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# Hemorrhagic Pituitary Adenomas of Adolescence

Tina Young Poussaint, Patrick D. Barnes, Douglas C. Anthony, Norman Spack, R. Michael Scott, and Nancy J. Tarbell

**PURPOSE:** To review the clinical and MR imaging findings in adolescents with hemorrhagic pituitary adenomas and to compare those findings with pathologic results and outcome. **METHODS:** We reviewed the clinical records, imaging examinations, surgical and pathologic findings, and follow-up studies in 11 girls and six boys (12 to 20 years old; mean age, 16 years) with pituitary adenomas who were treated at our institution between August 1986 and June 1995. **RESULTS:** Of the 17 adenomas, eight were macroadenomas (>1 cm) in patients 14 to 18 years old (three girls, five boys). Six of the macroadenomas were grossly hemorrhagic, and appeared as high-intensity intrasellar/suprasellar masses on all MR sequences obtained before definitive diagnosis and treatment. Clinical presentation in the patients with the hemorrhagic macroadenomas included headache (five), visual field deficits (three), and neuroendocrine symptoms (three). One patient was asymptomatic. The preliminary clinical and imaging diagnoses were craniopharyngioma or Rathke's cyst in five of the six cases. Pathologic diagnoses were prolactinoma in four patients, plurihormonal (prolactin/follicle-stimulating hormone) tumor in one patient, and nonfunctioning adenoma in one patient. Surgical resection was performed in all six hemorrhagic tumors and radiation therapy was required in three cases. **CONCLUSION:** Pituitary adenomas uncommonly occur in childhood and are usually seen in adolescence. The majority of the macroadenomas are hemorrhagic and often occur in male subjects. The clinical and MR imaging features may mimic craniopharyngioma or Rathke's cyst. These tumors often require surgery and/or radiation therapy.

**Index terms:** Adenoma; Children, neoplasms; Pituitary gland, hemorrhage; Pituitary gland, neoplasms

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Pituitary adenomas are uncommon in childhood, constituting less than 3% of all intracranial tumors (1, 2). The purpose of this study was to review the clinical aspects, imaging findings, and intermediate outcome in a series of adolescent patients with hemorrhagic adenomas.

## Materials and Methods

We retrospectively reviewed the medical records, imaging examinations, and pathologic findings from 17 consecutive patients in whom pituitary adenomas were iden-

tified during the period August 1986 through June 1995. Of the 17 patients with pituitary adenomas, eight (three girls, five boys; 14 to 18 years old; mean age, 16 years) had macroadenomas, of which six were grossly hemorrhagic, as determined by magnetic resonance (MR) imaging. None of the patients had been treated with bromocriptine at the time of imaging. For the purposes of this report, only the patients with hemorrhagic macroadenomas are described in detail.

The imaging studies included MR in five patients and computed tomography (CT) and MR in one patient. Axial 5-mm-thick CT sections were obtained through the posterior fossa with subsequent 10-mm-thick sections obtained through the entire brain without contrast enhancement. MR images were obtained with the use of a 1.5-T system in five patients and a 1.0-T system in one patient. In five patients, imaging parameters included 5-mm-thick sections, a 256 × 192 matrix, and a 24-cm field of view for sagittal T1-weighted conventional spin-echo (CSE) images (600/20/2 [repetition time/echo time/excitations]) and CSE double-echo axial T2-weighted (2000–2800/30,90) images. Fast spin-echo (FSE) axial proton density-weighted images (2000/17) and T2-weighted images (3200/85) were obtained in one patient. Additional coro-

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## Adolescents with hemorrhagic pituitary adenomas

Patient	Age, y/Sex	Clinical Presentation	Prolactin Levels, ng/mL	Pathologic Finding	Hemosiderin	Organized Clot	Outcome
1	14/M	Headache, pubertal delay and growth failure, decreased vision L eye	248	Adenoma, prolactin/FSH	+	—	Surgery; recurrence 7 mo later; surgery again; treated with radiation therapy; stable at 2 y
2	18/M	Headache, R homonymous hemianopsia	196	Adenoma, prolactin	+	+	Surgery; no recurrence at 5 y
3	15/F	Headache, amenorrhea	159	Adenoma, prolactin	+	—	Surgery; no recurrence at 6 mo
4	17/F	Headache, amenorrhea	73	Adenoma, prolactin	...	...	Surgery; recurrence 9 mo later; treated with bromocriptine; stable for 5 y
5	18/M	Headache, double vision	200	Adenoma, prolactin	...	...	Surgery; recurrence 6 months later; surgery again; radiation therapy; lost to follow-up
6	16/M	Asymptomatic, discovered on head CT for trauma	20	Adenoma, nonfunctioning	+	—	Surgery; refused radiation therapy for residual tumor, stable at 5-mo follow-up

