Brain Hemorrhage from Intracranial Tumor

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AND STIRLING CARPENTER, M.D.

SUMMARY Brain hemorrhage from an intracranial tumor was encountered in 7 males and 6 females during a 4-year period. In 5 patients, hemorrhage was responsible for the first signs of a previously unsuspected neoplasm. The intracranial lesion was demonstrated by computed tomography (CT scanning) in each patient. Characteristic CT scan findings included: a neoplastic core (high or low density); small, multifocal clots usually at the margin of the tumor; and, surrounding, often extensive, edema. Enhancement of the tumor tissue with intravenous injection of 60% Hypaque was observed in the 8 patients so studied. The regions which were enhanced had a peripheral distribution corresponding to the site of hemorrhage. Microscopic examination demonstrated 7 glioblastoma multiforme, 1 oligodendroglioma, 4 metastatic carcinomas (including 1 each of bronchogenic carcinoma, melanoma, hypernephroma, and adrenal carcinoma), and 1 hemangiopericytoma. High-grade malignancy and extensive, abnormal vascularity appeared to be predisposing factors.

BRAIN HEMORRHAGE from an intracranial tumor is a well-recognized entity. Prior to the introduction of computed tomography (CT scanning), clinical diagnosis and non-invasive confirmation were difficult. Since then a small number of patients diagnosed by CT scan have been reported. The object of this investigation was to study the clinical presentation, CT scan findings, and neuropathological changes in patients with a brain hemorrhage from an intracranial tumor.

Analysis of Cases

Thirteen adult patients with an intracranial tumor and concomitant brain hemorrhage were seen at the Montreal Neurological Institute from February 1974 to February 1978. The 6 females and 7 males ranged in age from 18 to 80 years (mean: 53 years). The intracranial lesion was demonstrated by CT scan in each patient and neoplasia was confirmed by microscopic examination of tissue obtained at operation and/or at postmortem examination.

Clinical Presentation

The clinical presentation of the 13 patients is summarized in table 1. Five were asymptomatic prior to hemorrhage and 8 had previous symptoms of progressive neurological dysfunction. Deterioration in the level of consciousness was the most common neurological finding following hemorrhage. Five patients became drowsy or obtunded and 7 became comatose. Progressive brain stem dysfunction, similar to that seen with uncal or central transtentorial herniation, developed in 9 patients. Only one patient remained alert and oriented without evidence of brain stem compression.

Arterial blood pressure was found to be elevated in 9 was multifocal with 2 or more clots in the vicinity of the tumor (figs. 1, 2). Usually they were located at the interface between tumor and surrounding edematous brain. A large homogeneous hematoma obliterating most of the tumor was observed in 1 patient only (case 8). This patient had a tumor arising from the diencephalic region. Brain hemorrhage distant from the tumor site was not seen, but extension into the ventricular system was present in 4 patients. Enhancement of the tumor with intravenous Hypaque was observed in the 6 patients so studied (fig. 3). The regions which enhanced generally had a peripheral distribution corresponding to the location of the hematoma.

During the period 1974–78 ten of 172 patients with brain hemorrhage diagnosed by CT scan were found to have an associated tumor.

CT Scan. The 13 patients had 26 scans. Intravenous infusion of 60% Hypaque was carried out on 9 occasions in 8 patients. The results of these studies are listed in tables 2 and 3. CT scans on 6 patients were obtained prior to hemorrhage. The findings were similar to those reported previously for brain tumors. Infusion studies in 3 of them revealed enhancement of tumor tissue, most marked at the periphery.

Ten patients had CT scans following hemorrhage, performed within 12 hours of the bleed in 9. The brain hemorrhage in 9 was multifocal with 2 or more clots in the vicinity of the tumor (figs. 1, 2). Usually they were located at the interface between tumor and surrounding edematous brain. A large homogeneous hematoma obliterating most of the tumor was observed in 1 patient only (case 8). This patient had a tumor arising from the diencephalic region. Brain hemorrhage distant from the tumor site was not seen, but extension into the ventricular system was present in 4 patients. Enhancement of the tumor with intravenous Hypaque was observed in the 6 patients so studied (fig. 3). The regions which enhanced generally had a peripheral distribution corresponding to the location of the hematoma.

