Child's Nervous System (2019) 35:2107–2118
https://doi.org/10.1007/s00381-019-04293-y

FOCUS SESSION

Pediatric pituitary adenomas

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Received: 26 June 2019 / Accepted: 30 June 2019 / Published online: 13 July 2019

Abstract

Background Pediatric pituitary adenomas are a rare medical entity that makes up a small portion of intracranial tumors in children and adolescents. Although benign, the majority of these lesions are secreting functional tumors with the potential for physiological sequela that can profoundly affect a child's development.

Focus of Review In this review, we discuss the medical and surgical management of these tumors with a focus on clinical presentation, diagnostic identification, surgical approach, and associated adjuvant therapies. We will also discuss our current treatment paradigm using endoscopic, open, and combined approaches to treat these tumors.

Summary The management of pituitary tumors requires a multidisciplinary team of surgeons, endocrinologists, and neuroanesthesiologists as well as neurocritical care specialists to deliver comprehensive care.

Keywords Skull base · Pediatric · Endonasal · Pituitary adenoma

Introduction

Epidemiology

Pediatric pituitary adenomas (PPA) represent only 2–8.5% of pituitary tumors in patients less than 20 years old [1–3]. Despite being one of the most common sellar tumors, they make up less than 3% of the supratentorial tumors in children. Incidence increases with age peaking in the third decade with an overall annual incidence of 0.1 case/100,000 [4, 5].

The differential diagnosis of intrasellar tumors includes craniopharyngiomas (only 25% are purely intrasellar), Rathke cleft cysts, and less common pathologies such as Langerhans cell histiocytosis, sarcoidosis, or dermoid/epidermoid cysts. PPA are categorized in the same fashion as their adult counterparts, either non-functional (or non-secreting) or functional (or secreting). The latter is much more common in children with only 5–10.5% of them presenting as non-secreting [2, 5–8]. In a meta-analysis of 37 surgical series (1284 patients), corticotropinomas (ACTH-secreting) were most commonly identified in 43% followed by prolactinomas (37%), somatotropinomas (12%), and plurihormomal adenomas (3%) [6]. In other series, prolactinomas are reported as being more frequent than Cushing's disease. This may represent a publication bias of surgical series [6]. Macroadenomas are not as frequent as in the adult population, most likely due to early clinical manifestations of hormonal disturbances of small secreting adenomas. If a child presents with macroadenoma, possibilities would include prolactinomas and somatotropinomas, while non-functional adenomas have such slow growth that they mainly become symptomatic at a later age [5]. When taken as a whole, PPA are more commonly diagnosed in females (2:1) [2, 6, 9, 10].

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Embryology

The development of the pituitary gland occurs with hormone signaling of SOX2-expressing progenitor cells. As pituitary stem cells develop, other signaling pathways, such as the *B-catenin/WNT* pathway, allow for further controlled differentiation [11, 12]. The general process has been described in four stages [13]. The initial stage, around the fifth week of gestation, is referred to as the pituitary placode. Second, the rudimentary Rathke pouch is formed, where the SOX2-expressing progenitors have been found. As Rathke's pouch continues to develop into the third stage (the definitive Rathke pouch), the connection between the oropharynx and the diencephalon is lost, progressing toward the development of the anterior pituitary as it connects with the posterior pituitary. The connection between the anterior and posterior portions is the pars intermedia. The final stage is the development of the pituitary gland and the differentiated cell types. Spatial/temporal development of the cell types occurs with *BMP2* and *FGF8* and develops from ventral to dorsal: gonadotropes, thyrotropes, lactotropes, and somatotropes [14].

It is thought that the majority of pituitary adenomas develop via somatic gene mutations. There are multiple genes associated with pituitary adenomas, both in specific differentiated cells and general shared components of the differentiated cells. Abnormally increased cAMP levels due to a mutation in the *GNAS* gene can be found in 40% of tumors stemming from somatotrophs. The increased cAMP activates promotor regions, leading to increased growth hormone (GH) secretion and cell proliferation [15]. Other studies have focused on the *pituitary tumor transforming gene* (*PTTG*) that has been attributed to development of functional adenomas. Overexpression of *PTTG* has been found in all secreting adenomas. Estrogen promotes tumor formation in the pituitary by activating *PTTG*; however, reduction in estrogen receptors can lead to more aggressive tumors, especially with regard to prolactinoma [12].

The majority of PPA are sporadic, but approximately 5% can be associated with genetic syndromes such as multiple endocrine neoplasia (MEN-1), McCune-Albright syndrome, Carney complex, familial isolated pituitary adenomas (FIPA) [6, 10, 15].

Presentation

Clinical manifestation of PPA will vary based on age and gender of the patient, type of adenoma (secreting vs. non-secreting), and size of the lesion.

Prolactinoma

The majority of pediatric prolactinomas will present during or after puberty. They occur mainly in females (5:1) and present with primary or secondary amenorrhea due to excessive prolactin (PRL) secretion [2, 6, 16, 17]. Visual deficits from compression of the optic chiasm apparatus by a macroprolactinoma can be seen in males [10, 18].

