Pediatr Nephrol (2000) 15:125–128

ORIGINAL ARTICLE

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Risk factors for urolithiasis in children on the ketogenic diet

Received: 28 May 1999 / Revised: 7 June 2000 / Accepted: 9 June 2000

Abstract Kidney stones have been associated with use of the ketogenic diet in children with refractory seizure disorders. We performed a case-control study examining risk factors for the development of stones on the ketogenic diet, and prospectively followed children initiating the ketogenic diet to evaluate the incidence of urolithiasis. Clinical characteristics of 18 children presenting with stones (8 uric acid stones, 6 mixed calcium/uric acid stones, 1 calcium oxalate/phosphate stone, 3 stones not evaluated) were compared with characteristics of non-stone-forming children initiating the ketogenic diet at Johns Hopkins since July 1996. Since July 1996, 112 children initiating the ketogenic diet have been followed for development of stones. Follow-up times on the diet range from 2 months to 2.5 years. Of 112 children, 6 have developed stones (3 uric acid, 3 mixed calcium/uric acid stones) (0.8 children developing stones/100 patient-months at risk). Comparisons of children presenting with stones on the ketogenic diet with characteristics of the entire cohort initiating the ketogenic diet suggest younger age at diet initiation and hypercalciuria are risk factors for the development of stones. Prospective evaluation of children initiating the ketogenic diet revealed that almost 40% of patients had elevated fasting urine calcium: creatinine ratios at baseline; this increased to 75% after 6 months on the diet. Median urine pH was 5.5 at diet initiation, and remained at 6.0 thereafter. In a subset of patients tested, urinary citrate excretion fell from a mean of 252 mg/24 h pre diet initiation to 52 mg/24 h while on the diet. Uric acid excretion remained normal. Patients maintained on the ketogenic diet often have evidence of hypercalciuria, acid urine, and low urinary citrate excretion. In conjunction with low fluid intake, these patients are at high risk for both uric acid and calcium stone formation.

Keywords Ketogenic diet · Seizures · Nephrolithiasis · Hypercalciuria · Hematuria

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Introduction

The beneficial effects of fasting on the frequency of seizures in patients with epilepsy have been noted since biblical times. Early in this century, it was observed that these effects could be mimicked by maintaining patients in a state of ketonemia [1] through a diet rich in fats and low in carbohydrates. The "ketogenic" diet was frequently used in select groups of patients with seizures through the 1930s, but fell in popularity with the discovery of diphenylhydantoin and other anticonvulsants beginning in 1939 [2].

In recent years, interest in the ketogenic diet as a potential treatment for pediatric epilepsy has re-emerged. Studies of the efficacy of the ketogenic diet have been published elsewhere [3, 4, 5]. Kidney stones have previously been reported in children initiated on the ketogenic diet [6, 7]. Prior case series have documented calcium oxalate and uric acid stones in this group of children. In order to evaluate which patients on the ketogenic diet were at greatest risk of stone formation, we retrospectively reviewed the clinical characteristics of children presenting with stones at our institution between 1995 and 1999 to identify risk factors for development of stones. Additionally, beginning in 1996, we undertook a prospective study to determine the incidence of stones in children initiating the ketogenic diet, and to describe how urinary pH, calcium, uric acid, and citrate excretion change after initiation of the ketogenic diet.

Table 1 Characteristics of stone patients and non-stone formers (*NS* not significant)

	Stone cases *n*=18	Non-stone formers *n*=106	*P* value
Mean age (SD) (months)	34.5 (23)	60.3 (49.9)	<0.05
Gender			
Female	33%	49%	NS
Severe motor delay	28%	32%	NS
Hypercalciuria[a]	89%	43%	<0.05
Urine pH <5.5	33%	30%	NS
History of medications increasing stone risk	28%	25%	NS
Family history of stones	17%	27%	NS

[a] Urinary calcium:creatinine ratios measured at stone presentation in patients and at diet initiation in controls

Patients and methods

Case-control study

The charts of all children on the ketogenic diet who were referred to the Harriet Lane Kidney Center were reviewed. All cases with stones or nephrocalcinosis were identified. From the charts, the following data were extracted: age at diet initiation, duration of diet at stone presentation, urinary studies and blood chemistries at stone presentation, stone composition if available, family history of stones, fluid intake, medications, and mobility (defined as ability to crawl, cruise, or walk). Medication lists were reviewed. Specifically, use of medications that might alter the risk of developing kidney stones (adrenocorticotropic hormone, acetazolamide, prednisone, and topiramate) was identified. Clinical characteristics of children presenting with stones were compared with the entire cohort of children initiating the ketogenic diet. Categorical data were compared using chi-squared analysis; continuous variables were compared using a *t*-test.

