Kidney Stones as an Underrecognized Clinical Sign in Pediatric Cushing Disease

Sara H. Rahman, BA[1,2], Georgios Z. Papadakis, MD[3], Margaret F. Keil, PhD, CRNP[1], Fabio R. Faucz, PhD[1], Maya B. Lodish, MD[1,*], and Constantine A. Stratakis, MD[1,*]

Objective To investigate the prevalence of kidney stones in a population of children with Cushing disease (CD) and to compare it with the prevalence of kidney stones in healthy children.

Study design Clinical and biochemical data from 139 pediatric patients with CD (68 females, 71 males) were analyzed retrospectively. Computed tomography scans were reviewed for kidney stones.

Results Among 139 patients, 27 with CD (19.4%) had either radiographic evidence and/or a history of kidney stones. Those with kidney stones had higher urine free cortisol (P = .008) and transsphenoidal surgery at an older age (P = .007). The average urinary calcium/creatinine ratio was elevated in patients with CD (0.22 ± 0.11). The prevalence of kidney stones was higher in children with CD than in normal children (19.42% vs 1.0%; $P < .001$).

Conclusion Our results illustrate that kidney stones are an underestimated complication of pediatric CD, especially when compared with the prevalence of nephrolithiasis in the general pediatric population. Long-term consequences for kidney function are not known and need to be studied. *(J Pediatr 2016;170:273-7)*.

Cushing syndrome (CS), resulting from chronic exposure to excess glucocorticoids, has an estimated incidence of 2-5 new cases per million people per year, with only 10% of these cases occurring in children.[1,2] The most common cause of endogenous CS is adrenocorticotrophic hormone (ACTH) overproduction from a pituitary adenoma, or Cushing disease (CD).[3,4] CD accounts for 75% of all cases of CS in children aged >7 years, and can have long-term effects on growth and development.[1] Early diagnosis and treatment are critical to prevent these consequences.[1,5,6]

Children with CD present with obesity, growth deceleration, striae, hirtsusim, hypertension, diabetes, and oligomenorrhea, with these symptoms not always presenting concurrently.[1,7,8] Kidney stones are a known complication of CS in adults, and previous studies have shown that approximately 50% of adult patients with CD have kidney stones.[8-10] Nephrolithiasis is found more frequently in adults with obesity, diabetes, and hypertension, all of which are common manifestations of CD in both adults and children.[5,11-14] In addition, excess glucocorticoid leads to bone reabsorption and disordered calcium metabolism in both adults and children and is associated with the development of kidney stones.[10,15,16]

Although the increased prevalence of kidney stones in adults with CD has been established, there is a paucity of literature evaluating nephrolithiasis in pediatric patients with CD. At the time of this literature review, only one published case report describes renal colic as a presenting sign of CS in children.[17] The National Institutes of Health (NIH) Clinical Center is a referral center for pediatric CS, and we have noted a large number of children with CD and kidney stones. In these children, the likely connection between the kidney stones and the underlying CD was not always apparent to the family or referring physician.

This study had 2 aims: first, to investigate the prevalence of kidney stones in a large population of pediatric patients with CD, and second, to compare the incidence of kidney stones in children with CD with the established incidence of kidney stones in healthy children. Early diagnosis is increasingly important to optimize long-term outcomes for children with CD; the presence of kidney stones may be an underused diagnostic marker that could aid clinicians in differential diagnosis.

ACTH	Adrenocorticotrophic hormone
Ca/Cr	Calcium/creatinine
CD	Cushing disease
CS	Cushing syndrome
CT	Computed tomography
MEN1	Multiple endocrine neoplasia 1
MRI	Magnetic resonance imaging
NIH	National Institutes of Health
TSS	Transsphenoidal surgery
UFC	Urine free cortisol

From the [1]Section on Endocrinology and Genetics, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, MD; [2]Frank H. Netter School of Medicine, Quinnipiac University, North Haven, CT; and [3]Radiology and Imaging Sciences, National Institutes of Health Clinical Center, Bethesda, MD

*Contributed equally.

The authors declare no conflicts of interest.

0022-3476/$ - see front matter. Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.jpeds.2015.11.045

Methods

Between January 1997 and January 2015, 139 pediatric patients (68 females and 71 males) were admitted to the NIH Clinical Center and received a diagnosis of CD. The records of these patients were reviewed retrospectively. All patients included in the study had newly diagnosed CD or CD not in remission before presenting at the NIH Clinical Center. Clinical confirmation of CD was made with standard testing including, but not limited to: (1) increased urine free cortisol (UFC); (2) lack of diurnal serum cortisol rhythm; (3) corticotrophin-releasing hormone stimulation test consistent with the diagnosis of CD; and/or (4) ≥69% suppression from an overnight administration of 8 mg dexamethasone.[18] Patients with magnetic resonance imaging (MRI) findings indicative of a pituitary adenoma then underwent transsphenoidal surgery (TSS). Other patients underwent inferior petrosal sinus sampling to confirm pituitary localization of the ACTH-producing adenoma. All 139 patients included in the study underwent TSS at the NIH Clinical Center.

