Risk Factors for Urolithiasis in Gastrostomy Tube Fed Children: A Case-Control Study

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KEY WORDS

case-control study, urolithiasis, gastrostomy, G-tube, percutaneous endoscopic gastrostomy (PEG) tube, feeding difficulties, risk factors, complications

ABBREVIATIONS

CCC—complex chronic condition

CI—confidence interval

G-tube—gastrostomy tube

GERD—gastroesophageal reflux disease

GTF—gastrostomy tube fed

i2b2—Informatics for Integrating Biology and the Bedside

ICD-9—International Classification of Diseases, Ninth Revision

OR—odds ratio

UTI—urinary tract infection

Dr Johnson conceptualized and refined the study design, designed the data collection instruments, performed a substantial portion of the data collection, performed the data analysis and interpretation, drafted the initial article, incorporated revisions from the senior authors, and approved the final article; and Drs Lightdale and Nelson conceptualized and refined the study design, contributed to the design of the data collection instruments and the interpretation of the data, and critically reviewed the article and approved the final article as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Patients who are fed via gastrostomy tube represent a heterogeneous, complex group of patients who may be at increased risk for kidney stones. To date, no previous studies have examined risk factors for kidney stone development in this population.

WHAT THIS STUDY ADDS: This case-control study of risk factors for urolithiasis in patients fed via gastrostomy suggests that topiramate use, urinary infections, and shorter length of time with a gastrostomy tube (possibly a marker for dehydration) are all associated with stone development.

abstract

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BACKGROUND AND OBJECTIVE: Pediatric patients who are fed primarily via gastrostomy tube (G-tube) may be at increased risk for urolithiasis, but no studies have specifically examined risk factors for stones in this population. We aimed to determine clinical differences between G-tube fed (GTF) patients with and without stones, in hopes of identifying modifiable factors associated with increased risk of urolithiasis.

METHODS: We conducted a retrospective case-control study, matching GTF patients with urolithiasis (cases) to GTF children without urolithiasis (controls) based on age (± 1 year) and gender. Bivariate comparisons and matched logistic regression modeling were used to determine the unadjusted and adjusted associations between relevant clinical factors and urolithiasis.

RESULTS: Forty-one cases and 80 matched controls (mean age 12.0 ± 6.5 years) were included. On bivariate analysis, factors associated with stone formation included: white race, urinary tract infection (UTI), topiramate administration, vitamin D use, malabsorption, dehydration, 2-year duration with G-tube, and whether goal free water intake was documented in the patient chart. On regression analysis, the following factors remained significant: topiramate administration (odds ratio [OR]: 6.58 [95% confidence interval (CI): 1.76–24.59]), UTI (OR: 7.70 [95% CI: 1.59–37.17]), and <2 years with a G-tube (OR: 8.78 [95% CI: 1.27–52.50]).

CONCLUSIONS: Our findings provide a preliminary risk profile for the development of urolithiasis in GTF children. Important associations identified include UTI, topiramate administration, and shorter G-tube duration, which may reflect subclinical chronic dehydration. Of these, topiramate use represents the most promising target for risk reduction. *Pediatrics* 2013;132:e167–e174

Pediatric patients who are fed primarily via gastrostomy tube (G-tube) may be at increased risk for urinary stone disease due to multiple factors associated with chronic illness and feeding difficulties, including immobility, inability to regulate free water intake, and atypical dietary content. Previous epidemiologic studies have suggested that low water intake,¹ high protein diets,^{2,3} and ketogenic diets^{4–6} are all associated with increased risk of urolithiasis in the general population. Although these and other factors may be important risk factors in G-tube fed (GTF) children, previous studies have not specifically examined possible associations.

A recent study by Smith et al⁷ compared GTF children with stones to non-GTF children with stones. This investigation noted a higher proportion of calcium phosphate stones, higher urine pH, lower bone mineral density z score, and a higher rate of re-treatment after extracorporeal shock wave lithotripsy in GTF patients. However, since only children with urolithiasis were included in this study, the investigators were unable to determine if modifiable factors exist among GTF patients that could decrease the risk of stone formation and the consequences thereof in this medically complex patient population.

Given the multiple potential risk factors for stones in our population of interest, we sought to understand clinical characteristics that could predispose GTF patients to urolithiasis. The aim of our study was to identify factors associated with urolithiasis in GTF children.

METHODS

With institutional review board approval, we conducted a retrospective matched case-control study comparing GTF children with urolithiasis (cases) to GTF children without urolithiasis (controls).

