Cerebral Ischemia in Young Patients: Is it Associated with Mitral Valve Prolapse and Abnormal Platelet Activity in Vivo?

Ruediger E. Scharf, M.D., Michael Hennerici, M.D., Viktor Bluschke, M.D., Juergen Lueck, M.D., and Rudolf G. Kladetzky, M.D.

SUMMARY The etiology of cerebrovascular disease (CVD) in young patients is difficult to establish if the common causes of a focal neurological deficit are excluded by appropriate investigations. Since in some observations prolapse of the mitral-valve (MVP), alterations of platelet function, or both have been linked with cerebral ischemic events, we studied the in vivo platelet release reaction and the incidence of MVP in 47 patients (12 males, 35 females) under 45 years of age with TIA or stroke of unknown cause and in an age- and sex-matched control group. The mean plasma beta-thromboglobulin (β-TG) level of the patients (mean = 54.9 ± 31.4 ng/ml) was significantly higher than that of the controls (mean = 20.6 ± 6.9 ng/ml, p < 0.001). MVP was demonstrated in 13 of 47 patients in contrast to 4 of the controls (p < 0.01). However, the β-TG levels of patients with MVP (n = 13, 52.9 ± 25.5 ng/ml) did not differ from those of patients without MVP (n = 34, 55.7 ± 33.7 ng/ml) significantly (p < 0.4). Our results confirm that the incidence of MVP is higher in young patients with cerebral ischemia of unknown cause than in asymptomatic controls. The significantly elevated plasma β-TG concentrations in the patient's group indicate an increased platelet activity in vivo. Since there was no significant difference between β-TG levels of patients with and without MVP, the mitral-valve abnormality cannot be the cause for the altered platelet activity.

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EXTRA- AND INTRACRANIAL ATHEROSCLEROTIC lesions are known to cause cerebrovascular disease in the later decades of life, but in young adults one of the major causes of TIA and stroke is cerebral embolism of cardiac origin.1-3 It has recently been suggested that one of the most common cardiac abnormalities, mitral valve prolapse (MVP), plays an important role in the pathogenesis of cerebral ischemia in patients under 45 years of age.4-6 However, the association of this disorder with stroke has met with some scepticism, because the pathogenetic mechanisms are still obscure6 and complications are relatively infrequent despite the incidence of MVP in a general population.7-9

Apart from cardiac abnormalities a wide range of blood disorders (anemia, polycythemia, leukemia, thrombocytosis and macroglobulinemia) are known to be associated with cerebrovascular accidents.10 According to recent opinion platelet abnormalities in particular underlie the thromboembolic mechanisms causing cerebrovascular accidents,11 hence platelet-suppressive drugs have increasingly been proposed for therapy in patients suspected to be at risk.12-14 Since no reliable and simple method has yet been available for quantitating platelet function in vivo, only some studies have been reported in patients with diabetes mellitus,15-16 vascular disease,17 acute myocardial infarction,18 deep venous thrombosis,19 and prosthetic heart valves using a beta-thromboglobulin (β-TG) radioimmunoassay kit.20

β-TG is a platelet specific protein stored within the alpha-granules in high concentrations and is released into the surrounding medium during platelet aggregation induced by thrombin or collagen.15, 19, 21 In order to examine whether an increased in vivo platelet activity as evaluated by the β-TG level, or the occurrence of MVP, or a combination of both abnormalities, could be considered to predispose to cerebrovascular disease in young people, 47 adults under 45 years of age with TIA or stroke of unknown etiology were studied.

Patients and Methods

Forty-seven patients, 45 years old or less, admitted for TIA or stroke (table 1), and a group of sex- and age-matched control subjects consisting of members of the medical staff (n = 22) and of patients without history, signs or symptoms of cerebrovascular disease (n = 25) were studied. The group of patients consisted of 12 males and 35 females. Their average age was 35.4 ± 6.6 yrs. Patients with extracranial arterial stenotic lesions, detected either by four-vessel ultrasound Doppler examination,22 cerebral angiography or both, were excluded from this study as well as patients with systemic diseases, generalized atherosclerosis manifested by coronary or peripheral arterial disease, renal failure, hypertension, diabetes mellitus, heart valve abnormalities other than MVP, infectious and thrombotic diseases, an increased mean platelet count or blood coagulation abnormalities.

