Night time versus daytime transient ischaemic attack and ischaemic stroke: a prospective study of 110 patients

Claudio Bassetti, Michael Aldrich

Abstract
Objective—Ischaemic stroke occurs only in 20%-40% of patients at night. The aim of the study was to compare sleep and stroke characteristics of patients with and without night time onset of acute ischaemic cerebrovascular events.
Methods—A consecutive series of 110 patients with transient ischaemic attack (n=45) or acute ischaemic stroke (n=65) was studied prospectively by means of a standard protocol which included assessment of time of onset of symptoms, sleep, and stroke characteristics. An overnight polysomnography was performed after the onset of transient ischaemic attack/stroke in 71 patients. Stroke and sleep characteristics of patients with and without cerebrovascular events occurring at night (between midnight and 0600) were compared.
Results—A night time onset of transient ischaemic attack or stroke was reported by 23 (21%) of 110 patients. Patients with daytime and night time events were similar in demographics; risk factors; associated vascular diseases; clinical and polysomnographic sleep characteristics (including severity of sleep apnoea); and stroke severity, aetiology, and outcome. Only the diastolic blood pressure at admission was significantly lower in patients with night time events (74 v 82 mm Hg, p<0.01).
Conclusions—Patients with night time and daytime transient ischaemic attack/stroke are similar in sleep and stroke characteristics. Diastolic hypotension may predispose to night time cerebrovascular events. Factors not assessed in this study probably account for the circadian variation in the frequency of transient ischaemic attack and acute ischaemic stroke.

Keywords: stroke onset; sleep apnoea; circadian rhythm; blood pressure

Possible explanations for the circadian pattern of cerebrovascular events have focused on circadian or postural changes in platelet aggregation, thrombolysis, blood pressure, heart rate, and catecholamine concentrations that occur after awakening with resumption of physical and mental activities.

In a minority of cases, which varies in the literature from less than 10% to as much as 44%, stroke occurs at night.² ³ This suggests that sleep, although “protective” for most cerebrovascular events, may represent a vulnerable state for a subset of patients at risk for stroke. Nocturnal blood pressure swings, cardiac arrhythmias, and sleep disordered breathing have been suggested as possible explanations for the nocturnal onset of stroke.

In the absence of systematic studies on daytime and night time onset of cerebrovascular events we performed a prospective analysis of stroke and sleep characteristics in a consecutive series of 110 patients with transient ischaemic attack or acute ischaemic stroke.

Patients and methods
A consecutive series of 120 adult patients admitted to the University of Michigan Hospitals with acute (retinal or cerebral) transient ischaemic attack or ischaemic stroke—defined by standard criteria—were considered for the study. The study protocol was approved by the institutional review board of the University of Michigan. Subjects were examined with a standard protocol by one of us (CB) usually within the first 2 days after admission to hospital. When a reliable history could not be obtained from a subject because of aphasia or confusion, information was obtained from relatives. Reliable clinical information including the time of onset of transient ischaemic attack or stroke was obtained in 110 (92%) of 120 patients. These 110 patients are the basis for the present analysis.

STROKE ASSESSMENT
Our stroke investigation included questions about such cardiovascular risk factors as family history of stroke, hypertension, diabetes, hypercholesterolaemia, smoking (pack-years), and alcohol consumption (drinks/week). Treatment with aspirin at the time of transient ischaemic attack/stroke onset was recorded. The presence of heart failure, coronary heart disease, and peripheral vascular disease was assessed. Estimated time of onset of transient ischaemic attack and stroke were noted. The time of onset for those patients who were well
at bedtime but woke up with symptoms was the time of awakening. Night time events were defined as transient ischaemic attack and stroke occurring between midnight and 0600. Clinical examination included assessment of body mass index and blood pressure at admission. Maximal severity of stroke was assessed with the Scandinavian stroke scale (range 0–58). The maximal score (no neurological deficit) is 58. A score>30 represents severe stroke. Stroke investigation included blood tests, 12 lead ECG, chest radiography, Doppler ultrasonography, and brain CT, or MRI, or both in all subjects. The presence of old strokes on brain CT or MRI was noted. Echocardiography was performed in 67 (61%) and conventional or MR angiography in 47 (43%) of 110 patients. Aetiology of stroke was classified according to the criteria of the Trial of Acute Stroke Treatment (TOAST) as large artery disease, small artery disease (microangiopathy), cardioembolism, other (cardotid dissection), and unknown. Outcome was classified at discharge from the hospital as good (no deficits or deficits without restriction of lifestyle, independent), or poor (deficits with restriction of lifestyle, dependent).

