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Kidney Stones as an Under-Recognized Clinical Sign in Pediatric Cushing Disease

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Abstract

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

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

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The authors declare no conflicts of interest.

Results—Of 139 patients, 27 children 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-value = 0.008) and a transsphenoidal surgery at an older age (p-value = 0.007). Average urinary calcium creatinine ratio was elevated in patients with CD (0.22 ± 0.11). The prevalence of kidney stones in children with CD was higher than in normal children (19.42% vs 1.0%, p-value <0.001).

Conclusion—Our results illustrate that kidney stones are an under-estimated 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.

Keywords

Nephrolithiasis; hypercalciuria; hypercortisolemeia; adolescent; pituitary tumor; Cushing's syndrome

Cushing syndrome (CS), which results from chronic exposure to excess glucocorticoids, has an estimated incidence of 2-5 new cases per million people per year; only 10% of these cases occur 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 over 7 years of age, and it can have long-term effects on their 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, and these symptoms may not always present 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 adult populations who have obesity, diabetes, and hypertension, all of which are common manifestations of CD in both adults and children.[5, 11-14] Also, excess glucocorticoids lead to bone reabsorption and disordered calcium metabolism in both adults and children and are 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 case report described renal colic as a presenting sign of CS in children.[17] Our institution, 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 who have kidney stones as part of their constellation of symptoms. In these instances, the connection that the kidney stones were likely related to the underlying CD was not always apparent to the patients' families or referring physicians.

The aim of this study was two-fold: 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 to the established incidence of kidney stones in healthy children. Early diagnosis is increasingly important in order to optimize long-term outcomes

for children with CD; the presence of kidney stones could be an under-utilized diagnostic marker that could aid clinicians in their differential diagnosis.

Methods

From January 1997 to January 2015, 139 pediatric patients (68 female, 71 male) were admitted to the NIH Clinical Center and received the diagnosis of CD. The records of these patients were retrospectively reviewed. All patients included in the study were newly diagnosed with CD or their disease was not in remission prior to coming to the NIH. Clinical confirmation of CD was made on the basis of previously evaluated literature including, but not limited to: (1) increased urine free cortisol (UFC); (2) lack of diurnal serum cortisol rhythm; (3) corticotrophin releasing hormone (CRH) stimulation test consistent with the diagnosis of CD; and/or (4) ≥ 69% suppression to an overnight 8 mg dexamethasone administration.[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 (IPSS) to confirm pituitary localization of the ACTH-producing adenoma. All 139 patients included in the study underwent TSS at the NIH. The study was conducted under clinical protocol 97- CH0076 that was approved by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Institutional Review Board. Informed consent from the patient's parents (and assent from older children) was obtained for all patients.

Data for the purpose of this work were collected retrospectively. For each patient, various measurements before the TSS were collected, including: age at surgery, height, weight, BMI, 24- hour UFC, midnight serum cortisol levels, morning serum cortisol levels, plasma ACTH levels, fasting insulin, fasting glucose, plasma total cholesterol, systolic blood pressure (BP), diastolic BP, serum urea, serum uric acid, serum calcium, and urine creatine. 74 patients were screened for Multiple Endocrine Neoplasia 1 (MEN1) gene using direct bidirectional sequencing and multiplex ligation-dependent probe amplification (MLPA).[19] Additionally, 36 patients had stored urine samples collected on dates prior to their TSS; spot urine calcium and creatinine were measured using the Dimension Clinical Chemistry system (Siemens Healthcare Diagnostics Inc).

Imaging in this study included MRI of the pituitary and computed tomography (CT) scans of the adrenals prior to TSS. Adrenal CTs were performed only when outside adrenal CT scans were not available as part of the diagnostic algorithm to localize the source of CS, as per 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 were able to 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 and medication history including insulin/metformin and/or anti-hypertensives. These documents were also reviewed for evidence of kidney stones, for example, a past history of nephrolithiasis, urolithiasis, etc. It was noted if the patient had

reported a symptomatic episode of kidney stones (i.e. visited the emergency room because of the kidney stones, complained of flank/back pain accompanied by a diagnosis of kidney stones, passed the stones, etc.).

