Pediatric sellar tumors: diagnostic procedures and management

JAY JAGANNATHAN, M.D., AARON S. DUMONT, M.D., JOHN A. JANE JR., M.D.,
AND EDWARD R. LAWS JR., M.D.

Department of Neurological Surgery, University of Virginia Health Science Center, Charlottesville, Virginia

The diagnosis and management of pediatric sellar lesions is discussed in this paper. Craniopharyngiomas account for the majority of pediatric sellar masses, and pituitary adenomas are extremely uncommon during childhood. The diagnosis of sellar lesions involves a multidisciplinary effort, and detailed endocrinological, ophthalmological, and neurological testing is critical in the evaluation of a new sellar mass. The management of pituitary adenomas varies depending on the entity. For most tumors other than prolactinomas, transsphenoidal resection remains the mainstay of treatment. Less invasive methods, such as endoscopic transsphenoidal surgery and stereotactic radiosurgery, have shown promise as primary and adjuvant treatment modalities, respectively.

KEY WORDS • pituitary adenoma • craniopharyngioma • pediatric tumor • sellar tumor • children

Pediatric sellar and parasellar lesions include a diverse group of tumors. More than 90% of purely intrasellar tumors are pituitary adenomas, although dysembryogenic lesions (that is, Rathke cleft cysts) also occur. Suprasellar lesions include craniopharyngiomas, germinomas, dermoid/epidermoid cysts, lipomas, teratomas, and hamartomas. Other sellar tumors such as meningiomas or gliomas are not usually symptomatic during childhood and adolescence. Over the last 30 years, significant advances in microneurosurgery, neuroimaging, and molecular biology have significantly changed the diagnosis and management of sellar lesions. In this review we focus on current concepts in the understanding of these diverse pathological entities.

EPIDEMIOLOGY

Prevalence of Craniopharyngiomas

Craniopharyngiomas account for the overwhelming majority (~90%) of neoplasms arising in the pituitary region (other than pituitary adenomas).¹¹ Most of these lesions arise from the Rathke pouch—a cystic diverticulum that originates from the roof of the stomodeum. Craniopharyngiomas constitute between 3 and 5% of all intracranial expanding lesions and account for 6% of all expanding lesions during the pediatric years.³⁴ Patients with these tumors show a bimodal age distribution during the first and second decade of life and then again in the fifth;⁵⁵ there is with no apparent predilection for either sex.¹⁶ Most originate in the intrasellar and suprasellar region (70%) with

suprasellar localizations (20%) or solely intrasellar lesions (10%) occurring less frequently.^{4,9}

Prevalence of Pituitary Adenomas

Pituitary adenomas are the most common cause of pituitary disease in adults but rarely present during childhood (although the incidence increases during adolescence).^{15,44} Pituitary adenomas constitute less than 3% of supratentorial tumors in children, with a mean annual incidence of approximately 0.1 per million children.⁸ Pituitary carcinomas are rare in adults and extremely rare in children.⁵⁰

An increased prevalence of pituitary adenomas in female patients has been reported,^{8,44} which most likely reflects the relative predominance of the two main types of adenomas (PRL- and ACTH-secreting adenomas). Prolactinomas are the most frequent adenoma subtype in children, followed by the corticotropin-secreting tumors and the somatotropinomas. Nonfunctioning pituitary adenomas, that is, null cell and gonadotropin-secreting adenomas, are very rare in children, accounting for only 3 to 6% of all pituitary tumors.^{1,8,44} As with adults, the presenting symptoms of pediatric pituitary tumors are generally related to endocrine dysfunction, such as growth delay and primary amenorrhea, rather than to mass effect.¹

Prolactin-Secreting Adenomas. Prolactinomas are the most frequent pituitary tumors in childhood and in adulthood, and their frequency varies with age and sex, occurring most often in women between 20 and 50 years of age.⁵⁵

Adrenocorticotropic Hormone-Secreting Adenomas. In children between 11 and 15 years of age, ACTH-secreting adenomas are the most frequent cause of adrenal hyperfunction and the second most frequent pituitary adenoma after prolactinomas.³¹ A macroadenoma is rarely the cause of CD in children.⁴⁶

Abbreviations used in this paper: ACTH = adrenocorticotropic hormone; CD = Cushing's disease; FSH = follicle-stimulating hormone; GH = growth hormone; LH = luteinizing hormone; MR = magnetic resonance; PRL = prolactin; TSH = thyroid-stimulating hormone.