Each patient underwent a detailed neurological and cardiovascular examination. Cerebral computerized tomography (CT) was performed in each patient. Twenty-six patients were subjected to cerebral angiography. Standard M-mode echocardiograms were carried out on each patient and on the control subjects by two trained and experienced cardiologists who did not know whether the recordings were from patients or controls. The diagnosis of mitral valve prolapse was made according to strict criteria, i.e. only in cases presenting an unequivocal late systolic prolapse of ≥ 2 mm of the mitral valve closure line or a pansystolic prolapse of ≥ 3 mm of the systolic closure line. Addi-
Table 1: The Incidence of Mitral Valve Prolapse (MVP) in 47 Patients with TIA and Stroke

<table>
<thead>
<tr>
<th>Condition</th>
<th>With MVP</th>
<th>Without MVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIA</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Hemispheres</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Brainstem</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Hemispheres + brainstem</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>8</td>
<td>26</td>
</tr>
<tr>
<td>Hemispheres</td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td>Brainstem</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Hemispheres + brainstem</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>34</td>
</tr>
<tr>
<td>Patients</td>
<td>28%</td>
<td>72%</td>
</tr>
</tbody>
</table>

Results

The Incidence of Mitral Valve Prolapse (MVP)

As can be seen from table 1, 13 of the 47 patients with cerebral ischemia (2 men and 11 women) had evidence of MVP, and the remaining 34 patients (10 men and 24 women) had normal echocardiograms.

Among the controls the echocardiograms revealed MVP in 4 subjects, this difference was significant at p < 0.01. Both patients and controls who had a negative echocardiogram also had negative auscultatory findings.

The incidence of TIAs was lower than that of strokes in patients with MVP (39% vs 61%) as well as in patients without MVP (24% versus 76%). Dysfunction of the hemisphere was far more frequent than dysfunctions of the brainstem or combinations of both. In those patients who underwent angiography only 2 in the MVP group and 4 in the non-MVP group revealed an isolated arterial occlusion in the main trunk or in a major branch of the middle cerebral artery of the type seen in cerebral arterial embolism. The remaining angiograms were normal (n = 20). On cerebral computerized tomography (CT) each patient with a history of hemispheric stroke and one with a history of recurrent TIAs showed hemispheric brain tissue lesions, while those with a previous stroke attributable to the brainstem or with recent hemispheric and/or brainstem TIAs showed no identifiable abnormalities. ECG recordings (at rest, maximal exercise and 24-hour recordings) revealed only low grade cardiac rhythm disturbances, but there was no significant difference either between patients and controls or between patients with and without MVP.

The Incidence of Abnormal Plasma β-Thromboglobulin (β-TG)

The results of the in vivo platelet activities studied, using β-TG as a marker of the platelet release-alpha-granule, are summarized in table 2. The main result is a statistically significant (p < 0.001) threefold higher mean plasma β-TG level (about 55 ng/ml) in the group of patients with cerebrovascular accidents versus control subjects (about 20 ng/ml), irrespective of the mean platelet count which showed no difference between the two groups.

The mean plasma β-TG concentration was abnormal (above the mean + 2 SD of the normal level, i.e. 35 ng/ml) in 35 of 47 patients (i.e. 75%) and in only one of 47 controls (i.e. 2%). Neither the incidence of abnormal platelet activity nor the absolute value of the β-TG level differed in patients with MVP (n = 13, 52.9 ± 25.5 ng/ml) as compared to those without MVP (n = 34, 55.7 ± 33.7 ng/ml). Furthermore, no difference existed between males and females in either the patients or the controls with respect to the mean β-TG level.

Although 80% of the female patients, i.e. 60% of the patient’s group were on oral contraceptives at the time the cerebral ischemic event occurred, no difference could be observed in the incidence of an increased β-TG level between those patients who had never taken oral contraceptives and those who had. Moreover, the β-TG level did not differ between those of the

Table 2: Mean Plasma β-Thromboglobulin Levels and Platelet Counts in 47 Patients with Cerebral Ischemia and in a Control Group

<table>
<thead>
<tr>
<th></th>
<th>β-Thromboglobulin (ng/ml)</th>
<th>Platelet-count/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(mean ± SD)</td>
<td>(mean ± SD)</td>
</tr>
<tr>
<td>Patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p &lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>with MVP</td>
<td>52.9 ± 25.5</td>
<td>19.5 ± 8.2</td>
</tr>
<tr>
<td>without MVP</td>
<td>55.7 ± 33.7</td>
<td>20.6 ± 6.9</td>
</tr>
<tr>
<td>Controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>263.180</td>
<td>263.880</td>
</tr>
<tr>
<td></td>
<td>±62.300</td>
<td>±51.950</td>
</tr>
</tbody>
</table>

Mean ± SD: Mean ± standard deviation.
female patients (n = 35), who were taking oral contraceptives (n = 8) and those who had been taking these prior to the time of investigation (n = 20). However, the β-TG level was even higher in the patients who were not taking oral contraceptives (58.2 ± 35.1 ng/ml) than in those who were taking these at the time of the investigation (44.4 ± 28.0 ng/ml). Among the controls women on oral contraceptives (n = 13) had higher β-TG levels (22.7 ± 5.1 ng/ml) than those who were not taking the pill (n = 22, 16.5 ± 4.4 ng/ml), but the difference was not significant.

