Pituitary apoplexy: its incidence and clinical significance


Department of Neurosurgery, University of Tokyo Hospital, Tokyo, Japan

The occurrence of hemorrhage from pituitary adenoma (so-called “pituitary apoplexy”) was investigated in a consecutive series of 560 cases operated on during the past 30 years. There were 93 cases (16.6%) in which hemorrhage from pituitary adenomas was confirmed either clinically or surgically. These patients were analyzed in terms of age, sex, symptoms and signs, size of tumor, hormonal function, and histological types of adenomas, and computerized tomography findings. In 90 cases (16.1%), hematoma or old bloody fluid was verified within the tumor tissue at surgery. Three other patients presented with subarachnoid hemorrhage, but there was no detectable intratumor hematoma in any of them. Among these 93 patients, 42 (7.5%) showed no evidence of clinical symptoms related to hemorrhage (asymptomatic hemorrhage). Fifty-one patients (9.1%) had definite histories of an acute episode that suggested sudden bleeding (symptomatic hemorrhage: pituitary apoplexy). Thirty-eight patients (6.8%) had a major attack manifested by disturbances of consciousness, hemiparesis, loss of vision, or ocular palsy. In two acromegalic patients, pituitary apoplexy developed during bromocriptine treatment. There was one case of sudden death due to massive hemorrhage from the tumor 14 months after the completion of postoperative radiation therapy. The other 13 symptomatic patients (2.3%) developed a minor attack which included headache, nausea, vomiting, and vertigo.

Bleeding from pituitary adenomas was not statistically correlated with any of the following factors: sex, hormonal function of adenomas, and histological types, but it was correlated with age. The number of asymptomatic cases in the third decade was significantly greater than that of the whole group of pituitary adenoma patients in the same decade. The present investigation revealed that the incidence of pituitary apoplexy was unexpectedly high: a major attack in 6.8% of pituitary adenoma patients, a minor attack in 2.3%, and asymptomatic hemorrhage in 7.5% of the cases. This risk of pituitary apoplexy should be kept in mind in treating pituitary adenomas.

Key Words • pituitary apoplexy • adenoma • hemorrhage • pituitary tumor

Pituitary apoplexy has been a well known clinical syndrome since Bleibtreu described the first case in 1905. It is characterized by the sudden onset of headache, vomiting, visual impairment, diplopia, disturbances of consciousness, and autonomic or hormonal dysfunction. This condition is considered to be caused by the sudden enlargement of a tumor mass due to spontaneous hemorrhage or hemorrhagic necrosis within the tumor tissue. Hundreds of such cases have been documented in the medical literature. However, the incidence of hemorrhage into pituitary adenomas varies between 1.5% and 27.7% of cases, and no systematic analysis is available regarding the symptomatology in relation to the severity of hemorrhage.

In the present report, we have investigated the occurrence of hemorrhage from pituitary adenoma in our personal series of 560 cases. We have analyzed its incidence and correlation of hemorrhage with the following factors: age, sex, tumor size, hormonal function, and the histological features of the adenomas.

Clinical Material and Methods

The clinical material consisted of 560 surgically verified cases of pituitary adenoma treated in our institute over a period of 30 years, from January, 1950, to July, 1980 (Fig. 1). All patients’ records and
operative reports were reviewed to detect the presence of any hematoma, old bloody fluid or xanthochromic fluid found at surgery, and histories of an acute episode such as a sudden onset of headache, nausea and vomiting, loss of vision, diplopia, or consciousness disturbances.

Cases of symptomatic hemorrhage were classified as having had a major attack, manifested by disturbances of consciousness, hemiparesis, loss of vision, ocular palsy, or a minor attack with only headache, nausea, vomiting, and vertigo.

Summary of Cases

Symptoms and Signs

In 90 cases (16.1%), intratumor hematoma or old bloody fluid was found at surgery (Group A, Table 1). Three other patients presented with subarachnoid hemorrhage (SAH), but there was no detectable hematoma within the tumor tissue in any of them, and angiography was unrevealing (Group D, Table 1). Among these 93 cases, 42 showed no evidence of clinical symptoms related to the hemorrhage (asymptomatic hemorrhage). The other 51 patients had definite histories of an acute episode that suggested sudden bleeding (symptomatic hemorrhage). The other 51 patients had definite histories of an acute episode that suggested sudden bleeding (symptomatic hemorrhage). The other 51 patients had definite histories of an acute episode that suggested sudden bleeding (symptomatic hemorrhage). The other 51 patients had definite histories of an acute episode that suggested sudden bleeding (symptomatic hemorrhage). The other 51 patients had definite histories of an acute episode that suggested sudden bleeding (symptomatic hemorrhage). The other 51 patients had definite histories of an acute episode that suggested sudden bleeding (symptomatic hemorrhage). The other 51 patients had definite histories of an acute episode that suggested sudden bleeding (symptomatic hemorrhage).

