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Cushing's syndrome in childhood: update on genetics, treatment, and outcomes

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Abstract

Purpose of review—To provide an update on the genes associated with Cushing's syndrome in children, as well as to familiarize the clinician with recent treatment guidelines and outcome data for children with Cushing's syndrome.

Recent findings—The list of genes associated with Cushing's syndrome continues to grow. In addition, treatment for childhood Cushing's syndrome is evolving. As long-term follow-up data on children becomes available, clinicians need to be aware of the issues that require attention.

Summary—Knowledge of the specific genetic causes of Cushing's syndrome has potential implications for treatment, surveillance, and counseling. Advances in surgical technique, radiation modalities, and medical therapies offer the potential for additional treatment options in Cushing's syndrome. Early identification and management of post-treatment morbidities in children treated for Cushing's syndrome is crucial in order to optimize care.

Keywords

childhood; Cushing's disease; medical therapy; pituitary adenoma; radiation

INTRODUCTION

Cushing's syndrome is a multisystem disorder resulting from the body's prolonged exposure to excess glucocorticoids. In children, it is characterized by truncal obesity, growth deceleration, striae, hypertension, and hirsutism [1]. Cushing's syndrome is most commonly caused by exogenous administration of glucocorticoids, whereas endogenous Cushing's syndrome is particularly rare in children. The overall incidence of endogenous Cushing's syndrome is approximately 2–5 new cases per million people per year, whereas only approximately 10% of these occur in children. The most common cause of endogenous Cushing's syndrome in children is adrenocorticotrophic hormone (ACTH) overproduction from a pituitary adenoma, or Cushing's disease, accounting for approximately 75% of all

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Conflicts of interest

None.

cases of Cushing's syndrome in children over 7 years. In children under 7 years, adrenal causes of Cushing's syndrome make up roughly 15% of childhood Cushing's syndrome, including bilateral hyperplasia, adenoma, or carcinoma. Ectopic ACTH and corticotropin-releasing hormone production is another rare cause of Cushing's syndrome that accounts for less than 1% of cases in adolescents [2]. Sources of ectopic ACTH include carcinoid tumors in the bronchus, pancreas or thymus, medullary carcinoma of the thyroid, pheochromocytoma, and small-cell carcinoma of the lungs.

Newly identified genetic alterations continue to be described in Cushing's syndrome. Knowledge of the natural history of these different genetic causes has important implications for patients and their families. Improved treatment modalities for Cushing's syndrome in children are being developed. However, Cushing's syndrome in children may be associated with late effects even after successful resolution of hypercortisolemia. Cushing's syndrome affects children and adolescents in many ways that are different than adults. The factors influencing the outcome of pediatric Cushing's syndrome will be reviewed, as well as the postoperative changes in parameters including metabolic syndrome, skeletal maturation, bone density, hypertension, and recovery of pituitary function. All of these factors impact the health-related quality of life, which is an important outcome measure to assess the burden of disease as well as the effect of treatment.

GENETICS

The underlying genetic cause of glucocorticoid excess is related to the source of disease, as summarized in the list below. Known genetic etiologies of Cushing's syndrome in children and young adults are as follows where applicable, the associated syndrome follows in parentheses.

1. Pituitary corticotropinoma:
 - a. *Menin* [multiple endocrine neoplasia type 1 (MEN-1)];
 - b. aryl hydrocarbon receptor interaction protein gene (*AIP*);
 - c. majority unknown;
2. Adrenal hyperplasia:
 - a. *Menin* (MEN-1);
 - b. gene coding for the stimulatory subunit alpha of the G-protein (G_{α}) *GNAS*: [McCune–Albright Syndrome (MAS)];
 - c. *ARMC5*;
 - d. protein kinase, cyclic AMP (cAMP)-dependent catalytic subunit (*PRKCA*);
 - e. protein kinase, cAMP-dependent regulatory type I alpha gene (*PRKARIA*; Carney complex);
 - f. phosphodiesterase 11A (*PDE11A*) gene;
 - g. phosphodiesterase 8B (*PDE8B*) gene;

3. Adrenal cancer:

- a. *P53* (Li–Fraumeni syndrome);
- b. *GNAS* (MAS);
- c. *Menin* (MEN-1);
- d. *IGF-II*, *H-19*, and *CDKI* (Beckwith–Wiedemann syndrome);
- e. adenomatous polyposis colii (*APC*; familial adenomatous polyposis).