Growth Hormone–Secreting Adenomas. In adulthood, these adenomas have a prevalence of 50 to 80 cases per million people;⁴⁴ gigantism, by contrast, is extremely rare, with approximately 100 reported cases to date.²³ In childhood, GH-secreting adenomas account for 5 to 15% of all pituitary adenomas. In less than 2% of the cases, excessive GH secretion is caused by a hypothalamic or ectopic GH releasing hormone–producing tumor (that is, a bronchial or pancreatic carcinoid).

Thyroid Stimulating Hormone–Secreting Adenomas. This tumor type is rare in adulthood and even rarer in childhood and adolescence, with only a few case reports in the literature.⁶ It is frequently a macroadenoma presenting with mass effect symptoms such as headache and visual disturbance, together with various symptoms and signs of hyperthyroidism. The TSH-secreting adenomas must be differentiated from thyroid hormone resistance.^{6,10} In most cases, the classic criteria of lack of TSH response to TRH stimulation, elevation of serum alpha-subunit levels, and a high alpha-subunit/TSH ratio, along with a pituitary mass on MR images, are diagnostic of TSH-secreting adenoma.

Gonadotropin-Staining Adenomas. The incidence of FSH- and LH-secreting tumors with a clinical picture of hormone hypersecretion is very rare in the pediatric population.^{3,32}

CLINICAL PRESENTATION AND DIAGNOSTIC TESTS

Diagnostic Criteria for Craniopharyngiomas

Neurological disturbances, such as headache and visual field defects, along with manifestations of endocrine deficiency such as growth retardation and delayed puberty are the common presenting symptoms of craniopharyngiomas. These tumors can stretch the diaphragma sellae and cause headaches.⁴³ Obstruction of the cerebral aqueduct and the foramen of Monro may also occur, making a shunt necessary.^{34,43} At diagnosis, endocrine dysfunction is found in up to 80% of patients.⁵⁵ Reduced GH secretion is the most frequent endocrinopathy and can be present in up to 75% of patients. This is followed by FSH/LH deficiency, which can be seen in 40% of patients, and then ACTH and TSH deficiency in 25%.⁵³

Despite the fact that craniopharyngiomas are frequently large at presentation, the pituitary stalk is usually not disrupted, and hyperprolactinemia secondary to pituitary stalk compression is found in only 20% of patients. Diabetes insipidus is relatively uncommon, occurring in 9 to 17% of patients.⁵⁵ The recent availability of high-resolution MR imaging has greatly improved the visualization and radiological diagnosis of craniopharyngiomas.²⁷

The neuroradiological diagnosis of craniopharyngiomas is based on the features of the lesion itself and on its relationship with the surrounding structures.²⁵ The diagnosis is mainly based on the three characteristic components of the tumor: cystic, solid, and calcified.^{44,52} The cystic component constitutes the most important part of the tumor, and shows variable signal depending on the chemical-physical properties of its content.⁵¹ A fluid content will appear hypointense in T₁-weighted and hyperintense in T₂-weighted images, whereas a lipid (due to cholesterol), methemoglobin, or protein content will appear as hyperintense in T₁ and T₂ se-

quences. The solid portion has an isointense signal in T₁- and a hyperintense signal in T₂-weighted images with an enhancement after Gd, at variance with the cystic component. Nevertheless, contrast enhancement is not a consistent feature.⁵² Calcifications can appear as areas of low signal in all sequences, but are generally visualized better with computerized tomography scans.^{24,44,52}