In order to test whether or not the increase in the β-TG level may be explained by platelet activation subsequent to the cerebrovascular incident itself, the intervals between the onset of the cerebral deficits and the time of β-TG measurement of each patient were revised (fig. 1): they range from 2 to 36 months with an average of 12 months (SD ± 16 months). Furthermore no correlation could be demonstrated between the extent and duration of the neurological deficit and the β-TG levels.

Neither the total cholesterol, the triglyceride nor the HDL cholesterol levels significantly differed between patients and controls.

Discussion

TIA and stroke are unusual occurrences in the early decades of life. However, if they do occur they frequently pose considerable difficulties in the search for an identifiable etiology, because risk factors or symptoms of atherosclerosis, commonly attributable to cerebral ischemia in later life, are usually absent in young people. The diagnostic problems are particularly intriguing if the common causes of a focal neurological deficit in young subjects like miscellaneous diseases of the cardio-vascular system, abnormalities

![Figure 1](http://stroke.ahajournals.org/)

**Figure 1.** Relationship between individual beta-thromboglobulin values (ng/ml) and the time of its measurement (interval from TIA and stroke). The correlation between both parameters is rather poor for patients with MVP (open circles, r = 0.245) as well as for those without MVP (dark circles, r = 0.435), which makes an explanation of the beta-TG levels subsequent to the cerebrovascular accident (CVA) very unlikely (A).

For comparison the beta-TG values of the control subjects (open triangles = medical staff, dark triangles = control patients without CVA) are indicated in B. The horizontal line marks the mean + 2 SD normal level of beta-TG.
of the blood and nonvascular lesions are not identified by appropriate investigations.

Comprehensive diagnostic investigations are then justified in order to elucidate the origin of cerebral ischemia in these patients and prevent renewed cerebrovascular events by medical treatment.

The observation of either a normal cerebral angiogram (n = 20) or an isolated arterial occlusion (n = 6) in our group of patients indicates transient isolated artery obstructions of the type seen in cerebral artery embolization, which is in good agreement with earlier reports. In search for a possible source of cardiac embolism Barnett et al. were the first to report a striking incidence (40%) of MVP in a group of 60 young patients with a history of previous TIA or stroke as compared to 6.8% in controls. If patients with recognizable potential causes of cerebral ischemia associated with MVP are excluded, the incidence of MVP still remains at 30%. This corresponds closely with the 28% presented in this paper from a similar number but differently selected group of patients with cerebral ischemia of unknown etiology. As the absence of a possibly relevant pathogenetic mechanism associated with the occurrence of MVP in our group of patients was evident — e.g. no marked arrhythmias could be detected, which had been reported to be associated with MVP to be a source of cerebral or retinal embolism. We tried to answer the question whether this valvular abnormality may be a stimulating factor in thromboembolic disorders, as was recently suggested by Steele et al. They demonstrated an abnormal platelet survival time in five patients with a previous cerebrovascular deficit and coexisting MVP. Since only a few attempts have yet been made, however, to examine platelet activity in vivo in patients with cerebrovascular disease, we evaluated β-TG as a marker of platelet alpha-granule release.

The results demonstrate the mean plasma β-TG level to be raised threefold in young adults with cerebral ischemia compared with that of an age- and sex-matched control group. However, the increased release of alpha-granule components, which may indicate an altered platelet activity in vivo, is not restricted to MVP patients but occurs in the majority of young patients with cerebral ischemia.

The altered platelet activity seems more likely to represent the cause than a consequence of the cerebral ischemic event itself in view of the lack of correlation between platelet activity and the onset, duration and extent of the neurological deficits. Moreover, no correlation was found to exist between the individual β-TG levels and oral contraceptives in our predominantly female series, as might have been suspected. No difference could be demonstrated between the β-TG levels in patients who had never been on oral contraceptives, those who had discontinued them after the ischemic event itself in view of the lack of correlation with an abnormal platelet activity in vivo, and those who continued taking them.

Cerebral infarction may be associated with intravascular platelet thrombi, but the nature of the stimuli for their production, as well as the coincidence with additional pathogenetic factors like MVP remain speculative. The present results support the hypothesis that cerebral infarction and TIA in young patients may coincide with an abnormal platelet activity in vivo, and thus support the present therapeutic use of antiplatelet drugs. However, non-steroidal antiinflammatory drugs such as aspirin or sulphinpyrazone may not only inhibit the arachidonic acid metabolism in platelets, but also reduce prostaglandin and thromboxane synthesis of the cerebral vasculature and the brain tissue.

The altered platelet activity in vivo may be a transient phenomenon at least for different pathogenetic mechanisms: The observation of an increase of β-TG and platelet factor 4 in patients with focal migraine at the time of their attacks supports such an assumption and indicates the possibility that activation of platelets in vivo could be related to transient spasms of cerebral blood vessels, a subject to be studied in the future.

Acknowledgments

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