaspirin group.

Five patients with cerebral ischemia as qualifying event were not treated with antithrombotic medication at the time of assessment. One of them had a thrombocytopenia, which prevented aspirin treatment; the other 4 had recurrent systemic bleedings (3 had gastric bleeding and 1 recurrent urinary tract bleeding). On the other hand, 5 patients with an intracerebral hemorrhage as qualifying event received antithrombotic treatment at the time of assessment, because they already had an indication for antithrombotic treatment before their hemorrhage. In 1 patient, oral anticoagulant treatment was restarted in the chronic phase after the bleeding because of a prosthetic aortic valve. In 2 patients with atrial fibrillation, 1 with a history of TIA and 1 a history of recurrent myocardial infarction, aspirin was started in the chronic phase after oral anticoagulant treatment was stopped in the acute phase of the hemorrhage. In 2 patients with a history of TIA, aspirin was restarted in the chronic phase.

Assessment of Cognitive Function and Dementia

Premorbid cognitive function was assessed by means of an interview with a close informant and the score on the Blessed Dementia Scale.¹⁵ Cognitive function was assessed through a neurological examination and by a series of neuropsychological screening instruments between 3 and 9 months after onset of stroke. We performed the Mini-Mental State Examination (MMSE),¹⁶ Geriatric Mental Status organic scale,¹⁷ and the Dutch version of the cognitive and self contained part of the Cambridge Examination for Mental Disorders of the Elderly, the CAMCOG.¹⁸ In patients in whom dementia was clinically suspected, extensive neuropsychological evaluation was performed. Based on information from a close relative, the results of extensive neuropsychological evaluation, and the clinical impression on examination, the diagnosis of dementia was assessed by a diagnostic panel that consisted of a neuropsychologist, 2 neurologists, and a physician of the Rotterdam Stroke Databank. For the diagnosis of dementia, the DSM-III-R criteria¹⁹ were applied. The NINDS-AIREN research criteria²⁰ were used to distinguish between patients with vascular dementia and those with Alzheimer's disease plus cerebrovascular disease. The latter were patients with progressive cognitive deterioration existing before the onset of stroke, without a history or signs of cerebrovascular disease until the present stroke occurred, thus fulfilling the clinical criteria for possible Alzheimer's disease.²¹ The degree of handicap was also assessed between 3 and 9 months after onset of stroke by means of the modified Rankin scale.²²

Measurements of Thromboxane Biosynthesis

Urine samples were collected 3 to 9 months after stroke, thus avoiding short-term fluctuations in thromboxane biosynthesis related to the acute phase of stroke.^{9,23} The creatinine concentration was measured, and samples of 50 mL were immediately frozen and stored at -20°C until extraction. Analytical measurements of 11-dehydro-TXB₂, a major enzymatic metabolite of TXB₂ in humans, were performed with blinding to the diagnosis of dementia. Immunoreactive 11-dehydro-TXB₂ was extracted from 10-mL aliquots of each coded urine sample (the pH was adjusted to 4.0 with formic acid) on SEP-PAK C18 cartridges (Waters Associates) and eluted with ethyl acetate. The eluates were subjected to silicic acid column chromatography and further eluted with benzene/ethyl acetate/methanol (60:40:30, vol/vol). Immunoreactive 11-dehydro-TXB₂ eluted from silicic acid columns was assayed at a final dilution of 1:30 to

TABLE 1. Clinical Characteristics of Stroke Patients in Relation to the Presence of Dementia