Patient Selection

We used our institution's Informatics for Integrating Biology and the Bedside (i2b2) query tool to identify patients aged 1 to 21 years who had a G-tube in place (presence of ≥ 1 of the following *International Classification of Diseases, Ninth Revision* [ICD-9] or *Current Procedural Terminology* codes: ICD-9 codes v44.1, 43.19, 43.11, 43.19, v55.1, 96.36, 97.02, 536.40, 536.41, 536.42, and 536.49; *Current Procedural Terminology* codes 43246, 43653, 43750, 43760, 43830, 43831, 43832, 49440, 49450, 49465, and 74350) and were evaluated for a first diagnosis of urolithiasis (presence of ≥ 1 of the following ICD-9 codes: 592.1, 592.2, and 592.9) between 2005 and 2011. Based on this initial query, medical record review was performed to identify eligible cases. Patients were excluded if they were classified as having a stone or G-tube incorrectly, if their stone history predated their G-tube placement, if they were outside of the study age range at

the time of stone diagnosis, if there were no data in the chart regarding tube feed formulation and/or timing, if they had received G-tube feeds for <3 months in the 12 months before the date of the stone diagnosis, or if they did not have at least 1 eligible control identified. The final selection of cases is illustrated in Fig 1.

Potential controls were also identified by using i2b2. The initial query identified all patients having ≥ 1 of the G-tube codes listed above. i2b2 was used to match cases with all potential controls based on age (± 1 year) and gender. Potential controls for each case were sorted randomly, and chart review was sequentially conducted for each set of potential controls until 2 controls were identified or all possible controls had been evaluated. The review verified that each control patient received G-tube feeds for at least 3 months in the 12 months before the stone diagnosis date of their matching case, and that each control had data available

FIGURE 1

Assembly of case cohort. ^a Outside age range (42); stone before 2005 (35); no stone or no G-tube (31); and tube and stone asynchronous (14).

regarding tube feed type and duration. Absence of urolithiasis was confirmed in controls through review of their available radiologic studies.

Data Abstraction

Demographic, laboratory, and comorbidity data were obtained by using i2b2. Comorbidities were identified by using ICD-9 coding for the presence or absence of the following conditions: seizure disorder (345.8 and 345.9), celiac disease (579.0), cystic fibrosis (277.0, 277.01, and 277.02), short gut (579.3, 579.8, and 579.9), Crohn disease (555.0, 555.1, and 555.9), gastroesophageal reflux disease (GERD; 530.81), diabetes insipidus (253.5 and 288.1), diabetes mellitus (249 and 250), diarrhea (787.91), primary hyperparathyroidism (252.01), pituitary dysfunction (253), adrenal dysfunction (255), and dehydration (276.51). A patient was considered to have a malabsorptive disorder if an ICD-9 code for cystic fibrosis, short gut, diarrhea, Crohn disease, and/or celiac disease was present.

Chart abstraction was then used to collect demographic and comorbidity data not available in i2b2, including insurance status, mobility status, documented urinary tract infection (UTI) in the 12 months before stone diagnosis, use of clean intermittent catheterization within 12 months of stone diagnosis, and presence of urologic abnormalities (ureteropelvic junction obstruction, vesicoureteral reflux, neurogenic bladder, and other anatomic abnormalities of the urinary tract). We documented use of anti-epileptics, diuretics, multivitamins, vitamin D, and calcium in the 24 months before stone diagnosis. Nutritional data were also obtained from the chart and included type of tube feed formulation, feeding schedule, free water administration, presence of nutrition consultation, and duration of time with G-tube. For cases, we obtained clinical

information regarding stone presentation, radiologic evaluation, burden, treatment, and family history. Data were managed by using REDCap (Research Electronic Data Capture).⁸

Data Analysis

Descriptive statistics were used to characterize cases and controls. Bivariate associations between potentially important clinical factors and the presence of stones were evaluated by using χ^2 testing. Matched (conditional) logistic regression modeling was used to determine the adjusted associations between relevant clinical factors and the presence of urolithiasis. Our final regression model was selected based on clinical relevance and observed bivariate associations. Data analysis was performed by using SAS version 9.3 (SAS Institute, Inc, Cary, NC), and a *P* value of $<.05$ was considered statistically significant.

RESULTS

A total of 41 cases and 80 matched controls were identified and deemed

eligible for the study. Two cases only had 1 available matched control; all other cases had 2 controls. All controls had no clinical history of urolithiasis. Imaging studies documenting lack of urolithiasis were identified in 88.8% (71/80) of controls; the negative imaging study was performed within 12 months of the date of stone presentation for their matched case in 42% (30/71) of controls with imaging. Demographic characteristics of the cases and controls are illustrated in Table 1. Cases and controls were well matched on age and gender. There were no statistically significant differences between the groups with respect to race, insurance status, or BMI. For the overall cohort, mean age was 12.0 ± 6.5 years, 76% were white, and 60% were boys.

