Quality of Life and Other Outcomes in Children Treated for Cushing Syndrome

Margaret F. Keil

Section on Endocrinology Genetics, Program on Developmental Endocrinology Genetics, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 20892

Context: Cushing syndrome (CS) in children is associated with residual impairment in measures of health-related quality of life, even after successful resolution of hypercortisolemia, highlighting the need for early identification of morbidities and improvements in long-term management of these patients.

Evidence Acquisition and Synthesis: A PubMed, Scopus, and Web of Science search of articles from 1900 onward identified available studies related to quality of life and complications of pediatric CS as well as important historical articles. This review summarizes studies through November 2012 and highlights recent developments.

Conclusions: A review of the literature identifies significant morbidities associated with CS of pediatric onset, which must not be treated in isolation. CS affects children and adolescents in many ways that are different than adults. Post-treatment challenges for the child or adolescent treated for CS include: optimize growth and pubertal development, normalize body composition, and promote psychological health and cognitive maturation. All these factors impact health-related quality of life, which is an important outcome measure to assess the burden of disease as well as the effect of treatment. Future research efforts are needed to improve management of the physical, psychological, and emotional aspects of this disease in order to diminish the residual impairments experienced by the pediatric CS patient population. ***(J Clin Endocrinol Metab* 98: 2667–2678, 2013)**

In the literature, the first pediatric-onset patient affected with Cushing syndrome (CS) was described by Dr Harvey Cushing as "Minnie G," who presented at age 23 years with onset of symptoms at age 16 years (abrupt cessation of menses, rounded face, abdominal stria, supraclavicular fat pad) (1). Dr Cushing performed a subtemporal decompression on this patient for "polyglandular syndrome," which is now known as a condition resulting from exposure to excess glucocorticoid. Since then significant progress has been made in our understanding of the etiology of CS, as well as the diagnosis, treatment, and management of patients affected with CS. As our knowledge and expertise in caring for patients affected by CS has advanced, the complexity of the disease and its pervasive effects demand our attention. Treatment success, as defined by remission of hypercortisolemia, often is accompanied by residual impairments that impact quality of life.

Prolonged exposure to excess glucocorticoids in childhood results in CS, which is a multisystem disorder characterized by truncal obesity, impaired linear growth, skin changes (acne, acanthosis, hirsutism, bruising, striae), delayed sexual development and amenorrhea (despite significant virilization and hirsutism), hypertension, glucose intolerance, and fatigue (Figure 1). In children, most cases of CS result from the exogenous administration of glucocorticoids (iatrogenic CS). Exogenous causes of CS include ACTH-secreting pituitary tumors, adrenal tumor(s), and rarely, ectopic ACTH or CRH-secreting tumors. In

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Abbreviations: BMD, bone mineral density; BMI, body mass index; CD, Cushing disease; CHQ, Child Health Questionnaire; CS, Cushing syndrome; HPA, hypothalamic pituitary adrenal; HRQL, health-related quality of life; LS, lumbar spine; PPNAD, primary pigmented nodular adrenocortical disease; TSS, transsphenoidal surgery.

