Mechanisms and Timing of Deaths from Cerebral Infarction

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SUMMARY Clinicopathologic correlations were reviewed in 100 cases of recent cerebral infarctions in the internal carotid artery distribution. The most frequent cause of death was transtentorial herniation, followed in frequency by pneumonia, cardiac causes, and pulmonary embolism. Thirty-six percent of all patients and 47% of those with transtentorial herniation died within 48 hours of cerebral infarction. Of the treatable extracerebral causes of death determined at autopsy, only 34% were recorded premortem in the clinician's death summary.

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ALTHOUGH CEREBRAL INFARCTION is a common cause of death in the United States, little is known about the actual mechanism of deaths during the immediate postinfarction period. Some authors have implicated acute brain swelling as a major contributor to death from cerebral infarction. Shaw et al. showed a negative correlation between the length of survival and the degree of midline shift resulting from swelling of infarcted brain in 17 autopsied patients with cerebral infarction in the middle cerebral artery distribution. Although postinfarction cerebral edema is usually considered as developing over several days, the authors noted that most patients with transtentorial herniation had disturbances in sensorium from the onset of their symptoms. Based on autopsy measurements of midline structure shifts, the authors further suggested that the edema reached a maximum after 3 to 5 days. However, 6 of the 17 patients studied died within the first 48 hours after cerebral infarction, and only 2 died between 3 and 5 days after infarction. In a similar autopsy study of massive cerebral infarction in the carotid artery distribution, Berry and Alpers found that death had occurred within 48 hours of infarction in 6 of the 18 patients and that only 2 deaths occurred between 3 and 5 days after infarction. They also found that patients who died early from transtentorial herniation had more profound initial neurologic deficits than did those who died after the first week of symptoms.

More recently, Brown and Glassenberg in a study of 200 autopsied patients with ischemic and hemorrhagic cerebrovascular disease, reported a high incidence of contributing extracranial factors, including cardiac, pulmonary, and infectious processes, many of which were potentially treatable. They emphasized that such non-neurologic causes were significantly more frequent in fatal cerebral infarction if the patient survived 8 days or more. Thus, the available data suggest that survival of patients who have evidence of brain swelling is shorter than that of patients who do not and that more patients with altered consciousness or severe neurologic deficit (or both) probably would die from cerebral causes rather than extracerebral causes.

The present study reviews the causes of death, length of survival, and presenting clinical signs in 100 autopsied patients with recent cerebral infarction in the internal carotid artery distribution.

Materials and Methods

The 100 patients were selected from a review of autopsy records of all autopsied patients at the Mayo Clinic from January 1966 through September 1975. Only those patients with clinical histories of focal neurologic dysfunction attributable to a lesion in the internal carotid artery distribution were included. In addition, only patients in whom death occurred within 35 days of cerebral infarction were included. The 35-day interval is derived from a clustering of patients during this time period. In all other patients reviewed, death occurred 60 days or more after the occurrence of cerebral infarction.

In all patients, a pathologic diagnosis of recent cerebral infarction had been made by a Mayo Clinic neuropathologist, and the gross specimens and histologic sections were reviewed by one of us (H.O.). Cases in which only the internal capsule-basal ganglia region was involved by infarction were excluded, because the arterial pathologic changes probably differ from those in larger infarcts and because these infarctions may be produced by occlusions in the vertebrobasilar system. Thus, the patients studied represent a sub-group of all cerebral infarctions including only fatal lesions, only those in the internal carotid artery distribution, and only those extending beyond the internal capsule-basal ganglia region.

Two of us (J.V.B. and H.O.) reviewed autopsy records to determine the cause of death. When the cause of death was more than one, we judged which condition was most pertinent. In general, chronic factors, such as hypertensive cardiovascular disease, were not designated as the primary cause of death. Instead, conditions compromising vital signs or tissue oxygenation (or both), such as acute myocardial infarction, pulmonary embolus, and severe pneumonia, were implicated as the likely mechanism of death.

Clinical charts were reviewed to identify contribut-
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ing systemic factors such as hypotension, hypoxia, and cardiac arrhythmias. Two clinical signs were considered as possible predictors of eventual cause of death and length of survival. These were alteration in level of consciousness and hemiplegia (as opposed to hemiparesis) contralateral to the ischemic cerebral lesion.

Premortem recognition of the cause of death was determined by reviewing the clinician’s final summary and diagnoses of apparent causes of death and contributing factors. The clinical record was not reviewed. If the autopsy diagnosis of cause of death was mentioned at any point in this clinical summary, the condition was considered to be recognized premortem regardless of therapy instituted. Only conditions potentially treatable by conventional methods (pneumonia, pulmonary embolus, and septicemia) were considered.

Results

Cause of Death. The causes of death in each of the 100 cases of cerebral infarction are summarized in table 1. When present, transtentorial herniation was considered the cause of death. Some patients with septicemia also had pneumonia, but causes of death were classified under septicemia because the patients’ vital signs were compromised directly by septic shock. Cardiac causes of death included acute myocardial infarction or fatal arrhythmia associated with pathologically documented cardiac disease. Patients with uncomplicated coronary artery or valvular disease were not included.

Two other features of table 1 deserve mention. First is the high frequency of transtentorial herniation, and second, a large percentage of deaths occurred owing to potentially treatable causes.

Length of Survival vs Cause of Death. Patients with transtentorial herniation had a particularly short mean survival time, especially when compared with patients who died of pneumonia (table 2). Since only patients who survived up to 35 days were included, all causes of death were associated with a relatively short mean survival.