Note.—+ indicates present; —, absent.

nal T1-weighted CSE or T2-weighted FSE sequences were performed through the sella and brain. In two patients, contrast material (gadoteridol) was administered intravenously at a dose of 0.1 mmol/kg. The CT and MR imaging features studied included tumor location, size, extent, density, signal intensity, and enhancement. Tissue samples from four patients (five surgical procedures) were available for detailed pathologic analysis. Examinations with light microscopy (including hematoxylin-eosin and Prussian blue staining) and immunohistochemistry were performed. Immunohistochemistry was performed to evaluate the following six pituitary hormones: luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyrotropin, human growth hormone (hGH), corticotropin, and prolactin. In one patient, pathologic analysis was done at an outside hospital; in another patient, pathologic reports were unavailable for further analysis.

## Results

Two of the eight patients with macroadenoma had nonhemorrhagic prolactin-secreting tumors (one pathologically proved and one presumed on the basis of laboratory and clinical findings). Clinical presentations were headache, nausea, vomiting, and visual field deficit in one patient (15 years old), and amenorrhea and galactorrhea in the other patient (14 years old). The macroadenomas were hypointense relative to gray matter on T1-weighted images and were hyperintense on T2-weighted images; the maximum diameters ranged from 1.3 to 5.0 cm (mean, 3.2 cm).

Six of the patients with macroadenomas (four boys, two girls; 14 to 18 years old; mean age, 16 years) had hemorrhagic tumors as determined by imaging, surgical, and pathologic findings (Table). The clinical presentations were headache in five patients (three boys, two girls); visual deficit in three boys; amenorrhea in two girls; and delayed growth in one boy. One patient was asymptomatic, and the pituitary adenoma was discovered on routine CT performed after head trauma. Pituitary apoplexy was not present in any patient.

Laboratory findings showed elevated prolactin levels in five patients (range, 116 to 248 ng/mL; mean, 184 ng/mL), growth hormone deficiency in two patients, and hypogonadotropic hypogonadism in one patient. The asymptomatic patient had only mild elevation of prolactin (20 ng/mL), thought to be the result of a mass effect on the pituitary stalk.

On imaging examinations, all six patients had tumors larger than 1.0 cm, with a maximum diameter ranging from 1.5 to 2.8 cm (mean, 1.7 cm). On T1-weighted MR images, the macroadenomas were of high intensity relative to gray matter, and on T2-weighted MR images the tumors had high and low signal intensity (Figs 1–3). Fluid levels were present in three patients. In the two patients who received intravenous contrast material for MR imaging, there was minimal enhancement of the mass in one and

