Stroke in Thyrotoxicosis With Atrial Fibrillation

Palle Petersen, MD, and Jens Mølholm Hansen, MD

Chronic atrial fibrillation is associated with an increased risk of stroke. In elderly patients with thyrotoxicosis, atrial fibrillation is frequently encountered, and the true risk of cerebrovascular events in these patients is controversial. We retrospectively studied 610 patients with initially untreated thyrotoxicosis, 91 (14.9%) of whom had atrial fibrillation, with the highest frequency in the elderly patients. The risk of cerebrovascular events, with special attention to the first year after the diagnosis of thyrotoxicosis, was calculated using logistic regression methods with age, sex, and atrial fibrillation as independent variables. Only age was an important risk factor (p<0.005), whereas sex and atrial fibrillation were not significant (p=0.09 and p=0.17, respectively) as independent risk factors. This is contrary to other studies of patients with thyrotoxic atrial fibrillation, and the need for further clarification of this issue is clear. From our study the indication for prophylactic treatment with anticoagulants for prevention of stroke in thyrotoxic atrial fibrillation seems doubtful, especially as no controlled studies of such treatment in patients with atrial fibrillation are currently available. (Stroke 1988;19:15-18)

Atrial fibrillation (AF) is found in 0.4% of the adult population\textsuperscript{1-3}; the prevalence increases with age, being 2-4% after 60 years of age.\textsuperscript{1,3}

A well known and often serious complication in AF is cerebrovascular events, occurring at an overall rate of 25%,\textsuperscript{4-7} with the highest frequency at the time of onset of AF.\textsuperscript{4,8,9}

Thyrotoxicosis may be complicated with AF,\textsuperscript{10} and several recent studies have found a high frequency of cerebral thromboembolism in such patients.\textsuperscript{11-14} Anticoagulation has been recommended for patients with thyrotoxicosis and AF to prevent embolic complications.\textsuperscript{15}

The above studies were not sufficiently controlled, and therefore, the aim of our study was to evaluate whether patients with thyrotoxicosis and AF have increased risk of cerebrovascular events compared with age-matched controls with thyrotoxicosis in sinus rhythm.

Subjects and Methods

Our study was retrospective and included a total of 610 consecutive patients with thyrotoxicosis admitted from 1976 to 1985 to a department of internal medicine and endocrinology in a hospital in Copenhagen. All patients had the diagnosis of thyrotoxicosis made according to established criteria.\textsuperscript{16} All except one patient had the type of goiter confirmed by thyroid scintigraphy, and all patients had an electrocardiogram (ECG) on admission. The patients were followed in the out-patient clinic at scheduled intervals, and they were examined by the same consultant physician. Patients followed for <1 year (n = 57) were excluded from the statistical analysis of cerebrovascular events, as were patients receiving anticoagulant treatment (n = 2). None of these excluded patients had cerebrovascular events during follow-up.

The criteria for cerebrovascular events were clinical signs or a medically confirmed history of the acute onset of a neurologic deficit of presumed vascular origin. The patients were grouped as having had a transient ischemic attack (TIA) if an episode of focal ischemia had clinically resolved within 24 hours and as having had a stroke if the neurologic deficit exceeded 24 hours.

According to ECG, the patients were also classified as having sinus rhythm, paroxysmal atrial fibrillation (PAF), or chronic atrial fibrillation (CAF). As the study was retrospective and based on out-patients, a further detailed analysis of the number of PAF episodes and the duration of PAF was impossible to calculate. Accordingly, the diagnosis of CAF was made when no episode of sinus rhythm was registered at any time on ECG during follow-up. If no episode of AF was noticed on admission or during follow-up, the patient was classified as having sinus rhythm.

There were 527 women (86.4%) and 83 men (13.6%). The mean age was 54 (range 13-93) years. The mean follow-up was 39 (range 0-108) months. On admission, 91 of the 610 patients (14.9%) had AF (75 women [82.4%], 16 men [17.6%]). The mean duration before the patients became euthyroid was 10 weeks.

The statistical analysis of cerebrovascular events within the first year after admission was based on logistic regression methods with age, sex, and AF as independent variables. The Goodman-Kruskall y test was used for the analysis of stroke versus TIA in the two groups of patients.