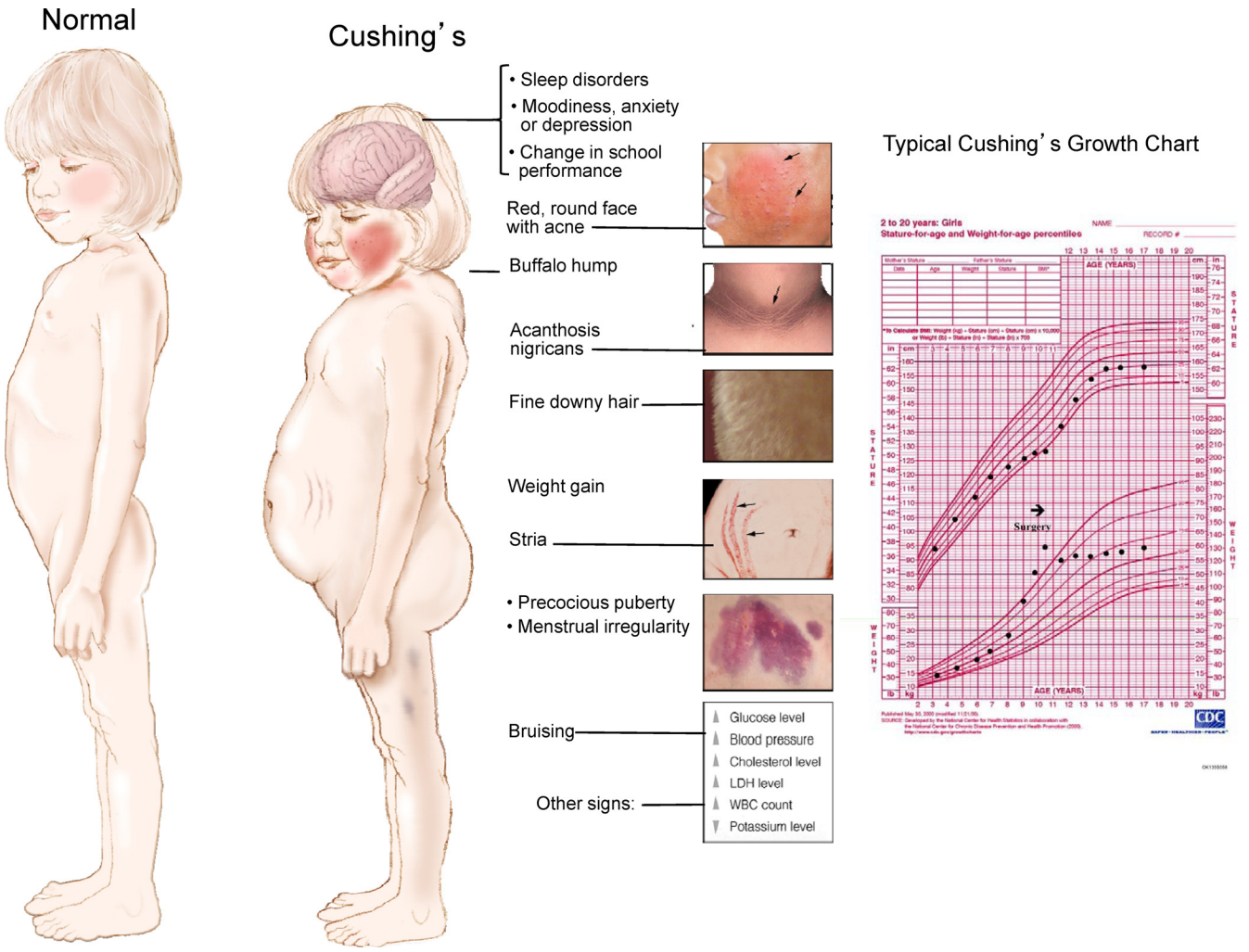

Figure 1. Clinical findings and typical growth chart in CS before and after treatment. The most common presentation in children is lack of height gain concomitant with persistent weight gain.

children and adolescents, symptoms that elicit the most concerns include: growth impairment, changes in physical appearance, fatigue/weakness, headaches, emotional lability, and sleep problems. The most common presentation in children is lack of height gain concomitant with persistent weight gain.

Etiology of Endogenous CS

ACTH-dependent CS

Corticotropinomas

In children and adolescents, an ACTH-secreting pituitary adenoma is the most common cause of endogenous CS in children over 7 years age. Similar to adults with CS, there is a female to male predominance that decreases with younger age. Data from large pediatric studies suggest that there may be a male to female predominance in prepubertal children (2, 3). Most pediatric ACTH-secreting tumors are microadenomas, although some macroadenomas have been reported in association with multiple endocrine neoplasia type 1. It may be that patients with multiple endocrine neoplasia type 1 and ACTH-secreting tumors can present with CS in childhood as GH- and prolactin-cosecreting adenomas (4), although there are very few cases to make any conclusive statements.

Ectopic CS

Ectopic causes of endogenous CS in children are extremely rare, with carcinoid tumors as the predominate etiology in children. Reported sites include bronchial, lung, thymic, thyroid, pancreas, renal, duodenum, pheochromocytomas, and neuroblastomas (2).

ACTH-independent CS

Adrenal causes of CS are the most common cause in children younger than 7 years, including adenoma, carcinoma, or bilateral hyperplasia. Adrenocortical neoplasms

account for 0.6% of all childhood tumors in young children. CS is a manifestation of approximately one third of all adrenal tumors, and unilateral adrenal tumors presenting with CS are associated with a high rate of malignancy (greater than 70%) in younger children (5, 6). There is a high prevalence of unilateral lesions; bilateral lesions are seen in 2 to10% of patients. Recent reports of bilateral nodular adrenal disease indicate that this cause of CS in childhood may occur more frequently than previously thought (6, 7).

