Cases of Psychiatric Morbidity in Pediatric Patients After Remission of Cushing Syndrome

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Endogenous Cushing syndrome (CS) may have different effects in children than what has been described in adults. Previous studies of children and adolescents with CS have identified cognitive decline despite reversal of brain atrophy after remission of CS. Although the observations of parents of children and adolescents with CS support personality changes, significant psychopathology has not been described in the literature. We report 9 children who underwent successful surgery (transsphenoidal surgery [TSS] or resection of bronchial carcinoid) for treatment of CS and subsequently developed significant affective pathology. Affective symptoms included anger–rage outbursts, suicidal ideation, irritability, anxiety, and depression. One child, who committed suicide 60 months after TSS, had recently discontinued antidepressant medication. She had a history of anxiety during active CS and was treated with an anxiolytic. The 7 patients with onset of symptoms within 7 months of TSS were on glucocorticoid replacement, and 1-year follow-up evaluation showed recovery of hypothalamic–pituitary–adrenal axis and biochemical evidence of remission. The 2 patients who presented with onset of symptoms at 48 months or later underwent endocrine evaluation that showed biochemical evidence of remission and normal anterior pituitary hormone levels. This is the first report of affective symptoms and behavioral dysregulation, including suicidal ideation, in a subgroup of children and adolescents after remission of CS. Health care providers caring for children with CS who have been cured should continue to screen for mental illness, monitor for changes in behavior, and refer as appropriate to mental health professionals.

Cushing syndrome (CS) is a multisystem disorder characterized by obesity, impaired growth, and cognitive and neuropsychiatric changes. In children, CS most often results from the exogenous administration of glucocorticoid. Endogenous causes of CS include adrenocorticotrophic hormone (ACTH)-secreting pituitary adenomas, adrenal tumors, or rarely, ectopic (ACTH) or corticotropin-releasing hormone–producing tumors.

CS affects children in many ways that are different from adults and is associated with residual impairment in quality of life (QoL) even after remission of hypercortisolemia.^{1,2} Adults with CS typically experience cognitive decrements; however, it is unusual for children to report problems. Also, studies in adult patients report improvements in cognitive function after remission of CS, whereas children may experience cognitive decrement³ (Table 1). Although the observations of

abstract

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Dr Keil participated in clinical data collection and analysis and drafted and revised the initial manuscript; Drs Zametkin, Lodish, and Stratakis saw the patients and critically reviewed and revised the manuscript; Ms Ryder participated in clinical data collection and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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TABLE 1 Comparison of Affective Symptoms and Cognitive Function Before and After Remission of Hypercortisolemia in Adults and Children

		Adult	Ref. No.	Pediatric	Ref. No.
Active CS	Affective symptoms	Depression, irritability, hypomania, mania, anxiety, panic, alcohol abuse, suicidality	4–7, 8–14	Irritability, moodiness, personality changes, labile affect, obsessive–compulsive behavior	1,3,15,16
	Cognitive function	Memory impairment, concentration difficulty, impaired performance on standard IQ measures	5,12,17, 18–22	Overachievement in school; No impairment in standard IQ and cognitive measures compared with controls	3,16,23
Remission CS	Affective symptoms	Amelioration of depression and affective symptoms; Residual anxiety, depression; Drug abuse, suicidality	4,24–28	No clinically significant psychopathology. Decreased prevalence of patient reported symptoms related to psychosocial health. Moodiness	1,3
	Cognitive function	Improvement in memory and concentration; Impaired cognitive function compared with controls	19,20,29	Decrement in standard IQ measures (magnitude of change associated with age at first evaluation); Problems with school performance; Difficulty with attention, memory, and concentration	1,3,16,23