Criteria for PRL-Secreting Adenomas

Prolactin-secreting adenomas are usually diagnosed at the time of puberty or in the postpubertal period,^{14,21} and clinical manifestations vary depending on the age and sex of the child. Girls of prepubertal age generally present with a combination of headache, visual disturbances, growth failure, and primary amenorrhea. The differential diagnosis of hyperprolactinemia should consider any process interfering with dopamine synthesis, its transport to the pituitary gland, or its action at lactotrophic dopamine receptors. A single measurement of PRL levels is unreliable because PRL secretion is markedly influenced by physical and emotional stress. To obtain a diagnostic value of PRL concentrations, at least three to six samples are necessary, with the mean value taken into consideration.

Criteria for CD

The clinical manifestations of CD are mostly the consequence of excessive cortisol production. The clinical presentation is highly variable, with signs and symptoms that can range from subtle to obvious. The diagnosis is generally delayed because a decrease in growth rate may be the only symptom for a long time. Growth failure in patients with CD may be due to a decrease of free insulin-like growth factor–I levels and/or a direct negative effect of cortisol on the growth plate.⁴¹

Other physical manifestations of CD include facial plethora; atrophic striae in the abdomen, legs, and arms; muscular weakness; hypertension; and osteoporosis. Results of bone mineral density or bone metabolism testing in children with CD have been reported only in some patients, and marked osteopenia was also found in affected children.⁴¹ Recent reports indicate that a long period of time (often > 2 years) is necessary to restore bone mass after the cure of CD, so other therapeutic approaches may be indicated to limit bone loss and/or accelerate bone recovery in these patients.²⁰

Children with CD may also have impaired carbohydrate tolerance (although diabetes mellitus is uncommon). Excessive adrenal androgens may cause acne and excessive hair growth, or premature sexual development in the first decade of life. On the other hand, hypercortisolism may cause pubertal delay in adolescent patients. Peculiarly, young patients with CD may present with neuropsychiatric symptoms that differ from those of adult patients. Frequently they tend to be obsessive and are high performers at school.⁴¹

The differential diagnosis of CD includes adrenal tumors, ectopic ACTH production (rare in the pediatric population), and ectopic CRH-producing tumors. In a child/adolescent with suspected CD, the diagnosis is based on measurement of basal and stimulated levels of cortisol and ACTH. Measurement of 24-hour urinary free cortisol is elevated, and a low dose of dexamethasone at midnight does

not induce suppression of morning serum cortisol concentrations.⁴⁶ Suppression of the spontaneous circadian variations of serum cortisol is another feature of CD. Suppression of cortisol by more than 50% after administration of high-dose dexamethasone given at midnight will confirm that hypercortisolism is due to an ACTH-secreting pituitary adenoma.^{20,41,46}

All patients with suspected CD should undergo pituitary MR imaging with the administration of Gd contrast. Nevertheless, ACTH-secreting pituitary adenomas are significantly smaller than all other types of adenomas, and therefore even high-quality pituitary MR images may fail to visualize the tumor. In some cases, the diagnosis of CD must be made based on the initial clinical and laboratory data.

For cases in which the diagnosis of CD is unclear, inferior petrosal sinus sampling can have a high specificity, but it carries a high rate of false-positive results.^{38,49} This procedure can also be difficult in children, both from a technical standpoint and because of the risk of morbidity from surgery and anesthesia.³⁷ If a patient without anomalous venous drainage patterns exhibits a lateralizing ACTH gradient of 2:1 or greater,^{37,38} removal of the appropriate half of the anterior pituitary gland will be curative in 80% of cases. Kunwar and Wilson³³ reported that in the presence of negative findings on surgical exploration, the use of inferior petrosal sinus sampling as a guide to the localization of a pituitary adenoma can be successful and curative.