Cerebral Angiography. Cerebral angiography was carried out in 6 patients, including 4 with a glioblastoma multiforme, 1 with an oligodendroglioma and 1 with a metastatic adrenal carcinoma. Abnormal tumor vessels and early venous filling were demonstrated in the patients with glioblastoma and metastatic carcinoma. Aside from tumor mass effect, no pathological vascularity was seen in the patient with the oligodendroglioma.

Investigations

In a previous study, we were able to determine the type of hemorrhage in 10 patients. 

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Treatment

Four patients did not have surgery because of extensive neoplastic disease. Treatment in these cases consisted of radiation and/or chemotherapy. Four other patients, including a 42-year old male with a
TABLE 1  
Clinical Presentation in Patients with an Intracranial Tumor and Concomitant Brain Hemorrhage

<table>
<thead>
<tr>
<th>Case number</th>
<th>Age/Sex</th>
<th>Symptoms prior to hemorrhage</th>
<th>Onset</th>
<th>Neurological findings following hemorrhage findings</th>
<th>Course (survival time)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>18/f</td>
<td>headache; lethargy; R. hemiparesis</td>
<td>acute</td>
<td>obtunded; pathological posturing</td>
<td>dead (2 weeks)</td>
</tr>
<tr>
<td>2.</td>
<td>48/f</td>
<td>personality changes; lassitude; seizures</td>
<td>acute</td>
<td>comatose; pathological posturing; oculomotor palsy</td>
<td>dead (2 days)</td>
</tr>
<tr>
<td>3.</td>
<td>53/m</td>
<td>L. homonymous hemianopsia; L. hemiparesis; hypertension</td>
<td>acute</td>
<td>comatose; pathological posturing; fixed pupils; BP 180/100 mm Hg</td>
<td>dead (1 day)</td>
</tr>
<tr>
<td>4.</td>
<td>56/m</td>
<td>none</td>
<td>acute</td>
<td>alert; L. homonymous hemianopsia; L. hemiparesis (mild)</td>
<td>dead (2 mos.)</td>
</tr>
<tr>
<td>5.</td>
<td>57/m</td>
<td>none</td>
<td>acute</td>
<td>comatose; pathological posturing; oculomotor palsy; BP 190/90 mm Hg</td>
<td>dead (5 days)</td>
</tr>
<tr>
<td>6.</td>
<td>68/m</td>
<td>L. facial weakness; unsteady gait</td>
<td>acute</td>
<td>drowsy; L. homonymous hemianopsia; L. hemiparesis; BP 180/100 mm Hg</td>
<td>dead (5 weeks)</td>
</tr>
<tr>
<td>7.</td>
<td>80/f</td>
<td>confusion; hypertension</td>
<td>subacute</td>
<td>drowsy; L. hemiparesis; meningismus</td>
<td>dead (1 mo.)</td>
</tr>
<tr>
<td>8.</td>
<td>19/f</td>
<td>headache; diplopia</td>
<td>acute</td>
<td>comatose; pathological posturing; oculomotor palsy; BP 160/110 mm Hg</td>
<td>dead (3 weeks)</td>
</tr>
<tr>
<td>9.</td>
<td>71/m</td>
<td>headache; R. hemiparesis; seizures</td>
<td>subacute</td>
<td>drowsy; R. hemiparesis</td>
<td>dead (3 weeks)</td>
</tr>
<tr>
<td>10.</td>
<td>52/m</td>
<td>confusion; dysphasia</td>
<td>acute</td>
<td>comatose; pathological posturing; fixed pupils; BP 150/130 mm Hg</td>
<td>dead (1 day)</td>
</tr>
<tr>
<td>11.</td>
<td>55/f</td>
<td>none</td>
<td>acute</td>
<td>drowsy; dysarthria; R. facial palsy; Babinski responses; BP 180/110 mm Hg</td>
<td>alive (1 year)</td>
</tr>
<tr>
<td>12.</td>
<td>71/m</td>
<td>none</td>
<td>acute</td>
<td>comatose; pathological posturing; Cheyne-Stokes respiration; BP 200/100 mm Hg</td>
<td>dead (1 day)</td>
</tr>
<tr>
<td>13.</td>
<td>42/m</td>
<td>none</td>
<td>acute</td>
<td>comatose; pathological posturing; absent oculocephalic and oculovestibular responses; BP 240/100 mm Hg</td>
<td>dead (2 days)</td>
</tr>
</tbody>
</table>

hemangiopericytoma, were not treated surgically because of severe brain stem injury secondary to cerebral herniation.

