Stroke in the Lehigh Valley: Seasonal Variation in Incidence Rates

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We investigated the seasonal pattern of stroke using the Lehigh Valley Stroke Register. This register includes all patients hospitalized with stroke or transient ischemic attack (TIA) from among the 600,000 Lehigh Valley residents. Meteorological data were obtained from the National Oceanic and Atmospheric Administration. The study, which uses 18 months of data, included 1,944 cases. Using single harmonic regression analysis, the seasonal pattern of TIA and infarction, but not hemorrhage, fit a sine-cosine wavefunction with a 12-month period ($R^2 = 41\%$ and $36\%$, respectively). For infarction, the strongest seasonal pattern was exhibited for women of all ages and for both sexes in the age groups 65-74 and 75-84, but only the sine component was significant. The peak months for TIA were June-August, while the peak months for infarcts were February-April. Correlations between ambient temperature and each type of stroke were computed. A significant positive correlation for TIA was found ($r = 0.57, p = 0.01$). After adjusting for a 2-month lag between the low for infarction and the peak for temperature, a significant negative correlation was found ($r = -0.64, p = 0.01$). No significant correlation was found for hemorrhage. Possible reasons for the opposite relations of TIA and infarct are discussed. (Stroke 1987;18:38-42)

S EASONAL variation in the rate of strokes, with a peak in the winter-spring and a trough in the summer-autumn, has been reported in many areas, including the United States,1-4 England,5-9 Canada,10 Japan,11,12 and Australia.13,14 The seasonal pattern in these countries is thought to be related to ambient temperature. However, in other countries, for example Mexico,15 Brazil,15,16 and Yugoslavia,17 no relation between stroke rate and ambient temperature has been found.

Acceptance of claims of seasonal patterns in stroke incidence rates in some studies is difficult because of a lack of statistical analysis showing that the presumed seasonal pattern was unlikely to be due simply to chance. Other studies averaged monthly meteorologic conditions in a region over several years and compared these monthly averages with the average monthly frequency of strokes. Wide variations in both meteorologic conditions and stroke frequency could, of course, be obscured by using average values, since the number of strokes and the climatic conditions during the same month in different years can be quite different. Thus, a pattern discerned by months in one year would not necessarily be duplicated in subsequent years. Another problem pertains to the limited age groups or small total number of cases in some studies. Because of inconsistencies in the seasonal pattern of stroke rates reported and the methodologic problems cited, we conducted another study of the seasonal occurrence of stroke in the Lehigh Valley using a large population and more appropriate statistical techniques.

Subjects and Methods

The Lehigh Valley is 60 miles north of Philadelphia and 90 miles southwest of New York City. It has about 600,000 inhabitants according to the 1980 census.18 The Lehigh Valley has an age and sex distribution similar to that of the United States (U.S.) as a whole and a socioeconomic status above the U.S. median. About 95% of the population is white, so inferences about nonwhites based on Lehigh Valley data may be inappropriate. The distribution of strokes by type in the Lehigh Valley is similar to that reported for the United States in the National Survey of Stroke.19

The population is served by 8 acute care hospitals and 1 chronic care facility. Virtually all strokes that occur in the Valley, including those where stroke is only suspected, are admitted to one of the acute care hospitals. Medical facilities in the Lehigh Valley are excellent and, therefore, there is very little, if any, loss of cases due to hospitalization outside the Valley. Since 1982, we have maintained a community-wide, hospital-based stroke/transient ischemic attack (TIA) register. Individuals trained in abstracting medical records identify all patients admitted with even a suspicion of having had a stroke or discharged with a diagnosis of stroke. Patients with a suspicion of having had a TIA or a diagnosis of TIA or those with stroke-like symptoms are also identified. All these patients are included in the register. A neurologist using standardized criteria similar to that used by the Pilot Stroke Data Bank20 reviews all registered cases and assigns a definitive diagnosis. Approximately 1,000 cases of stroke and 300 cases of TIA are registered each year. We have previously reported the incidence18 of initial...
and recurrent stroke as well as risk factors for recurrent stroke in this population.¹⁹

TIA was diagnosed after careful review of the medical protocol by the study neurologist, taking clinical and laboratory data into account.¹⁸ While not all patients with TIA were referred to the hospital, the estimated frequency of TIA derived from the register was higher than that based on a population survey of Rochester, Minn.²¹ Physicians in the community whom we interviewed assured us that there is a strong tendency to refer patients with TIA to a hospital for investigation rather than to allow them to remain at home.

Meteorologic data were obtained from the National Oceanic and Atmospheric Administration (NOAA) for 1982–83 for Allentown, which is centrally located in the Valley and has a representative climate.