Corticotropinomas

Corticotropinomas (ACTH-secreting adenomas), better known as Cushing's disease, peak at the onset of puberty with a predilection for female gender (3:1) [6, 19, 20]. Interestingly, the gender discrepancy is not as pronounced before puberty [20]. In a large prospective observational study of 200 pediatric corticotropinomas, mean age at presentation was 10.6 years [20]. Primary chief complaints include rapid and significant weight gain as well as growth failure [20–22]. The majority of patients also present with typical adult Cushing syndrome manifestations including atrophic striae, generalized muscle weakness, acne, hirsutism, and osteoporosis. Other complications can result from hypercortisolism such as hypertension and glucose intolerance although frank diabetes mellitus is rare [19].

Somatotropinomas

In comparison to prolactinomas and corticotropinomas, growth hormone–secreting adenomas are rare in children (only 5–15% of PPA) and are mainly found in males [2, 6, 23]. The manifestation of increased growth is referred to as gigantism if it occurs before the fusion of long bone growth plates or to acromegaly if it presents after [6]. These tumors can often co-secrete PRL and thyroid-stimulating hormone (TSH) and can be associated with other syndromes such as McCune-Albright syndrome or Carney complex [10].

Thyrotropinomas

TSH-secreting adenomas are rare in children. In addition to general signs of hyperthyroidism, they usually manifest as macroadenomas with symptoms of mass effect including visual defects and headaches [24, 25].

Non-functioning pituitary adenomas

The benign nature and slow growth of these lesions generally lead to a diagnosis later in life and are rarely diagnosed in childhood. The visual deficits frequently identified in adult patients are only noted in 10% of children [26–28]. The majority of these lesions are discovered incidentally on imaging done for other reasons. Overall, these are approached and managed like in adults [8].

Pituitary apoplexy

Pituitary apoplexy, consisting of an abrupt onset of infarction and/or hemorrhage of a pituitary adenoma [29, 30], is rarely seen in children. Case series have reported this occurring in prolactinomas, corticotropinomas, non-functional adenomas,

and more frequently in macroadenomas [29, 31]. The clinical syndrome generally involves a sudden severe headache and is occasionally accompanied by cranial neuropathies from compression of the cavernous sinus or optic chiasm apparatus. It is critical to identify rapidly this entity due to the possible acute hypopituitarism that requires urgent steroid replacement. It has been suggested that pediatric patients might be less sensitive to the acute insult and less likely to suffer hypopituitarism [29]. Surgical intervention is generally recommended, with emphasis on those with neurological deficits [32].

Diagnostic evaluation

Imaging

Magnetic resonance imaging (MRI) using protocols centered on the pituitary gland is the favored modality. Most protocols will include thin (1–3 mm) coronal slices through the sella turcica. Dynamic techniques using quick repeated scans after the injection of intravenous gadolinium contrast show a time-dependent pattern that allows better delineation of the lesion from the normal gland. Figure 1 demonstrates a case example of an adenoma in Cushing's disease captured with dynamic pituitary imaging with rapid sequencing of slices through the pituitary gland demonstrating a small adenoma on the right side of the gland. Normal adenohypophysis (anterior pituitary gland) is usually isointense to brain parenchyma on T1-weighted sequences and homogeneously enhances early after the injection of contrast. In comparison, adenomas are usually T1-hypointense and show a slower, delayed contrast enhancement [33]. Other imaging features such as deviation of the infundibulum and asymmetry of the gland will help identify the lesion. Lonser et al. showed that MRI was 99% accurate in identifying corticotropinomas which are notorious for being difficult to visualize on imaging [20]. On the other hand, inferior petrosal sinus sampling was only accurate in 55–72% of patients when used to identify the laterality of an ACTH-secreting microadenoma [20]. This invasive endovascular procedure, although easily and safely feasible in children, is rarely used in this population. It is reserved for children in which the endocrinological labwork is equivocal in determining the central vs. ectopic origin of ACTH [20, 34].

In children, a special consideration toward the osseous and vascular anatomy is critical. A CT scan without contrast and/or a CT angiography is commonly obtained in our practice. When considering a transsphenoidal approach, it is important to identify the degree of sphenoid sinus pneumatization in order to plan the drilling needed to create a corridor to the sella. In addition, it is equally important to identify the trajectory of the carotid arteries as well as the intercarotid distance, which will dictate if the transsphenoidal approach is safely feasible. We generally obtain thin sliced sequences to use in our intraoperative neuronavigation guidance system. These images also serve to narrow the differential diagnosis and can, for example, identify calcifications suggestive of craniopharyngioma or bone hyperostosis in meningiomas [33, 35].