Craniotomy with evacuation of the clot and subtotal removal of a cerebral glioblastoma multiforme was done in 2 patients (cases 4 and 5). Another patient (case 11) had a suboccipital craniectomy with evacuation of a cerebellar hematoma and excision of a hypernephroma nodule. In these 3 patients, the hematomas were found to be multifocal and appeared to arise at the margin of the tumors. Hemorrhage had extended into surrounding edematous brain tissue. Two patients with diencephalic tumors had insertion of a ventricular drain to relieve acute obstructive hydrocephalus.

Results

The length of survival is listed in table 1. None of the patients receiving medical therapy alone lived longer than 4 weeks. Two of the 3 patients decompressed surgically left the hospital. One subsequently died 2 months later from progressive growth of a glioblastoma multiforme. The other is alive 1 year following resection of a hypernephroma nodule and associated cerebellar hematoma, but multiple brain

TABLE 2  
CT Scan Findings Prior to Hemorrhage

<table>
<thead>
<tr>
<th>Case number</th>
<th>Location</th>
<th>Tumor</th>
<th>Appearance</th>
<th>Edema</th>
<th>Enhancement with hypaque infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>hypothalamus; L. thalamus</td>
<td>low density; ? cystic</td>
<td>+</td>
<td>not done</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>R. temporal; R. basal ganglia</td>
<td>isodense lesion</td>
<td>0</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>R. frontal</td>
<td>low density lesion</td>
<td>++</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>hypothalamus</td>
<td>cystic lesion</td>
<td>++</td>
<td>not done</td>
<td></td>
</tr>
<tr>
<td>9.</td>
<td>L. parieto-occipital; R. frontal; R. temporal</td>
<td>multiple isodense lesions</td>
<td>++</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>10.</td>
<td>L. frontal</td>
<td>low density lesion</td>
<td>++</td>
<td>not done</td>
<td></td>
</tr>
</tbody>
</table>

0 = none; + = mild; ++ = moderate; +++ = marked.
metastases subsequently have been identified. The 2 patients with a diencephalic tumor died 2 and 3 weeks following hemorrhage without apparent benefit from ventricular drainage.

Pathology
The results of the microscopic examination of tumor tissue are listed in table 4. The gross findings in the 11 patients undergoing postmortem examination correlated closely with the CT scan findings.

Discussion
Intracranial tumors are a well-established cause of hemorrhage into brain tissue. However, hemorrhage is believed to occur infrequently. Tumors were found in 2% of the 461 autopsied cases of "spontaneous" intracerebral hemorrhage reported by Russell and less than 1% of the 225 reported by Mutlu et al.10 In our series, bleeding originated from an intracranial tumor in 6% of patients with brain hemorrhage diagnosed by CT scan. Diagnosis of brain tumor was made in 3 other patients having a CT scan only prior

TABLE 3 CT Scan Findings Following Hemorrhage

<table>
<thead>
<tr>
<th>Case number</th>
<th>Location</th>
<th>Hematoma</th>
<th>Findings after hemorrhage</th>
<th>Edema</th>
<th>Enhancement with hypaque infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>hypothalamus; L. thalamus</td>
<td>multifocal</td>
<td>+</td>
<td>not done</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>R. parietal</td>
<td>multifocal</td>
<td>++</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>R. parieto-occipital</td>
<td>multifocal</td>
<td>++</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>R. frontal</td>
<td>multifocal</td>
<td>++</td>
<td>not done</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>R. temporal</td>
<td>multifocal</td>
<td>+++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>hypothalamus; R. basal ganglia</td>
<td>discrete; homogeneous</td>
<td>+ +</td>
<td>not done</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>L. parieto-occipital</td>
<td>multifocal</td>
<td>+++</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>R. cerebellum</td>
<td>multifocal</td>
<td>+++</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>L. parieto-occipital</td>
<td>multifocal</td>
<td>+++</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>R. parieto-occipital</td>
<td>multifocal</td>
<td>+</td>
<td>not done</td>
<td></td>
</tr>
</tbody>
</table>

0 = none; + = mild; ++ = moderate; +++ = marked.

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Discussion
Intracranial tumors are a well-established cause of hemorrhage into brain tissue. However, hemorrhage is believed to occur infrequently.1, 7, 10, 12 Intracranial tumors were found in 2% of the 461 autopsied cases of "spontaneous" intracerebral hemorrhage reported by Russell and less than 1% of the 225 reported by Mutlu et al.10 In our series, bleeding originated from an intracranial tumor in 6% of patients with brain hemorrhage diagnosed by CT scan. Diagnosis of brain tumor was made in 3 other patients having a CT scan only prior

FIGURE 1. CT scan of patient 1 following hemorrhage shows a multifocal hematoma surrounding a low density, left thalamic tumor. There is moderate ventricular dilatation and periventricular edema.