<table>
<thead>
<tr>
<th>Case</th>
<th>Mean survival (days)</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herniation</td>
<td>3.7</td>
<td>31</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>13.7</td>
<td>29</td>
</tr>
<tr>
<td>Cardiac</td>
<td>6.9</td>
<td>17</td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>5.2</td>
<td>13</td>
</tr>
<tr>
<td>Septicemia</td>
<td>11.8</td>
<td>10</td>
</tr>
<tr>
<td>Other</td>
<td>8.3</td>
<td>100</td>
</tr>
</tbody>
</table>

Of all deaths, 47% occurred within 3 days after clinical evidence of infarction (fig. 1). Transtentorial herniation was associated with a particularly early clustering of deaths — 62% of deaths occurred within 3 days of infarction (fig. 2). However, there was little early clustering of deaths from pneumonia (fig. 3). Sixty-nine percent of the patients who died of pneumonia died more than 1 week after infarction.

Presenting Clinical Signs vs Cause of Death. Causes of death were correlated with 2 presenting clinical signs: 1) alteration in consciousness and 2) hemiplegia contralateral to infarction (table 3). Notably, 50% of
Table 4: Premortem Recognition of Treatable Causes of Death

<table>
<thead>
<tr>
<th>Cause</th>
<th>No. of cases</th>
<th>Cases with correct clinical diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>29</td>
<td>11</td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Septicemia</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>47</td>
<td>16 (34%)</td>
</tr>
</tbody>
</table>

Discussion

Our finding of 31% of patients with transtentorial herniation is considerably greater than the frequency of 13% reported by Ng and Nimmannitya. However, in some smaller series of selected infarctions, herniation is more frequent than in our series. Berry and Alpers found severe swelling in 48% of their patients of occlusions of the internal carotid artery in which death occurred during the first 12 days, and Adams and Graham noted a herniation rate of 83% for patients with fatal cerebral infarction. Although we would emphasize the importance of transtentorial herniation, more than two-thirds of our patients died of extracerebral disease.

Most patients who died within 35 days of their infarction did so early during that time period. Pneumonia was the only cause of death that did not show a high frequency during the first week. This finding is slightly different from that of Brown and Glassenberg, who noted a number of conditions that were more frequent after the first week of survival. However, in our study, we considered only infarction rather than both infarctive and hemorrhagic cerebrovascular diseases. Furthermore, we cited only the primary cause of death rather than all associated extracerebral conditions.

The present study indicates that when postinfarction cerebral edema results in transtentorial herniation and death, it often does so within 48 hours. More patients died during the first 2 days than in any other 2-day period after cerebral infarction.

These findings are at odds with the prevailing clinical concept that postinfarction cerebral edema becomes maximal at 3 to 7 days. This concept is based largely on autopsy studies that use shifts of midline cerebral structures or increases in brain water content as standards of measurement; both of these are suboptimal criteria. Supratentorial mass lesions produce midline transtentorial herniation and death, with little or no shift of midline cerebral structures. Furthermore, a bias is inherent in autopsy measurements of midline structure shifts because lesser shifts are more likely to be present when death occurs within 2 to 3 days. Patients who survive the first few days with lesser shifts have a low probability of dying from the infarction. Changes of brain water content in cerebral infarction are complicated by concomitant losses of tissue solids and ischemic changes in other tissue components. Therefore, an increase in percentage of water content need not be due to a net gain in fluid.

Table 3: Presenting Clinical Signs and Causes of Death

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Altered sensorium only</th>
<th>Hemiplegia only</th>
<th>Altered sensorium &amp; hemiplegia</th>
<th>Cases with altered sensorium or hemiplegia (or both)</th>
<th>Cases without altered sensorium or hemiplegia</th>
<th>Total cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herniation</td>
<td>7</td>
<td>2</td>
<td>12</td>
<td>21</td>
<td>10</td>
<td>31</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>18</td>
<td>11</td>
<td>29</td>
</tr>
<tr>
<td>Cardiac</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>6</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>5</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>5</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>9</td>
<td>24</td>
<td>55</td>
<td>45</td>
<td>100</td>
</tr>
</tbody>
</table>
The introduction of computed tomography (CT) offers another possible method for defining the course of postinfarction cerebral edema. Bruce and Hurtig have stressed the lack of correlation between the decreased x-ray absorption coefficients on CT and the increased tissue water content in cerebral infarction. Campbell et al. found that distortion or displacement of the ventricular system was a more useful indicator of brain swelling. Although the authors did not comment on the timing of maximal edema, they reported that mass effect was occasionally seen on the day of cerebral infarction.

In most patients with transtentorial herniation, either altered level of consciousness or hemiplegia was initially present. When both of these signs existed, herniation was 3 times more frequent than any other cause of death. Nevertheless, approximately one-third of patients who died of herniation had neither altered sensorium nor hemiplegia initially, and either condition alone proved to be a poor predictor.

The low frequency of premortem recognition of the cause of death may reflect the method of assessing the clinician's impressions. In addition, in patients with pulmonary embolism, the condition may have been sudden and terminal, thereby precluding a correct premortem diagnosis. However, prophylactic treatment with low-dose heparin might have prevented a pulmonary embolus. Regardless of the possible underestimation of correct clinical diagnoses, the large number of patients for whom the eventual cause of death was not noted in the clinician's summary before autopsy deserves attention. It is exceedingly difficult to medically evaluate hemiparetic-hemiplegic or semicomatose (or both) patients. Also, medical diagnoses may not have been sought with the same thoroughness employed in patients with a better overall prognosis. Nonetheless, the clinician must be particularly pains-taking in seeking treatable medical illnesses in patients with ischemic stroke.

References
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