Morning Increase in Onset of Ischemic Stroke

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The time of onset of ischemic stroke was determined for 1,167 of 1,273 patients during the collection of data by four academic hospital centers between June 30, 1983, and June 30, 1986. More strokes occurred in awake patients from 10:00 AM to noon than during any other 2-hour interval. The incidence of stroke onset declined steadily during the remainder of the day and early evening. The onset of stroke is least likely to occur in the late evening, before midnight. (*Stroke* **1989;20:473–476)**

Stroke is a life-threatening condition that deserves rapid and aggressive treatment to impede, or even prevent, the progression from ischemia to cerebral infarction. It is important to know all we can about conditions that immediately precede a stroke and when a stroke is most likely to occur. Recognizing the increasing evidence of circadian periodicity in cardiovascular disorders such as myocardial infarction[1] and sudden cardiac death,[2] we studied the relation between time of day and the onset of stroke. Knowledge of any periodicity in the time of stroke onset may be relevant to primary stroke prevention and treatment and may help elucidate the pathophysiologic mechanisms of stroke.

Subjects and Methods

At four academic hospital centers, neurologists collected information about stroke patients for the Stroke Data Bank supported by the National Institute of Neurological and Communicative Disorders and Stroke.[3] These neurologists reported data on all their patients admitted for the treatment of acute stroke, which includes ischemic stroke, intraparenchymal hemorrhage, and subarachnoid hemorrhage. We report data for 1,273 patients who had ischemic strokes between June 30, 1983, and June 30, 1986.

The physician who took the neurological history determined the date and time of stroke onset by questioning the patient or a person who may have observed the onset. If no estimate of the time of onset could be obtained, a value of 0 was entered. The presence of any stroke symptoms on the patient's awakening was recorded as "No," "Yes," or "Unknown," as were the presence at the time of stroke onset of vomiting, seizures, and severe headache with nuchal rigidity. Data from the neurological history included the patient's use of antiplatelet agents (aspirin or dipyridamole) or anticoagulants (heparin or warfarin) at the time of the stroke.

After the results of tests such as angiography, computed tomography, and Doppler ultrasound became available, one of the study neurologists determined the etiology of the patient's stroke as ischemia due to unknown cause, infarct with normal angiogram, tandem arterial pathology, embolism attributed to cardiac or transcardiac source, cerebral infarction due to atherosclerosis, lacune, parenchymatous hemorrhage, subarachnoid hemorrhage, or other. These diagnostic categories have been defined elsewhere.[3]

To investigate the time of stroke onset, we assumed that if it had no relation to time of day, then the time of stroke onset would be evenly distributed throughout the day. We compared the observed frequency of stroke onset in 12 2-hour intervals with the expected frequency using a χ^2 test.

Analysis of the extent of bias as a result of stroke symptoms present on the patient's awakening required three steps. First, the distinction was ignored and the data were analyzed without regard

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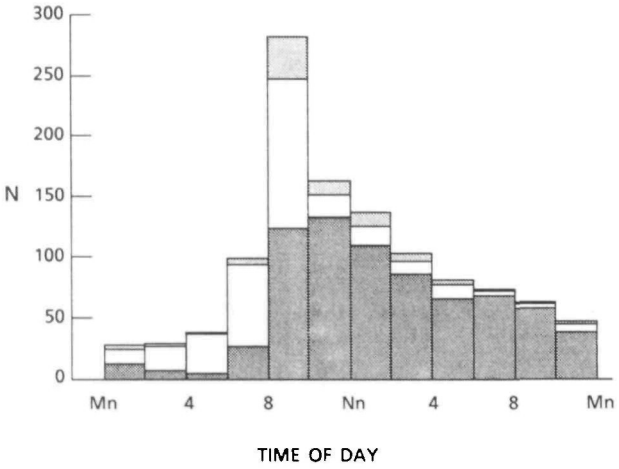

FIGURE 1. *Frequency, in 2-hour intervals, of onset of ischemic stroke for 1,167 patients. Mn, midnight; Nn, noon; N, number of patients. Filled areas, 744 patients with onset while awake; open areas, 331 patients with stroke symptoms present on awakening; shaded areas, 92 patients for whom time of stroke onset was unknown. Hypothesis for uniform distribution of time of onset was rejected on basis of* χ^2 *test* (χ^2=558.34, df=11, p<0.005).