**Sleep characteristics**

We assessed sleep-wake habits and disturbances preceding transient ischaemic attack and stroke including estimated total sleep/24 hours, history of insomnia (disturbed or insufficient sleep), snoring, and hypersomnia (excessive daytime sleepiness). Snoring was considered habitual when it was reported to occur often or always. The habitual use of hypnotic drugs was also recorded. Sleepiness was estimated with the Epworth sleepiness scale. Polysomnography was recorded whenever possible and scored according to international criteria as described elsewhere. An overnight polysomnography was performed within a mean of 7 days (range 1–45 days) after the onset of the cerebrovascular event in 71 (65%) of 110 patients. In the remaining 39 patients the examination was refused (n=17) or unavailable (n=22). The number of apnoeas and of apnoeas plus hypopnoeas/hour of sleep was expressed as apnoea index and apnoea-hypopnoea index (AHI). We also noted maximal and average duration of respiratory events, minimal oxygen saturation (SaO2) and percentage of sleep time spent with SaO2<90%.

**Statistical analysis**

Nominal data were analysed with the χ² test. For continuous data, we used the unpaired t test and the Mann-Whitney U test. Continuous values are given as mean (SD). Statistical significance was set at p<0.05.

**Results**

There were 48 women and 62 men with a mean (SD) age of 59 (15) years (range 19–80). There were 45 patients with transient ischaemic attack and 65 with acute ischaemic stroke. The percentage of cerebrovascular events per 2 hour period were the following: 23 (21%) between 0000 and 0559, 46 (42%) between 0600 and 1159, 26 (24%) between 1200 and 1759, and 14 (13%) between 1800 and 2359. This circadian pattern was similar in patients with transient ischaemic attack and stroke; eight (18%) of the transient ischaemic attack patients and 15 (23%) of the stroke patients had a night time onset of the cerebrovascular event. The distribution of time of onset of transient ischaemic attack/stroke in the 110 patients is shown in figure 1.

**Cardiovascular risk factors**

Patients with (n=23) and without (n=87) night time onset of transient ischaemic attack/stroke were similar in all demographic variables, type of cerebrovascular event, risk factors, associated vascular diseases, and use of aspirin at the time of the cerebrovascular event (table 1). Only the diastolic blood pressure at admission was significantly lower in patients with night time onset of stroke (74 v 82 mm Hg, p=0.01).

**Sleep characteristics**

All clinical sleep variables evaluated including history of habitual snoring (11 patients (48%) v 43 patients (49%)) and hypersomnia (eight patients (35%) v 33 patients (38%)); Epworth sleepiness score (8.6 (0.7) v 8.4 (0.5); and habitual use of hypnotic drugs (three patients (13%) v 11 patients (13%)) preceding the acute cerebrovascular event were similar in patients with (n=23) and without (n=87) night onset of cerebrovascular event. The distribution of time of onset of transient ischaemic attack/stroke in the 110 patients is shown in figure 1.
Night time versus daytime transient ischaemic attack and ischaemic stroke

Preceding the onset of the acute cerebrovascular event, often-

None of the differences between the two groups were statistically significant.

*Preceding the onset of the acute cerebrovascular event, †often-

Table 3 Stroke and transient ischaemic attack (TIA) at night and during the day: polysomnographic sleep characteristics*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Stroke/TIA at night</th>
<th>Stroke/TIA during the day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interval to recording (days)</td>
<td>10.6 (3.4)</td>
<td>6.7 (0.9)</td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>276.9 (23.4)</td>
<td>269.4 (10.3)</td>
</tr>
<tr>
<td>% NREM sleep 1</td>
<td>23.7 (3.9)</td>
<td>21.8 (1.8)</td>
</tr>
<tr>
<td>% NREM sleep 2</td>
<td>30.4 (4.5)</td>
<td>29.7 (1.8)</td>
</tr>
<tr>
<td>% NREM sleep 3-4</td>
<td>1.1 (0.5)</td>
<td>3.9 (0.8)</td>
</tr>
<tr>
<td>% REM sleep</td>
<td>9.0 (1.6)</td>
<td>10.0 (1.0)</td>
</tr>
<tr>
<td>Apnoea-hypnoea index</td>
<td>22.9 (9.9)</td>
<td>27.4 (4.2)</td>
</tr>
<tr>
<td>Apnoea index</td>
<td>13.9 (8.1)</td>
<td>7.8 (2.4)</td>
</tr>
<tr>
<td>Minimal SaO2*</td>
<td>85.5 (1.4)</td>
<td>80.8 (1.5)</td>
</tr>
<tr>
<td>Mean apnoea duration (s)</td>
<td>17.4 (1.2)</td>
<td>17.1 (1.0)</td>
</tr>
</tbody>
</table>

Values are mean (SD).

None of the differences between the two groups were statistically significant.

*After the onset of the acute cerebrovascular event.

Table 4 Stroke at night and during the day: distribution, severity, and outcome

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Stroke at night</th>
<th>Stroke during the day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid/vertebrobasilar</td>
<td>11:2</td>
<td>34:13</td>
</tr>
<tr>
<td>Scandinavian stroke scale</td>
<td>36.5±6.1</td>
<td>40.2±2.2</td>
</tr>
<tr>
<td>Old strokes on CT</td>
<td>3/11</td>
<td>8/24</td>
</tr>
<tr>
<td>Good outcome*</td>
<td>7/13</td>
<td>19/39</td>
</tr>
</tbody>
</table>

Values in parentheses are SD.