We examined the frequency of all strokes and TIA for each month during an 18-month period. We also examined the frequency of infarction by sex and by 4 age groups. We did not analyze the seasonal variation of other types of stroke by sex and age because the numbers in such subgroups were small.

To quantify the periodicity of the seasonal distribution of occurrence of stroke and TIA, a single harmonic regression model was fit to the data. The period of oscillation was taken to be 12 months. The model’s goodness of fit was evaluated by F test for the overall model and the R² value. The single harmonic regression equation for the frequency of occurrence of strokes or TIA is

\[ y_t = \mu + \beta_1 \sin(2\pi t/12) + \beta_2 \cos(2\pi t/12) \]

where \( \mu \) is the mean monthly frequency of stroke or TIA, \( t \) is month 1, 2, 3, …, 18, and \( y_t \) is the predicted number of stroke/TIA cases for month \( t \). This is the general representation for a function with a 12-month periodicity and a single peak and trough. It is possible that the pattern is more complicated. However, only a major yearly seasonal pattern is under investigation in this report. For additional information on harmonic regression see Bloomfield.²²

The Pearson correlation coefficient was used to estimate the relation between average monthly ambient temperature and the occurrence of each type of stroke and of TIA.²³

### Results

The present study, pertaining to July 1982 through December 1983, included 1,944 cases of stroke or TIA as diagnosed after review by the register’s neurologist. Of these, 68% were cerebral infarction (thrombosis, embolus, and lacune), 7% were cerebral hemorrhage, 2% were subarachnoid hemorrhage, and 23% were TIA. There were 659 women and 672 men who had an infarction, 67 women and 66 men who had a cerebral hemorrhage, and 263 women and 204 men who had TIA. The age distribution for each type of stroke and TIA is shown in Table 1.

The monthly frequency of TIA is presented in Figure 1, along with the monthly average ambient temperature. Per year, the mean monthly number of cases of TIA during the 18 months was 24.4. The number of cases of TIA in each month did not vary significantly from the monthly average using the \( \chi^2 \) test (\( \chi^2 = 5.489, df = 17, p > 0.05 \)). This test, however, is not sensitive for detecting periodicities with narrow amplitudes. The regression model with a sine–cosine function is more sensitive. Using this model, the rate of TIA was shown to be periodic with a peak rate in June–August and low rates in December–February (Table 2 and Figure 1). Forty-one percent of the variation in the TIA data was explained by the sine–cosine model, and both estimated coefficients (\( \beta_1, \beta_2 \)) were significant (\( p < 0.05 \)). The mean monthly number of TIA’s (\( \mu \)) was estimated to be 23.9. When there is no difference between maximum and minimum monthly frequency, the ratio is 1. The larger the ratio, the larger the (relative) variation. In the present study, the predicted ratio of maximum to minimum monthly frequency was 1.6 for TIA.

Correlations between ambient temperature and TIA are given in Table 3. A significant positive correlation for TIA’s (\( r = 0.57, p = 0.01 \)) was found. The seasonal pattern for TIA’s and ambient temperature were in phase, with peaks for TIA’s corresponding to peaks for temperature.

A seasonal pattern was also observed for infarction with the peak incidence during February–April and the trough during August–October (Table 2 and Figure 1). Thirty-six percent of the variation in the infarction data was accounted for by the sine–cosine model, and

### Table 1. Age Distribution of Stroke by Type in the Lehigh Valley From July 1982 to December 1983*

<table>
<thead>
<tr>
<th>Age</th>
<th>Thrombosis</th>
<th>Embolus</th>
<th>Lacune</th>
<th>ICH</th>
<th>SAH</th>
<th>TIA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>%</td>
<td>No</td>
<td>%</td>
<td>No</td>
<td>%</td>
</tr>
<tr>
<td>&lt;45</td>
<td>15</td>
<td>1.5</td>
<td>6</td>
<td>2.8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>45–64</td>
<td>189</td>
<td>18.8</td>
<td>51</td>
<td>24.2</td>
<td>30</td>
<td>33.0</td>
</tr>
<tr>
<td>65–74</td>
<td>314</td>
<td>31.3</td>
<td>69</td>
<td>32.7</td>
<td>35</td>
<td>38.5</td>
</tr>
<tr>
<td>75–84</td>
<td>332</td>
<td>33.1</td>
<td>64</td>
<td>30.3</td>
<td>18</td>
<td>19.8</td>
</tr>
<tr>
<td>&gt;85</td>
<td>154</td>
<td>15.3</td>
<td>21</td>
<td>10.0</td>
<td>8</td>
<td>8.8</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1004</td>
<td>211</td>
<td>91</td>
<td>130</td>
<td>41</td>
<td>424</td>
</tr>
</tbody>
</table>

¹ICH = intracerebral hemorrhage, SAH = subarachnoid hemorrhage, TIA = transient ischemic attack.