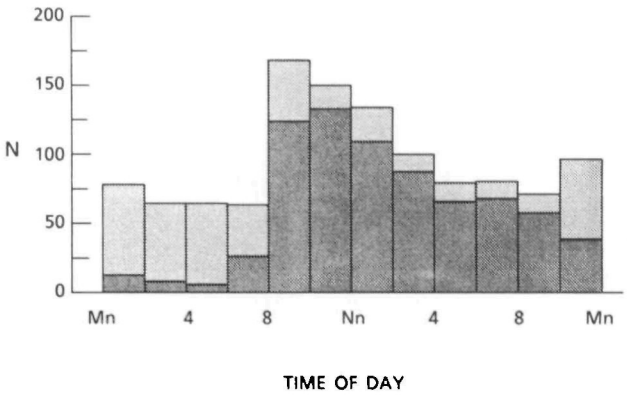

FIGURE 2. *Frequency, in 2-hour intervals, of onset of ischemic stroke in 1,167 patients after redistribution of strokes with symptoms present on awakening and time of onset unknown over preceding 8 hours. Mn, midnight; Nn, noon; N, number of patients. Filled areas, 744 patients with stroke onset while awake (same as in Figure 1); shaded areas, 423 patients with stroke symptoms present on awakening or in whom time of stroke onset was unknown. Hypothesis for uniform distribution of time of onset was rejected on basis of* χ^2 *test* (χ^2=143.90, df=11, p<0.01).

to whether stroke onset was before or after awakening. Second, the data were analyzed omitting cases in which stroke symptoms were unknown or present on awakening. Third, assuming that symptoms present on awakening indicated a stroke occurring at times distributed evenly over the preceding 8–10 hours, the times of onset for these strokes were distributed evenly between the hour of awakening and the preceding 8 hours, and we analyzed the redistributed data using a χ^2 test.

Results

The median age of all 1,273 patients was 68 (range 18–99) years. For 106 patients, the time of stroke onset was not determined. For the remaining 1,167 patients, onset occurred in 744 awake patients (64%). Stroke symptoms were present on awakening in 331 patients (28%). For 92 patients (8%) it was unknown whether symptoms were present on awakening.

Figure 1 shows the frequency, in 12 2-hour intervals, of onset of strokes occurring in awake patients, strokes in patients awakening with symptoms already present, and strokes for which it was unknown whether symptoms were present when the patient awakened. In awake patients, more strokes occurred between 10 AM and noon than during any other 2-hour interval. From 8:00 to 10:00 AM, stroke symptoms were present on awakening in 44% of the patients; for 12% of the patients, it was unknown whether symptoms were present on awakening. Even when only those patients in whom the stroke was known to have occurred after awakening are considered, the number of strokes observed between 8:00 and 10:00 AM (124) significantly exceeds the number expected (62) if the time of onset were uniformly distributed throughout the day (χ^2=357.77, *df*=11, p<0.001).

Figure 1 also shows that during the day and early evening (8:00 AM–8:00 PM), more strokes occurred in awake patients from 8:00 AM to noon, with a declining incidence during the remainder of the day and early evening. Presumably, all strokes present on awakening and all strokes for which the presence of symptoms on awakening was unknown could have occurred at any time while the patient was asleep. Therefore, if the time of onset for these strokes were distributed evenly over the preceding 8 hours of sleep, the results would be as shown in Figure 2. With such a distribution, the rate of stroke onset, in patients awake or asleep, is greater between 8:00 AM and noon, with significant deviation from a uniform distribution remaining (χ^2=143.90, *df*=11, p<0.001). The same preponderance of strokes that occur between 8:00 AM and noon remains when strokes present on awakening are distributed over the preceding 6 and even 4 hours.