TABLE 2 Clinical Characteristics of Patients Before Surgery

Subject	Age Before Surgery, y	Gender	CS Duration, y	Midnight Serum Cortisol, mcg/dL	Ht z Score	BMI z Score	Tanner Stage	School Grades
1	12.3	F	2	14.2	−2.1	0.85	II	A
2	13.9	M	2.5	14.7	−2.2	2.4	I	A
3	10.5	M	2	15	−1.1	2.4	I	A
4	8.6	F	2	11.5	−0.7	2.5	II	A
5	13	M	3	13.2	−2.1	2.6	II	A–B
6	15.8	M	1	23	−0.7	2.0	IV	A, recent decline
7	13.4	F	1.5	24.6	−1.5	1.0	III	Homeschool, doing well
8	12	M	2.5	19.9	−0.5	1.75	II	A
9	16.9	F	8	8.2	−1.9	2.29	V	A

parents of children with CS support personality changes, significant psychopathology has not been described.

We report 9 children (5 male, 12.9 ± 2.5 years old), who underwent successful surgery (transsphenoidal surgery [TSS] [8 children] or resection of bronchial carcinoid [1 child]) for treatment of ACTH-dependent CS and subsequently developed significant affective symptoms after resolution of hypercortisolemia. Affective symptoms included anger–rage outbursts, suicidal ideation, irritability, anxiety, and depression. Children also reported cognitive changes and a decline in school performance. This is the first documentation of suicidal ideation

after surgical cure of CS in children and adolescents.

SUBJECTS AND CLINICAL PROTOCOL

All patients were enrolled in a National Institutes of Health clinical trial (97-CH-0076) for evaluation and treatment of ACTH-dependent CS between 2003 and 2014 (total number of pediatric patients with CS evaluated = 149). CS was confirmed as previously described³⁰ and was confirmed by histology. Serum cortisol was measured starting on day 2 postoperatively. Dexamethasone (glucocorticoid replacement [GR]) was administered starting day 6 until discharge, when hydrocortisone was initiated. All patients were

defined as cured of disease by postoperative serum cortisol (<3 mcg/dL) or adrenocortical insufficiency, for which they received GR.^{31–34} Clinical evaluation 1 year postoperatively showed recovery of the hypothalamic–pituitary–adrenal (HPA) axis after GR (patients 1–6). Tables 2 and 3 summarize the clinical characteristics of the subjects before and after surgical cure.

Case Histories

Patient 1

A 12-year, 3-month-old white girl with CS underwent TSS. Preoperative symptoms included anxiety, depression, and mood swings; an antidepressant was prescribed. After surgery, she complained of fatigue, difficulty concentrating, anxiety, and

TABLE 3 Clinical Characteristics of Patients After Surgical Cure

Subject	Age at Follow-Up, y	Gender	8 AM Cortisol Serum, mcg/dL	HPA Axis Recovery at 1 y	Ht z Score	BMI z Score	Tanner Stage	Endorse Academic Difficulty	Parent Report of Mood–Behavior Disturbance, Postoperative mo
1	13.4	F	23	+	−2	−0.3	II	+	60
2	14.9	M	8.5	+	−1.3	0.9	III	+	48
3	11.7	M	3.4	+	−0.8	1.9	II	+	4
4	9.6	F	7.7	+	−0.05	1.7	II	—	4
5	14	M	2.3	+	−2.1	0.5	III	+	7
6	16.7	M	11.1	+	−0.5	0.8	IV	+	5
7	14	F	<1	n/a	−2	0	III	—	2
8	12.7	M	<1	n/a	−0.62	1.6	II	+	4
9	17.3	F	1.6	n/a	−1.9	2.2	V	+	3

Age at follow-up (years); HPA axis recovery at 1 year (+ biochemical evidence of HPA axis normalization); Endorse academic difficulty (+ patient endorsed problem with academic performance); —, patient denied problem with academic performance); n/a, not available.

depression. Her symptoms worsened 6 years later. Symptoms improved with antidepressant medications and counseling. However, she discontinued the antidepressant medications and 6 months later committed suicide by asphyxiation. Family history is significant for maternal diagnosis of anxiety disorder.

Patient 2

A 14-year, 9-month-old white boy with CS underwent TSS. Preoperatively he endorsed mild depressive symptoms. Five years postoperatively he developed symptoms of depression and was admitted to an inpatient psychiatric facility for suicidal ideation. There is a positive maternal family history of anxiety and depression.