Prospective cohort study

From July 1996 through September 1999 all children initiating the ketogenic diet as inpatients at Johns Hopkins University were followed prospectively for the development of stones. Children were eligible to begin the ketogenic diet if they were between 1 and 16 years old, and had a seizure disorder refractory (>2 seizures/week) to at least two anticonvulsant medications [4, 5]. After informed consent was obtained, medication history, patient height and weight, and family history of kidney stones was documented. Children had begun fasting, as part of initiation of the ketogenic diet, the evening prior to admission. On admission, serum electrolytes and a baseline urine was examined for pH (by dipstick). A fasting voided urine specimen for uric acid and calcium:creatinine ratio was ordered. When possible, repeat samples from patients with abnormal urine calcium:creatinine ratios were requested. In addition, when possible without urinary catheterization, a 24-h urine collection for calcium, uric acid, creatinine, citrate, and oxalate was obtained. All studies were not performed on each patient.

While on the diet, parents were instructed to test the urine at home for hematuria. Children returned for follow-up visits at 3 months if possible, and also at 6, 12, 18 and 24 months if still on the ketogenic diet. Serum electrolytes, urine studies for uric acid, and calcium:creatinine ratio were obtained at subsequent visits.

The development of persistent microscopic hematuria (heme positive by urinalysis on three occasions), or gross hematuria, dysuria, flank or loin pain while on the ketogenic diet, prompted liberalization of fluids and evaluation for hypercalciuria or evidence of stones by renal ultrasonography. If a patient had hematuria and hypercalciuria on a random urine specimen, oral calcium intake was decreased to 75% of the U.S. Recommended Daily Allowance. If patients had persistent hematuria with hypercalciuria, oral citrate therapy was started. If renal sonography revealed evidence of stones, the patient was referred to a pediatric urologist, and any stones passed were retrieved and sent for evaluation. Appropriate therapy in these cases was initiated on an individual basis.

For purposes of this study, hypercalciuria was defined as a fasting urine calcium:creatinine ratio of >0.2 (mg/mg) for patients 1 year of age or older, >0.6 for patients between 6 months and 1 year, and >0.8 for patients <6 months [8, 9]. Uric acid excretion was normalized for glomerular filtration rate, and normal was defined as <0.57 [8, 9]. Normal citrate excretion was defined as >400 mg/g creatinine [9, 10]. Mean values of citrate excretion/24-h obtained pre and post diet initiation were compared with a one tailed *t*-test. Normal oxalate excretion was considered <50 mg/1.73 m^2 per 24 h. The statistical significance of the development of hypercalciuria on the ketogenic diet was tested with the McNemar test [11] for paired observations. If a patient had a normal calcium:creatinine ratio at baseline and any of multiple follow-up urinalyses for calcium:creatinine were above the normal level for the patient's age, we defined that patient as having developed hypercalciuria.

Results

Case-control study

Between 1995 and 1999, 18 children on the ketogenic diet presented to the Harriet Lane Kidney Center with kidney stones. Characteristics of patients presenting with stones are compared with the entire cohort initiating the ketogenic diet in Table 1. The mean age at stone presentation was 34.5 months (range 9 months to 8 years). The median time on the ketogenic diet for children presenting with stones was 15 months (range 3–35 months). On average, children who presented with stones took only 70% of maintenance fluids (as calculated by the Holliday-Segar method [12]). At the time of stone presentation, all children had normal renal function and normal serum calcium. The median urine pH at the time of stone presentation was 5.5, range 5–8, by urine dipstick. Younger age at initiation of the ketogenic diet (P<0.05) appeared to be a risk factor for stone development in simple bivariate analysis. Patients with stones were more likely to have evidence of hypercalciuria on a random urine calcium:creatinine estimation for evaluation of causes of stones than were all patients initiating the ketogenic diet (P<0.05) (Table 1). There were no differences in family history of stones, use of medications that may increase the risk of stone formation, or severe delay in motor skills such that patients could not crawl, cruise, or walk.

Prospective cohort study

Baseline patient characteristics, blood and urine studies

Between July 1996 and September 1999, 112 patients [88% white, 47% female, mean age 5 years (SD 4.2)] started the ketogenic diet at our institution. Of these patients, 91 had baseline urinalyses and/or blood studies. Not all tests were obtainable in all patients. Demographic characteristics of patients on whom baseline blood and/or urine studies were obtained [87% white, 44% female, mean age 4.9 years (SD 4.1)] did not differ from those not studied.

