

Pediatric Pituitary Adenomas

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• **Context.**—Pituitary adenomas are relatively rare occurrences in the pediatric population, and there are few studies documenting the profile of these tumors in this age group.

Objective.—To study the clinical and pathologic features of pediatric pituitary adenomas in conjunction with a review of the available literature.

Design.—A retrospective clinicopathologic review of 20 pediatric patients (younger than 20 years of age) with pituitary adenomas resected during a 24.5-year period (1981–2005).

Results.—A total of 20 patients, including 12 females and 8 males, comprise the study group. Mean age at onset of symptoms was 14.0 years (range, 5–18 years). Four patients had onset of symptoms before the age of 12 years. The majority of patients presented with headaches (n = 12), visual disturbances (n = 12) or, in females, menstrual

dysfunction (n = 9/12). Tumor size based on radiographic data was known for 19 tumors; 12 adenomas were greater than 1 cm in greatest dimension, and 7 were less than 1 cm. On follow-up, 2 patients with total gross tumor resections had recurrent adenomas; time to recurrence was 5 months and 17 months, respectively. Nine adenomas stained solely for prolactin, 5 for adrenocorticotrophic hormone, and 3 for growth hormone. Two stained for growth hormone and prolactin. One did not stain with hormone antibodies.

Conclusions.—Most pediatric pituitary adenomas present after the onset of puberty and present with frequent headaches, changes in visual acuity and, in females, menstrual dysfunction. Most (19/20) were secretory, with prolactinomas being the most common type.

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Pituitary adenomas in children are relatively infrequent occurrences.^{1–8} Most studies report the incidence of these tumors to be between 1% and 10% of all childhood brain tumors^{9–12} and between 3% and 6% of all surgically treated adenomas.^{9,11,13} Variation in reported incidence is, to a certain degree, a matter of a lack of consensus on an age range for defining a pituitary adenoma as pediatric. Cutoff ages vary between 16 and 20 years of age, depending on the study. Despite the rarity of these tumors, they can have a significant effect on the quality of life of the patient, especially during childhood, when growth rates and development are at a peak. Few characteristics of these tumors have been consistently demonstrated in different studies. Variation among studies has been reported regarding age and sex predilection, tumor size, hormonal production, and recurrence rates. We report one institution's experience with pediatric pituitary adenomas. The clinical features of these patients and the pathology of their tumors are described and the literature reviewed.

MATERIALS AND METHODS

Following institutional review board approval, a computer search of the surgical pathology files was performed for pituitary adenomas diagnosed between 1981 and 2005. Only patients who had symptoms and were initially examined prior to the age of

20 years were considered for this study (slightly less than 2% of all adenomas). All available microscopic slides, including immunostains for follicle-stimulating hormone, luteinizing hormone, thyroid-stimulating hormone, prolactin (PRL), adrenocorticotrophic hormone (ACTH), and growth hormone (GH) were reviewed to confirm the prior diagnosis and document information on tumor histology and hormonal immunoreexpression. If neither slides nor immunostains were available, tissue blocks were used to create new slides with a full set of immunostains. If no prior slides or blocks were available, the patient was excluded from this retrospective analysis. Patients were also excluded from the study if histologic evidence of an adenoma was not identified, despite clinical data to suggest the presence of a pituitary adenoma. A total of 20 patients were identified that met our inclusion criteria and formed the study group.

Patient records were examined for clinical information. Tumor size was based on radiologic information. A microadenoma was defined as a tumor that measured less than 1 cm in greatest dimension. Tumor recurrence was defined as recurrent disease after a complete gross resection of the original tumor and was based on the clinical judgment of the treating physician as documented in the patient's record. Increasing size of residual disease after an incomplete resection was not classified as recurrent disease. Information for comparative purposes concerning patient age at diagnosis, sex, symptoms and physical findings were based on documentation provided in the medical record at the patient's initial visit with the treating physician. All other pertinent information concerning the patient's surgery and follow-up were gathered from the patient's medical record.

