Cerebral Arterial Thrombosis Preceding Ulcerative Colitis

To the Editor:

Some clinical observations suggest a relationship between inflammatory bowel disease and a prethrombotic state, which may result in thromboembolic complications, especially during the acute phase of the disease. Large series reveal an incidence of thromboembolic complications ranging from 1.3% to 6.4% in patients with inflammatory bowel disease. We recently observed two unusual cases that suggested this association.

A 31-year-old man was admitted with abdominal cramps and bloody diarrhea for the past week. Colonoscopy showed an inflammation of the colon and rectum but not the ileum, and colon biopsy confirmed the diagnosis of ulcerative colitis. The patient was first treated with sulfasalazine. Intravenously administered corticosteroids were added because of worsening of the disease. One week after admission, the patient developed sudden right-sided hemiparesis. Computed tomography (CT scan) of the brain revealed recent ischemic infarction of the left internal capsule and an old ischemic lesion in the left basal ganglia. An intensive search for a hypercoagulable state revealed an association with transient protein C, protein S, and factor II deficiencies, probably reflecting vitamin K deficiency due to impaired vitamin K colonic absorption or synthesis.

A gradual improvement of his clinical, biochemical, and hematologic status occurred in the months after this dramatic event. One year later, a left carotid arteriogram showed incomplete occlusion at the origin of the left carotid artery. The patient had a history of a transient right-sided hemiparesis 10 years before this admission, but CT scan of the brain and panarteriography performed at that time were negative.

The second patient was a 32-year-old man with a history of uncomplicated migraine, who was admitted because of sudden left-sided hemiparesis, stupor, and hemiataxia. These regressed in 12 hours. Normal arteriography and cardiac echocardiography; biochemical, immunological, and hematologic screening; and physical examination excluded known systemic or hereditary causes of cerebral arterial thrombosis. Successive CT scans of the brain revealed a temporoparietal cerebrovascular ischemic lesion. Three months later, the patient was readmitted because of bloody diarrhea. Colonoscopy revealed an inflammation of the distal 30 cm of the colon and rectum. Several stool cultures were negative.

Sulfasalazine treatment induced remission of the symptoms and regression of the colonoscopic findings.

Although deep venous thrombosis and pulmonary embolism are relatively often reported in patients with inflammatory bowel disease, arterial thrombosis (and, especially, stroke due to cerebral arterial thrombosis) is much less common in ulcerative colitis. Thromboembolitis; elevated factor V, factor VIII, factor IX, and fibrinogen concentrations; and a fall in antithrombin III concentration have all been reported in patients with inflammatory bowel disease. None of these factors has been definitely recognized as the cause of this observed hypercoagulability. We were the first to report deficiencies of protein C and protein S, both vitamin K-dependent plasma anticoagulants, in a patient (case 1) with cerebral arterial thrombosis during the acute phase of ulcerative colitis.

Cerebral arterial thrombosis is relatively rare in young persons. Cerebral vascular occlusions were seen on cerebral angiography in a few patients whose inflammatory bowel disease was complicated by a cerebral infarction. On the other hand, a cerebrovascular ischemic lesion preceded the occurrence of ulcerative colitis in our two cases, by 10 years in one and by 3 months in the other. We are unaware of any case in the literature in which arterial thrombosis occurred before inflammatory bowel disease.

Physicians should be aware of the possibility of thromboembolic complications of ulcerative colitis not only long after definitive surgery has been performed, but even preceding active ulcerative colitis. Our observations suggest that studies are needed to investigate the underlying pathophysiology of the hypercoagulability during inflammatory bowel disease or perhaps before the symptomatic stage of the disease.

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References
TABLE 1. Frequency of Hemorrhagic Strokes in Placebo-Controlled Clinical Trials of Effectiveness of Aspirin for Prevention of Stroke