Ophthalmologic evaluation

As part of the standard evaluation of a newly diagnosed pituitary lesion, an ophthalmology evaluation should be

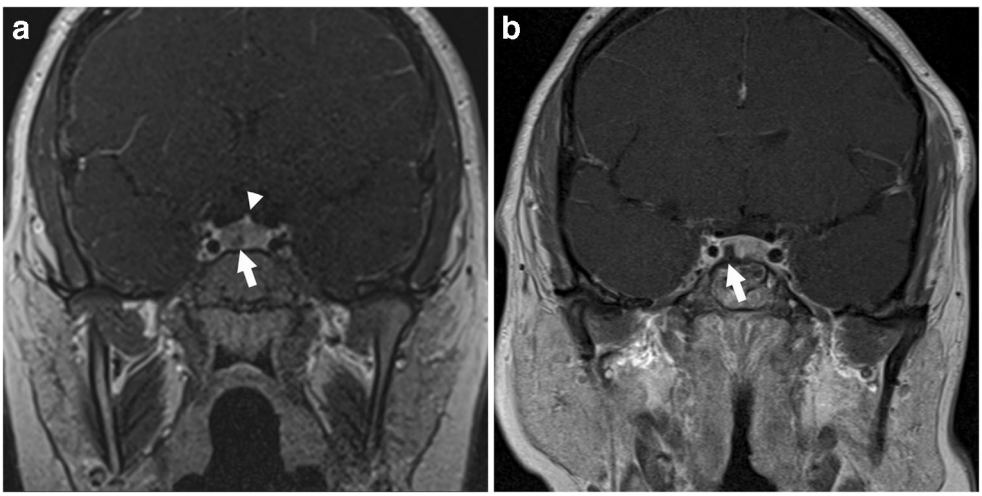

Fig. 1 **a** Imaging localization of an adenoma in Cushing's disease. In this coronal T1-weighted MRI with contrast, rapid sequencing of slices through the pituitary gland during contrast administration demonstrates delayed or absent uptake of contrast in the adenoma. Arrow indicates adenoma, positioned in the inferior right aspect of the gland. Arrowhead indicates the pituitary stalk. **b** Resection of secretory adenoma via an endonasal approach in the management of Cushing's disease. Preoperative localization using acquired thin slices of the pituitary gland allowed for targeted dissection and resection of the right inferiorly positioned adenoma. In this T1-weighted contrasted dynamic acquisition MRI, the resection cavity is indicated by the arrow. Dissolvable packing is noted in the sphenoid sinus inferior to the resection cavity

completed including visual field testing documentation [6]. As previously mentioned, children rarely present with macroadenomas and thus will infrequently have visual complaints. A detailed evaluation could suggest mild abnormalities not described by the child. This will also help in identifying any post-operative deficits and/or recurrence or progression of an adenoma over time.

Endocrinologic evaluation

Collaboration with pediatric endocrinology is at the cornerstone of the evaluation of all PPA.

Prolactinomas are confirmed with serum PRL measurements. Normal levels vary between 5 and 25 ng/mL and 5–15 ng/mL in females and males, respectively, and are usually at their highest during puberty [16, 18]. Levels greater than 200–250 ng/mL are generally considered diagnostic [17]. Levels between 100 and 200 ng/mL could result from a decreased tonic dopaminergic inhibition of PRL if the infundibulum is compressed by a lesion [36]. A high-dose "hook effect" should be considered with normal or mild PRL elevation and severe clinical presentations. Although less frequent with more recent technology, this false negative is due to a saturation of the two-site binding ELISA technique in the setting of high serum PRL [37].

Corticotropinomas are mainly diagnosed in a two-step pattern. First, Cushing syndrome is confirmed by measuring the basal levels of cortisol. An elevated 24-h urinary free cortisol or serial 11 pm salivary cortisol levels will identify hypercortisolism. A low-dose dexamethasone suppression test done at midnight (15 μg/kg dose) will confirm Cushing's syndrome if the morning serum cortisol remains elevated. The second step involves identifying the origin of ACTH secretion, pituitary (or central) vs. ectopic ACTH. A high dose of dexamethasone (120 μg/kg) is administered at midnight, and the morning serum cortisol measured. If the level decreases by more than 50%, or if it is less than 5 μg/dL, it confirms a pituitary origin [38]. If uncertain, an intravenous injection of CRH should lead to a significant increase in ACTH and cortisol within 45 min of the injection in Cushing's disease [39]. On the other hand, ectopic ACTH-secreting lesions will not suppress to high-dose dexamethasone and will not respond to injections of CRH. As previously described, inferior petrosal sinus sampling is reserved for cases where doubt remains in regard to central vs. ectopic excess ACTH (97% sensitivity). Measures of ACTH sampled in the inferior petrosal sinus are compared with peripheral venous samples, and a ratio of 2:1 or more has a 95% sensitivity and 93% specificity in diagnosing Cushing's disease [40].

GH-secreting adenomas are highly suspected based on clinical features and confirmed by measuring insulin-like growth factor-1. The latter correlates well with general levels of GH secreted in the previous 24–48 h [41]. Direct measurements of GH are usually unreliable given its normal diurnal variations and variability in response to normal physiologic activities like exercise, stress, and sleep. The oral glucose tolerance test is a useful confirmatory test (75-g glucose load). An abnormal response involves a failure of GH to suppress to less than 1 ng/mL within 2 h of ingestion. A paradoxical increase with a GH level of greater than 2 ng/mL is considered diagnostic. The range between 1 and 2 ng/mL is highly suggestive of an abnormal GH-secreting lesion [42, 43]. It is recommended to measure PRL, TSH, and T4 in these patients due to possible co-secretion of these hormones. Figure 2 demonstrates an extensive growth hormone–secreting pituitary adenoma that has expanded the sella and extended into the suprasellar space.