Primary pigmented nodular adrenocortical disease (PPNAD) is a genetic disorder that in many cases is associated with Carney complex (syndrome of multiple endocrine gland overactivity, lentigines, and myxomas). Periodic, cyclical, or atypical CS is commonly seen in children and adolescents with PPNAD. In a large series of pediatric patients with adrenal CS, most PPNAD findings were associated with Carney complex (53%) and isolated micronodular disease with pigmentation (21%) (8). Other types of rare adrenal CS seen in children and adolescents include massive macronodular adrenal hyperplasia or bilateral macronodular or primary bimorphic adrenal disease (seen in McCune Albright syndrome, usually in infantile period). Aberrant cAMP signaling has been linked to almost all genetic forms of adrenal-dependent cortisol excess; for example, PPNAD is associated with mutations in the *PRKAR1A* gene (9).

Protocols for the evaluation and differential diagnosis of CS in children and adolescents are available (2, 10).

Long-Term Effects and Complications of CS in Childhood

Post-treatment challenges in caring for the child or adolescent treated for CS include: optimize growth and pubertal development, normalize body composition, and promote psychological health and cognitive maturation. This review of morbidities related to pediatric-onset endogenous CS addresses the following four categories: treatment-related, clinical, neuropsychiatric, and quality of life (Table 1).

Studies of outcome measures of treatment of CS typically include the frequency and duration of remission of hypercortisolemia, recovery of the hypothalamic pituitary adrenal (HPA) axis, and other clinical parameters (11). An important caveat in the interpretation of outcome measures of treated CS is the criteria used by a study to define cure of CS. In the immediate postoperative period, depending on the surgical center (2, 12–14), biochemical remission has been categorized as hypocortisolism if the persistent morning serum cortisol nadir is between <1.8 and 5 μg/dL, with serum morning cortisol < 2 μg/dL associated with low recurrence rates (15, 16). Measurement of 24-hour urine free cortisol is also reported in cases where serum cortisol levels are equivocal, with values < 20 μg/24 hours suggestive of remission (15). Long-term follow-up studies of patients treated for CS (ie, $>$ 1-y after treatment) typically define remission or cure as biochemical evidence of eucortisolemia, normal circadian rhythm,

Table 1. Summary of Outcomes and Long-Term Comorbidities Described in Children Treated for CS

	Outcome/Comorbidity	Refs.
Treatment related		
TSS	Partial/complete panhypopituitarism, neurocognitive decrement, recurrence of CS, pseudotumor cerebri	[2, 13, 14, 17, 22–29, 32–36]
Pituitary irradiation	Partial/complete panhypopituitarism, neurocognitive decrement, cranial neuropathies, tumors	[19, 37–39, 40–42]
Adrenalectomy	Adrenal insufficiency, Nelson syndrome	[8, 21, 27, 43–47]
Medical therapy	Recurrence of CS, hepatotoxicity, hypertension, hypokalemia, endometrial hyperplasia	[54–59]
Long-term clinical effects		
Growth	Compromised final height	[2, 8, 17, 32, 33, 60–62]
Metabolic	Increased BMI, visceral obesity, impaired glucose metabolism, hyperlipidemia	[2, 8, 17, 60–64, 73]
Cardiovascular	Hypertension, increased arterial rigidity	[2, 8, 65, 66, 73]
Bone	Osteopenia, osteoporosis, vertebral fractures, avascular necrosis, bone age perturbation	[2, 17, 60–63, 74, 75, 79, 81–84]
Other	Autoimmune disease, nephrolithiasis	[28, 85]
Cognitive and psychological	Cerebral atrophy, amygdala and hippocampus hypofunction, cognitive decrement, memory and concentration impairment, personality changes, depression or anxiety, decline in school performance	[17, 90, 93–95, 100–102]
Quality of life	Residual deficits in physical (physical function, role physical), or psychosocial scores (global health perception, parent emotional impact)	[101]

and/or recovery of the HPA axis (normal response to ACTH stimulation test, suppression of serum cortisol to low-dose dexamethasone) (14, 15, 17–19). Despite successful resolution of cortisol excess, physical recovery is often slow and/or incomplete, and it is not uncommon to find residual impairments, such as pituitary hormone deficiency, loss of final height, obesity, hypertension, cognitive decrement, osteoporosis/osteopenia, etc (20, 21). The persistence of physical and/or psychological impairments may affect quality of life, despite evidence of long-term biochemical remission of CS.

Treatment-related long-term effects

Transsphenoidal surgery

Studies of adults and children with Cushing disease (CD) report a wide range of success rates of transsphenoidal surgery (TSS) due to neurosurgeon expertise, definition of remission, and length of follow-up. Initial remission rates of 60–98% and long-term remission rates of 50–98% have been reported (mean follow-up range, 22 to 96 mo) (2, 14, 17, 22–29). Recent improvements in imaging technologies have augmented the success of TSS (30, 31).