<table>
<thead>
<tr>
<th>Reference/Author/Country</th>
<th>Dose (mg/day)</th>
<th>% Male</th>
<th>Months of follow-up</th>
<th>Age (yr)</th>
<th>No. hemorrhagic strokes/no. subjects randomized</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/Atrial Fibrillation Study Group* USA</td>
<td>325</td>
<td>71</td>
<td>24</td>
<td>67</td>
<td>Aspirin: 1/517, Placebo: 0/528</td>
</tr>
<tr>
<td>7/UK-TIA Study Group†</td>
<td>300, 1,200</td>
<td>73</td>
<td>48</td>
<td>60</td>
<td>Aspirin: 13/1,621, Placebo: 3/814</td>
</tr>
<tr>
<td>8/Swedish Cooperative Study‡</td>
<td>1,500</td>
<td>62</td>
<td>24</td>
<td>68</td>
<td>Aspirin: 3/253, Placebo: 2/252</td>
</tr>
<tr>
<td>9/Sorensen et al§/Denmark</td>
<td>1,000</td>
<td>73</td>
<td>25†</td>
<td>39</td>
<td>Aspirin: 1/101, Placebo: 1/102</td>
</tr>
<tr>
<td>10/Bousser et al/France‡</td>
<td>300</td>
<td>70</td>
<td>36</td>
<td>63</td>
<td>Aspirin: 2/198, Placebo: 2/204</td>
</tr>
<tr>
<td>11/Fields et al/USA†</td>
<td>1,300</td>
<td>66</td>
<td>24</td>
<td>≥45</td>
<td>Aspirin: 1/88, Placebo: 0/90</td>
</tr>
<tr>
<td>12/Gent et al/Canada∥</td>
<td>1,400</td>
<td>NE</td>
<td>42</td>
<td>NE</td>
<td>Aspirin: 0/143, Placebo: 0/137</td>
</tr>
<tr>
<td>13/Reuthe and Dorndorf#W. Germany</td>
<td>1,500</td>
<td>65</td>
<td>24</td>
<td>NE</td>
<td>Aspirin: 0/60, Placebo: 0/60</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Aspirin: 21/2,981, Placebo: 8/2,187</td>
</tr>
</tbody>
</table>

Age, mean age unless otherwise indicated; NE, not estimable.
*Warfarin group excluded.
†Two doses of aspirin.
‡Median length of follow-up.
§Group with both aspirin and dipyridamole excluded.
∥Postsurgical treatment groups excluded.
#Number of hemorrhagic strokes inferred from article.

Aspirin and Hemorrhagic Stroke

To the Editor:

We have noted an increasing rate of hemorrhagic stroke in the Province of Quebec, Canada, and are concerned that this rise may be due in part to increased consumption of aspirin.

Recently, there has been much discussion about the use of aspirin for the primary prevention of myocardial infarction, arising mainly from findings from two recent clinical trials. Not only were these two studies discordant on the degree to which aspirin was beneficial, attributed in part to differences in study design and in the characteristics of the two populations, but they also differed on the extent to which aspirin was associated with hemorrhagic strokes. In the study of British physicians, there was no difference in number of hemorrhagic strokes in the group taking aspirin compared with the group avoiding aspirin (relative risk [RR] = 1.1). In the American Physicians' Health Study, the group taking aspirin experienced twice as many hemorrhagic strokes as those taking a placebo (23 cases versus 12 cases; RR = 2.14, p < 0.06).

Estimates of the risk of hemorrhagic stroke associated with the use of aspirin can also be gleaned from the many clinical trials evaluating the effectiveness of aspirin for the primary and secondary prevention of myocardial infarction and stroke. Clinical trials for the prevention of myocardial infarction, for the most part, did not enumerate hemorrhagic strokes as separate events and thus do not permit an opportunity to assess risk. The studies on the prevention of stroke do provide this opportunity, but in no one trial were there enough hemorrhagic events to raise concern; taken collectively, the possibility of an increased risk emerges.

In Table 1, we have compiled the findings on the occurrence of hemorrhagic stroke events from eight placebo-controlled randomized clinical trials of aspirin for the prevention of stroke. There were a total of 21 hemorrhagic strokes occurring among the 2,981 persons who were randomized to receive aspirin compared with seven hemorrhagic strokes among the 2,187 persons randomized to placebo (RR = 1.93, 95% confidence interval 0.82–4.54). The confidence interval was calculated from the estimate of standard error derived using logistic regression, which modeled the logarithm of the odds of hemorrhagic stroke by assignment to aspirin or placebo groups.

Owing to the large variability associated with this estimate of risk and to potential biases we were unable to measure or control, these data do not provide convincing evidence that aspirin is associated with increased risk of hemorrhagic stroke. However, because of the increasing prevalence of aspirin use and the twofold excess risk estimated from these clinical trials, it might be prudent to consider testing the hypothesis that aspirin use is a risk factor for hemorrhagic stroke.

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