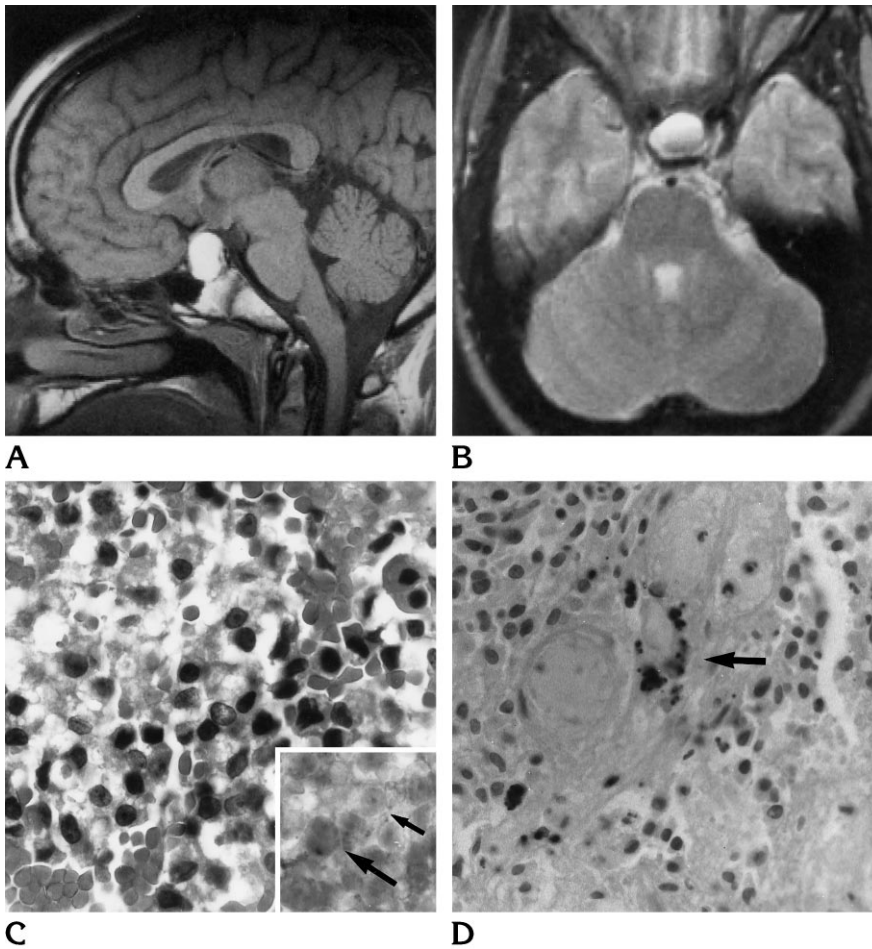


Fig 1. Patient 2: 18-year-old boy with headache and visual field deficit.

A, Sagittal T1-weighted MR image shows a hyperintense sellar mass extending into the suprasellar cistern and abutting the optic chiasm.

B, Axial T2-weighted MR image shows fluid level with hyperintense signal anteriorly and hypointensity posteriorly.

C, The histologic features include uniform cells with abundant eosinophilic or vacuolated cytoplasm and regular nuclei (hematoxylin-eosin, original magnification  $\times 900$ ). *Inset* illustrates variable prolactin expression within this tumor, with some cells showing only faint expression (*small arrow*) and others showing such dense expression that the nucleus is obscured by the cytoplasmic staining (*large arrow*).

D, Iron is detectable within the tumor, often adjacent to blood vessels (*arrow*) (Prussian blue iron stain, original magnification  $\times 600$ ).

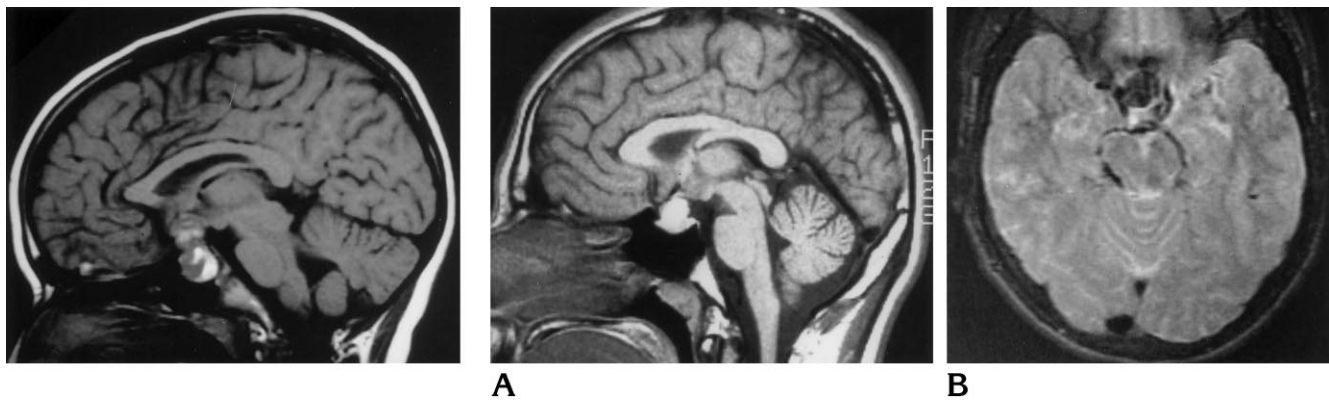


Fig 2. Patient 1: 14-year-old boy with headache, visual impairment, short stature, and delayed puberty. Sagittal T1-weighted image shows mixed areas of isointensity and hyperintensity within the sellar mass, which abuts the optic chiasm.