Patient 3

An 11-year, 7-month-old white boy with CS underwent TSS. Four months postoperatively, he developed episodes of anxiety, depression, and suicidal ideation. A child psychiatrist evaluated him and psychological support was initiated.

Patient 4

A 9-year, 6-month-old white girl with CS underwent TSS. Four months postoperatively, she developed episodes of irritability, anger–rage outbursts, and suicidal ideation. A child psychologist evaluated her, and counseling

was initiated. Family history is significant for paternal diagnosis of anxiety disorder.

Patient 5

A 14-year-old black boy with CS underwent TSS. After surgery he experienced episodes of irritability and anger–rage outbursts, which resulted in a school suspension. He verbalized suicidal ideation. He was evaluated by a child psychologist and received counseling. He acknowledged marijuana use after surgery.

Patient 6

A 16-year, 7-month-old Asian boy with CS underwent TSS. He noted a decline in school and athletic performance several months before surgery, which did not improve postoperatively. Seven months after surgery he developed irritability and anger outbursts and verbalized suicidal ideation.

Patient 7

A 13-year, 4-month-old Hispanic girl with ACTH-dependent (ectopic) CS due to bronchogenic carcinoma underwent surgical excision at primary hospital and then was referred to the National Institutes of Health; she underwent a second surgery a month later. Postoperatively, she reported mood swings, irritability, and depression and sought mental health services; her antidepressant dosage was

increased. Three months after discharge she attempted suicide by taking an overdose (acetaminophen) and was admitted to a psychiatric unit. She received a diagnosis of major depressive disorder and was referred to group therapy. She had a previous history of suicidal ideation at 9 years of age. Family history is significant for suicide of a paternal grandparent and suicidal ideation of her father.

Patient 8

A 12-year-old white boy with CS underwent TSS. Four months postoperatively, he developed episodes of severe mood swings, irritability, depression, and suicidal ideations. The patient underwent psychiatric evaluation, and psychological support was initiated. Family history is significant for paternal diagnosis of anxiety disorder.

Patient 9

A 16-year, 9-month-old black girl with CS underwent TSS. Three months postoperatively, she developed irritability, severe depression, difficulty with concentration and schoolwork, and suicidal ideation. She underwent psychiatric evaluation, and psychological support was initiated. Her family history includes an

aunt diagnosed with an affective disorder.

DISCUSSION

There is substantial evidence that adults with CS suffer a high incidence of psychopathology, most commonly depression or affective disorder, with gradual improvement of symptoms after remission and recovery of the HPA axis.^{4,17} However, many patients do not achieve a premorbid level of functioning and experience persistent impairment of QoL and cognitive function.^{24,35} Brain morphologic changes, including cerebral atrophy and decreased hippocampal volume associated with cognitive decrement and depressive symptoms, have been reported in adults with active CS and are partially reversible after cure.^{5,36,37} These data highlight the need for prospective research to investigate the long-term psychological and cognitive morbidities.

In children, excess glucocorticoid exposure appears to affect the brain differently. Children with CS were described to have compulsive behavior, with overachievement in school.^{3,15,16} Studies of children with CS have reported alterations in behavior such as compulsivity, emotional lability, irritability, and depression.^{15,16} In contrast to adults, a large pediatric series reported cognitive decrement after cure of CS despite reversal of brain atrophy, with younger age at first evaluation associated with greater deterioration in IQ scores.³

As with hypertension in CS, factors other than hypercortisolemia may play a role in the etiology of cognitive and psychological changes, including genetic predisposition, developmental changes (ie, puberty), multiple hormone imbalances, neuronal changes, and alterations in gene expression and protein synthesis.³⁸ Brain morphologic changes, such as altered amygdala and hippocampal function in

adolescents with CS that were not associated with memory impairments, contrast with adult studies.²³ Puberty is also associated with an increased incidence of mood disorders. Two patients were prepubertal, 5 were early to midpuberty, and 2 were in late puberty; all had normal pubertal progression after treatment. There is a paucity of data regarding neuropsychiatric sequelae in children treated for CS and a need for prospective studies to formally evaluate for psychopathology.