The study was conducted under clinical protocol 97-CH0076, which was approved by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Institutional Review Board. Informed consent from parents (and assent from older children) was obtained for all patients.

Data for this work were collected retrospectively. For each patient, data obtained before TSS included age at surgery, height, weight, body mass index, 24-hour UFC, midnight serum cortisol levels, morning serum cortisol levels, plasma ACTH levels, fasting insulin, fasting glucose, plasma total cholesterol, systolic blood pressure, diastolic blood pressure, serum urea, serum uric acid, serum calcium, and urine creatine. A subset of patients (n = 74) were screened for the multiple endocrine neoplasia 1 (MEN1) gene using direct bidirectional sequencing and multiplex ligation-dependent probe amplification.[19] In addition, 36 patients had stored urine samples collected before undergoing TSS; in these samples, spot urine calcium and creatinine were measured using the Dimension Clinical Chemistry system (Siemens Healthcare Diagnostics, Tarrytown, New York).

Imaging in this study included MRI of the pituitary and computed tomography (CT) scans of the adrenals before TSS. Adrenal CT was performed only when outside adrenal CT scans were not available as part of the diagnostic algorithm to localize the source of CS, in accordance with our protocol. Although these CT scans were not performed for the purpose of evaluating kidney stones, in 124 of the 139 patients in our cohort, the kidneys could be visualized in the field of study. MRIs were evaluated by a neuroradiologist, and adenoma size and invasion of cavernous sinus, if visualized on MRI, were recorded. CT scans were read by a single radiologist, blinded to clinical details, to evaluate for the presence of kidney stones.

Clinical documents of all patients were reviewed to determine the period of active disease before the diagnosis of CD as well as medication history, including insulin/metformin and/or antihypertensives. These documents were also reviewed for evidence of kidney stones, such as a past history of nephrolithiasis or urolithiasis. Whether the patient had reported a symptomatic episode of kidney stones (eg, visited the emergency room because of the kidney stones, complained of flank/back pain accompanied by a diagnosis of kidney stones, passed stones) was noted as well.

Statistical Analysis

Data were analyzed using simple descriptive statistics or frequency distributions and are presented as mean ± SD or number and percentage. Independent *t* and Mann-Whitney *U* tests were used for normally and abnormally distributed data, respectively. Categorical data were compared using the χ^2 and Fisher exact tests as appropriate. In addition, a *Z* test for proportions was used to evaluate differences between our population and the general pediatric population. Statistical analyses were performed using SPSS for Mac version 20.0 (IBM, Armonk, New York). A 2-sided *P* value <.05 was considered statistically significant.

Results

In our cohort of 139 patients, 124 had CT scans reviewed. In 24 of these patients, the CT showed kidney stones, and 1 patient whose CT did not show kidney stones had a history of symptomatic nephrolithiasis. Of the 15 patients without a CT assessed because of a gadolinium contrast–only image or unavailability of a scan, 2 patients reported episodes of symptomatic kidney stones. A total of 27 patients with CD out of the 139 (19.4%) in our cohort had kidney stones present on CT and/or after clinical documentation; 10 of these 27 (37.0%) reported having symptomatic kidney stones before being evaluated for CD (**Figure**; available at www.jpeds.com).

Characteristics of the 139 children with CD are summarized in **Table I**. The majority were Caucasian (70.5%), 6.5% were African American, 4% were Asian, and the remainder were other/unknown race. Twenty-five percent of the children were of Hispanic/Latino ethnicity. There was an equal distribution of males and females, and no significant sex-based difference in the presence and absence of kidney stones. Two patients had CD associated with a family history of genetically confirmed MEN1, and 1 patient had a family history of clinical features of MEN1. Genetic confirmation revealed known mutations in *MEN1* in each of these patients, as described previously.[19] None of these patients with MEN1 had kidney stones at the time of TSS; however, 1 patient later developed parathyroid hyperplasia and underwent parathyroidectomy 2 months after TSS.

A statistical analysis of the patients with kidney stones and those without kidney stones revealed that those with kidney stones had higher UFC levels (mean, 903.1 ± 2906.6 μg/dL vs 336.9 ± 471.4 μg/dL; $P = .008$) and underwent TSS at an older age (mean, 13.9 ± 2.3 years vs 12.4 ± 3.3 years;