Fig 3. Patient 5: 18-year-old boy with headache and double vision. A, Sagittal T1-weighted MR image shows a hyperintense sellar mass. B, Axial T2-weighted MR image shows hypointensity within the sellar mass.

inhomogeneous enhancement in the other. In one patient who also had CT, there were heterogeneous mixed densities with some areas of high attenuation. Another patient had CT; however, the scans were unavailable for retrospective analysis. The preoperative diagnosis in five of the six patients was craniopharyngioma or Rathke's cyst.

Three patients underwent transphenoidal hypophysectomy and three had subtemporal craniotomy. Brownish, bloody fluid/material was aspirated from the masses in all cases. Microscopically, each of the tumors had the histologic features of a pituitary adenoma (Fig 1C). The hemorrhagic pituitary adenomas were prolactinomas in four patients, plurihormonal (prolactin/FSH) tumor in one patient, and nonfunctioning in one patient with no expression of LH, FSH, thyrotropin, prolactin, or hGH. In the nonfunctioning adenoma there was a faint blush of corticotropin without elevation in serum levels.

Histologically, the tumors were composed of uniform cells with abundant eosinophilic or vacuolated cytoplasm (Fig 1C). The cells were arranged in large, patternless sheets, which were at times interrupted by rudimentary organoid formations or linear festoons of cells. The nuclei were regular and round to oval in shape. The nuclei often contained a single dark focus of staining, but the chromatin was otherwise evenly dispersed in a finely granular distribution throughout the nucleus. In some instances, only a few cells scattered throughout the tumor expressed the hormone. In other instances, a substantial proportion of the tumor cells expressed the hormone, most often prolactin (Table). Because the hemorrhage identified grossly may have occurred at the time of surgery, a search for evidence of a cellular reaction to intratumoral hemorrhage was undertaken. In two cases, hemosiderin was readily detected on sections stained with hematoxylin-eosin, while in the other cases hemosiderin was detected only with Prussian blue stain (Fig 1D). However, in all cases in which hemorrhage was detected by imaging there was pathologic evidence of hemosiderin deposition. In one case, there was also a proliferation of connective tissue around an organizing blood clot (Table).

Tumor recurrence was observed in three of the six patients (two boys, one girl) on follow-up studies. In one patient, the tumor recurred 9 months after the initial surgery, with rising levels of prolactin, and was subsequently treated with

bromocriptine. In two patients, the recurrences were 6 months and 7 months after initial surgery, respectively, and required further surgery and subsequent radiation therapy. The other three patients have been stable for 5 months, 6 months, and 5 years after surgery, respectively, without recurrence. In the patients who had tumor recurrence and further therapy, one patient has been lost to follow-up and the two other patients have been stable for 2 years and 5 years, respectively. Radiation therapy was recommended in one patient (case 6), but the family refused. Of the patients with nonhemorrhagic pituitary adenomas, one patient had subtotal resection then bromocriptine therapy and another had treatment alone with bromocriptine, and both have been stable without recurrence on bromocriptine at 2 years and 1.9 years, respectively.

## Discussion

Pituitary adenomas are uncommon in childhood, representing less than 3% of all intracranial tumors. As in our series, the majority of cases occur in adolescence (1–4). In our series, the pituitary adenomas were macroadenomas in 47% of the patients, compared with a range of 36% to 78% in the literature (1, 2, 5–8). Of the eight patients with macroadenomas in our series, six (75%) were prolactinomas, one (12.5%) was a plurihormonal tumor with immunohistochemical detection of both prolactin and FSH, and one (12.5%) was a nonfunctioning adenoma. These findings concur with the literature involving pediatric pituitary tumors, in which the majority of macroadenomas were prolactinomas (1, 2, 5–8).