Adrenocortical hyperplasias

Genetic forms of Cushing's syndrome have been linked to abnormalities in the cAMP signaling pathway [3]. Bilateral macronodular adrenal hyperplasia may be associated with MAS, in which a somatic mutation of the *GNAS1* gene leads to constitutive activation of the Gs α protein and dysregulated cortisol overproduction [4–6]. Cushing's syndrome in MAS usually presents before 6 months of age and may resolve spontaneously [7,8]. Primary pigmented nodular adrenocortical disease (PPNAD) is another type of bilateral nodular adrenal disease that may present in childhood. PPNAD occurs most frequently in association with Carney complex, an autosomal dominant multiple neoplasia and lentiginosis syndrome. PPNAD is associated with germ-line inactivating mutations of the *PRKARIA* gene that codes for the regulatory subunit of the cAMP-dependent protein kinase A (PKA), whereby inactivation of *PRKARIA* leads to unregulated PKA function [9,10]. We recently reported the gain-of-function mutations in *PRKACA*, the catalytic alpha subunit (C α) of PKA, in adrenal Cushing's syndrome associated with both bilateral adrenal hyperplasia and adrenal adenomas [11[¶]]. Massive macronodular adrenal hyperplasia (MMAD) is another rare type of Cushing's syndrome; this disorder may be sporadic or familial [12]. A recent study elucidated inactivating mutations of a putative tumor suppressor gene, *ARMC5*, in 33 cases of MMAD with Cushing's syndrome [13[¶]]. Mutations in phosphodiesterase genes *PDE11A* and *PDE8B* are also implicated in adrenocortical hyperplasia leading to Cushing's syndrome [14–17]. Screening for these genetic alterations may identify the family members who have subtle or early forms of disease. For example, the first-degree relatives of individuals with Cushing's syndrome may have hypertension or glucose intolerance and diabetes mellitus, but may not be aware that these are the early manifestations of Cushing's syndrome.

Adrenal cancer

In the case of pediatric adrenocortical tumors, recent advances have identified germline *TP53* mutations in over 70% of cases of adrenocortical tumors in children [18]. Adrenal cancer can be associated with Li–Fraumeni syndrome, Beck-with–Wiedemann syndrome, familial adenomatous polyposis, McCune–Albright syndrome, and MEN-1 (see list above) [19].

Pituitary corticotropinoma

Although ACTH-producing pituitary adenomas are the most common cause of Cushing's syndrome in childhood, thus far, no genetic defect has been found to account for the majority of cases of Cushing's disease. Cushing's disease is usually sporadic, yet may be

familial, and is known to occur in the context of MEN-1 and rarely because of mutations of the *AIP* gene [20,21,22^{¶¶}]. MEN-1 includes ACTH secreting pituitary adenomas in 5–10% of cases [23]. ACTH-secreting tumors have also been associated with mutations in cyclin E (*CCNE*), *EGFR*, *CMP1k*, and *LAPTM4B* in adults, yet these defects are rare in the pediatric Cushing's disease population [20,24]. The prevalence of germline mutations in MEN-1, *AIP*, *PRKARIA*, *CDKN1B*, and *CDKN2C* was studied in 74 pediatric patients with isolated Cushing's disease, yet only one *AIP* mutation and two MEN-1 mutations were found [20]. In the aggregate, these conditions explain only a small proportion of Cushing's disease cases. The finding of a mutation associated with Cushing's disease may have clinical implications. Pituitary tumors associated with *AIP* mutations are larger and present earlier in life [25]. Cushing's disease with underlying MEN-1 often involves multiple pituitary adenomas, which may be larger and more aggressive [19,26]. As a portion of patients continue to have refractory Cushing's disease after surgery, genetic predictors of outcome would be useful for determining the prognosis.

Treatment

Treatment of Cushing's syndrome depends on the source of disease, as outlined below.