For two subgroups of patients, the times of stroke onset reported may be more accurate than for the total group. One such subgroup is the 283 patients whose stroke worsened after they had been hospitalized for an initial stroke. For these patients, information concerning the time of worsening was taken from the notes of physicians and assisting personnel; whether the patient was awake or asleep at the time of symptom progression was not recorded. The other subgroup comprises 171 patients who had a sudden headache, seizure, or vomiting at stroke onset; more accurate estimates of the time of onset of their symptoms may have been obtained because the onset was dramatic. As shown in Figures 3 and 4, the same preponderance of strokes occurred from 8:00 AM to noon in both subgroups.

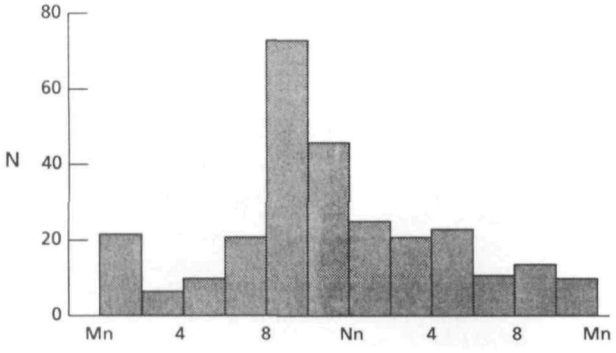

FIGURE 3. *Frequency, in 2-hour intervals, of progression of ischemic stroke for 283 patients whose strokes worsened while in the hospital. Mn, midnight; Nn, noon; N, number of patients. Hypothesis for uniform distribution of time of worsening was rejected on basis of* χ^2 *test* (χ^2=*163.54*, df=*11*, p<*0.01*).

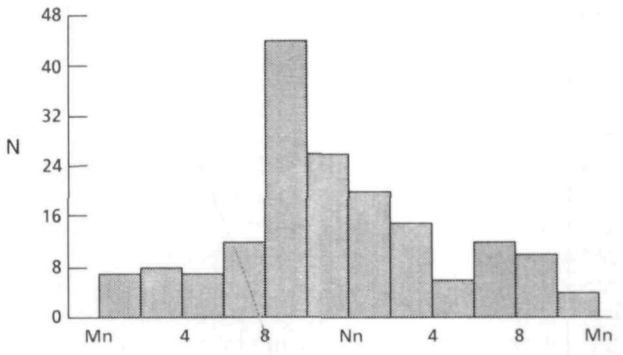

FIGURE 4. *Frequency, in 2-hour intervals, of onset of ischemic stroke for 171 patients who had prominent signs or symptoms (severe headache, seizures, or vomiting) at onset. Mn, midnight; Nn, noon; N, number of patients. Hypothesis for uniform distribution of time of onset was rejected on basis of* χ^2 *test* (χ^2=*98.40*, df=*11*, p<*0.01*).

For each ischemic stroke subtype, the hypothesis that strokes occur with equal frequency in 2-hour intervals throughout the day was generally rejected, with two exceptions. For infarcts with normal angiogram, the sample size was too small for a valid χ^2 test. For the 139 embolic strokes in awake patients from 8 AM to midnight, the hypothesis that the strokes occurred with equal frequency in each 2-hour interval was not rejected (χ^2=5.40, *df*=7, *p*=0.61).

The observed pattern of occurrence from 8:00 AM to noon was not altered in the 158 patients who received aspirin, dipyridamole, or warfarin before their stroke. Similarly, the pattern of occurrence was not related to age, sex, blood pressure at admission, history of hypertension, and severity of the consequences of the stroke.

Discussion

As summarized in Table 1, the results of at least six studies of the time of onset of ischemic stroke have been published. Our results agree well with those of Agnoli et al,[4] Jovičić,[5] Tsementzis et al,[6] and Kaps et al,[7] who reported a peak occurrence of ischemic stroke between 6:00 AM and 2:00 PM, between 8:00 and 11:00 AM, between 10:00 AM and noon, and between 7:00 AM and 7:00 PM, respectively. Our results do not agree with those of Marshall[8] and Hossmann,[9] who reported the peak of stroke onset to be several hours earlier, between midnight and 6:00 AM and between 1:00 and 5:00 AM, respectively. Although the results of these studies are not the same, all support the conclusion that stroke is least likely to occur in the late evening, before midnight.