Thyrotropinomas are confirmed via thyroid function tests showing elevated TSH and T4 levels. Also, if needed, a thyrotropin-releasing hormone stimulation test can be done to eliminate the differential diagnosis of central thyroxine T4 resistance. Failure to respond to this test would suggest an adenoma as the cause [24]. Figure 3 demonstrates the case of a 17-year-old male with a TSH-secreting macroadenoma and progressive vision loss found after failing a driver's license vision and was managed surgically via an expanded endoscopic endonasal approach (EEA).

Management

Medical therapy

While most pituitary adenomas require surgical management, the preferred first-line treatment for prolactinoma is with

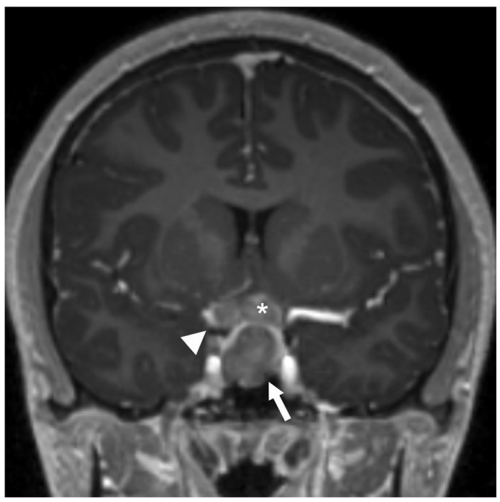

Fig. 2 Extensive growth hormone–secreting pituitary adenoma. This adenoma expanded the sella (arrow) and extended into the suprasellar space (asterisk). Note lateral extension of the adenoma toward the temporal fissure (arrowhead)

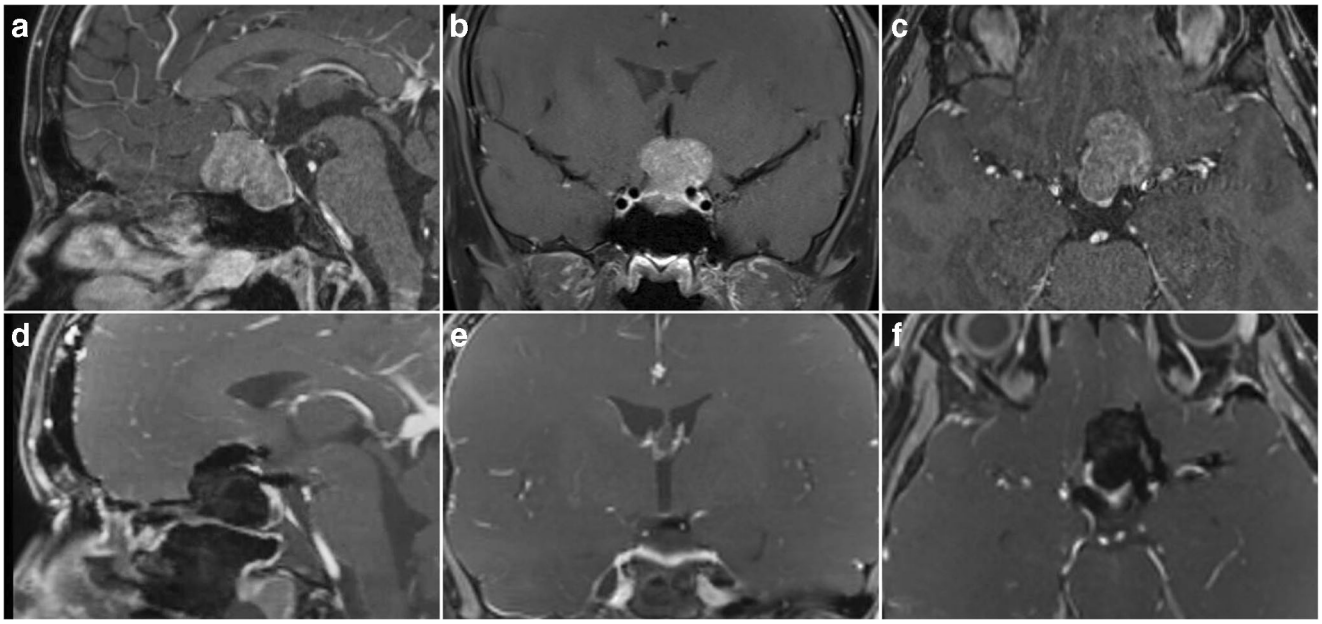

Fig. 3 A case of a 17-year-old male who presented with a progressive vision loss and a TSHoma that was managed surgically via an expanded endoscopic endonasal approach. Images demonstrated here are pre-operative and post-operative MRI scans. **a** Sagittal, **b** coronal, and **c** axial T1-weighted MRI images with contrast demonstrating a macroadenoma with suprasellar extension. **d** Sagittal, **e** coronal, and **f** axial T1-weighted MRI images with contrast of the same patient post-operatively demonstrating gross total resection and good approximation of the nasoseptal flap to the skull base opening

dopamine agonists due to their efficacy and favorable side effect profile [44]. All children presenting with a new pituitary mass should have their prolactin level assessed [27, 45]. In adults, cabergoline is the preferred drug for management of prolactinoma according to a recent consensus statement due to higher efficacy reducing hyperprolactinemia and larger reduction in tumor size [46]. No recommendations have been made on the preferred dopamine agonist in the pediatric population although several studies have shown improved efficacy with cabergoline, with remission achieved in 80–90% of microadenomas and 70% of macroadenomas [6, 47]. Relative contraindications to medical therapy are the presence or progression of cranial nerve deficits or vision loss due to mass effect. These findings warrant surgery for decompression with potentially curative intent [6, 48].