Adrenal source of Cushing's syndrome—Benign adrenal tumors are best treated with surgical resection; in the case of bilateral micronodular or macronodular adrenal disease, bilateral total adrenalectomy is the treatment of choice. In familial cases of PPNAD, linear growth, weight gain, and cortisol excess and its associated comorbidities should be monitored in children to help guide the timing of surgery. Treatment guidelines for children with adrenal cancer are lacking because of the rarity of this disease. A protocol was developed in 2006 to investigate the role of surgery and chemotherapy including mitotane and cisplatin, etoposide, and doxorubicin for adrenal cancer in children, however the study is ongoing and final results are pending. (Children's Oncology Group ARAR0332) [18].

Cushing's disease treatment in children—The first-line treatment for almost all children with Cushing's disease remains transsphenoidal surgery (TSS) (Fig. 1) [27^{¶¶}]. In specialized centers with experienced neurosurgeons, the success rate of the first TSS is close to or even higher than 90% [28,29^{¶¶}]. Endonasal endoscopic transsphenoidal pituitary surgery (ETES) is a newer surgical approach; experience in children is limited, but preliminary data are promising [30]. Although it is the preferred initial treatment, pituitary surgery may not be successful, and disease may recur years after initial surgery. Treatment failures are generally because of a macroadenoma or a small tumor invading the cavernous sinus. The success rate of repeat TSS is worse, closer to 60%. Postoperative complications include transient diabetes insipidus and, occasionally, syndrome of inappropriate anti-diuretic hormone secretion, central hypothyroidism, hypogonadism, growth hormone deficiency, bleeding, infection, and pituitary apoplexy. The mortality rate is extremely low, at less than 1%. Permanent complete or partial hypopituitarism is infrequent; however, it is more likely after repeat TSS or macroadenomas. If initial TSS is unsuccessful, the clinician is faced with the challenging task of deciding the course of action. The best strategy is not always clear, especially in childhood which is the window for growth and development [31^{¶¶}]. Repeat pituitary surgery should be considered if there is a clear anatomical target.

The second-line treatment for refractory Cushing's disease includes pituitary irradiation, especially useful in cases in which there is a localized site of disease. In up to 80% of cases, patients will have remission of Cushing's disease within a few years after radiation therapy; however, radiation therapy in children is known to take effect more rapidly than in adults [32,33]. Unfortunately, hypopituitarism is commonly encountered, and children receiving pituitary radiotherapy require frequent assessment of anterior pituitary function [34]. The traditional dose of radiation therapy is 4500–5000 cGy given over a 6-week period. However, innovative types of stereotactic radiotherapy are now available for the treatment of corticotropinomas. These approaches include linear particle accelerator (LINAC), Gamma Knife stereotactic radiosurgery (SRS), and proton beam therapy – though long-term follow-up studies in children are lacking. In adults, recent evidence shows that SRS provides an effective and well tolerated treatment option for patients with pituitary adenomas. Stereotactic radiosurgery offers the benefit of shorter time required for the procedure and the potential for lower rates of side-effects. In a recent retrospective review of 262 patients treated with SRS, tumor control rate was 89%, but the majority of patients were adults. Higher margin radiation dose to the adenoma and suprasellar extension were two independent predictors of SRS-induced hypopituitarism [35]. In a recent study of 96 patients with Cushing's disease, remission at 5 years after SRS was 78% [36]. In another long-term study of radiation therapy in pituitary adenomas, including individuals as young as age 10, radiation therapy was seen to increase the quality of life in 95% of patients, and local progression-free survival following radiation therapy was 90% at 2 years. The authors conclude that early initiation of radiation therapy after surgery instead of reserving it for recurring adenomas improved the outcome [37^{***}]. SRS may lead to radiation-induced optic neuropathy and associated blindness when the dose to the anterior visual pathway is greater than 8 Gy [38]. Postoperative radio-therapy does not seem to be associated with an increased incidence of second tumors and mortality in adults with pituitary adenomas [39].