| Characteristic | n | Demented, n (%) | Control, n (%) | P |
|---|-----|--------------------|-------------------|--------|
| Age, mean±SD, y | 131 | 73.8±7.9 | 73.6±8.2 | 0.90 |
| Gender | | | | |
| Male | 69 | 29 (47) | 40 (58) | 0.20 |
| Female | 62 | 33 (53) | 29 (42) | |
| Type of stroke | | | | |
| TIA | 12 | 3 (5) | 9 (13) | 0.10 |
| Cerebral infarction | 99 | 46 (74) | 53 (77) | 0.73 |
| Intracerebral hemorrhage | 20 | 13 (21) | 7 (10) | 0.09 |
| Clinical subtype of cerebral infarction | | | | |
| TACS | 11 | 7 (15) | 4 (35) | 0.22 |
| PACS | 46 | 20 (44) | 26 (49) | 0.58 |
| LACS | 30 | 11 (24) | 19 (8) | 0.20 |
| POCS | 12 | 8 (17) | 4 (8) | 0.13 |
| Severity | | | | |
| Rankin score of ≤3 at follow-up | 103 | 38 (61) | 65 (94) | <0.001 |
| Rankin score of >3 at follow-up | 28 | 24 (39) | 4 (6) | |
| Anti-thrombotic medication | | | | |
| Aspirin | 77 | 36 (58) | 41 (59) | 0.90 |
| Oral anticoagulant | 34 | 12 (19) | 22 (32) | 0.10 |
| Neither aspirin nor oral anticoagulant | 20 | 14 (23) | 6 (9) | 0.03 |

n indicates number of patients; TACS, total anterior circulation stroke; PACS, partial anterior circulation stroke; LACS, lacunar stroke; and POCS, posterior circulation stroke.

1:1000, as described previously.²⁴ The urinary excretion rate of 11-dehydro-TXB₂ was expressed as picomoles per millimole of creatinine.

Statistical Analysis

Data were analyzed by means of the Statistical Package for the Social Sciences (SPSS Inc) and Egret statistical software. Values of 11-dehydro-TXB₂ between groups were compared with the Mann-Whitney *U* test. Differences in baseline characteristics between demented and nondemented patients were compared with use of the Student *t* test, χ^2 test, and Fisher exact test where appropriate. Values of $P < 0.05$ (2-sided testing) were considered statistically significant. A logistic regression analysis, in which potential confounders such as age, gender, use of antiplatelet medication, cardiovascular risk factors (hypertension, hypercholesterolemia, atrial fibrillation, smoking habit), and type and site and of stroke were taken into account, was performed to investigate whether 11-dehydro-TXB₂ was independently related to the presence of dementia.

Results

Dementia was diagnosed in 71 (23.7%) of the 300 stroke patients. Three (6.5%), 54 (25%), and 14 (39%) of the patients with TIA, ischemic stroke, and intracerebral hemorrhage, respectively, were demented. Patients with an intracerebral hemorrhage had a higher risk of dementia (OR 2.31, 95% CI 1.04 to 5.08) and patients with TIA a lower risk (OR 0.19, 95% CI 0.06 to 0.67). The mean age of the demented patients was 73.3±7.7 years and that of the nondemented patients 62.8±8.0 years ($P < 0.001$). Of the demented patients, 52% were female compared with 37% of the controls ($P = 0.03$).

Urine samples were available from 62 demented patients and 69 controls. Table 1 shows the baseline characteristics in relation to dementia for both groups. No statistically significant differences in age, gender, type of stroke, and clinical subtype of cerebral infarction existed between the 2 groups, although patients with TIA were numerically more frequent in the control group and more patients with intracerebral hemorrhage were present in the group with dementia. Patients who used neither oral anticoagulant nor antiplatelet medication were more frequent in the dementia group ($P = 0.03$). However, no statistically significant difference existed between the 2 groups in the numbers of patients using aspirin or anticoagulant medication.

Patients with dementia had a significantly higher 11-dehydro-TXB₂ excretion (median 399, range 89 to 2105 pmol/mmol creatinine) than nondemented patients, (median 273, range 80 to 1957, $P = 0.01$), as detailed in Table 2. No difference in 11-dehydro-TXB₂ excretion was found between the 2 major types of dementia median 404, range 89 to 2105 pmol/mmol creatinine for vascular dementia and median 399, range 96 to 1467 for Alzheimer's disease plus cerebrovascular disease. Impaired performance on cognitive screening tests was associated with increased 11-dehydro-TXB₂ excretion ($P = 0.003$ for the MMSE and $P = 0.03$ for the CAM-COG). The correlation, however, between cognitive scores and level of 11-dehydro-TXB₂ was only modest: $r^2 = 0.10$ ($P < 0.001$) and $r^2 = 0.05$ ($P < 0.001$) for MMSE and CAM-COG, respectively. Patients with severe strokes, defined as a