Surgical therapy

Open approaches

The use of open approaches has been used less frequently in pediatric pituitary adenoma due to their midline sellar location, direct access with transsphenoidal endonasal approach, and excellent visualization with endoscopy. The transsphenoidal approach to the sella was initially popularized in the early twentieth century but later largely abandoned due to poor visualization with existing technology in favor of the open subfrontal approach [49]. Subsequent development of the operating microscope and fluoroscopy brought the microscopic transsphenoidal approach back into favor in the 1960s [50]. This approach can be accessed either via a transnasal route or via a transseptal route utilizing a sublabial incision. Sphenoid pneumatization is variable in the pediatric population with final pneumatization occurring at ages 9–12, though complete pneumatization may not occur [51–53]. Even if the sphenoid is partially pneumatized, the transsphenoidal approach can still be used with judicious drilling of the non-pneumatized bone [7, 54, 55]. Many surgeons now favor endoscopic technique over the microscopic transsphenoidal approach which will be discussed in further detail below.

Although the transsphenoidal approach is used for the majority of pediatric patients, open or combined approaches have a role in tumors with significant suprasellar and/or ventricular extension, or Sylvian fissure involvement, although these are less common in pediatric patients [56, 57]. Some authors suggest using a pterional or orbitozygomatic approach for addressing a pre-fixed chiasm due to the short working distance of this approach and a subfrontal or transbasal approach for patients with a post-fixed chiasm [6, 58]. For tumors that have grown extremely large, anterolateral approaches are sometimes required for adequate exposure and less frontal lobe retraction [58, 59].

Endoscopic approaches

In parallel to the growing popularity of the microscopic transsphenoidal approach, the use of endoscopes to

visualize the sella was also being developed. Advantages of the technique include improved visualization, no facial or scalp incisions, and potentially shorter recovery from the approach. Disadvantages include the need for dural reconstruction, challenges with hemostasis, and the learning curve of endoscopic techniques [60]. Only a few studies compare EEA with microsurgical resection in adults and even fewer in the pediatric population. Early reports suggest that EEA is as safe as microscopic resection, and some note improved visual outcomes, less hormonal insufficiency, decreased post-operative pain, and improved rates of gross total resection (GTR), although a higher rate of carotid injury has been reported [6, 61–66]. Of note, these reports discuss adult endonasal experience. Massimi et al. assessed 31 pediatric patients undergoing EEA or microscopic resection and found that the EEA group had fewer intensive care unit admissions, shorter hospitalization, and less pain. They found no difference in symptom resolution, operative time, and immediate post-operative complications [67]. Initial reports of EEA raised concern for increased rates of CSF leak, but more recent surgeons' series suggest that CSF leak rate, endocrine outcomes, and extent of resection are equivalent between microsurgery and EEA [55, 65, 68, 69].

Specific to the pediatric population, there was initial concern for disruption of craniofacial growth with EEA. However, the series with the longest term results have not identified abnormalities of facial growth following pediatric EEA [68, 70, 71]. Smaller nasal passages and septal length could be concerning for difficult creation of a nasoseptal flap (NSF) in children [72]. A study of CT scans of the sinuses suggested that NSF width is unlikely to be a problem at any age. The same study suggested that NSF length may be insufficient for all clival defects regardless of age but is expected to be sufficient for transsellar/transplanum defects after 6–7 years of age and for transcribriform defects after ages 9–10 [73]. Ghosh et al. retrospectively reviewed the CT scans of 16 pediatric patients undergoing repair of suprasellar defects and found that the NSF was feasible in all, even in those under 6 years of age [74]. NSF has been used in patients as young as 4 years old in published series, and the authors' clinical experience has demonstrated adequate coverage for anterior fossa defects as low as 2 months of age [75]. The learning curve can be significant with worse outcomes immediately after adopting endoscopic resection that improves after the first 15–20 procedures [76, 77]. Further data on long-term outcomes and comprehensive endoscopic training for surgeons will be critical to ensuring good outcomes. Figure 4 depicts an endoscopic view of the surgical montage of the thyrotropinoma case presented in Fig. 3. It required an expanded EEA to the sellar and suprasellar compartments.

Post-operative management

All pediatric patients are admitted to the hospital after skull base surgery. Patients can be admitted to the floor or neurological care step down unit unless they have undergone open craniotomy for tumor resection, in which case they are admitted to the pediatric intensive care unit. In our practice, prophylactic antibiotics are administered for 7 days post-operatively if absorbable packing is placed following skull base reconstruction. If there is non-absorbable packing that requires later removal, antibiotics are continued until the packing is removed. Antibiotics are primarily given to decrease the risk of post-operative meningitis and toxic shock syndrome (TSS) due to packing material. A fourth-generation cephalosporin is most commonly used as it provides good central nervous system coverage of staphylococcal and streptococcal bacteria, common culprits for TSS. In patients with penicillin allergies, vancomycin with trimethoprim-sulfamethoxazole is an alternative treatment regimen. The authors adopt this practice despite limited prospective data to guide antibiotic selection and duration. Two studies demonstrated no intracranial infection with only 24–48 h of antibiotic prophylaxis following EEA for skull base surgery in adults, suggesting that this may be sufficient [78, 79]. Further studies are needed to better define the optimal duration and selection of antibiotics following skull base surgery in children.