In adults with active CS, suicidal ideation has been reported in ~17% of subjects, and although psychopathology was associated with elevated cortisol levels, it was not uncommon for a delay in resolution of psychiatric symptoms for months or years after resolution of the hypercortisolemia.^{6,7} Also, there is evidence that adults and children endorse compromised QoL measures for many years after resolution of CS.^{1,2,24–26,35,39,40} Experimental models have demonstrated long-term changes in neuronal function caused by excess glucocorticoid exposure,^{41,42} and this mechanism has been suggested as a possible cause of neurocognitive sequelae.

In our cohort of patients, 6% of children experienced suicidal ideation after surgical cure (of a total of 141 who had sustained remission). The 3 children with suicidal ideation and either a suicide attempt or psychiatric hospitalization endorsed emotional disturbance (anxiety, depression [3 children], and suicidal ideation [1 child]) in the prodromal phase of CS. Two developed psychiatric symptoms 48 to 60 months after surgical cure, and the third developed behavioral disturbances within 3 months postoperatively, while taking GR. Six of the 9 children in this cohort had a family history of affective disorder, including 1 who had a family history of suicide. None had

clinical evidence of recurrence. These data are consistent with known risk factors that are significant predictors of suicidal ideation among adolescents: history of mood disorder, previous suicide attempt, chronic illness, and family history of mood disorder or suicide. We did not formally evaluate for psychopathology throughout the follow-up period in this cohort; however, we previously reported (including some patients in this cohort) that 1 year after remission, despite improvement, there was residual impairment in QoL, emotional health concerns, and cognitive decrement (particularly in younger children).¹

Risk factors for suicide in the general population include personal or family history of suicidal ideation, mental disorders, history or trauma or abuse, impulsive or aggressive tendencies, serious medical illness or pain, and other factors.⁴³ Indeed, 1 child in this group had a previous history of suicidal ideation and attempted suicide 3 months after surgery, and 6 children had relatives with a diagnosis of affective disorder.

Patients prescribed exogenous steroids for autoimmune or antiinflammatory medical conditions report similar neuropsychiatric side effects, including irritability, fatigue, mood changes, insomnia, and difficulty with concentration and attention,^{38,44,45} that typically resolve after discontinuation of glucocorticoid medication. However, because of the variability in underlying medical disease and amount and type of glucocorticoids used, it is difficult to make causal inferences. In our cohort of patients, it is unlikely that behavioral symptoms were caused by overreplacement with glucocorticoid because 4 were either off GR completely or taking a dosage ≤ 8 mg/m² per day at the time of report of concerns about behavior. It is possible that cortisol withdrawal syndrome may have been a contributing factor. It is

unlikely that mild growth hormone deficiency, as has been reported to persist up to 1 year after surgical cure of CS, contributed significantly to the behavioral symptoms, because patients had normal insulin-like growth factor-1 levels and experienced significant catch-up growth during the first postoperative year. In addition, all patients were euthyroid 1 year after surgical cure. However, it is possible that normalization of the HPA axis may unveil or trigger psychopathological manifestations not precipitated by hypercortisolemia or vice versa.³⁸

CLINICAL IMPLICATIONS

Clinicians caring for children with CS should provide anticipatory guidance that after surgery, mood and behavior may not normalize for months or years. It is imperative for clinicians to carefully review the psychosocial history, including a family history of mental illness and suicidal ideation, because patients may not spontaneously mention neuropsychiatric symptoms. Health care providers should screen for risk factors for suicide and suicide ideation in children with CS and refer to mental health professionals.

These case reports highlight the need for controlled prospective studies with validated measures of psychopathology.

ABBREVIATIONS

ACTH: adrenocorticotrophic hormone
CS: Cushing syndrome
GR: glucocorticoid replacement
HPA: hypothalamic-pituitary-adrenal
QoL: quality of life
TSS: transsphenoidal surgery

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