Evaluation of baseline electrolyte studies revealed normal serum calcium, creatinine, and phosphate levels in these patients. The mean serum uric acid level was 5.7 mg/dl (SD 2.3). Eight patients had elevated uric acid levels at baseline; 5 were normal when repeated. The mean serum bicarbonate was 18.3 (SD 4.5). At the time of baseline electrolyte studies, most patients had been fasting overnight. The median urine pH of patients initiating the ketogenic diet was 5.5 (range 5–8.0). At diet initiation, 26 of 60 patients tested (43%) had elevated urine calcium:creatinine ratios on fasting specimens.

Follow-up urinary studies on the ketogenic diet

In follow-up at 3, 6, and 12 months on the diet, 25 of 35 (71%), 24 of 32 (75%), and 10 of 16 (63%) patients had random urine tests that revealed elevated calcium:creatinine ratios ($P<0.05$ McNemar test comparing paired proportions). Median urine pH at follow-up visits remained at 6.0. Uric acid excretion was normal and remained normal on the diet ($P>0.05$ McNemar test for paired proportions).

Nine patients had 24-h urine studies for citrate. The mean citrate excretion was 252 mg/24 h pre diet initiation (SD 223.7). The mean citrate excretion fell to 52 mg/24 h on the diet ($P<0.05$ one-tailed *t*-test). Nine patients had 24-h urine studies for oxalate. All patients studied had normal oxalate excretion.

Six patients whom we had followed since diet initiation, aged 9 months to 4.5 years, developed kidney stones during the follow-up period (760 patient-months at risk). Three patients had uric acid stones and 3 had mixed calcium oxalate, uric acid stones. Notably, 3 of these patients had hypercalciuria at baseline; the other 3 patients developed hypercalciuria after beginning the ketogenic diet. None had a family history of kidney stones. Patients developed stones 7–22 months after initiation of the ketogenic diet.

Discussion

Urolithiasis is an uncommon problem in pediatrics, with renal stones occurring in only 1 in several thousand otherwise healthy children. Between 1995 and 1999, 18 children maintained on the ketogenic diet at multiple institutions were referred to our clinic because of kidney stones. Since 1996, we have prospectively evaluated the risk of stones in patients initiated on the ketogenic diet at our institution to treat intractable seizure disorders. Of 112 children initiated on the diet with up to 2.5 years of follow-up, 6 have developed stones (0.8 cases of urolithiasis/100 patient-months at risk).

Of the 18 patients with stones identified since 1995, 15 had stone analysis. Eight stones were uric acid stones, 1 was a calcium oxalate stone, and 6 were mixed calcium oxalate, calcium phosphate/uric acid stones. Our study suggests that younger age at initiation of the ketogenic diet and hypercalciuria are risk factors for stones in this population.

We found a remarkably high percentage of children tested when initiating the ketogenic diet had hypercalciuria on a fasting baseline urine calcium:creatinine ratio. Additionally, the proportion of patients with hypercalciuria increased with time on the diet. Patients who did not have evidence of hypercalciuria at baseline were likely to develop it on the ketogenic diet.

Possible causes of hypercalciuria in this group of normocalcemic patients include idiopathic hypercalciuria, drug side effects, immobilization, and acidosis. It is possible that we observed an unusually high incidence of idiopathic hypercalciuria in this group, as they were predominantly of white race and a relatively high percentage had a positive family history of kidney stones. Although limited by sample size, our case-control study did not suggest a higher prevalence of drugs that increase the risk of stones or of immobility in children who developed stones compared with the larger cohort of children initiating the ketogenic diet.

Acidosis, which is frequently seen in children on the ketogenic diet, is likely related to fasting and may contribute in several ways to the increased risk of stones seen in this population. Blood chemistries in this cohort of patients were normal, except for elevated uric acid levels in 3 patients and low median serum bicarbonate. Children may have had elevated uric acid levels because of protracted seizures, dehydration, and acidosis. Acidosis could explain the hypercalciuria we observed on the diet, as acidosis decreases renal tubular calcium reabsorption [12], and therefore increases urinary calcium excretion. The increased urine calcium excretion in acidosis is not associated with an increase in intestinal calcium absorption, but rather results from bone mineral resorption to buffer the acid load.