Cerebrospinal diversion is not typically utilized after endonasal adenoma resection. The adult literature supports the avoidance of lumbar drain (LD) placement for standard endonasal approaches, but there is no pediatric-specific data to recommend for or against LD placement. In the absence of an intraoperative CSF leak, LD would not be entertained. However, if there is an intraoperative leak encountered, additional factors should be considered. The success of the skull base reconstruction does rely to some extent on the patient's ability to comply with nasal precautions and avoidance of activity that increases intracranial pressure. As such, the younger pediatric age group may represent a unique population at higher risk for failure of reconstruction due to inability to comply with post-operative restrictions—an indication for CSF diversion in a recent review [80]. A randomized control trial performed in adult patients found that LD placement was not indicated unless the patient was at high risk for post-operative CSF leak, defined as dissection into the ventricle or cistern, extensive arachnoid dissection, or dural defect greater than 1 cm^2 [81]. Accordingly, the decision to place a lumbar drain in a pediatric patient is made on an individual basis, but an effort is made to avoid LD placement in the majority [80].

Nasal precautions are instituted following skull base surgery with the patient instructed to sneeze with their mouth open and avoid nose blowing until the reconstruction is well healed, generally 4–6 weeks post-operatively.

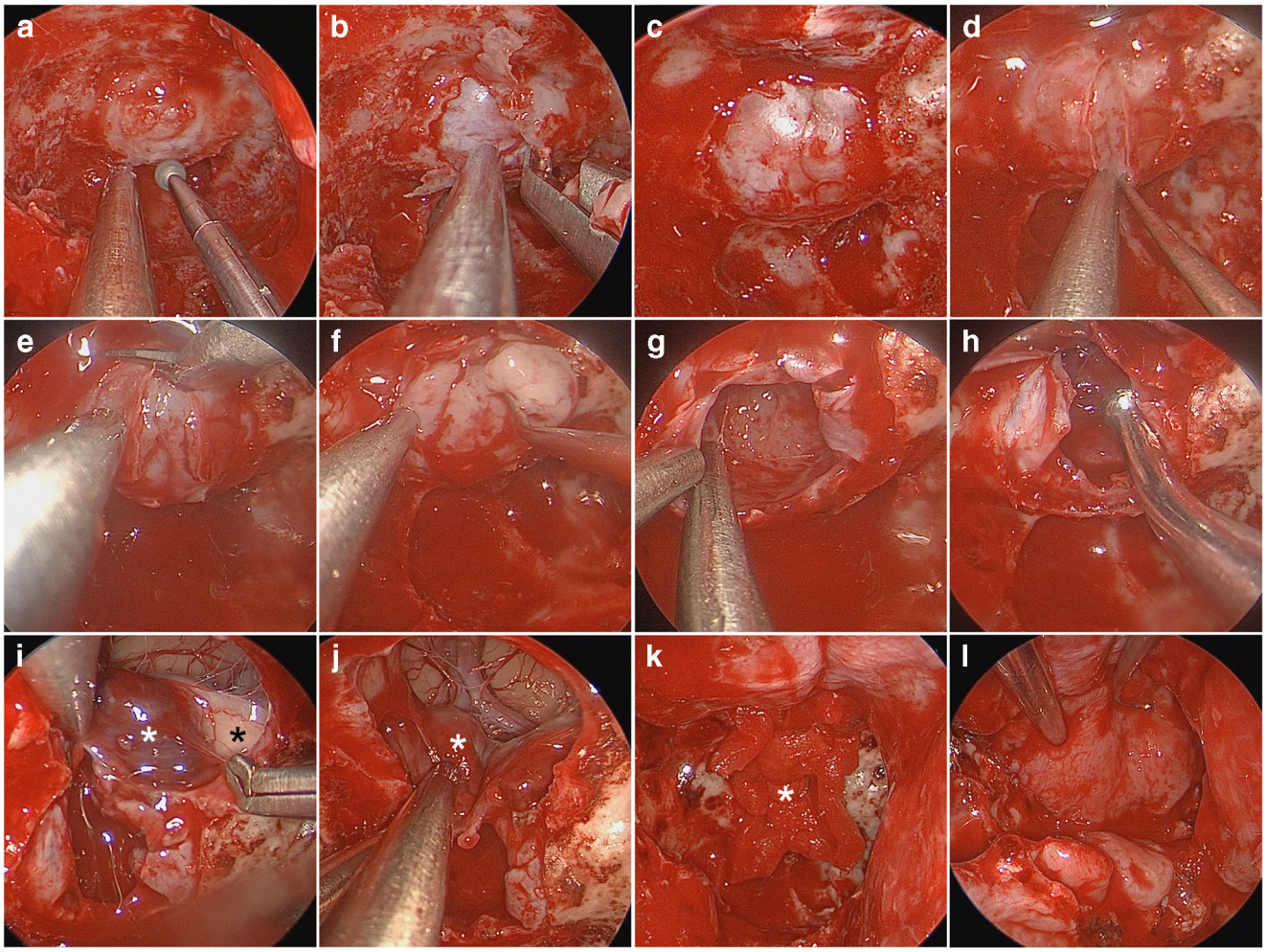

Fig. 4 Surgical still photographs taken with an intraoperative endoscope of the TSHoma case presented in figure 3 via a transsphenoidal approach. (**a**) Endoscopic view of drilling of the face of the sella from a transsphenoidal approach (**b**) Removal of bone for an expanded sellar opening (**c**) Exposing the necessary dura for access to the tumor in the pituitary compartment (**d**) Incision of the dura and early identification of tumor (**e**) Expanded dural opening to expose the pituitary compartment (**f**) Resection of the tumor using microinstruments in a piecemeal fashion (**g**) Resection of the tumor using aspiration taking care not to injure the posterior gland (**h**) Resection of the tumor from the suprasellar compartment using directional aspiration (**i**) Resection of tumor (white asterisk) and decompression of the left optic nerve (black asterisk) (**j**) View of the suprasellar space after gross total resection of the tumor demonstrating a herniated diaphragma (white asterisk) and the anterior cerebral arteries in the background (**k**) Reconstruction of the dural opening and skull base using a duragen inlay placed in a gasket seal type arrangement (**l**) Elevation of the nasoseptal flap with good approximation to the skull base.

Nasal cannula is avoided to prevent nasal crusting and drying, and humidified face tent is used if supplemental oxygen is required. The head of bed is elevated 15–30°, and nasal tubes of all types (nasogastric tubes, impedance probes, nasopharyngeal airways, and deep nasal suctioning) are strictly avoided to prevent damage to the repair and subsequent complication [82].

Nasal saline spray is started the day of surgery to assist with nasal hygiene and clearance of crusts and mucous. Nasal saline irrigations are instituted after splints and non-absorbable packing are removed. Many children > 6 years of age are able to comply with nasal irrigations with appropriate parental encouragement and oversight. The nasal cavity is cleaned of excess crust and mucous so that the graft can be visualized 5–7 days after surgery. Older compliant children and teens may be able to tolerate this procedure at the bedside, while younger less compliant patients may require return to the operating room for debridement and packing removal [82].