RESULTS

The 20 study patients included 12 females and 8 males who ranged in age at the time of initial surgery from 8 to 19 years (mean, 15.6 years). The clinicopathologic features of the patients and their adenomas are summarized in the Table. The clinical presentation was quite variable, but cer-

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Summary of Clinicopathologic Features of Pediatric Pituitary Adenoma Patients*

Patient	Age, y/Sex	Tumor size, cm	Symptoms	Hormone status	Recurrence
1	16/F	3	Headache, galactorrhea, visual changes, weight loss, hot flashes, mood alteration	PRL	Recurrence at 16 mo per MRI
2	13/F	<1	Headache, nausea/vomiting, amenorrhea, galactorrhea, visual changes, fatigue	PRL	...
3	19/F	0.8	Amenorrhea, galactorrhea	PRL	...
4	15/M	1.8	Headache, visual changes	PRL	...
5	19/F	<1	Headache, amenorrhea, galactorrhea	PRL	...
6	17/F	5	Amenorrhea, galactorrhea, visual changes	PRL	...
7	17/F	3.5	Amenorrhea, headache, visual changes	PRL	...
8	15/F	2.8	Amenorrhea, headache, visual changes	PRL	...
9	16/M	2	Headache, syncope, weight loss	PRL	...
10	17/F	1.5	Headache, amenorrhea, visual changes, Cushing syndrome	ACTH	...
11	14/F	0.9	Cushing syndrome, amenorrhea	ACTH	...
12	15/F	Unknown	Hirsutism, hot flashes, Cushing syndrome	ACTH	...
13	14/F	0.8	Amenorrhea, Cushing syndrome	ACTH	Second surgery 5 mo after first
14	16/M	0.2	Short stature, Cushing syndrome	ACTH	...
15	19/M	2.8	Headache, weight loss	GH	...
16	16/M	0.8	Visual changes, increased stature	GH	...
17	13/M	4	Visual changes, increased stature	GH	...
18	17/M	3.6	Headache, visual changes, epistaxis, increased stature	GH, PRL	...
19	8/M	1.6	Headache, visual changes, increased stature, polydipsia	GH, PRL	...
20	16/F	2	Headache, syncope, visual changes	Nonsecretory	...

* Age shown is age at time of initial surgery. PRL indicates prolactin; MRI, magnetic resonance imaging; ACTH, adrenocorticotrophic hormone; GH, growth hormone; and . . . , no recurrence.

tain symptoms occurred with greater frequency. The most common initial complaints were headache (n = 12) and visual disturbances (n = 12), including decreasing visual acuity and field defects. Menstrual irregularities were noted in 9 of 12 females; 5 females complained of galactorrhea. Five patients presented with various symptoms of Cushing syndrome, including weight gain (n = 5), round facies (n = 4), striae (n = 4), hirsutism (n = 3), fatigue (n = 2), mood lability (n = 2), acne (n = 2), and excessive bruising (n = 1). Other presenting complaints included increased stature (n = 4), syncope (n = 2), hot flashes (n = 2), weight loss (n = 1), polydipsia (n = 1), epistaxis (n = 1), short stature (n = 1), and nausea/vomiting (n = 1).

Tumor size ranged between 0.2 and 5.0 cm (mean, 2.0 cm), with 12 macroadenomas and 8 microadenomas. Surgical intervention was attempted in all 20 cases, with 12 reported gross total resections and 8 subtotal resections. Four patients who underwent subtotal resection required additional surgical intervention between 24 and 72 months after the initial surgery. Of these 4, 1 remained symptomatic after surgery until lost to follow-up 10 years after the second surgery, 1 received gamma knife therapy after a second surgery with successful results, and 2 were lost to further follow-up after an additional operation. An additional patient who underwent subtotal resection received adjuvant radiation therapy 10 months after the initial resection with only limited results before being lost to follow-up 57 months after the initial resection.