Our study and several others showing a late-morning onset of stroke challenge the hypothesis that stroke onset coincides with low blood pressure, which is well known to occur early in the morning, when most people are asleep. In fact, the onset of ischemic stroke seems to be maximal when blood pressure is well documented to be highest for the day, late in the morning.[10,11] The onset of intracerebral hemorrhage and subarachnoid hemorrhage is more obviously related to blood pressure. In fact, these two types of stroke have also been reported to occur late in the morning.[6]

In view of the several well-known circadian rhythms in humans, it is not surprising that several parameters associated with events that may lead to the onset of a stroke have been shown to fluctuate with a predictable periodicity. The 24-hour variation in cortisol secretion is perhaps the best known. Available data suggest that this secretion rhythm is not passively driven by environmental events but, rather, is the product of an endogenous "clock" within the organism.

Other examples of well-documented biologic periodicity in humans include time of death, onset of

TABLE 1. **Previous Studies of Time of Onset of Ischemic Stroke**

Study	Year	*n*	Population	Peak onset
Hossmann[9]	1971	131	Germany	1:00 AM–5:00 AM
Agnoli et al[4]	1975	256	France	6:00 AM–2:00 PM
Marshall[8]	1977	707	England	Midnight–6:00 AM
Jovičić[5]	1983	85	Yugoslavia	8:00 AM–11:00 AM
Kaps et al[7]	1983	545	Germany	7:00 AM–7:00 PM
Tsementzis et al[6]	1985	245	England	10:00 AM–noon

spontaneous labor, and attacks of asthma. Most deaths occur between 5:00 and 9:30 AM,[12] whereas the incidence of cardiac death peaks between 8:00 and 11:00 AM.[13] Onset of labor occurs most frequently between 1:30 and 2:30 AM.[12] Dyspnea with attacks of asthma occur most frequently between 11:00 PM and 6:00 AM.[14,15] In addition to variations in serum cortisol concentrations, several other processes as determined by laboratory tests have been reported to vary with the time of day: blood viscosity, hematocrit, blood pressure, activated partial thromboplastin time, prothrombin time, and platelet aggregation.[9,16,17] For example, Ehrly and Jung[16] have demonstrated a considerable diurnal, and substantially parallel, fluctuation in blood viscosity, plasma viscosity, hematocrit, and protein concentration that peaks between 8:00 AM and noon. These changes are considered to be secondary to changes in hemoconcentration and hemodilution, which may in turn reflect variations in the renin-angiotensin-aldosterone system. Peak plasma viscosity and hematocrit coincide approximately with the peak of thrombosis, a finding that might be significant in relation to the increased hematocrit in patients at the time of transient ischemic attacks and infarction.

Petralito et al[18] compared data from healthy volunteers and from those with vascular disease reflected by chronic-phase myocardial infarction and arteriopathy of the lower extremities. Petralito et al observed an increased tendency to clotting in normal subjects between 9:00 AM and noon. Especially noteworthy is the increased aggregability of platelets between 9:00 AM and noon, which, when coupled with the other processes mentioned, demonstrates several conditions that together increase the tendency to thrombosis during the midmorning. Miller-Craig et al[11] demonstrated a peak in blood pressure at 10:00 AM in hypertensive patients that is not as prominent in healthy individuals. It may also be that the late morning onset of stroke has little to do with endogenous circadian rhythms but, rather, is a response to the physiologic stress or activities of the morning.

Also relevant are reported variations in response to medical therapy during the day. For stroke therapy, Decousus et al[19] reported circadian changes in the anticoagulant effect of heparin infused at a constant rate. Activated partial thromboplastin times were maximum at night and minimum in the morning. Thus, comparing results of the studies reported here with those of others in related medical areas may provide a different perspective that would be of value in elucidating the pathogenesis, or even aiding in the prevention, of stroke.

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KEY WORDS • cerebral ischemia • circadian rhythm • stroke onset

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