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Pituitary apoplexy

TABLE 2
Classification of 93 cases with hemorrhage from a pituitary adenoma

<table>
<thead>
<tr>
<th>Classification*</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
</tr>
<tr>
<td>symptomatic</td>
<td>51</td>
</tr>
<tr>
<td>major attack</td>
<td>38</td>
</tr>
<tr>
<td>minor attack</td>
<td>13</td>
</tr>
<tr>
<td>asymptomatic</td>
<td>42</td>
</tr>
<tr>
<td>total cases</td>
<td>93</td>
</tr>
</tbody>
</table>

* For definition of major and minor attack, see text.

more severe than the first. The first episode was minor in three cases and major in four cases. The second episodes were all major attacks. In 13 other symptomatic cases, the episodes were minor, with symptoms of headache, nausea, vomiting, and vertigo (Table 2).

The acute symptoms in the 51 symptomatic patients included the following in order of frequency: headache, loss of vision, nausea and vomiting, ocular palsy, disturbances of consciousness, vertigo, fever, and hemiparesis (Table 4).

Distribution of Age in Both Sexes

Ages ranged from 15 to 63 years, with a mean age of 37.7 years for the symptomatic cases, 32.4 years for the asymptomatic, and 35.3 years for all cases (Fig. 2). Difference of mean age between the two groups was statistically significant (p < 0.05). The mean age for all cases of pituitary adenomas reviewed (37.3 years) was significantly different from that for asymptomatic hemorrhage cases (p < 0.05). The incidence of asymptomatic cases in the third decade was significantly greater than that of the total group of pituitary adenoma cases in the same decade (p < 0.01).

There was no difference in the incidence of hemorrhage from pituitary adenoma between both sexes: 28 males and 23 females in the symptomatic group; 21 males and 21 females in the asymptomatic group; 49 males and 44 females in the total group with hemorrhage; and 281 males and 279 females in the whole series of pituitary adenoma cases.

Size of Tumor

In acute cases among the symptomatic group (Table 1), the size of the adenomas could not be determined because the patients had no histories suggesting a pituitary tumor. However, most of the tumors might have been intrasellar or at least of modest size. In the

TABLE 3
Symptoms and signs in 38 cases with a major attack*

<table>
<thead>
<tr>
<th>Symptoms &amp; Signs</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>loss of vision</td>
<td>14</td>
</tr>
<tr>
<td>loss of vision &amp; headache</td>
<td>11</td>
</tr>
<tr>
<td>loss of vision, ocular palsy, &amp; headache</td>
<td>3</td>
</tr>
<tr>
<td>loss of vision &amp; ocular palsy</td>
<td>1</td>
</tr>
<tr>
<td>ocular palsy &amp; headache</td>
<td>2</td>
</tr>
<tr>
<td>consciousness disturbance &amp; headache</td>
<td>4</td>
</tr>
<tr>
<td>consciousness disturbance, loss of vision, &amp; headache</td>
<td>1</td>
</tr>
<tr>
<td>consciousness disturbance &amp; hemiparesis</td>
<td>1</td>
</tr>
<tr>
<td>hemiparesis</td>
<td>1</td>
</tr>
</tbody>
</table>

* For definition of major attack, see text.

TABLE 4
Symptoms and signs in 51 symptomatic cases of hemorrhage from pituitary adenoma

<table>
<thead>
<tr>
<th>Acute Symptoms</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
</tr>
<tr>
<td>headache</td>
<td>32</td>
</tr>
<tr>
<td>loss of vision</td>
<td>30</td>
</tr>
<tr>
<td>nausea &amp; vomiting</td>
<td>16</td>
</tr>
<tr>
<td>ocular palsy</td>
<td>16</td>
</tr>
<tr>
<td>disturbance of consciousness</td>
<td>6</td>
</tr>
<tr>
<td>vertigo</td>
<td>4</td>
</tr>
<tr>
<td>fever</td>
<td>4</td>
</tr>
<tr>
<td>hemiparesis</td>
<td>2</td>
</tr>
</tbody>
</table>
**TABLE 5**


<table>
<thead>
<tr>
<th>Hormonal Function</th>
<th>Total Cases</th>
<th>Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>nonfunctioning</td>
<td>107</td>
<td>10 (9.3%)</td>
</tr>
<tr>
<td>producing GH</td>
<td>65</td>
<td>4 (6.2%)</td>
</tr>
<tr>
<td>prolactinoma</td>
<td>66</td>
<td>8 (12%)</td>
</tr>
<tr>
<td>producing ACTH</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>total</td>
<td>248</td>
<td>22 (8.9%)</td>
</tr>
</tbody>
</table>

* GH = growth hormone; ACTH = adrenocorticotropic hormone.