Two patients who underwent gross total resections had additional surgical intervention. One patient with an ACTH-secreting adenoma maintained elevated cortisol levels after surgery, despite no radiographic evidence of residual disease. A second operation 5 months after the first surgery revealed a miniscule amount of additional tumor. The second patient had recurrence of disease symptoms at 7 months after the initial resection and had recurrent disease identified by magnetic resonance imag-

ing 16 months after the initial resection. The patient transferred care to a different institution before additional therapy was initiated. A total of 13 patients had no documented residual or recurrent tumor with an average follow-up of 50 months (range, 1–130 months). Of these 13, however, 3 patients did have symptoms suggestive of, but never conclusively linked to, disease recurrence. Of the 7 patients with documented residual or recurrent disease, 3 had microadenomas, 3 had macroadenomas, and 1 had no information available on tumor size.

Microscopic review of the adenomas revealed 14 acidophilic tumors (Figure 1), 5 chromophobic tumors, and 1 basophilic tumor. Mitotic activity was 0 to 1 mitotic figures per 10 high-powered fields in 16 of the adenomas (Figure 2). Four adenomas had increased mitotic activity (4 to 5 mitoses per 10 high-powered fields). One tumor contained focal necrosis. Calcifications were focally noted in 3 adenomas (Figure 3), and 1 adenoma demonstrated microcystic degeneration. Immunohistochemical staining revealed 19 secretory adenomas and 1 nonsecretory adenoma. Of the secretory adenomas, 9 stained positively for PRL (Figure 4), 5 stained for ACTH (Figure 5), 3 stained for GH alone (Figure 6), and 2 stained for both PRL and GH. None of the adenomas stained positively with antibodies to follicle-stimulating hormone, luteinizing hormone, or thyroid-stimulating hormone.

COMMENT

The vast majority of pituitary adenomas arise in adults. In most studies, pediatric pituitary adenomas represent only 3% to 5% of all adenomas. Differences in incidence among studies in part are related to how "pediatric" is defined (ie, age at the time of initial surgery or age at actual presentation).

In the current series, patient age at onset of symptoms seemed to vary slightly according to tumor type. Those patients with ACTH-secreting tumors presented earlier,