Criteria for GH-Secreting Adenomas

In adults, chronic GH hypersecretion causes acromegaly, which is characterized by hyperostosis. In children and adolescents it leads to gigantism because of associated secondary hypogonadism, which delays epiphyseal closure, thus allowing long-bone growth. The two disorders may be considered part of a spectrum of GH excess, with principal manifestations determined by the developmental stage during which such excess originates.¹⁷ Supporting this model has been the observation of clinical overlap between the two entities, with approximately 10% of patients with acromegaly exhibiting tall stature,³³ and the majority of those with gigantism eventually demonstrating features of acromegaly.¹⁸

The diagnosis of acromegaly and gigantism is usually clinical and can be readily confirmed by measuring circulating insulin-like growth factor-I concentrations that correlate with the integrated 24-hour GH secretion levels.⁵

The presence of different GH isoforms in patients with gigantism/acromegaly may represent a diagnostic problem.^{47,48} A greater sensitivity of the GH assay may facilitate the distinction between patients and healthy volunteers, as shown by the use of a chemiluminescence GH assay.^{13,57} It may also help in demonstrating the persistence of GH hypersecretion after surgery or during medical therapy. In case of clinical and laboratory findings indicative of a GH-producing adenoma, pituitary MR imaging must be performed to localize and characterize the tumor.

TREATMENT

Management of Craniopharyngiomas

In small intrasellar or enclosed tumors, total resection is most easily achieved, and adjunctive radiotherapy is unnec-

essary.²⁴ Radiotherapy is required in cases of incomplete tumor removal, which occurs frequently with extrasellar craniopharyngiomas (the majority of cases).^{27,28,40,53} Surgical morbidity depends on tumor size and invasiveness, the experience of the surgeon, and the route of surgical approach. The risk of hypothalamic damage is significantly greater in large invasive tumors treated via the transcranial approach. Near-total excision of the tumor by an experienced pituitary surgeon sparing the hypothalamus, carotid arteries, and visual apparatus, followed by fractionated radiotherapy, provides the best hope of low long-term morbidity and longer survival.^{28,29,40} Regardless of the approach, the incidence of endocrine dysfunction is high following surgical treatment,²⁹ although it is lower after the transsphenoidal approach.²⁴ Localized intracavity yttrium, phosphorus-32, and other radioactive implants, given as additional treatment, have proven useful for recurrent tumors with a predominant cystic component. Hyperfractionated multiportal stereotactic radiotherapy and gamma knife radiosurgery are promising therapeutic adjuncts to standard radiotherapy, due to their potential ability to reduce treatment-associated morbidity in this condition. In children, however, the benefit of any additional radiotherapy treatment should be balanced against the relatively high risk of inducing hypopituitarism later in life.²⁴

Management of PRL-Secreting Adenomas

In the absence of complications that need immediate surgery, such as rapidly progressing visual loss, hydrocephalus, or a cerebrospinal fluid leak, pharmacotherapy with dopamine agonists should be considered the first treatment approach. Treatment with dopamine agonists is effective in normalizing PRL levels and shrinking the tumor mass in the majority of adult patients with prolactinoma.^{16,45,56} In children and adolescents, bromocriptine has been used successfully by several investigators to decrease tumor volume.⁹

Quinagolide and cabergoline are two selective dopamine receptor subtype-2 agonists that have also been reported to be effective in reducing PRL secretion and tumor size in adult patients with prolactinoma, even in those previously shown to be poorly responsive to or intolerant of bromocriptine.¹⁴ Cabergoline in particular has received attention for its tolerability and high compliance rates^{7,17,56} and has been shown to be effective also in patients whose tumors are poorly responsive or resistant to bromocriptine. Cabergoline has a longer half-life than bromocriptine, and it normalizes serum PRL levels and restores gonadal function in the majority of patients with microprolactinomas.^{16,45} Its convenient weekly administration also makes it an excellent therapeutic alternative in children with prolactinomas.⁵⁶