None of the differences between the two groups were statistically significant.

*Independent at discharge from hospital.

Table 5 Estimated time of onset of stroke/transient ischaemic attack (TIA) according to aetiology

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Stroke/TIA at night</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macroangiopathy (n=22)</td>
<td>5/22</td>
</tr>
<tr>
<td>Microangiopathy (n=14)</td>
<td>4/14</td>
</tr>
<tr>
<td>Cardioembolic (n=14)</td>
<td>3/14</td>
</tr>
<tr>
<td>Other causes (n=20)</td>
<td>3/20</td>
</tr>
<tr>
<td>Unknown (n=36)</td>
<td>7/36</td>
</tr>
</tbody>
</table>

None of the differences between the groups were statistically significant.

*Four patients with incomplete diagnostic work up and unknown aetiology of stroke were excluded from this analysis.

Discussion

The present study assesses stroke and sleep characteristics in 110 consecutive patients with transient ischaemic attack or acute ischaemic stroke according to time of onset of the cerebrovascular event. As we studied a cohort admitted to hospital with an average age of 59 years our patients may not be fully representative of stroke and transient ischaemic attacks in the population. Despite this potential limitation, we confirm and expand previous data showing that not only acute ischaemic stroke but also transient ischaemic attack have a circadian pattern with a peak of onset between 0600 and 1200 and about 20% of events occurring at night time. Furthermore, it is shown for the first time that patients with daytime and night time onset of transient ischaemic attack/stroke are similar in most cardiovascular risk factors; clinical and polysomnographic sleep characteristics; and stroke parameters.

ONSET OF TRANSIENT ISCHAEMIC ATTACK/STROKE AND CARDIOVASCULAR RISK FACTORS

We found that patients with and without night time cerebrovascular events are similar in cardiovascular risk factors and associated vascular diseases. Similarly, Palomäki et al found that age, history of hypertension, diabetes, smoking, alcohol consumption, and body mass index did not differ in 59 male patients with sleep related and 108 male patients with sleep unrelated stroke. We also confirmed that aspirin does not modify the circadian pattern of stroke onset.

The only difference found between patients with daytime and night time onset of transient ischaemic attack/stroke in our series was a lower diastolic blood pressure on admission in the second group. This finding suggests that low diastolic blood pressure values may predispose to night time onset of cerebrovascular events enhancing the sleep related fall in blood pressure. This finding is in line with previous reports suggesting a relation between night time hypotension and silent stroke and recurrent stroke.

The link between blood pressure and stroke severity or outcome remains, conversely, unclear. Some studies have shown an adverse
effect of high nocturnal blood pressure on outcome of cerebrovascular diseases. On the other hand, low admission blood pressure values found to correlate with lower stroke mortality and morbidity, but also with worse outcome and higher risk of stroke progression.

ONSET OF TRANSIENT ISCHAEMIC ATTACK/STROKE AND SLEEP CHARACTERISTICS.

Sleep disordered breathing is present in about 50% of patients with acute cerebrovascular diseases. Furthermore, at least one paper suggested habitual snoring as an independent risk factor for sleep related stroke. To our surprise, however, we did not find any significant difference in time of onset of cerebrovascular events in patients with and without sleep disordered breathing. This was also true when comparing patients with normal sleep breathing with patients with severe sleep apnoea (AHI>30). This finding confirms data presented in abstract form by Kapen et al in a series of 48 patients with acute stroke. Similarly, Spriggs et al found that a history of habitual snoring increases the risk of stroke but not the risk for strokes to occur at night. These data suggest that sleep apnoea—while being a risk factor for stroke due to patients who awaken with severe sleep apnoea, which was more pronounced in the morning than in the afternoon. In the literature we found only one case report—presented in abstract form—of an acute cerebrovascular event occurring immediately after a witnessed apnoeic event. It is nevertheless conceivable that in a patient with severe sleep apnoea swings in blood pressure, decreased cerebral blood flow, and cardiac arrhythmias produced by respiratory events may trigger cardiovascular and cerebrovascular events during sleep.

ONSET OF TRANSIENT ISCHAEMIC ATTACK/STROKE AND STROKE CHARACTERISTICS.

In all characteristics assessed—including severity, topography, aetiology, and short term outcome of cerebrovascular events—patients with and without night time onset of transient ischaemic attack/stroke were found to be similar. It is noteworthy that in our study all stroke aetiologies had a morning peak of onset and that microangiopathy was the most common stroke subtype with a night time onset (29%). In a study of 1233 patients Lago et al also found a higher frequency of all types of stroke during the day and a higher night time onset in macroangiopathy and microangiopathy compared with other stroke subtypes. Macroangiopathic and microangiopathic strokes may be particularly susceptible to nocturnal haodynamic changes and decreased cerebral per-
We thank Dr Douglas Quint for reviewing the neuroradiological studies. This research was supported by the Swiss National Science Foundation Grant 32--49853.96.

7 Johns MW. Sleepiness in different situations measured by the Epworth sleepiness scale. Sleep 1994;17:703–10.
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