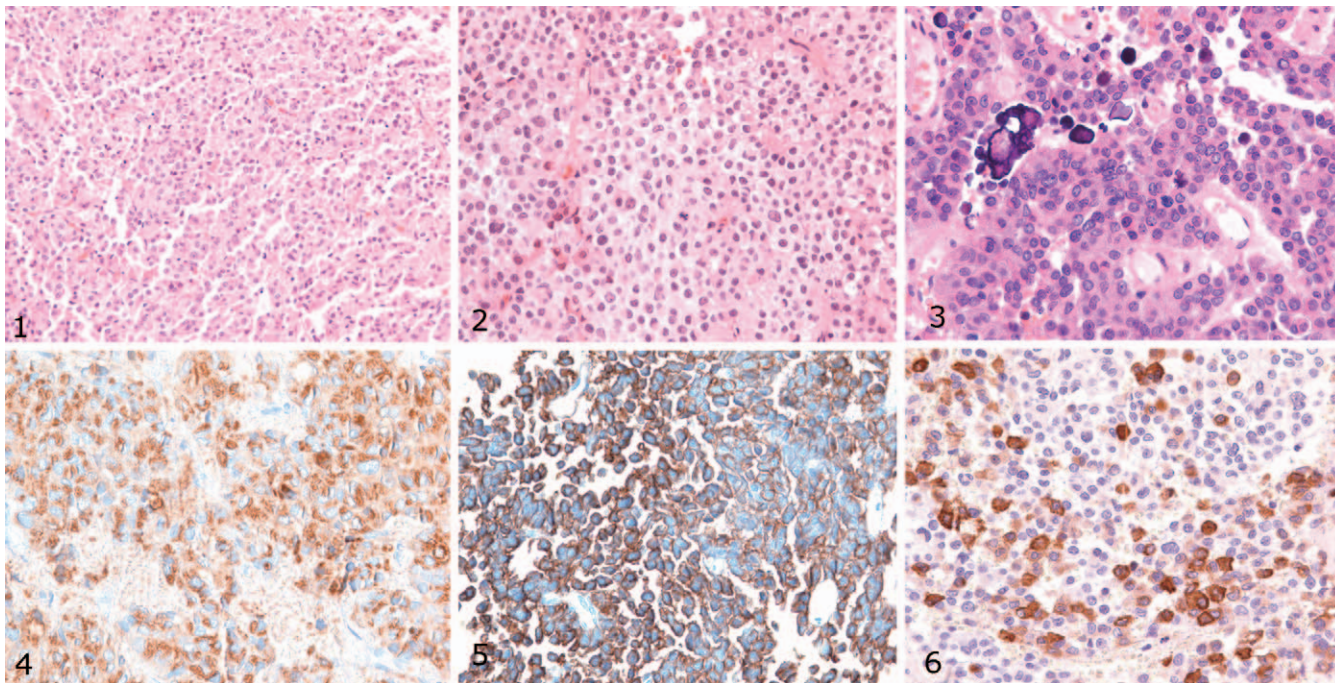


Figure 1. Acidophilic pituitary adenoma in patient 1 marked by a proliferation of cells with abundant eosinophilic cytoplasm (hematoxylin-eosin, original magnification $\times 200$).

Figure 2. Adenoma in patient 17 demonstrating mitotic activity (hematoxylin-eosin, original magnification $\times 400$).

Figure 3. Chromophobic adenoma in patient 19 displaying prominent calcifications (hematoxylin-eosin, original magnification $\times 400$).

Figure 4. Adenoma from patient 9 with positive immunostaining for prolactin (original magnification $\times 400$).

Figure 5. Adenoma in patient 14 with positive immunostaining for adrenocorticotropic hormone (original magnification $\times 400$).

Figure 6. Adenoma from patient 18 with positive immunostaining for growth hormone (original magnification $\times 400$).

with a median age of 14 years (range, 10–17 years), whereas patients with GH-secreting tumors and prolactinomas presented slightly later, with a median age of 15 years (ranges, 11–18 years for GH adenomas and 11–17 years for prolactinomas). While our results do not show striking differences in age of onset, they do fit with the overall trend of other studies, which show a tendency for ACTH-secreting tumors to present at an earlier age than other tumor types.^{12,14,15}

Within our study, females represented 60% of all cases, outnumbering males 12 to 8. This is consistent with the female predominance found in multiple large studies.^{10,11,13} Only a few published studies have had male-female ratios skewed toward male predominance, but these studies have contained smaller sample sizes.^{16,17} In compiling male-female ratios from 6 different studies^{5,10–12,14,16} in addition to the current study within the context of hormone secretion, females clearly represent the vast majority of prolactinomas (162 females to 34 males) and a slight majority of ACTH-secreting tumors (60 females to 49 males). Pure GH-secreting tumors are slightly more likely to arise in males (25 males to 19 females).

In our series of patients, the number of macroadenomas ($n = 12$; 60%) was higher than that of microadenomas ($n = 7$; 35%). Tumor size was not known for 1 patient. This ratio is comparable to that of Kane et al,¹³ who reported that macroadenomas accounted for 59% of total tumors. Other large studies, however, show more equal numbers of macroadenomas and microadenomas.^{11,14}

Tumor size appears to be related to hormone secretion.