TSS can lead to disruption of HPA function and may occasionally lead to partial or complete panhypopituitarism (2, 17, 32, 33). Studies of pediatric CD patients report an incidence of 19–25% of 1 or more endocrine deficiencies after initial TSS (diabetes insipidus, GH deficiency, central hypothyroidism, and central hypogonadism) (2, 17, 33). Mild suppression of thyroid function occurs frequently in children and adolescents before and for a few months after TSS, and typically resolves within 6 months (34). Recently, Lodish et al (35) reported in a large series of pediatric CD patients that the average time to recovery of HPA axis post-TSS was 12.6 ± 3.3 months and that early recovery of the HPA axis (within 6 mo) was associated with recurrence.

A recent retrospective review of 941 TSS (218 children) performed at 2 surgical centers identified 3% occurrence of pseudotumor cerebri in children (none in adults) noted within 1 year after successful cure of CD (36).

Pituitary irradiation

Pituitary irradiation was the treatment of choice for children with CD until TSS became widely available. There are a number of concerns related to the use of pituitary radiation in children and adolescents because the pituitary is radiosensitive and the surrounding neural tissue has not fully matured. Potential morbidities include: neurocognitive deficits, cranial neuropathies, hypopituitarism, and radiation-induced tumors (37–39).

Lack of long-term follow-up data is a major limitation in evaluation of treatment efficacy literature on radiotherapy (conventional, fractionated dose) and radiosurgery (stereotactic, high dose, single treatment) in children and adolescents. A seminal paper on the treatment of children with CD treated with external pituitary irradiation reported that remission was achieved in 12 of 15 patients within 18 months—with resumption of linear growth, normal gonadal function, no visual deficit, or deterioration in cognitive function (19). However, 3 patients required bilateral adrenalectomy for treatment failure. A recent review of this literature by Jagannathan et al (40) identified 5 studies with pediatric patients treated with radiotherapy (ie, conventional, fractionated dose), with a follow-up range of 18–56 months and remission rate ranges of 50–100%. Hypopituitarism was the major morbidity associated with radiotherapy, with GH axis being the most sensitive to late effects of treatment (19, 41).

There is a paucity of data on treatment outcomes using gamma knife irradiation or proton-beam irradiation in children or adolescents. The postulated advantage of radiosurgery is the ability to use higher dose radiation targeted to the tumor, with low exposure to normal pituitary tissue and surrounding vascular and neural structures. In a large series of adult and pediatric patients treated with radiosurgery for CD, remission of hypercortisolemia was achieved in 54% of patients, with a mean time to remission of 13 months, and post-treatment anterior pituitary hormone deficiencies were found in 22% of patients, most commonly hypothyroidism and GH deficiency (42).

Adrenalectomy

Surgical resection is the treatment of choice for benign adrenal tumor(s). Historically, transperitoneal or retroperitoneal approaches have been used, although laparoscopic adrenalectomy is preferred in eligible surgical candidates. Medical treatment with mitotane, an adrenocytolytic agent, may be used as an adjuvant therapy or in the case of an inoperable tumor. In some patients, glucocorticoid antagonists or steroid synthesis inhibitors are indicated to treat the hypercortisolism.

A recent retrospective study of operative management of CS secondary to micronodular adrenal hyperplasia (56% presented as children) reported no difference in cure rate between laparoscopic and open approaches, although open laparotomies were associated with higher morbidity. In studies of adult and pediatric patients, postoperative complications included acute renal failure, bacteremia, wound infection, bleeding requiring reoperation, and

pneumonia, whereas mortality from pancreatitis occurred for 1 pediatric patient (8). Long-term morbidity associated with bilateral adrenalectomy includes acute adrenal insufficiency that was usually associated with minor acute illness, and Nelson syndrome (8, 43–45).

Data from studies after curative resection of adrenal tumors in adult patients with CS report a median time of 9–15 months for symptom resolution (21, 46, 47). There is a paucity of data regarding symptom resolution after adrenalectomy for CS in children and adolescents.