Results

Of the 610 patients, 91 (14.9%) had AF. The frequency of AF rose with increasing age, being higher after 60 years of age, when >25% of the patients had
AF. In patients <50 years of age, AF was found infrequently; i.e., only 0.9% had AF (Table 1). (Table 2 shows the ECG diagnoses in the patients excluded from the statistical analysis of cerebrovascular events.) In 46% of the AF patients sinus rhythm developed after treatment of thyrotoxicosis (Table 1), but the frequency of reversion to sinus rhythm varied from 100% in the AF patients during the first year, 5 in the AF and 8 in the sinus rhythm class (Table 4). All these 13 events occurred before the patients became euthyroid. As the majority of the 610 patients were in sinus rhythm, the results in Table 3 may give the impression that AF carried a higher risk of cerebrovascular events. Using logistic regression methods to analyze age, sex, and AF as independent variables, only age was a significant risk factor, whereas sex and AF were not (Table 5). This result is based on the events that occurred among 551 patients during the first year after the diagnosis of thyrotoxicosis, but even when the whole follow-up period was considered, there was no statistical evidence for AF being an independent risk factor for cerebrovascular events, although a tendency toward more events in the AF class was seen.

Thirteen patients had stroke and 14 had TIA. There was no significant difference between CAF and PAF, but there were significantly more strokes in patients with AF compared with patients in sinus rhythm (p = 0.03, one-sided test) (Table 6). Two patients in sinus rhythm died subsequent to the cerebrovascular event.

**Table 2. Patients Excluded From the Study**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Patients followed &lt;1 year</th>
<th>Patients on anticoagulation</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>11</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>46</td>
<td>0</td>
<td>46</td>
</tr>
<tr>
<td>Total</td>
<td>57</td>
<td>2</td>
<td>59</td>
</tr>
</tbody>
</table>

**Discussion**

It is well established that AF carries an increased risk of stroke. In the Framingham study,12 CAF was associated with an increased risk of stroke. AF in the absence of rheumatic heart disease (RHD) was associated with a more than fivefold increase in stroke incidence, whereas AF with RHD had a 17-fold increase compared with controls without AF. In that study the frequency of thyrotoxicosis was not calculated, but there was a high frequency of strokes in so-called lone AF, which may have included some patients with thyrotoxicosis. During the last decade several studies11-14 have found an increased stroke risk in thyrotoxicosis with AF, contrary to older studies18,19 in which the rarity of embolism in thyrotoxic AF was commented upon.

In our study we found a tendency toward more cerebrovascular events in AF but without statistical evidence of AF being an independent risk factor during the first year after the diagnosis of thyrotoxicosis; age was the only significant risk factor. This is in contrast with the study of Staffurth et al,11 in which 26 episodes of arterial embolism were found in 262 patients with thyrotoxic AF. Seventeen embolic events were cerebral, underscoring the serious character of the events. However, that study included no control group. The study of Yuen et al12 included 210 patients with thyrotoxicosis, but no comparisons were made with a control group. Twenty-one patients had AF, and 5 of these had systemic emboli. Hurley et al13 found 8 arterial embolic episodes (6 cerebral) in 68 patients with AF and thyrotoxicosis, but insufficient data were provided on the 311 patients with thyrotoxicosis and in sinus rhythm. Recently Bar-Sela et al14 found 12 embolic complications in 30 patients with thyrotoxic AF and no episodes in 112 patients in sinus rhythm. However, this might be explained by the fact that the mean ages in the AF and sinus rhythm classes were markedly different.
Table 5. Significance of Risk Factors for Cerebrovascular Events During First Year in 551 Patients With Thyrotoxicosis

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Probability</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Sex</td>
<td>0.09</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.17</td>
</tr>
</tbody>
</table>

*Significance assessed using logistic regression methods.

Table 6. Type of Cerebrovascular Events in 610 Patients With Thyrotoxicosis

<table>
<thead>
<tr>
<th>Atrial fibrillation</th>
<th>Stroke</th>
<th>Transient ischemic attack</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Chronic</td>
<td>5</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Sinus rhythm</td>
<td>5</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>14</td>
<td>27</td>
</tr>
</tbody>
</table>

increased compared with age-matched controls with thyrotoxicosis and in sinus rhythm, and since the cost/benefit ratio of anticoagulation in AF with or without thyrotoxicosis has not been established, we suggest that recommendation of such treatment should await further studies of stroke occurrence in thyrotoxic AF and the results of controlled studies of anticoagulants for prevention of stroke in patients with AF.

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