Statistical analyses

Data were analyzed using simple descriptive statistics or frequency distributions and are presented as mean and standard deviation (SD) or percents. Independent *t*-tests and Mann-Whitney U tests were used for normally and abnormally distributed data, respectively. Categorical data were compared by Chi Square and Fischer Exacts tests when appropriate. Additionally, a Z-test for proportions was used to evaluate differences between our population and the general pediatric population. IBM SPSS Statistics for MAC Version 20.0 was used for statistical analysis. A two-sided p-value of less than 0.05 was considered statistically significant.

Results

In our cohort of 139 patients, 124 had CT scans that were reviewed. 24 of these patients' CTs showed kidney stones, and 1 patient, whose CT did not show kidney stones, did have a history of symptomatic nephrolithiasis. Of the 15 patients whose CT could not be assessed because of gadolinium contrast-only images or unavailability of the scans, 2 patients reported episodes of symptomatic kidney stones in their histories. In total, 27 pediatric patients with CD out of the 139 (19.4%) in our patient population had kidney stones present on their CT and/or after clinical documentation; 10 of these 27 (37.0%) reported having had symptomatic kidney stones prior to their evaluation for CD (Figure; available at www.jpeds.com).

Patient characteristics are summarized in Table I. Of the 139 children with CD, 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 in our patient population and no significant difference between sex and patients with and without evidence of kidney stones. Two pediatric patients had CD associated with a family history of genetically confirmed MEN1, and 1 had a family history of clinical features of MEN1. Genetic confirmation revealed known mutations in MEN1 in each of these patients, as previously described.[19] None of these patients with MEN1 had kidney stones at the time of their TSS. However, one patient later went on to develop parathyroid hyperplasia and underwent parathyroidectomy 2 months after TSS.

Statistical analysis of the cohort of patients with kidney stones and cohort of patients without kidney stones revealed that those with kidney stones had higher UFCs (903.1 μg/dL ± 2906.6 *vs* 336.9 μg/dL ± 471.4, p-value = 0.008) and a TSS at an older age (13.9 years ± 2.3 *vs* 12.4 ± 3.3, p-value = 0.007) (Table II). No significant differences were found between the patients with kidney stones and the patients without kidney stones in any of the other variables, including time period of disease before diagnoses, invasion of the cavernous sinus, and adenoma size (Table II).

Overall, patients with CD had evidence of hypercalciuria with an average calcium/creatinine (Ca/Cr) ratio of 0.22 ± 0.11, which is considered high (normal in children is defined as ≤ 0.22). [20] Half of the patients (18 of 36, 50%) with urine samples had a higher than normal Ca/Cr ratio; of those 36 patients, 6 of 8 (75.0%) patients with kidney stones had a higher than normal Ca/Cr ratio and 10 of 28 (35.7%) patients without kidney stones had a higher than normal Ca/Cr ratio, but this was not statistically significant (p-value = 0.114). When comparing the cohort of patients with available random urine samples and those without available random urine samples, the patients with random urine samples were representative of the larger cohort in terms of demographics and disease severity.

In order to evaluate the incidence of kidney stones in our population of pediatric CD patients, we looked to the current literature to find the incidence of kidney stones in children. 50 per 100,000 children are estimated to have kidney stones.[21] The prevalence of kidney stones in our pediatric patients with CD was significantly higher than the prevalence of kidney stones in the general pediatric population, as measured by Z-test for proportions (19.42% vs 1.0%, p-value ≤0.001).

Discussion

This comprehensive study of children with CD investigated nephrolithiasis in pediatric patients with CD. Our large group of 139 patients illustrates that kidney stones are indeed an under-estimated complication of pediatric CD, especially when compared with the incidence of nephrolithiasis in the general pediatric population. Our study results are in alignment with the findings of increased prevalence of kidney stones in adults with CD.[9]

The clear relationship between nephrolithiasis and CD could have many explanations. Hypercalciuria is an especially common cause of kidney stones in pediatric patients.[22, 23] Studies have shown that increased bone resorption occurs in patients with high levels of cortisol, including in children with CD, which likely contributes to their hypercalciuria.[14, 24] Additionally, the effects of hypercortisolemia can lead to hyperuricosuria and hypercystinuria, all of which are also common effects in CD and further increase the risk of kidney stone formation.[25] Our cohort of children with CD with kidney stones had a significantly higher levels of UFC, supporting this argument. Overall, our entire patient population had high levels of urine calcium. Although though the data for hypercalcuria between the cohort of patients with kidney stones and without kidney stones was not stastically significant, this was perhaps due to a small sample size. Furthermore, abdominal obesity, insulin resistance, hypertension, and high cholesterol increase the likelihood of nephrolithiasis in children and adolescents.[26] Our previous study showed that pediatric patients with CD are at higher risk for metabolic syndrome, and all of the patients in our cohort had at least one, if not more, of these syndromes.[5] The development of nephrolithiasis in these pediatric patients with CD most likely had a multifactorial pathogenesis.