FIGURE 2. CT scan of patient 11 following hemorrhage shows a multifocal hematoma in the right cerebellar hemisphere. Extensive edema is demonstrated.
to hemorrhage. The higher incidence of tumor hemorrhage reported here is related to the more accurate and reliable identification of brain hematoma with CT scanning. It suggests that this phenomenon is more common than previously believed.

The mechanism of bleeding has not been defined, but high-grade malignancy and extensive, abnormal vascularity appear to be predisposing factors. Brain hemorrhage from metastatic and primary intracranial malignant tumors is encountered approximately with equal frequency. Hemorrhage from a benign neoplasm, such as a meningioma, is rare and usually is attributed to angiomatous tumor vessels. Hypertension and/or coagulopathy could be important contributing factors in these patients. Elevated systemic arterial pressure was observed in 8 of our patients during or shortly following hemorrhage, however, it was not possible to determine whether the hypertension was the cause or result of the intracranial bleed. None of our patients had clinical evidence of a generalized bleeding disorder and none had received anticoagulants prior to the hemorrhage.

Glioblastoma multiforme was found in 7 of our 8 patients with glial neoplasia. The hemorrhagic propensity of glioblastomas has been described previously. According to Zulch, the pathogenesis of ruptured blood vessels is understandable in view of the "huge, disorderly, fistulous vessels" invariably present. Proliferation of endothelium, clusters of dilated thin-walled vessels, and areas of necrosis were common findings in tumor tissue examined microscopically.

Hemorrhage into a well-differentiated astrocytoma is uncommon and was not seen in our investigation. This is likely related to the infrequent occurrence of pathological blood vessels and absence of necrosis.
in these tumors. Oligodendrogiomas appear to produce bleeding more frequently than astrocytomas. The reason for this is unclear, although the presence of numerous dilated, thin-walled vessels (i.e., glomeruloid formation) and endothelial proliferation as observed in our patient have been implicated as important predisposing factors.

Bronchogenic carcinoma, melanoma, and hypernephroma each occurred in one patient. These tumors, as well as choriocarcinoma, are implicated most frequently when brain hemorrhage results from a metastatic lesion. The incidence of bleeding from metastatic choriocarcinoma, a rare tumor usually found in young females, is particularly high, occurring in more than 50% of patients with a brain metastasis. In most instances of metastatic tumor, hemorrhage is thought to arise from the rapidly growing peripheral portion of the tumor or from adjacent, damaged, brain tissue. The inherent capacity of choriocarcinoma for vascular invasion appears to be a particularly important factor in the pathogenesis of hemorrhage with this neoplasm.

Benign meningeal tumors constitute a rare but important cause of intracranial hemorrhage. Highly vascular meningothelial and angioblastic meningiomas are most frequently involved. Gruszkiewicz et al. stated that “nearly all reported cases of meningioma associated with intracranial hemorrhage deal with subarachnoid hemorrhage rather than intracerebral hemorrhage or hemorrhage within the substance of the tumor itself.” One patient with extensive intracerebral hemorrhage from a hemangiopericytoma arising from the falx cerebri was included in our series. Numerous thin-walled vessels were observed on microscopic examination of this tumor.

Bleeding from a tumor usually is symptomatic and may be responsible for the first signs of a previously unsuspected neoplasm. The bleeding simulates a primary vascular disorder such as hypertensive hemorrhage or ruptured saccular aneurysm. Five of our 13 patients were asymptomatic prior to hemorrhage. Likewise, the existence of a tumor was not clear-cut in 8 of the 13 patients described by Padt et al. with bleeding into a brain tumor. Similar findings have been reported by other investigators.

The presence of tumor was not clear-cut in 8 of the 10 non-infusion CT scans performed following hemorrhage. A high density or low density neoplastic core with small, multifocal clots at its periphery were consistently demonstrated. Usually there was extensive surrounding edema. These features were useful in differentiating tumor hemorrhage from the other more common causes of brain hemorrhage (i.e., hypertension, saccular aneurysm, etc.). The location of the hematomas (i.e., in the cerebral hemispheres) was not typical of hypertensive hemorrhage, the most common cause of “spontaneous” intracerebral hemorrhage.