TABLE 2. Median and Range of 11-Dehydro-TXB₂ Excretion Rates as a Function of Dementia, Cognitive Function, Severity of Stroke, and Medication

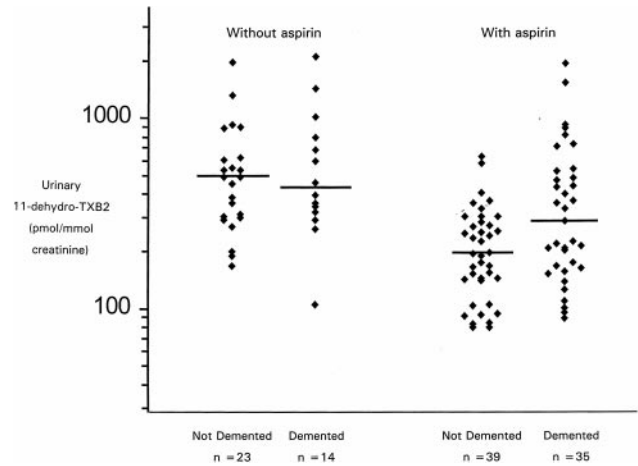
| Variable | n | 11-Dehydro-TXB ₂ | P |
|----------------------------------|-----|-----------------------------|----------|
| Dementia | | | |
| No | 69 | 273 (80–1957) | 0.01 |
| Yes | 62 | 399 (89–2105) | |
| Type of dementia | | | |
| Alzheimer's disease with CVD | 18 | 399 (96–1467) | 0.04* |
| Vascular | 44 | 404 (89–2105) | 0.04* |
| Possible | 4 | 396 (220–796) | 0.23* |
| Probable | 40 | 404 (89–2105) | 0.06* |
| Cognitive function | | | |
| MMSE ≤24 | 64 | 399 (89–2105) | 0.003 |
| MMSE >24 | 67 | 269 (80–1313) | |
| CAMCOG ≤76 | 60 | 380 (89–2105) | 0.03 |
| CAMCOG >76 | 71 | 272 (80–1957) | |
| Severity of stroke | | | |
| Rankin score of ≤3 at follow-up | 103 | 286 (80–1313) | 0.0002 |
| Rankin score of >3 at follow-up | 28 | 635 (89–2105) | |
| Antithrombotic medication | | | |
| No oral anticoagulant or aspirin | 20 | 610 (188–1467) | <0.0001# |
| Aspirin | 77 | 214 (80–1935) | |
| Oral anticoagulant | 34 | 479 (105–2105) | |

*Vs nondemented patients.

#Vs no oral anticoagulant or aspirin.

Rankin scale score of >3 at follow-up, had significantly higher metabolite excretion levels than patients with minor stroke ($P=0.0002$). The group of patients treated with aspirin had significant lower excretion levels of 11-dehydro-TXB₂ than untreated patients ($P<0.0001$).

Because aspirin treatment has a major impact on urinary 11-dehydro-TXB₂, by largely suppressing platelet TXA₂ biosynthesis⁸ we investigated the relationship between metabolite excretion and dementia both in the presence and in the absence of aspirin therapy. To avoid an imbalance in the subgroups, patients with an intracerebral hemorrhage were excluded, because almost none of them used aspirin. The Figure depicts the individual values, with and without aspirin, of 11-dehydro-TXB₂ for patients with cerebral ischemia. Only in the aspirin group were 11-dehydro-TXB₂ excretion rates significantly higher in demented patients than in controls ($P=0.01$). When hemorrhagic stroke patients were added, the results remained the same ($P=0.007$). In patients not on aspirin therapy, the median values were 494 (range 167 to 1957), and 431 (range 105 to 2105), for nondemented and demented patients, respectively ($P=0.73$). For the aspirin group the corresponding values were 196 (range 80 to 631) and 290 (range 89 to 1935), respectively ($P=0.01$). Thus, in patients who did not have dementia at follow-up, aspirin treatment was associated with 60% lower rate of thromboxane biosynthesis than in the absence of antiplatelet therapy, and only 2 of 39 aspirin-treated subjects had metab-



Individual urinary 11-dehydro-TXB₂ excretion rates depicted on a logarithmic scale for demented and nondemented patients with cerebral ischemia, as a function of aspirin therapy. The horizontal bars represent median values for each subgroup of patients.

olite excretion in excess of the median value of untreated subjects. In contrast, in patients who were demented at follow-up, aspirin treatment was associated with a 33% lower rate of TXA₂ biosynthesis, and 13 of 35 treated subjects had metabolite excretion in excess of the median value of untreated subjects. However, no firm conclusions can be drawn because of the relatively small numbers and the large variability.