It is important to point out that three of our study population had MEN1; hyperparathyroidism and kidney stones are known complications of MEN1.[27] Interestingly, our MEN1 patients were not found to have kidney stones on CT and had no clinical

documentation of a history compatible with nephrolithiasis. Clinical guidelines for the management of pediatric patients with MEN1 include surveillance for hypercalcemia.[28] It is, however, possible that these patients did have kidney stones that were asymptomatic and never discovered. Another point that emerged from our study is that sex did not influence the risk of forming kidney stones. Previous studies have reported girls as having a higher likelihood of nephrolithiasis;[13] however, it has also been shown that sex does not influence severity of CD in children.[5]

The retrospective design of our study has a number of limitations. For example, many patients had missing data for values such as urine calcium. We did not have blood or urine stored from all patients to run PTH levels, serum phosphate, etc. Some of the patients did not have CT scans available or their CT scans were not able to be evaluated for kidney stones because of artifact from contrast. Also, some of the available adrenal CT scans did not visualize the entire left and right kidneys. We would like to note that for future kidney stone evaluation in children, ultrasound is the preferred modality due to radiation exposure.[29] Finally, we did not systematically survey patients for history of symptomatic nephrolithiasis, so we may have underestimated the number of individuals with a history of kidney stones.

In conclusion, pediatric patients with CD are highly predisposed to form kidney stones, and nephrolithiasis is an under-recognized clinical sign of CD that could help in early detection of the disease. The consequences of this complication for kidney function remain unknown and need to be studied.

List of Abbreviations

CS	Cushing syndrome
ACTH	Adrenocorticotrophic hormone
CD	Cushing disease
NIH	National Institute of Health
UFC	Urine Free Coritsol
CRH	Corticotrophin Releasing Hormone
MRI	Magnetic Resonance Imagine
TSS	Transsphenoidal Surgery
IPSS	Inferior Petrosal Sinus Sampling
BP	Blood Pressure
MEN1	Multiple Endocrine Neoplasia 1
MLPA	Multiplex Ligation-dependent Probe Amplification
CT	Computed tomography
SD	Standard Deviation

Ca/Cr calcium/creatinine

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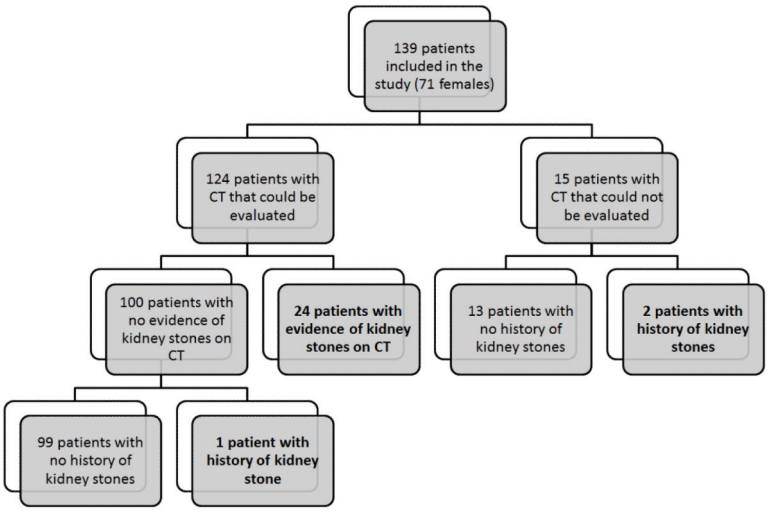

Figure.

Flow diagram regarding evidence of and/or history of kidney stones. A total of 27 patients were found to have kidney stones.