Medical therapy

Regardless of the etiology of endogenous CS, surgery is usually the treatment of choice for children and adults. However, medical treatment may be indicated in instances when a patient may not be a surgical candidate, or with adjunctive therapy where remission of hypercortisolemia takes months to years, or in patients with acute potentially life-threatening complications of CS (eg, severe hypertension, psychosis, opportunistic infections) (48–50). Options for medical treatment of CS include pituitary-targeted therapies (ie, dopamine or somatostatin analogs, glucocorticoid or progesterone antagonists), or adrenal-targeted therapies (ie, adrenal steroidogenesis inhibitors: mitotane, etomidate, metyrapone, ketoconazole). Studies of pituitary-directed therapies (eg, pasireotide, cabergoline) report success in approximately 25–30% in adult patients with CS (49, 51–53); however, there is a paucity of data regarding their use to treat children with CS. Adrenal steroidogenesis inhibitors are useful agents to control cortisol levels; however, limitations of ketoconazole or mitotane include a need for dose escalation to control cortisol blockade, tolerability, and hepatic toxicity (54–56). Recently, mifepristone (a progesterone receptor antagonist with glucocorticoid receptor antagonist activity at higher doses) was approved by the Food and Drug Administration (FDA) for treatment of adults with CS to control hyperglycemia (57). Studies of mifepristone to treat adults with CS show improvement in clinical, metabolic, and psychosocial outcome measures (57). Potential serious side effects include worsening of hypertension, hypokalemia, and endometrial hyperplasia. There are limited data on the use of medical therapies to treat CS in children and adolescents (58, 59). Currently, mifepristone is the most promising option for long-term medical treatment of refractory CS in children because safety and efficacy data are available, and it was recently approved by the FDA for treatment of adults with CS.

Clinical effects of childhood-onset endogenous CS

Growth and metabolic

Catch-up growth, final height, and body mass index (BMI) standard deviation scores are the most commonly reported outcome measures after surgical cure of CS in children and adolescents. Factors affecting catch-up growth include GH deficiency post-cure and long-term effects of chronic hypercortisolemia on pituitary and growth plate physiology (60, 61). A retrospective review by Magiakou et al (60) of children with CS (CD = 50, adrenal disease = 6, ectopic = 3) reported that 1 year after cure most children had decreased body weight and body mass, and their height and growth velocity increased. However, final adult height was compromised compared to midparental height (60). These and other reports suggest that early-onset CS may increase the risk for compromised final height (17, 60). Although studies of adults with CS report a high rate of vertebral fractures, in children with CS there is a paucity of data—primarily case studies and clinical observations—so vertebral fractures may be an unrecognized factor in compromised final height in this population (62). Children and adolescents with poorer than expected catch-up growth after treatment of CS should undergo testing to confirm ongoing remission of hypercortisolemia and evaluation of GH axis recovery.

Normalization of body composition in children and adolescents after cure of CS may not occur (17, 62, 63). Davies et al (62) followed 14 children with CD treated with TSS and pituitary radiotherapy and noted that the majority attained sufficient catch-up growth to reach within range of target height; although BMI standard deviation scores decreased from time of diagnosis, they remained greater than the normal population at 3.9 years after cure. This is consistent with other studies of CD in children and adolescents reporting that total body fat, ratio of visceral to sc fat, and waist circumference remained elevated (63, 64). In a study of children with adrenal causes of CS, height and weight for age improved at 1-year follow-up (mean follow-up was 6.7 $\pm$ 1.2 y); however, weight-for-age remained above average for 74% of patients 1 year after bilateral adrenalectomy (taking standard glucocorticoid and mineralocorticoid replacement doses), suggesting that normalization of waist circumference and body weight does not typically coincide with resolution of hypercortisolemia (8). Similar to what has been reported in adults, adverse long-term effects of chronic hypercortisolemia include residual negative effects on waist circumference and BMI standard deviation after cure of endogenous CS. There is a need for long-term follow-up studies to elucidate any differences in long-term effects of childhood-onset CD vs adrenal CS on growth, BMI, and risk for metabolic syndrome.

Hypertension is a common finding in children with endogenous CS, with an incidence of up to 60% (2, 17). Prior studies of childhood-onset CS report an incidence of 44–74% of systolic hypertension and approximately 25% of diastolic hypertension (65, 66). There is a paucity of data on long-term follow-up of blood pressure in children treated for CS. Several studies report a significant improvement of blood pressure in the immediate postoperative period and at 1-year follow-up. Recently, Lodish et al (66) reported that systolic hypertension persisted in 16% of CD and 21% of ACTH-independent CS, and diastolic hypertension was found in approximately 4% of all pediatric patients 1 year after cure (66). In this series, hypertension appeared to be related to the degree of hypercortisolemia pretreatment. Of note, 2 patients suffered serious hypertension-related sequelae (multiple infarcts, hypertensive encephalopathy). The finding of residual hypertension in a significant number of children after cure of CS may be due in part to vascular remodeling and/or genetic factors, and it highlights the importance of follow-up of cardiovascular morbidity associated with hypertension.