Medical therapy is a second option in the case of surgical failure for Cushing's disease or unlocalizable ectopic ACTH [40,41^{***}]. Currently, three categories of pharmacologic therapies exist, including those directed at the pituitary gland, steroidogenic inhibitors targeting the adrenal gland, as well as those that antagonize the glucocorticoid receptor. The main caveat is that none of these therapies are approved for the use in children, and all have significant side-effects. Pasireotide (targeting somatostatin receptors) and cabergoline (targeting dopamine receptors) have shown success in up to 30% of adults with Cushing's disease. Adrenal enzyme inhibitors, such as mitotane, metyrapone, or ketoconazole, may also be used alone or in combination to control hypercortisolism. Ketoconazole, an adrenolytic that inhibits several enzymatic steps in steroidogenesis, has limited effectiveness in reducing the cortisol levels, is not well tolerated because of gastrointestinal side-effects, and can cause significant hepatotoxicity. In addition, steroidogenesis inhibitors lead to adrenal insufficiency, and patients must be started on replacement with hydrocortisone. The US Food and Drug Administration (FDA) conducted a comprehensive benefit–risk assessment of the safety and efficacy of ketoconazole which resulted in the changes to the drug's label in July 2013, including monitoring for hepatotoxicity with weekly ALT levels [42]. For patients with Cushing's disease requiring medical therapy, careful monitoring is necessary; however, some argue that the potential benefits of ketoconazole are likely to

outweigh the risks [43]. The glucocorticoid receptor antagonist mifepristone has been used in adults with Cushing's syndrome [44]. However, adverse events include hypokalemia, adrenal insufficiency, and endometrial thickening. Although medical therapy may show reasonable efficacy in select patients, none of these therapies are approved for the treatment of Cushing's disease in children, and further study of these medications in patients with glucocorticoid excess is needed. In addition, even in adults, the FDA has approved only two drugs for the treatment of Cushing's disease or hyperglycemia associated with endogenous hypercortisolemia (pasireotide and mifepristone, respectively).

Adrenalectomy is an option for refractory Cushing's disease or ACTH-dependent Cushing's syndrome. A recent retrospective review out of MD Anderson Cancer Center including both pediatric and adult patients looking at 4 decades of treatment for refractory Cushing's syndrome concluded that early bilateral adrenalectomy in patients with uncontrolled Cushing's syndrome improved adverse events [45]. However, a potential complication after bilateral adrenalectomy in individuals with Cushing's disease is growth of the corticotropinoma, elevated ACTH levels, and hyperpigmentation (Nelson's syndrome). Adrenal crisis is another lifelong risk in these patients. Recent approximations from two systematic reviews in adults found that Nelson's syndrome occurred in 21–24% of the patients [46,47]. The exact rate of Nelson's syndrome in children is not known.

FOLLOW-UP

Endogenous Cushing's syndrome, regardless of the cause, has the potential for long-term health effects in children. In addition, the surgical or radiation treatment itself for Cushing's disease has specific short and long-term complications. Chronic hyper-cortisolemia has been associated with a number of morbidities, including poor growth, obesity, insulin resistance, hypertension, dyslipidemia, hypercoagulability, impaired bone mineral density, and psychiatric disorders. Recent research has looked into the short-term and long-term sequelae in children and adults with Cushing's syndrome.

Following successful TSS, intermittent adrenal insufficiency is expected until the hypothalamic pituitary adrenal axis recovers. Physiologic glucocorticoid replacement is initiated at discharge (12–15 mg/m²/day b.i.d.) and the adrenocortical function should be periodically assessed with a one hour ACTH stimulation test to guide further weaning [48]. Following bilateral adrenalectomy, patients require lifetime replacement with both glucocorticoids and mineralocorticoids.

Cushing's syndrome is associated with an increased risk of venous thromboembolism in adults; however, little is known about the risk in children [49]. The hypercoagulable state in adult patients with Cushing's disease is not always reversible upon after successful medical therapy [50]. In order to evaluate the natural history of the coagulation status of children with Cushing's disease, we are investigating the parameters of coagulation and fibrinolysis before and after the cure of disease. Children with Cushing's syndrome are at high risk of metabolic abnormalities including dyslipidemia, adiposity insulin resistance, and hypertension prior to cure; however, even after the cure of Cushing's syndrome these symptoms may persist [51]. In this study, 30 children with Cushing's syndrome were

evaluated prior to and 1 year after treatment and compared to 14 years of age and BMI-matched controls – there was persistence of an elevated waist circumference and fasting insulin despite the remission of Cushing’s syndrome, suggesting that children with a history of Cushing’s syndrome may have an increased risk for adverse long-term effects related to increased abdominal fat mass. Children with Cushing’s syndrome are at risk for residual hypertension despite showing a significant improvement after surgical cure, and hypertension appears to correlate with the degree of hypercortisolemia [52]. Other groups have looked at arterial distensibility in children affected by Cushing’s syndrome and have found increased rigidity, as well as early markers of cardiovascular dysfunction even after successful cure [53,54]. Cardiovascular remodeling may be a permanent sequelae of longstanding Cushing’s syndrome and underscores the importance of early detection and treatment in children.