In the logistic regression analysis, increased urinary excretion of 11-dehydro-TXB₂ remained independently related to the presence of dementia, with an OR of 1.12 (95% CI 1.03 to 1.22) per 100 pmol/mmol creatinine.

Discussion

The main finding of the present study is that patients with poststroke dementia more often show increased thromboxane biosynthesis than nondemented controls. Elevated levels of circulating platelet microparticles have been described earlier in a small study of patients with multi-infarct dementia.²⁵ However, the interpretation of blood indexes of platelet activation is hampered by sampling-related artifacts.²⁶

Among other factors associated with increased 11-dehydro-TXB₂ in our univariate analysis were atrial fibrillation, unfavorable outcome, and absence of antiplatelet treatment, which is consistent with the results of a previous study in patients with acute ischemic stroke.⁹ Atrial fibrillation was also identified as risk factor for dementia in a population-based study²⁷ as well as in a stroke population.²⁸ However, in a multiple logistic regression analysis in which these confounders were taken into account, increased urinary excretion of 11-dehydro-TXB₂ remained independently related to the presence of dementia.

Increased thromboxane biosynthesis may also reflect severe vascular disease, which may lead to dementia. However, this seems unlikely in light of a recent study in patients with peripheral arterial disease,²⁹ which has clearly demonstrated that vascular disease per se is not associated with enhanced thromboxane biosynthesis.

The role of aspirin in our setting remains puzzling, because the association between dementia and increased thromboxane biosynthesis was most prominent in patients with aspirin treatment. This may reflect the play of chance, because the subgroup analysis included a small number of patients. On the other hand, this finding may suggest that stroke patients who show increased thromboxane biosynthesis that cannot be completely suppressed by aspirin have an increased risk of dementia. This might imply that patients with poststroke dementia have an important aspirin-insensitive source of thromboxane biosynthesis. The involvement of prostaglandin H synthase-2 (cyclooxygenase [COX]-2) in producing the substrate for thromboxane synthase within the context of an ongoing inflammatory process in the brain would be compatible with this working hypothesis. Among the cell types endowed with thromboxane synthase and capable of expressing COX-2 in response to inflammatory cytokines and growth factors are monocytes and macrophages.³⁰ Moreover, transcellular biosynthesis of TXA₂ may occur through the biochemical cooperation of cells expressing COX-2 (eg, vascular endothelial cells) with aspirinated platelets.³¹ Aspirin is considerably less potent in inhibiting human monocyte COX-2 than platelet COX-1 activity.³² Thus, plasma aspirin concentrations achieved at conventional antiplatelet dosage are inadequate to suppress COX-2-dependent eicosanoid biosynthesis. Cipollone et al³² have recently reported that in unstable angina, episodes of aspirin-insensitive TXA₂ biosynthesis may reflect extraplatelet sources possibly expressing COX-2 in response to a local inflammatory milieu. If the same mechanism is operative in the setting of cerebral ischemia and inflammation, this might explain the rather conflicting results obtained with aspirin in observational studies^{2,4,5} as well as the apparent protection against Alzheimer's disease associated with nonaspirin NSAIDs.³ These drugs (eg, ibuprofen) are equally potent in inhibiting human platelet COX-1 and monocyte COX-2.³⁰

We conclude that (1) patients with poststroke dementia more often show increased thromboxane biosynthesis than nondemented stroke patients; (2) increased thromboxane biosynthesis is not associated with the type of poststroke dementia; and (3) the association between thromboxane biosynthesis and the presence of poststroke dementia is particularly apparent in patients on aspirin treatment, which suggests that patients with poststroke dementia have an aspirin-insensitive source of thromboxane biosynthesis, possibly related to COX-2 expression in the brain. The availability of specific COX-2 inhibitors offers the opportunity to test this hypothesis with a properly designed randomized trial.

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