GH-secreting tumors tend to present as macroadenomas. Of the 12 GH-secreting tumors reported by Mindermann and Wilson,¹¹ 11 were macroadenomas. In our series, all 3 GH-secreting tumors and both GH/PRL-secreting tumors were macroadenomas. The ACTH-secreting tumors tend to present as microadenomas.^{11,14} In our series, 3 were microadenomas, and only 1 was a macroadenoma (information was not available for 1 additional ACTH-secreting tumor).

The most common presenting complaints in the current series were headaches and visual disturbances. Headaches were reported by 12 (60%) of the 20 patients. Of these 12, all but 2 had macroadenomas. The literature is divided on the occurrence of headaches. In the study of non-ACTH-secreting tumors by Kane et al,¹³ 34 (60%) of 56 patients reported headaches. Partington et al,¹² however, reported the occurrence of headaches in only 10 (28%) of 36. In the current study, visual disturbances were also reported by 12 patients (60%), 9 of whom also reported headaches. The occurrence of visual field defects in many studies is much less (10%–20%).^{10,12,13} Of the 12 patients with macroadenomas, all of them had at least one symptom attributable to mass effect. Nine females presented with menstrual dysfunction, including all 7 females with prolactinomas and 2 of the 4 females with ACTH-secreting tumors. Five females presented with galactorrhea, all of whom had prolactinomas.

Presenting complaints among patients did correlate well with tumor type. All 5 patients with ACTH-secreting tumors presented with Cushingoid features including but

not limited to central obesity, moon facies, ease of bruiseability, hyperpigmentation, hirsutism, fatigue, skin striae, depression, and mood instability. Mindermann and Wilson¹¹ similarly reported Cushingoid features in 38 of 42 patients with ACTH-secreting tumors. Of the 5 patients with GH-secreting tumors or GH/PRL-secreting tumors, 4 presented with increased stature for age. All 5 presented with symptoms of mass effect (headaches or visual disturbances). Increased stature among patients with GH-secreting tumors was also reported with high frequency by Partington et al¹² (3/3) and Mindermann and Wilson¹¹ (7/12). Of the 9 patients with prolactinomas, all but 1 presented with symptoms of mass effect. As mentioned previously, menstrual irregularities and galactorrhea occurred with increased frequency, as expected.

The largest group was the prolactinomas, accounting for 45% of tumors in the current study. This predominance of prolactinomas roughly corresponds to the findings of Kane et al¹³ (52%) and Mindermann and Wilson¹¹ (52.9%). ACTH-secreting tumors comprised 25% of adenomas, GH-secreting tumors 15%, and GH/PRL-secreting tumors 10%. There were no tumors in the current series that secreted luteinizing hormone, follicle-stimulating hormone, or thyroid-stimulating hormone. Of the 20 adenomas in the current series, only 1 was nonsecretory. These additional results are also similar to findings of other studies. Haddad et al¹⁴ and Kane et al¹³ failed to report any nonsecretory adenomas. Kunwar and Wilson¹⁵ and Mindermann and Wilson¹¹ reported 4 nonsecretory adenomas of 150 and 136 adenomas, respectively.

Tumor behavior depended largely on whether the patient underwent total or subtotal resection. Of the 8 patients in this series who underwent subtotal resection, 5 required additional surgical/medical intervention for symptomatic disease. Only 2 (17%) of the 12 patients who underwent total resection had documented recurrent disease. This compares with 10% tumor recurrence documented by Mindermann and Wilson¹¹ and 25% tumor recurrence after initial remission reported by Partington et al.¹² Kane et al¹³ reported tumor recurrence in 8 (14%) of 56 patients.

CONCLUSIONS

Pediatric pituitary adenomas are relatively infrequent and are quite variable in their presentation. Among pediatric patients, those most at risk for the development of pituitary adenomas tend to be postpubertal and more commonly females. Most pediatric pituitary adenomas appear to be secretory, with prolactinomas being the most common type. Tumor behavior tends to be linked closely with the results of the primary resection. Patients undergoing subtotal resection have a higher likelihood of residual disease effects from the remaining tumor.

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