**TABLE 6**

Comparison of histology and incidence of hemorrhage in cases of pituitary adenoma*

<table>
<thead>
<tr>
<th>Histology</th>
<th>With Hemorrhage</th>
<th>Without Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Percent</td>
</tr>
<tr>
<td>diffuse</td>
<td>41</td>
<td>66.2%</td>
</tr>
<tr>
<td>sinusoidal</td>
<td>18</td>
<td>29.0%</td>
</tr>
<tr>
<td>papillary</td>
<td>3</td>
<td>4.8%</td>
</tr>
<tr>
<td>total</td>
<td>62</td>
<td>100%</td>
</tr>
</tbody>
</table>

* Specimens of only 62 of 93 cases were available for histological evaluation.

"acute to chronic" cases in the symptomatic group (Table 1), five patients had no visual disturbance before hemorrhage from their pituitary adenoma; their tumors were considered to be intrasellar in location. The tumor in two of three cases presenting with SAH ("acute to chronic," Table 1, Group D) was confirmed at surgery to be limited within the sella. It was not possible to assume the size of tumor before bleeding in 42 asymptomatic cases. Thus, the occurrence of hemorrhage could not be correlated with the size of the tumor.

**Hormonal Function**

Measurement of serum prolactin levels became possible in our hospital in 1971. Since then, there have been 248 cases of pituitary adenoma, in which 22 had evidence of intratumor hemorrhage. Table 5 shows the number of adenomas with and without hemorrhage in relation to endocrinological function of the tumor. The incidence of hemorrhage including both symptomatic and asymptomatic cases appeared to be higher in prolactinomas than in growth hormone (GH)-producing and nonfunctioning adenomas; however, the difference was not statistically significant.

**Histological Evaluation**

Sixty-two of 93 specimens were available for histological evaluation. There were 41 diffuse (66.2%), 18 sinusoidal (29.0%), and three papillary (4.8%) adenomas. This shows nearly the same distribution as that of pituitary adenomas without hemorrhage; 97 diffuse (69%), 34 sinusoidal (24.3%), and nine papillary (6.4%) adenomas. These are shown in Table 6.

**Computerized Tomography Findings**

There were 15 cases of hemorrhage from pituitary adenomas examined with computerized tomography (CT). Ring enhancement was noted in nine patients (Fig. 3), seven of whom were symptomatic. Their CT scans were taken from 2 weeks to 3 months after the bleeding episode. In all these cases, liquefied hematoma or old bloody fluid was identified at surgery. A high-density mass was observed on precontrast CT scans in two symptomatic cases (Fig. 4); in these cases, CT was performed within 1 to 2 weeks after bleeding, and blood clot was evacuated at surgery. Intratumor low-density areas were seen in two asymptomatic patients, in whom surgery revealed a moderate amount of bloody fluid. Two cases had negative CT findings: one was an intrasellar tumor producing GH, and the other was an intrasellar prolactinoma with SAH, without any detectable hematoma in the tumor.

**Discussion**

The present investigation demonstrated that the incidence of hemorrhage from pituitary adenoma was unexpectedly high (16.6%): 38 had a major attack (6.8%), 13 had a minor attack (2.3%), and 42 had asymptomatic hemorrhage (7.5%). The first two groups (hemorrhage with major or minor symptoms) are categorized as cases of "pituitary apoplexy" (9.1% in this series). There has been a marked variation in the incidence of pituitary apoplexy reported in the literature, ranging from 1.5% to 27.7%. This diversity in incidence is due to incomplete analysis of the symptomatology and surgical findings. Some reports dealt with only severe cases and others included mild or asymptomatic cases as well.

Several investigators emphasized the higher incidence of apoplexy in patients with acromegaly or adrenocorticotropic hormone (ACTH)-producing tumors, but in our series the incidence of the apoplectic syndrome was not significantly different among patients with prolactinoma, GH-secreting tumor, and nonfunctioning adenoma. No case presented with this condition in 11 ACTH-secreting tumors.