Table 1

Pediatric CD patient characteristics and data at surgery date

Patient Characteristics (*N*=139)	**Mean ± SD**
Males/Females (*n*)	68/71
Age at Surgery(years)	12.7 ± 3.1
BMI Z-score	2.0 ± 0.8
Height Z-score	−1.4 ± 1.4
Systolic BP Z-score	1.8 ± 1.2
Diastolic BP Z-score	0.9 ± 1.0
Midnight Cortisol (μg/dL) (*n=138*) (normal 3.0-17.0 μg/dL)	18.3 ± 14.6
AM Cortisol (μg/dL) (*n=89*) (normal 4.0-22.0 μg/dL)	19.0 ± 10.2
Plasma ACTH (pg/mL) (normal 5.0 – 46.0 pg/mL)	56.6 ± 56.6
UFC (μg/dL) (*n=136*) (normal 2.1 - 38.0 μg/24 hr)	449.3 ± 1362.5
Urine Calcium/Creatinine Ratio (*n*=36) (normal < 0.22)	0.22± 0.11
Urine Calcium/Creatinine Ratio Z-score (*n=36*)	1.06 ± 1.01
Period of disease before diagnoses (years) (*n=119*)	2.72 ± 1.77
MEN1 gene (yes) (*n*)	3 (2.2%)

Table 2

Comparison of CD pediatric patients with kidney stones and without kidney stones

Patient characteristics	Kidney stones (*N* =27) Mean ± SD	No Kidney stones (*N*=112) Mean ± SD	*P*-value
Males/Females (*n*)	12/15	56/56	.604
Age at surgery (years)	13.9 ± 2.3	12.4 ± 3.3	.007
BMI Z-score	1.9 ± 1.0	2.1 ± .8	.280
Height Z-score	−1.4 ± 1.1	−1.4 ± 1.5	.905
Systolic BP Z-score	1.9 ± 1.2	1.8 ± 1.2	.553
Diastolic BP Z-score	1.0 ± 0.7	0.88 ± 1.0	.526
Adenoma size (mm) (*n*=75)	8.2 ± 7.9 (*n=14*)	6.6 ± 4.9 (*n=61*)	.335
Midnight Cortisol (μg/dL) (*n*=138)	22.9 ± 23.7	17.1 ± 11.2 (*n=111*)	.065
AM Cortisol (μg/dL) (*n*=89)	18.8 ± 7.3 (*n=20*)	19.0 ± 10.9 (*n=69*)	.938
Plasma ACTH (pg/mL)	59.7 ± 46.0	55.8 ± 59.0	.752
UFC (μg/dL) (*n=136*)	903.1 ± 2906.61	336.9 ± 471.4 (*n=109*)	.008
Fasting glucose (mmol/L)	99.6 ± 40.2	98.5 ± 32.6	.883
Fasting insulin (mcU/mL) (*n*=74)	27.9 ± 12.9 (*n=19*)	33.7 ± 32.8 (*n=55*)	.454
Total cholesterol (mg/dL) (*n*=105)	192.1 ± 35.7 (*n=21*)	184.7 ± 53.2 (*n=84*)	.547
Serum urea (mg/dL) (*n*=138)	13.7 ± 4.3 (*n=26*)	12.4 ± 3.7	.146
Serum Uric Acid (mg/dL) (*n=71*)	4.9 ± 2.2 (*n=18*)	4.4 ± 1.5 (*n=53*)	.331
Urine Calcium/Creatinine Ratio (*n=36*)	0.28 ± 0.12 (*n=8*)	0.20 ± 0.10 (*n=28*)	.069
Urine Calcium/Creatinine Ratio Z-score (*n=36*)	0.45 ± 0.97 (*n=8*)	1.23 ± 0.97 (*n=28*)	.054
Serum Calcium (mmol/L) (*n*=132)	2.3 ± 0.1 (*n=26*)	2.3 ± .1 (*n=106*)	.351
Period of disease before diagnoses (years) (*n=119*)	2.3 ± 2.4 (*n*=19)	2.6 ± 1.6 (*n*=100)	.148
Invasion of Cavernous Sinus (yes) (*n=91*)	3 (11.1%) (*n*=18)	6 (5.4%) (*n*=73)	.373
MEN1 Gene (yes)	0 (0%)	3 (2.7%)	1.00