*Age was missing in 43 cases.
Table 2. Seasonal Distribution of Stroke/TIA by Type, Age, and Sex in the Lehigh Valley From July 1982 to December 1983

<table>
<thead>
<tr>
<th>Stroke type</th>
<th>Subgroup</th>
<th>Parameter estimates</th>
<th>R² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarction</td>
<td>—</td>
<td>75.9, -8.9*</td>
<td>1.1*</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>—</td>
<td>7.5, -0.7</td>
<td>0.03</td>
</tr>
<tr>
<td>TIA</td>
<td>—</td>
<td>23.9, 3.5*</td>
<td>4.0*</td>
</tr>
<tr>
<td>Infarction</td>
<td>Females</td>
<td>37.7, -4.9*</td>
<td>1.6</td>
</tr>
<tr>
<td>Infarction</td>
<td>Males</td>
<td>38.1, -4.0</td>
<td>-0.5</td>
</tr>
<tr>
<td>Infarction</td>
<td>&lt;64 yrs</td>
<td>16.3, -1.2</td>
<td>-1.8</td>
</tr>
<tr>
<td>Infarction</td>
<td>65-74 yrs</td>
<td>24.2, -4.5*</td>
<td>0.9</td>
</tr>
<tr>
<td>Infarction</td>
<td>75-84 yrs</td>
<td>23.8, -3.3*</td>
<td>1.3</td>
</tr>
<tr>
<td>Infarction</td>
<td>&gt;85 yrs</td>
<td>10.2, 0.1</td>
<td>0.8</td>
</tr>
</tbody>
</table>

*p < 0.05.
†Significant (p < 0.05) only for sine function.

The estimated coefficient for the sine function (β₃) was significant (p < 0.05). The estimated peak incidence in women was February-April, and the trough incidence was August-October (i.e., the same as for both sexes combined). The estimated mean monthly frequency of infarction in women was 37.7 and the ratio of predicted maximum to minimum monthly frequency for women was also 1.3.

For infarction, only the age groups 65-74 and 75-84 exhibited a significant seasonal pattern and only the sine function parameter estimates (β₃) were significant (p < 0.05) (Table 2). The R² values were 28.5 and 28.0 for the decades beginning at 65 and 75, respectively. The estimated peak incidence for these age groups was February-April and the estimated trough was August-October, while the estimated mean monthly number of infarctions were 24.2 and 23.8, respectively, for the 2 age groups. The ratio of estimated maximum to minimum monthly frequencies for the decades beginning age 65 and 75 were 1.5 and 1.4, respectively.

No seasonal pattern was discernible for the occurrence of hemorrhage and no correlation was found between hemorrhage and ambient temperature (Tables 2 and 3 and Figure 2). In addition to temperature, precipitation was examined but the correlation with stroke was not significant (Table 3).

Discussion

The present study of seasonal variation in the incidence of stroke and TIA was based on a larger popula-
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...tion than most previous studies and therefore allowed more detailed analyses by gender and age, at least for thrombotic strokes. Our investigations in the Lehigh Valley showed that infarction and TIA had different seasonal patterns and that hemorrhage had no seasonal pattern. For infarction, a seasonal pattern was also demonstrated in the 65-74 and 75-84 age groups. Similar results for cerebral infarction by age were reported by Bull.5

The reason for admission of the patients registered was almost always the cerebrovascular event itself and not an intercurrent infection, so the seasonal differences in stroke and TIA frequency cannot be attributed to seasonal variation in the frequency of infection in the community. In the oldest and youngest groups studied, no seasonal pattern emerged. However, the monthly number of cases over age 85 was small, and this may account for our inability to find a seasonal pattern in this age group. In the younger age group, compared with those over age 65, cerebral infarction usually has different mechanisms such as cardiac valvular disease and vasculitis, which may not be influenced by seasonal factors. When infarcts were examined by gender, the seasonal pattern was significant only for women. A reason for sex-specific seasonal variation in infarcts is not immediately apparent, and this observation needs confirmation.

It seems unlikely that physicians hospitalized patients with cerebral infarction less frequently in the summer than in the winter. If they had, the in-hospital mortality rate and duration of hospitalization would be expected to increase since there would be a tendency to refer the more severe cases. In fact, there was no significant seasonal variation in mortality rate or length of hospitalization.