The major clinical presentations in our series of adenomas included headache, visual field deficits, and neuroendocrine symptoms, with no patient presenting with pituitary apoplexy. One patient was asymptomatic at presentation, with the pituitary adenoma noted on imaging studies done subsequent to trauma. The majority of patients with hemorrhagic pituitary macroadenomas (83%) presented with headache, which may have been related to mass effect. This compares with a 50% frequency of headache in patients with nonhemorrhagic pituitary macroadenomas. There was no difference in the prevalence of visual field deficits in the patients with and without hemorrhagic adenomas. The patients who had endocrine dysfunction were

more often girls, a finding also reported in a previous series and not surprising considering the sensitivity of the menstrual cycle (2). Patients with visual field deficits were boys, primarily with symptoms related to compression of the optic chiasm, a finding also confirmed in a previous series in which the male patients had suprasellar tumor extension (2). In other series, however, no apparent association between gender and symptoms could be found (1, 9), although focal neurologic deficit was more common in patients with pituitary prolactinomas than in those with other pediatric adenomas (8). The laboratory findings of elevated prolactin in our series concurs with that reported in the literature (8).

Hemorrhage within pituitary adenomas has been previously described in the absence of pituitary apoplexy (10–14). The association of bromocriptine with intratumoral hemorrhage in pituitary adenomas has also been reported (14). The frequency of hemorrhage in our 17 untreated patients was 47% as compared with a frequency of 7% to 8% in the literature (13–15). A later study by Yousem et al (16), however, showed a prevalence of subacute intratumoral hemorrhage in 43% of nonsurgically treated pituitary adenomas, but it is not clear whether these patients received bromocriptine. The frequency of hemorrhage in our series of untreated macroadenomas (75%) exceeds that reported for adults (14.5%) (13, 14). As in our series, most of the previously reported hemorrhagic adenomas were prolactinomas (13, 14). Imaging findings in our study concur with other published studies in which mixed density has been noted on CT scans and high intensity noted on T1- and T2-weighted MR images, reflecting subacute hemorrhage (11–14, 16–18) (Figs 1–3).

It is unclear how hemorrhage occurs in pituitary adenomas. Several hypotheses have been advanced, including outgrowth of blood supply, impaction of the growing pituitary adenoma against the diaphragmatic hiatus impairing blood supply (19), and increase of intracapsular pressure with tumor growth leading to infarction and hemorrhage (13). Perhaps growth of the pituitary adenoma compromises blood supply, leading to endothelial cell damage and ischemic change, leading to leakage of red cells. Another hypothesis has suggested tumoral factors that cause hemorrhage (10). In that study, the finding of hemorrhage was significantly associated with invasiveness. In reported series of pediatric

pituitary tumors, an increased prevalence of hemorrhage has not been specifically emphasized. However, it is known that growth factors such as growth hormone and insulinlike growth factor-1 (IGF-1) are increased in puberty (20–22) and both IGF-1 and growth hormone through IGF-1 are known to increase endothelial proliferation (23), which speculatively may play a role in hemorrhage. Vascular endothelial growth factor is known to increase endothelial proliferation, vascular permeability, and fragility (24–27). It is unclear whether this factor is increased in puberty, and the relationship between IGF-1 and vascular endothelial growth factor is unknown. Further research into the association between these growth factors and pediatric pituitary adenomas may be helpful for elucidation of the cause of hemorrhage in these lesions.

In our series, the tumor recurred in two (50%) of the four boys and in one (50%) of the two girls. Pituitary adenomas, and specifically prolactinomas, have been noted in previous series (28) to be larger in boys at the time of detection and may require bromocriptine and/or radiation therapy to control disease (2, 5, 7, 29). In one study, adolescent patients were found to have larger pituitary adenomas and a shorter mean time to progression than adult patients (7). In other studies, pituitary adenomas in children have not been described as particularly invasive or extrasellar (30, 31). Yet, in the study by Fraioli et al (3), the age at presentation (ie, prepubertal, pubertal, or postpubertal) was important. In nine patients in that series with the onset of symptoms at puberty (ages 11 to 15), seven had pituitary adenomas that were invasive. In a more recent study, although boys had larger tumors and higher preoperative and immediately postoperative prolactin levels, tumor recurrence rates and invasion did not differ as compared with girls (8).

In summary, pituitary adenomas, although uncommon in childhood, may be seen as hemorrhagic macroadenomas and mistaken for other lesions, such as craniopharyngioma or Rathke's cyst, on MR studies. The presence of hemorrhage in these tumors may be an additional indicator of potentially aggressive behavior.

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