Almost all patients affected with CS are obese or overweight and have abdominal visceral adiposity, and many have findings consistent with metabolic syndrome, including glucose metabolism abnormalities, hypertension, and/or hyperlipidemia. Studies of adults treated for CS report an increased incidence of diabetes and premature atherosclerosis and increased morbidity, especially cardiovascular, compared to general population. Studies of adults with CS report increased risk of metabolic syndrome due to the presence of interrelated risk factors including hypertension, dyslipidemia, increased waist circumference, and insulin resistance (67–72). A prospective study by Faggiano et al (72) reported an increased incidence of residual metabolic syndrome, vascular damage, and atherosclerotic plaques 1 year after disease remission in adults with CS. There is a paucity of data on late effects of childhood-onset endogenous CS on risk for the development of metabolic syndrome. Recently, Bassareo et al (73) reported early markers of cardiovascular dysfunction and decreased arterial distensibility associated with abnormal 24-hour ambulatory blood pressure levels in young girls after surgical cure of CS.

Bone

The detrimental effect of chronic exposure to excess glucocorticoids on bone and collagen turnover is well established (17, 32, 63, 74, 75). Osteopenia is a common finding in adults with CS, with a prevalence of approximately 30–50% (74, 76–79). In pediatric CS, osteoporosis is the result of a multifactorial process, including effects of excess glucocorticoid on bone, hypogonadism, GH deficiency, and decreased calcium absorption and renal calcium reabsorption (80). Because bone mass acquisition occurs during puberty, delayed puberty and hypogonadism are associated with decreased bone density (17, 60). There are few long-term studies regarding bone effects of CS in children before and after treatment. Several small studies report impaired bone mineral density (BMD) before treatment of CS, with dramatic improvement 3–4.5 years after remission of hypercortisolemia (17, 81). In a prospective study of children with CD, the prevalence of osteopenia in the lumbar spine (LS) and femoral neck was 38 and 23%, respectively, with the average BMD z-score of the LS lower than the femoral neck (82). Follow-up of these patients 12–18 months after successful cure of CD showed a significant improvement in LS BMD z-sores, which is consistent with studies of adults with CS that report a more pronounced effect on trabecular vs cortical bone (74, 82–84).

Bone age in children at presentation has been reported to be on time, delayed, or, less frequently, advanced and may reflect the combined effects of cortisol, which has an inhibitory effect, and adrenal androgens/gonadal steroids, which should have a stimulatory effect (2, 60, 62).

Other

Resolution of hypercortisolism has been associated with the emergence or exacerbation of autoimmune disease, such as Hashimoto's thyroiditis, Graves' disease, celiac, and vitiligo (28). Nephrolithiasis has been reported in approximately 15–50% of adult patients with CS (85), and this risk is associated with coexisting factors, such as systemic hypertension, high BMI, and hyperuricosuria. Although the risk of nephrolithiasis decreases, it remains a concern after cure.

Cognitive and psychological

It is well established that excess glucocorticoid exposure affects brain function and mood. Memory, attention, and/or concentration deficits have been reported in studies of adults with active CS (86–91). Cerebral atrophy has been reported in a few studies of adults with CS, and Bourdeau et al (92) noted that it was partially reversible in some patients. In addition, experimental models have shown that prolonged exposure to excess glucocorticoids is toxic to hippocampal neurons due to the high concentration of glucocorticoid receptors (93–95), which likely has a role in the changes in cognitive function in patients with CS. Studies of long-term follow-up of adults with remission of CS report general improvement in cognitive function; however, residual impairment in visual and verbal memory has been reported (96–99).

In children and adolescents, excess glucocorticoid exposure appears to have different effects on the brain than what is described in adults. In a large series of children and adolescents, Merke et al (100) identified cognitive decline despite reversal of brain atrophy after remission of CS, and psychopathology was not reported. Compared to adults affected with CS, verbal and performance IQ scores have been reported to decline after resolution of CS (90, 100, 101), with younger age at first evaluation associated with greater deterioration in IQ scores from pre- to post-treatment (Figure 2). In addition, Maheu et al (102) reported altered amygdala and hippocampus function in adolescents with CS compared to healthy controls that was not associated with affective or memory systems, which contrasts with findings of studies of adults with CS. Results of these studies highlight the importance of additional research to investigate the role of age and related brain maturational stage and exposure to chronic excess glucocorticoids.

