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

Margaret F. Keil, PhD, CRNP, a Alan Zametkin, MD, b Celia Ryder, MS, RN, c Maya Lodish, MD, d Constantine A. Stratakis, D(med)Sci d

aProgram on Developmental Endocrinology & Genetics and Pediatric Endocrinology Inter-institute Training Program, National Institute of Child Health & Human Development, National Institutes of Health, Bethesda, Maryland; bPrivate practice, Kensington, Maryland; and cClinical Center Nursing Department, National Institutes of Health, Bethesda, Maryland

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.

This trial has been registered at www.clinicaltrials.gov (identifier NCT00001595).

DOI: 10.1542/peds.2015-2234

Accepted for publication Dec 21, 2015

Address correspondence to Margaret F. Keil, PhD, CRNP, 10 Center Drive, Building 10, NIH–Clinical Research Center, Room 1-3330, MSC1103, Bethesda, MD 20892. E-mail: keilm@mail.nih.gov

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2016 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported by the Intramural Research Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Funded by the National Institutes of Health (NIH) Intramural project Z01-HD-000642-04 to Dr. Stratakis.


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 adrenocorticotropic 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 hypercortisolism.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...
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 hypercortisolism. 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 described 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. 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 depression.
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. Family history is significant for paternal diagnosis of anxiety disorder.

**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

---

**TABLE 3 Clinical Characteristics of Patients After Surgical Cure**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age at Follow-Up, y</th>
<th>Gender</th>
<th>8 am Cortisol Serum, mcg/dL</th>
<th>HPA Axis Recovery at 1 y</th>
<th>Ht z Score</th>
<th>BMI z Score</th>
<th>Tanner Stage</th>
<th>Endorse Academic Difficulty</th>
<th>Parent Report of Mood–Behavior Disturbance, Postoperative mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13.4</td>
<td>F</td>
<td>23</td>
<td>+</td>
<td>−2</td>
<td>−0.3</td>
<td>II</td>
<td>+</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>14.9</td>
<td>M</td>
<td>8.5</td>
<td>+</td>
<td>−1.3</td>
<td>0.9</td>
<td>III</td>
<td>+</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>11.7</td>
<td>M</td>
<td>3.4</td>
<td>+</td>
<td>−0.8</td>
<td>1.9</td>
<td>III</td>
<td>+</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>9.6</td>
<td>F</td>
<td>7.7</td>
<td>+</td>
<td>−0.05</td>
<td>1.7</td>
<td>II</td>
<td>—</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>14.5</td>
<td>M</td>
<td>2.3</td>
<td>+</td>
<td>−2.1</td>
<td>0.5</td>
<td>III</td>
<td>+</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>16.7</td>
<td>M</td>
<td>11.1</td>
<td>+</td>
<td>−0.5</td>
<td>0.8</td>
<td>IV</td>
<td>+</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>14.5</td>
<td>F</td>
<td>&lt;1</td>
<td>n/a</td>
<td>−2</td>
<td>0</td>
<td>III</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>12.7</td>
<td>M</td>
<td>&lt;1</td>
<td>n/a</td>
<td>−0.62</td>
<td>1.6</td>
<td>II</td>
<td>+</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>17.3</td>
<td>F</td>
<td>1.6</td>
<td>n/a</td>
<td>−1.9</td>
<td>2.2</td>
<td>V</td>
<td>+</td>
<td>3</td>
</tr>
</tbody>
</table>

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.
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.48 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 antinflammatory 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

**POTENTIAL CONFLICT OF INTEREST:** The authors have indicated they have no potential conflicts of interest to disclose.

**REFERENCES**

32. Lindsay JR, Oldfield EH, Stratakis CA, Nieman LK. The postoperative basal cortisol and CRH tests for prediction of long-term remission from Cushing’s disease after transphenoidal surgery. *J Clin Endocrinol Metab.* 2011;96(7):2057–2064
41. Sapolisky RM. Potential behavioral modification of glucocorticoid damage to the hippocampus. *Behav Brain Res.* 1995;57(2):175–182
Cases of Psychiatric Morbidity in Pediatric Patients After Remission of Cushing Syndrome
Margaret F. Keil, Alan Zametkin, Celia Ryder, Maya Lodish and Constantine A. Stratakis

Pediatrics 2016;137; originally published online March 29, 2016;
DOI: 10.1542/peds.2015-2234

Updated Information & Services
including high resolution figures, can be found at:
/content/137/4/e20152234.full.html

References
This article cites 44 articles, 3 of which can be accessed free at:
/content/137/4/e20152234.full.html#ref-list-1

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Endocrinology
/cgi/collection/endocrinology_sub
Psychiatry/Psychology
/cgi/collection/psychiatry_psychology_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
/site/misc/Permissions.xhtml

Reprints
Information about ordering reprints can be found online:
/site/misc/reprints.xhtml
Cases of Psychiatric Morbidity in Pediatric Patients After Remission of Cushing Syndrome
Margaret F. Keil, Alan Zametkin, Celia Ryder, Maya Lodish and Constantine A. Stratakis

*Pediatrics* 2016;137;; originally published online March 29, 2016;
DOI: 10.1542/peds.2015-2234

The online version of this article, along with updated information and services, is located on the World Wide Web at:
/content/137/4/e20152234.full.html