Cushing’s syndrome has psychosocial implications that may continue after recovery. We recently reported that children with Cushing’s syndrome experience a decline in the cognitive and school performance 1 year after surgical cure [55]. Although most self-reported Cushing’s syndrome symptoms showed improvement, forgetfulness, unclear thinking, and decreased attention span did not improve even after the cure of Cushing’s syndrome [56]. Our recent study on health-related quality of life reported that active Cushing’s syndrome, particularly in younger children, was associated with low physical and psychosocial scores. Although individuals showed improvement from before surgery as compared to one year after cure, residual impairment in the physical function and role-emotional impact score was found in Cushing’s syndrome survivors compared to the normal population [57^{***}].

Growth and development are affected by childhood Cushing’s syndrome; however, studies have shown differing outcomes in terms of final height and catch-up growth [58–60]. Individuals who develop Cushing’s syndrome during puberty or who have had a longer course of disease prior to receiving treatment are at higher risk of poor growth; early diagnosis and treatment of growth hormone deficiency, when appropriate, leads to optimal outcomes. In our recent study looking at skeletal maturity in 124 children with Cushing’s syndrome, we found the majority of patients had normal or even advanced skeletal maturation. When present, bone age advancement in Cushing’s syndrome is related to obesity, insulin resistance, and elevated adrenal androgen levels [61]. This finding may have significant implications for treatment decisions and final height predictions in these children. In children with Cushing’s disease, bone mineral density of the lumbar spine improved significantly after TSS, suggesting that osteopenia may be reversible [62].

A number of recent studies addressing the long-term outcome of Cushing’s syndrome treatment have been published; however, the majority focus on the adult population. In a large series examining mortality in 418 patients with Cushing’s syndrome with long-term follow-up, the mortality was significantly increased [standardized mortality ratio 9.3; 95% confidence interval (CI), 6.2–13.4, $P < 0.001$], even after apparently successful treatment. Children as young as 10 years of age at diagnosis were included in this study; however, the median age of the individuals was 40, making it difficult to draw conclusions relative to children alone [63^{*}]. In another large series of 318 patients, mortality was twice as high in

Cushing's syndrome patients (hazard ratio 2.3, 95% CI 1.8–2.9) compared with controls; mortality and risk of myocardial infarction remained elevated during long-term follow-up [64]. In a recent study examining the features influencing the outcome of surgery for pediatric Cushing's disease, 195 out of 200 patients (98%) achieved remission after surgery, whereas 8% of patients with at least 1-year follow-up had recurrence of disease after surgery [29].

CONCLUSION

Although many genes have recently been identified to account for the cause of adrenal hyperplasias leading to Cushing's syndrome, currently, very little is known about the involvement of genetic factors in Cushing's disease. The first-line therapy for Cushing's disease is neurosurgery at a center with expertise in TSS. In children, the optimal choice of second-line treatment is not always clear-cut and must be individualized to the specific patient. Post-treatment monitoring for disease recurrence, as well as for the comorbidities associated with hypopituitarism and cortisol excess, is mandated.

The use of whole-exome sequencing may serve to identify the additional genetic factors associated with Cushing's disease. The evaluation of Cushing's disease in children is challenging, particularly in the early stages, because the diagnosis is not obvious. Finding the genetic markers associated with Cushing's disease could make it easier for the clinicians to rule in or perhaps rule out the diagnosis. Further studies of targeted radiation modalities and medical therapies in children are necessary.

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KEY POINTS

- Cushing's syndrome is increasingly becoming identified as a genetic disease; clinicians need to be aware of the growing scope of genetic causes.
- Treatment of children with Cushing's syndrome presents many unique challenges and is best performed at a center with experience in the management of these patients.
- Post-treatment challenges for the child or adolescent treated for Cushing's syndrome include optimization of growth and pubertal development, normalization of body composition, and promotion of psychological health and cognitive maturation.
- Early identification of the morbidities associated with Cushing's syndrome is crucial for the improvement of long-term management of these patients.

FIGURE 1.

Algorithm for the management of children with confirmed Cushing's disease.