Lopez and Wright, et al., stated that pituitary apoplexy occurred about 1.6 to 2 times more in male than female patients. In our data, however, both sexes were almost equally affected by this condition.
incidence of asymptomatic cases of hemorrhage from pituitary adenomas in the third decade was significantly greater than that of all the pituitary adenoma cases in the same decade \((p < 0.01)\), and the mean age for asymptomatic cases was younger than that for cases with symptomatic hemorrhage and for the total series of pituitary adenomas \((p < 0.05)\). There is, however, no adequate explanation for these differences.

Mohanty, et al.,\(^3\) described intratumor hemorrhage or necrosis as related to the size and vascularity of adenomas, and suggested that the high incidence of hemorrhage in their series \((27.7\%)\) might be due to the large size of tumors seen by them. There was no correlation between the size of adenomas and the occurrence of hemorrhage; bleeding occurred even in small tumors that were considered to be confined within the sella. The incidence of hemorrhage was not related to any particular histological type of adenoma, although the sinusoidal type is known to be abundant in vascularity.

Several reports have suggested some factors that precipitate pituitary apoplexy: head trauma,\(^6\) estrogen,\(^1\) anticoagulant therapy,\(^4\) angiography,\(^5\) and radiotherapy,\(^6\) particularly preoperative radiotherapy.\(^6,5\) None of the patients in our series had received preoperative irradiation, but in three cases apoplectic episodes occurred shortly after the completion of postoperative radiotherapy. Dingley\(^1\) reported a patient who died suddenly due to massive hemorrhage from the tumor 14 months after irradiation.

Two acromegalic patients in the present series developed pituitary apoplexy during bromocriptine treatment. There have been no other similar reports. In recent years, an increasing number of GH-secreting tumors and prolactinomas have been treated by bromocriptine.\(^2,5\) This agent is known to reduce the secretion of GH and prolactin from functioning adenoma cells and to diminish the size of tumors as well.\(^1,6,19,34,5\)

In our experience, adenomas have sometimes shown necrosis at surgery after bromocriptin treatment. This may be the cause of hemorrhage in the two acromegalic patients mentioned above. In any event, those who treat pituitary adenomas medically should keep in mind the possibility of pituitary apoplexy.

Three of our cases had evidence of SAH, but no hematoma was detected in the tumor. Subarachnoid hemorrhage has been reported as a presenting picture of pituitary adenoma,\(^1,6,17,18,30,57,6\) and it is important to differentiate this condition from SAH caused by ruptured intracranial aneurysm,\(^6,5\) especially when there is a coincidental aneurysm associated with a pituitary adenoma.\(^3,6\) Our previous study has demonstrated that the incidence of aneurysm associated with pituitary adenomas is significantly increased in patients with SAH.\(^1,3,6\)
with pituitary adenoma was very high (7.4%).\(^6\) A patient with pituitary adenoma presenting with SAH due to ruptured aneurysm was reported in that article. In comparison, the present series includes a case of pituitary adenoma with associated aneurysm in which the SAH was due to the adenoma.

Computerized tomography was found to be an excellent tool for detecting pituitary adenomas as well as intratumor hemorrhage.\(^4\) Scans taken within 1 or 2 weeks of hemorrhage show a high-density mass which corresponds to the intratumor blood clot. However, if taken after 2 weeks, it will show either a low-density area or ring enhancement. Ring enhancement appears to last for a long period, the longest in our experience was 3 months. This may be explained by the fact that the pituitary gland has a capsule around it,\(^8,9\) or that the blood-brain barrier does not exist in either pituitary adenomas or the pituitary gland.\(^2\)

In addition to the cases with acute episode due to hemorrhage from adenomas, there were many cases with acute episodes similar to pituitary apoplexy but without evidence of hemorrhage at surgery. About half of them (17 cases, Table 1) had xanthochromic fluid in the tumor or empty sella. This might be a late sequela of pituitary apoplexy or infarction. The other 16 cases had solid tumors, most of which were soft in consistency. Acute symptoms such as those of pituitary apoplexy could be caused by a solid tumor that might have expanded rapidly as a result of infarction.\(^6,10,12,21,27\) This condition is difficult to differentiate from pituitary apoplexy on clinical grounds alone, and should be managed as if it were pituitary apoplexy. Therefore, any cases of pituitary adenoma with acute symptoms similar to pituitary apoplexy should be treated surgically, and any patients with a major attack must be considered as a neurosurgical emergency.

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Pituitary apoplexy


Address reprint requests to:
Susumu Wakai, M.D., Section of Neuro-Ophthalmology, Dept of Neurological Surgery, Kyorin University School of Medicine, 16-2 (Shindenbashi 4-chome), Shinagawa-ku, Tokyo 141, Japan.

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