If stroke has a seasonal pattern, the major causative factors should also be modified by seasonal variables. After TIA, the most powerful stroke risk factor is hypertension, both systolic and diastolic. This applies to all types of stroke, to both sexes, and to all ages.24 According to Hachinski et al.,24 incidence of hypertension in 820 patients with completed stroke admitted to the Toronto Stroke Unit was 50% for cerebral infarction and 48% for cerebral hemorrhage while, in matched controls, it was only 22%. A seasonal variable that correlated with TIA and infarction in our study was ambient temperature. It is noteworthy, therefore, that a significant negative correlation between ambient temperature and blood pressure was reported in Japan.11 The average blood pressure of people measured in winter was higher than that measured in summer.11 An increase in arterial pressure during mild surface cooling was also reported.26

Thus, low temperature was associated with higher blood pressure and may perhaps explain the peak in infarcts during colder months. However, no seasonal pattern for cerebral hemorrhage was discerned. If an effect of temperature on blood pressure mediates seasonal variation in stroke rates, then hemorrhagic as well as occlusive strokes should have shown a seasonal pattern. It is unlikely, therefore, that the seasonal pattern observed for infarcts is attributable to an effect of ambient temperature on blood pressure alone.

TIA is another powerful risk factor, particularly for infarction. Hachinski et al.25 reported a prior history of TIA in 33% of patients with cerebral infarction, 18% of those with hemorrhage, and none of the matched controls. The risk of developing stroke after TIA in the Toronto study was about 6 times that of the normal population. In the Lehigh Valley, the estimated relative risk for recurrent stroke for those with a history of TIA was 41.4. In comparison, hypertension was associated with a relative risk of recurrent stroke of only 4.5.26 In the present study, we found a seasonal pattern for TIA. Thus, it may be that the seasonal pattern for infarcts that was observed in the Lehigh Valley reflects an effect of ambient temperature on TIA and the seasonal pattern for infarcts was at least in part due to conditions related to TIA set in motion a few months earlier. In a recent population-based study, Schoenberg et al.27 reported that over 50% of all strokes that occurred in a TIA cohort occurred within 1 year of the first transient ischemic episode. In the present study, the estimated peak in TIA's anticipated the estimated peak in infarction by about 8 months.

As an alternate hypothesis, the factor(s) that causes TIA may be influenced by warm temperature (e.g., relative dehydration) while the factor(s) that influences thrombosis may be affected by cooler temperatures. For example, increases in platelet and red cell counts, blood viscosity, and catecholamine secretion occur with cooler temperatures.26 Clotting factor VII, antithrombin III, and cholesterol levels decrease with colder temperatures, while fibrinolytic activity increases.27 On the other hand, if TIA were more likely to lead to early infarction in the winter than in the summer, the seasonal differences in peak frequency of TIA and cerebral infarction might be explained. However, we do not yet have sufficient data to examine this point.

Of course, the seasonal effect we observed may not depend on temperature per se but on other factors that also show periodic changes. Such factors might include changes in blood volume, electrolyte concentrations in blood or tissues, or amine or fatty acid metabolism.28 Plasma cortisol levels that vary seasonally may also affect the risk of stroke. No direct evidence is available on these points, but a similar range of possibilities was offered recently to explain a diurnal pattern in frequency of myocardial infarction.29 Variation in dietary habits and alcohol consumption and seasonal variation in protein-bound iodine levels might also be considered,4 but for none of these conditions is the seasonal pattern very marked.28,30

The duration, phase, and amplitude of production of the pineal hormones and of melatonin and serotonin, both of which are vasoactive,31 are regulated by the changing environmental light cycle via the central nervous system.32 Seasonal variations in day length and photoperiod result in rhythmic release of pineal hormones in all mammalian species. In seasonally breeding mammals, changes in the gonads are controlled by...
melatonin rhythm. Some physiologic processes that could induce stroke, such as activity of the sympathetic nervous system, fibrinolytic activity of the blood, metabolism of pharmacologic doses of heparin, plasma levels of catecholamines, and arterial pressure may have a circadian rhythm. Perhaps, these physiologic processes not only exhibit circadian rhythm but also seasonal cycles. Thus, endogenous seasonal cycles could be related to the seasonal variation in stroke frequency. Moreover, seasonal variations of serotonin uptake and neurotransmitter have been reported.

By conducting studies in areas where the climate is different or the reverse of that in the Lehigh Valley, it may be possible to shed further light on the seasonal periodicity we observed. For example, in Melbourne, Australia, the peak incidence of strokes occurred in July, which is, of course, winter in the southern hemisphere. This observation lends weight to the idea that low ambient temperature is associated with an increase in at least some types of stroke. Identification of the cause(s) of seasonal variation in the incidence of stroke might lead to measures that could help prevent stroke. Therefore, the risk factors for stroke that can be modified by seasonal variables are worthy of further study.

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