Numerous studies of adults with CS report a high incidence of psychopathology, most commonly depression and/or major affective disorder, with gradual improvement of symptoms after correction of hypercortisolism and recovery of the HPA axis (103–109). Although there is evidence to suggest that symptoms of depression abate with remission of hypercortisolism, a significant number of patients experience residual psychological sequelae, which highlights the need for prospective studies of psychopathology in adults with CS (98, 99, 110, 111). In a large series of children/adolescents with active CS, Devoe et al (17) reported personality changes in 23–29%. In children and adolescents, typical personality changes include: compulsive behavior, overachievement in school, moodiness, and irritability (2, 17, 100, 101), although there are case reports of significant psychopathology, including mania and psychosis (112, 113). There is a paucity of data regarding neuropsychiatric sequelae in children and adolescents treated for CS

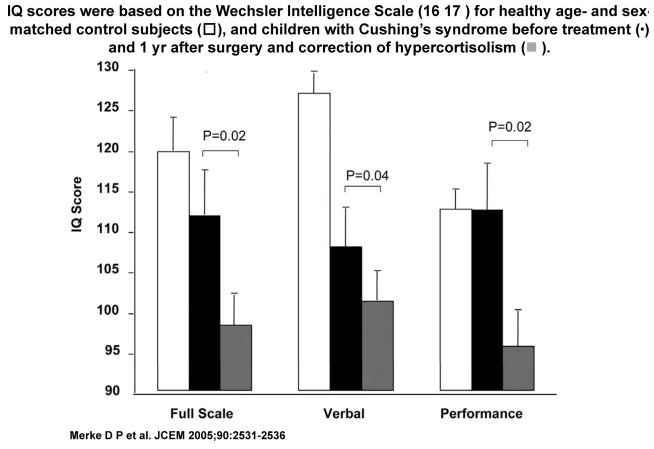

Figure 2. IQ scores were based on the Wechsler Intelligence Scale for healthy age- and sex-matched control subjects (white bars), and children with CS before treatment (black bars), and 1 year after surgery and correction of hypercortisolism (gray bars). The T-bars indicate standard error values (100).

Quality of life

It is well established that CS is debilitating both physically and mentally, and often emotionally. The development of a chronic illness in childhood often impacts both the achievement of normal developmental tasks of childhood and the child's ability to perform age-appropriate activities of daily living as well as the ability of the family to function. Quality of life assessment is an important outcome measure to assess the impact of a chronic illness, such as CS, as well as the effect of any treatment. Quality of life in pediatrics has been defined by the Committee of Evaluation of Children's Health of the National Academies of Sciences and the Institute of Medicine as the extent to which children are able (or enabled) to develop their potential, satisfy their needs, and develop their ability to interact with their biological, physical, and social environments (http://www.iom.edu/Reports/2011/Child-and-Adolescent-Health-and-Health-Care-Quality/Report-Brief.aspx). Many health-related quality of life (HRQL) tools are available that include an assessment of the patient's sense of well-being and physical, emotional, social, and intellectual function.

HRQL in CS is influenced by many factors, including physical and psychological changes, as well as the direct effect of glucocorticoids on the brain. There are few prospective studies of quality of life in adults with CS and a paucity of studies with children. A majority of studies of quality of life in adults with CS use a generic quality of life questionnaire, such as the Short Form-36 (SF-36) (15), often in conjunction with assessment of mental state and/or cognitive function. One advantage of a generic HRQL tool, such as the SF-36, is the ability to compare the patient population of interest to healthy normative controls, as well as to patients with other common chronic conditions (ie, asthma, headache). In studies of adults with active CS, control groups typically include patients with other types of pituitary tumors and/or published population normative controls.

Studies of quality of life in adults after cure of CS report residual impairment in physical and social functioning and limitations in their ability to perform normal activities of daily living due to physical and emotional problems, pain, and general feeling of health (11, 16, 21, 43, 52, 99, 104–106, 114–116). Low scores did not correlate with the severity of disease or the time elapsed since treatment (106, 117) except for physical function scores, which the time since treatment did

show had an effect (114). Studies differ in findings related to whether panhypopituitarism or adrenal insufficiency influenced quality of life scores likely due to variables such as sample size, length of follow-up, and quality of life questionnaire utilized (99, 106, 117).