The fall in urinary citrate excretion that we observed in those patients able to collect 24-h urine samples has been previously described [7]. The fall in urinary citrate is also likely related to acidosis from fasting. Acidosis increases proximal tubule citrate absorption and decreases its excretion. In conjunction with hypercalciuria, low urinary citrate may predispose children on the ketogenic diet to stone formation. Citrate normally binds urine calcium in the urine, lowering its concentration, and acts as an inhibitor of crystallization. Thus, an acidosis-induced reduction in urinary citrate excretion not only increases the available calcium, but also decreases an important crystallization inhibitor.

Over half of the stones we observed in children on the ketogenic diet were uric acid stones. Our study documents several risk factors for uric acid stones in patients on the ketogenic diet: low urine pH and low fluid intake. At low urine pH, as seen in children on the ketogenic diet, urine may become supersaturated with respect to uric acid, even at normal rates of uric acid excretion. In our study we documented normal uric acid excretion, but a low median urine pH of 5.5–6.0 while maintained on the ketogenic diet. Fluid restriction in the youngest patients may put these patients at greatest risk, as the fluid restriction may be tighter in these patients with a higher body surface area and relatively increased fluid requirements. Additionally, the ketosis associated with the ketogenic diet interferes with the normal thirst mechanism, and we have found that frequently patients do not even meet their fluid restriction, unless constantly encouraged by their parents or caretakers to drink.

Our study suggests that the risk of stone formation on the ketogenic diet is increased in the youngest patients, particularly those with hypercalciuria. Acidosis on the ketogenic diet is likely to promote hypercalciuria, hypocitraturia, and low urine pH. It is likely that the urine of these patients with low fluid intake on the ketogenic diet becomes supersaturated with respect to calcium or uric acid as a consequence of the factors noted above, and crystals of one of these supersaturated ions adhere to one another to ultimately become clinically significant stones.

Our study is limited by the fact that we were unable to confirm random fasting urine calcium:creatinine ratios with 24-h collections in these young, often developmentally delayed patients. A subset of abnormal random fasting urine samples was duplicated, and abnormal ratios were reproducible. It is possible that if these patients had low muscle mass, perhaps their creatinine excretion was low, causing falsely elevated calcium:creatinine ratios. Additionally, due to the difficulties in obtaining urine specimens in these delayed young children with severe seizure disorders, not all subjects initiating the ketogenic diet at out institution had urine studies performed. However, patients studied did not differ in systematic ways from those who did not have urine or blood studies checked.

We were not able to obtain 24-h citrate and oxalate excretions on a large number of patients over time; however, our results documenting a fall in urinary citrate levels are consistent with previous reports. Because patients entered this protocol over 3 years, and patients discontinued the ketogenic diet for multiple reasons [4] at varying time points, we have varying lengths of follow-up for patients studied. Therefore, estimates of the prevalence of hypercalciuria after longer periods of time on the diet may be biased.

Despite these limitations, in view of our findings of the increased risk of stones in this patient group, we recommend that patients initiating the ketogenic diet be evaluated for hypercalciuria. The fluid intake for children initiating the diet should be maximized. We have increased the fluid limits of many patients on the ketogenic diet to maintenance requirements (using the Holiday-Seager method) without increasing seizure frequency. Any evidence of dysuria, crystalluria, hematuria, or increased seizures (which may be secondary to pain) should prompt evaluation with a renal sonogram to look for kidney stones. If calcium or uric acid stones are found, referral to a pediatric urologist or nephrologist should be made. Management of stones should proceed on an individual basis. If patients on the ketogenic diet have evidence of symptomatic hypercalciuria or crystalluria, fluid intake should be increased, and consideration should be given to the use of oral potassium citrate to complex urine calcium and alkalinize urine to a pH of 6.5 to improve the solubility of uric acid. Fluid liberalization has not diminished the efficacy of the ketogenic diet in controlling seizures in children we have seen at our institution. Commercial preparations of potassium citrate may contain sugars not allowed on the ketogenic diet, so sugar-free solutions can be specially made. With these recommendations, we do not feel that the development of hypercalciuria or kidney stones is an absolute contraindication to continuing the ketogenic diet. If the ketogenic diet is associated with clinical improvement in the child's seizure frequency, we maximize fluid intake, alkalinize the urine, and monitor children closely with serial renal ultrasonography for further development of nephrocalcinosis or stones. In view of the prevalence of hypercalciuria in children maintained on the ketogenic diet, evaluation of bone metabolism may also be indicated in this patient group.

Acknowledgement Funded by a grant from The Charlie Foundation to Cure Pediatric Epilepsy, Santa Monica, California, USA.

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