Pediatric endocrinology is consulted in all patients with pituitary adenoma pre- and post-operatively to aggressively address hypopituitarism. While all of hormone levels are followed on an outpatient basis, patients are monitored closely for diabetes insipidus, hypocortisolemia, and hypothyroidism in the post-operative periods so that deficits can be addressed rapidly to prevent morbidity. Once the patient has stabilized from an endocrinologic and surgical perspective, he or she is discharged with close follow-up.

Radiation therapy

Radiation therapy has a defined role in the management of adult recurrent pituitary adenoma, but the role of radiation in the pediatric population is less clear with many physicians attempting to avoid or postpone radiation therapy after puberty to avoid hypopituitarism and growth delay [6]. Prior to radiation administration, revision surgery or medical management (if not already attempted) should be considered. Revision surgery, if the lesion is surgically accessible, can successfully cure 14–57% of patients in pediatric and adult series, respectively [6, 83, 84]. Many pediatric patients with progression of their disease have cavernous sinus involvement, which complicates revision surgery. Some patients may benefit from medical treatment including cabergoline or octreotide if revision surgery is not successful or not feasible, while some physicians use medical therapy to forestall radiation therapy until after puberty [6].

If revision surgery and medical management are not indicated, radiation therapy for recurrent or progressive disease may be entertained, although its use in the pediatric population is not well studied. Local control of secretory pituitary adenomas with radiation has been reported to be very high with 64–100% control rates including all tumor subtypes [6, 19, 85, 86]. Almost all pediatric patients who undergo radiation therapy suffer some amount of growth hormone (GH) deficiency (86–100%) with resulting short stature, while panhypopituitarism occurs more rarely. The hypothalamus is more sensitive to radiotherapy and results in the common finding of GH deficiency, while the anterior pituitary is relatively more radioresistant [87]. There is a strong correlation between the overall dose of radiation and the development of pituitary deficits [88, 89]. Age at treatment and time since treatment also correlate with pituitary function [87]. The form of radiation therapy used (external beam, stereotactic radiosurgery, and proton beam) in the pediatric population has not been well studied. In aggressive pituitary adenomas that do not respond to therapy or pituitary carcinomas, there may be a role for chemotherapeutics, although there are no guidelines in the pediatric age group and decisions to treat must be made on an individualized basis [90].

Outcomes

Disease control

Perry et al. performed a review of the pediatric case series regarding pediatric pituitary adenoma managed surgically and found that surgical cure was obtained in 46% of their cases and 65% of cases in the studies they reviewed [6]. Surgical outcomes were comparable in a study by Barzaghi et al. that identified a 6-month surgical cure rate of 55.6 to 72.1% (depending on the type of adenoma with nonfunctioning pituitary adenoma being the lowest and Cushing's disease being the highest) [5]. Remission rates are reportedly higher in Cushing's disease patients with Lonser et al. noting a 98% early remission rate after surgical intervention in a pediatric series with 8% subsequent recurrence [20]. A smaller study by Yordanova et al. specific to Cushing's disease found a surgical cure rate of 71% while other reviewed studies reported surgical cure as low as 60%, largely due to differences in the definition of surgical cure [22, 91].