Management of CD

Transsphenoidal resection is the treatment of choice for ACTH-secreting adenomas. Surgical removal is successful in the majority of children, with initial remission rates of 70 to 98% and long-term cure rates of 50 to 98% in most studies.^{41,48} The success rate decreases when the patients are followed for more than 5 years, and the outcome cannot be predicted by pre- or postoperative tests.^{41,42} The morbidity is low when the procedure is performed by an experienced

neurosurgeon. Transsphenoidal microsurgery is considered successful when it is followed by remission of signs and symptoms of hypercortisolism and by normalization of laboratory values. Surgery is usually followed by adrenal insufficiency, and patients require hydrocortisone replacement for 6 to 12 months. After normalization of cortisol levels, resumption of normal growth or even catch-up growth can be observed. Generally, the patient's final height is compromised compared with their target height.³⁸ Some children, however, do achieve a normal final stature.³¹

The choice of treatment modality in patients who have relapses after transsphenoidal adenomectomy is still controversial. Some authors recommend repeated surgery,²⁶ whereas others favor radiation therapy.^{19,29} Radiotherapy with or without concomitant mitotane treatment may be indicated in patients with macroadenoma.²⁹ Although surgery can induce panhypopituitarism or permanent diabetes insipidus, hypothalamic-pituitary dysfunction is an early and frequent complication of radiation.^{22,54} Bilateral adrenalectomy may be the last therapeutic option in case of failure of both surgery and radiotherapy. Stereotactic radiosurgery with the gamma knife and linear accelerator includes promising new modalities that minimize the toxic effects of radiation on the brain, while still controlling tumor growth and ACTH secretion.⁵⁴

Management of GH-Secreting Adenomas

The objectives in the treatment of excess GH are tumor removal with resolution of its mass effect, restoration of normal basal and stimulated GH secretion, relief of symptoms caused by GH excess, and prevention of disease sequelae (that is, hypertension, insulin resistance, diabetes mellitus, and lipid abnormalities). The currently available treatment options for acromegaly include surgery, radiotherapy, and pharmacological suppression of GH levels by means of dopamine agonists or somatostatin analogs. Transsphenoidal resection remains the first treatment choice for GH-secreting tumors. In the case of macroadenomas, particularly when they exhibit extrasellar growth, persistent postoperative hypersecretion of GH occurs frequently. In most surgical series, only approximately 60% of patients with acromegaly achieve normal GH levels, but the success rate improves when the surgeon is a specialist in pituitary surgery.^{3,39} In pediatric patients with gigantism, transsphenoidal surgery was found to be as safe as it is in adults.²

Management of Clinically Nonfunctioning Adenomas

The first approach to these adenomas is transsphenoidal resection to debulk the tumor and decompress parasellar structures.³⁶ As in the other histological types of adenoma, surgery has a low morbidity rate and leads to an improvement of visual symptoms in the majority of cases.³⁵ The recent development of the endoscopic transsphenoidal approach to the pituitary,^{30,12} which has indications similar to conventional transsphenoidal microsurgery, overcomes many of the potential problems associated with the surgical route, due to its minimal invasiveness. This procedure involves no fractures of the facial bones or sublabial incisions. Furthermore, a wider surgical view of the operating field is obtained, which potentially improves the likelihood of a better and safer tumor removal. Endoscopic treatments can result in shorter hospitalization times and a rapid recovery for the child.^{12,30}

CONCLUSIONS

The management of pituitary adenomas and other sellar lesions must account for both the endocrine and neurological sequelae of these tumors. Patients require thorough pre- and posttreatment evaluation by neuroendocrinologists, neurosurgeons, neuroophthalmologists, and neuroradiologists. Medical treatment is the primary therapy for prolactinomas and recent advances have brought forward the expectation of effective pharmacotherapy for GH adenomas as well. Transsphenoidal surgery offers effective relief of mass effect and not only restoration but the preservation of normal endocrine function in the majority of patients. Radiation therapy can offer remission for some patients with medically and surgically refractory tumors, but patients must be observed closely for evidence of radiation necrosis and the presence of new endocrinopathies. With improved understanding of the molecular pathogenesis, future therapy will treat these tumors more effectively.

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Address reprint requests to: Edward R. Laws Jr., M.D., Department of Neurological Surgery, University of Virginia, PO Box 800212, Charlottesville, Virginia 22908-00212. email: el5g@virginia.edu