Enhancement with an intravenous Hypaque injection was observed in 8 patients. This technique was useful in confirming the diagnosis of tumor prior to hemorrhage and demonstrated the abundant vascularity of the neoplasms involved. The location of the hematomas generally corresponded to the areas of enhancement, that is, at the periphery of the tumor.

Five of the 6 patients with peritumoral enhancement following hemorrhage had the study within 24 hours of the bleed. Consequently, the enhancement seen was considered the result of abnormal vascularity existing prior to the hemorrhage and not the enhancement commonly present 6 days or longer following hemorrhage from other causes. The patient (case 4) who had infusion and plain CT scans 1 week following hemorrhage, had a complete ring of enhancement around the tumor which included areas distant from the clot. Although enhancement in the vicinity of the hematoma could have been the result of the hemorrhage, the more distant enhancement likely was related to abnormal tumor vessels at the tumor-brain interface.

Emergency surgical decompression is sometimes helpful in those patients without previous demonstration of extensive malignant disease and without clinical findings of severe brain stem injury secondary to herniation. The hemispheric location of most of these tumors and associated hematomas allows relatively easy access and removal. The excision of an occasional benign tumor, such as a meningioma, or solitary metastatic nodule, may result in long-term survival.

References

Effect of Altered Availability of Energy-Yielding Substrates Upon Survival from Hypoxia in Mice

JEFFREY R. KIRSCH, B.S. AND LOUIS G. D'ALECY, D.M.D., PH.D.

SUMMARY  The duration of survival during a hypoxic or ischemic incident can be altered by barbiturate anesthesia. If this effect on the brain results from a reduction in lactic acid production by hypoxia, then a similar protective effect may be produced by altering substrate availability. Six groups of mice were subjected to hypoxia (4 to 5% O₂, balance N₂) at 30 to 35°C: 1. Hypoglycemia was induced by 2 U insulin injected ip 30 min prior to hypoxia. 2. Ketotic hypoglycemia was induced by fasting 85 to 90 hours prior to hypoxia. 3. Hyperglycemia was induced by iv dextrose. 4. Diabetic-ketotic-hyperglycemia was induced by iv alloxan 5 days prior to hypoxia. 5. One group was given both the insulin and dextrose in the above sequence. 6. In control, saline was given iv or ip when appropriate. The mean survival time for ketotic-hypoglycemic and diabetic-ketotic-hyperglycemic mice was significantly higher than control. The mean survival time for the insulin-hypoglycemic mice was significantly lower than control. The remaining groups showed no difference from control. The observed improvement in survival time from hypoxia seen in the ketotic animals suggests that during hypoxia, the brain metabolizes ketones selectively and minimizes the production of lactic acid to maintain neuronal viability.

BARBITURATE ANESTHESIA and alterations in blood glucose have been reported to modify survival time or brain damage in various animal models of brain hypoxia and ischemia. If the increase in survival time and the decrease in brain injury are related to a reduction in hypoxia-induced production of lactic acid, then supplying the brain with a substrate other than glucose may afford protection from hypoxia. Under normal circumstances, the mammalian brain is an obligatory glucose user. During a prolonged fast, or in the uncontrolled diabetic state, ketosis develops and the brain adapts by metabolizing acetoacetate and beta-hydroxybutyrate. The metabolism of these ketones requires the consumption of oxygen, but does not involve the production of lactic acid. Lactic acid, itself, or the hydrogen ion changes associated with the production of lactic acid have been suggested as a possible mediator of the neuronal damage associated with ischemia or hypoxia. It is assumed in the present study and previous studies using this animal model that neuronal metabolic derangements are responsible for the death of the animal during hypoxia. We tested the hypothesis that an alteration in the type or amount of substrate available for energy production could increase survival time during hypoxia.

Materials and Methods

The animal model used has been previously described by Wilhjelm and Arnfred and Steen and Michenfelder. Adult, male Sprague-Dawley albino mice (ICR-ARS-HA) weighing between 15 and 30 g were pretreated and then subjected to hypoxia (4 to 5% oxygen). The pretreatment involved a modification of dextrose infusion, insulin injection, fasting, or experimental alloxan-diabetes. For each group the survival time, and blood glucose and ketone levels were determined.
Brain hemorrhage from intracranial tumor.
J R Little, B Dial, G Bélanger and S Carpenter

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