Recently, 2 groups developed CS-specific quality of life assessment tools for adults (117–119). The first CS-specific questionnaire, the CushingQoL, was developed by Webb (120). This is a unidimensional instrument that demonstrated significant correlation to the patients' perceived health, clinical parameters, and SF-36 scores. However, a limitation of tools with global scores is a lower sensitivity to detect changes in the multifactorial mechanisms involved in determining HRQL, which is relevant to direct intervention(s). Recently, Milian et al (119) developed a tool for patients with CD that includes 6 subdomains correlated with quality of life, including depression, sexual activity, environment, eating behavior, bodily restrictions, and cognition. Interestingly, correlation was noted between 24-hour urine free cortisol levels and cognition subscale scores before treatment. These tools are welcome additions to the field of research in patients with CS to address aspects of disease and impact of treatment of concern to this patient population. However, neither questionnaire was developed or validated for use with children or adolescents with CS.

To date, there is only 1 prospective study of quality of life in children and adolescents with CS, which reported that active CS was associated with low summary scores (using the Child Health Questionnaire [CHQ]) (121) for both physical and psychosocial measures (compared to age-matched U.S. population norms) (101) (Figure 3). Despite improvement from before cure to 1 year after cure, residual impairment persisted in several quality of life measures. After cure, the subscale domains that remained significantly below the normative data included physical function, role-physical, global health perception, and emotional impact. Incomplete recovery of the HPA axis (measured response to ACTH stimulation test) at 1 year after cure was associated with impairment of scores for physical function, global health perception, physical summary, and emotional impact (parent) (3). In addition, BMI standard deviation scores 1 year after treatment were a significant predictor of residual impairment in physical function score. This finding is consistent with studies of healthy obese adolescents, where there is an inverse relationship between BMI SD and physical function score (101, 122).

Data from the developers of the CHQ report that the time and emotional impact parent scales are considered the most sensitive to both physical and psychosocial

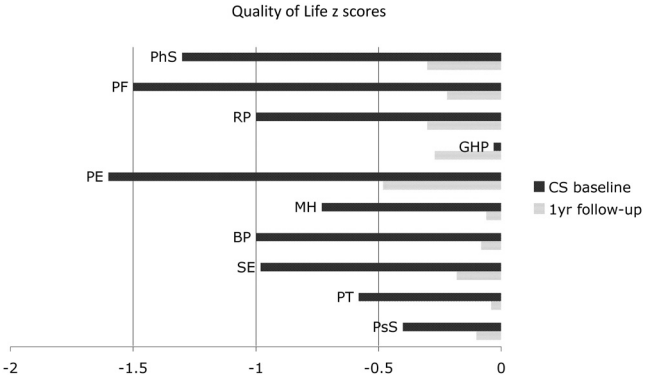

Figure 3. Before and 1 year after treatment CHQ (quality of life tool) individual domain z-scores in 40 children with CS treated with either TSS or adrenalectomy. Results are expressed as z-scores compared to age-matched normative data from the U.S. population. The CHQ domains represented are those that showed significant improvement from before to after treatment and include: physical summary score (PhS), physical function (PF), role-physical (RP), global health (GHP) (note: GHP was the only score that declined from before to after treatment), emotional impact on parent (PE), mental health (MH), bodily pain (BP), self-esteem (SE), time impact-parent (PT), and psychosocial summary score (PsS). $P < .05$ for differences between all domains and U.S. norms before treatment; $P < .01$ for differences between PhS, PF, RP, GHP, and PE post-treatment scores and U.S. norms (101).

outcomes of children because chronic illness affects not only the patient but also the entire family (121). Keil et al (101) reported residual impairment in parent scores for emotional impact 1 year after treatment, which suggests that parents of children recovering from CS express a great deal of unresolved emotional concern as a result of this disease. Interestingly, global health perception scores were the only subscale scores that declined from before to after treatment, which is likely related to the unresolved emotional concern of the parent, experience of surgery, and period of recovery between pre- and post-measures.

Conclusion

The available evidence provides support to show that children and adolescents treated for CS experience residual impairments after successful treatment and that many of the morbidities related to CS are manifested differently in the growing child compared to adults. Future research is needed to identify improvements in the management of the physical, psychological, and emotional aspects of this disease in order to reduce residual impairments experienced by the pediatric CS patient population. The identification of additional factors that contribute to diminished HRQL in pediatric-onset CS may lead to a revised paradigm of care for clinicians.

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Address all correspondence and requests for reprints to: Margaret F. Keil, PhD, Program on Developmental Endocrinology Genetics, National Institute of Child Health and Human Development, National Institutes of Health, Building 10, CRC, Room I-3330 (East Laboratories), 10 Center Drive, MSC1103, Bethesda, Maryland 20892. E-mail: keilm@mail.nih.gov.

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