While it is encouraging that many pediatric patients respond well to surgery, the rates of recurrent or progressive disease remain significant. As noted above, revision surgery is the preferred modality for residual disease if anatomically accessible. Previous studies in adults have suggested a 57% revision surgical cure in adults with secretory pituitary adenoma, although the available rates of surgical cure in pediatric pituitary adenoma are only 14% in a revision setting [6, 83, 84]. The underlying mechanisms for the decreased rate of cure in the pediatric population are unclear. As noted in the radiation section, pediatric pituitary adenomas do respond well to radiation therapy, with local control rates being reported at 64–100% following radiation therapy [19, 85, 86].

Vision

Close collaboration with a pediatric ophthalmologist is recommended in the pre- and post-operative setting to diagnose any unrecognized visual field deficits and to monitor response to therapy. Post-operative permanent visual dysfunction was found to be 6% in a pooled review of 39 case series on pediatric pituitary adenoma treated surgically [6]. While this may be an acceptable risk given the complexity of the disease process, patients and families should be counseled about this risk pre-operatively and aggressively screened for visual disturbances in follow-up.

Endocrine function

Hypopituitarism remains a significant problem in pediatric pituitary adenoma management. Rates of permanent hypopituitarism vary. While a rate of 23% was reported in a review of the literature, more recent data suggest a rate of 67% [6]. The authors of the more recent study note that previous studies show a wide range of reported hypopituitarism (4–80%) and were limited by short follow-up and potentially underreporting [6]. The true rate is elusive but does seem to be higher than the 5–22% hypopituitarism rate in adult series [92, 93]. Rates of hormone deficiency for specific adenoma subtypes have not been detailed in previous studies apart from Lonser et al. who reported a 97% rate of hypocortisolemia following pituitary surgery for Cushing's disease [20]. Following surgery for all subtypes of pituitary adenoma, GH

deficiency is most common, with corticotropin and thyroid-stimulating hormone being less common and easily replaced. Gonadotropin deficiency is uncommon, but if encountered, gonadotropin replacement is needed if fertility is desired later in life. [23, 94]. Patients are routinely monitored post-operatively for diabetes insipidus (DI). Consultation with pediatric endocrinology is essential to tailor the treatment to the pediatric patient; however, management relies on desmopressin (DDAVP) administration and correction of sodium aberrations [95]. For most patients undergoing resection of a pituitary adenoma, DI is transient, although around 3–5% will require chronic DDAVP administration [6, 20].

Other complications

CSF leak remains relatively uncommon. Surgical series using an operating microscope cite rates of 0.5–3% [20, 96]. Data regarding EEA CSF leak rates specific to pituitary adenoma are less robust due to EEA being a relatively recent development in skull base surgery and pediatric adenomas being rare in incidence. Chivukula et al. reported on 11 adenomas and found 1 CSF leak (9.1%) [68]. Another study found an 8.3% risk of CSF leak rate but only included 12 patients with pituitary adenoma [55]. A larger study by Zhan et al. of 49 pediatric patients over the age of 10 years found a lower 3.5% rate of CSF leak [69]. This would suggest that the rate of CSF leak is roughly equivalent between EEA and microscopic techniques, a finding that has been demonstrated in the adult population, although further study on EEA CSF leak in pituitary adenoma is needed [65, 97].

In the event of CSF leak, lumbar drain placement may be trialed, though most advocate for early return to the operating room for localization of the leak and multilayered repair [98]. LD placement requires anesthesia in many pediatric patients, which should be considered when weighing the risks and benefits of CSF rhinorrhea management. Skull base repair can be challenging in patients with a history of multiple intranasal procedures and radiation therapy; however, attempts should be made to perform a multilayered, water tight seal. Free mucosal grafts and vascularized tissue grafts, such as NSF, are options for revision skull base reconstruction, although NSF may not be available if the patient is very young or has had previously had skull base reconstruction [99, 100].

A feared complication of management of pituitary adenomas is carotid artery injury. Fortunately, rates of carotid artery injury during endoscopic or open surgical tumor resection remain very low. A carotid injury rate of 0.55–0.9% has been reported in the adult population. Immediate control with isolation of the injury and temporization with crushed muscle plug should be performed and the patient transported for immediate endovascular stenting or embolization. This management method is advocated to prevent patient mortality [101]. In pediatric patients, a rate of 0.75% for carotid injury has been reported [68]. While carotid injury is an emergency in any patient, the smaller circulating blood volume in pediatric patients reduces the amount of time surgeons have to act prior to the patient succumbing to hemorrhagic shock. Even so, the management pattern is similar to injury in adults.

Conclusion

The management of pituitary adenomas in pediatric patients mimics patterns of management in the adult population, with a transition to endonasal techniques with decreased overall morbidity despite increased potential for CSF rhinorrhea related to open approaches. Outcomes following meticulous surgical resection of the adenoma result in generally good long-term outcomes, though monitoring of endocrine function for post-operative dysfunction and for recurrence is required.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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