Patient Comorbidities

Highly prevalent diagnoses among all GTF children included immobility (74% of cases and 64% of controls were wheelchair bound), GERD (80% of cases, 91% of controls), and seizures (68% of cases, 56% of controls). On bivariate

TABLE 1 Demographic Characteristics of Cases and Controls

	Cases (Stones) (<i>N</i> = 41)	Controls (No Stones) (<i>N</i> = 80)	<i>P</i>
	<i>N</i> (% of Cases)	<i>N</i> (% of Controls)	
Age in y (mean $\pm$ SD)	12.2 $\pm$ 6.4	11.8 $\pm$ 6.7	.80
Gender			.92
Boy	25 (61.0)	48 (60.0)	—
Girl	16 (39.0)	32 (40.0)	—
Race			.32
White	34 (82.9)	52 (65.0)	—
African American	1 (2.4)	9 (11.3)	—
Asian	1 (2.4)	5 (6.3)	—
Hispanic	0 (0)	2 (2.5)	—
Other or mixed	3 (7.3)	6 (7.5)	—
Unknown	2 (4.9)	6 (7.5)	—
Insurance status			.19
Private	3 (7.3)	11 (13.8)	—
Public	10 (24.4)	28 (35.0)	—
Both	28 (68.3)	41 (51.3)	—
BMI category ^a			
Underweight	5 (12.2)	11 (13.8)	.93
Normal weight	19 (46.3)	36 (45.0)	—
Overweight	4 (9.8)	5 (6.3)	—
Obese	1 (2.4)	2 (2.5)	—
Dual-energy X-ray absorptiometry z-score (mean $\pm$ SD) ^b	−3.63 $\pm$ 1.84	−3.47 $\pm$ 1.72	.82

^a BMI data available for 83 patients.

^b Dual-energy X-ray absorptiometry scores available for 12 cases and 15 controls.

analysis (Table 2), factors significantly associated with stones included the following: white race (compared with nonwhite: 87% of cases, 70% of controls, $P = .04$), UTI (24% of cases, 6.3% of controls, $P < .01$), topiramate administration (39% of cases, 12.5% of controls, $P < .01$), vitamin D use (22% of cases, 8% of controls, $P = .02$), malabsorption (56% of cases, 36% of controls, $P = .04$), dehydration (44% of cases, 24% of controls, $P = .02$), ≤ 2 -year duration with G-tube (32% of cases, 13% of controls, $P = .01$), and whether goal free water intake was documented in the patient chart (46% of cases, 21% of controls, $P < .01$). Mobility status, presence of a urologic abnormality, tube feed formulation, and feeding schedule were not associated with urolithiasis on bivariate analyses. Although increased documentation of free water needs was associated with the presence of urolithiasis, several other subjective and calculated measures of hydration status were not (laboratory data not shown).

On regression analysis (Table 3), topiramate administration (odds ratio [OR]: 6.58 [95% confidence interval (CI): 1.76–24.59]), UTI (OR: 7.70 [95% CI: 1.59–37.17]), and having G-tube in place for < 2 years (OR: 8.78 [95% CI: 1.27–52.50]) were all significantly associated with the formation of stones. Of note, controls taking topiramate had a longer mean duration on the drug compared with cases (8.5 ± 3.0 years vs 4.4 ± 3.2 years, $P < .01$).

Of the 15 patients with a UTI in the 12 months before stone diagnosis, 3/10 cases (30%) and 3/5 controls (60%) had evidence of infection with a urea-splitting organism (*Klebsiella*, *Pseudomonas*, *Proteus*, and/or staphylococcus). An equal proportion (40%) of cases and controls with UTI had recurrent infection (> 1 UTI) in the year before the stone diagnosis date for the

TABLE 2 Bivariate Associations of Clinical Characteristics and Stone Formation in GTF Patients

	Cases (Stones) (N = 41)	Controls (No Stones) (N = 80)	P
	N (% of Cases)	N (% of Controls)	
Race			.04
White	34 (82.9)	52 (65.0)	—
Nonwhite	5 (12.2)	22 (27.5)	—
Unknown	2 (4.9)	6 (7.5)	—
Comorbidities			
UTI			$< .01$
Yes	10 (24.4)	5 (6.3)	—
No	31 (75.6)	75 (93.8)	—
Clean intermittent catheterization			.21
Yes	6 (14.6)	6 (7.5)	—
No	35 (85.4)	74 (92.5)	—
Urinary tract abnormality			.23
Yes	11 (26.8)	14 (17.5)	—
No	30 (73.2)	66 (82.5)	—
Seizures			.20
Yes	28 (68.3)	45 (56.3)	—
No	13 (31.7)	35 (43.8)	—
GERD			.09
Yes	33 (80.5)	73 (91.3)	—
No	8 (19.5)	7 (8.8)	—
Malabsorptive disorder			.04
Yes	23 (56.1)	29 (36.3)	—
No	18 (43.9)	51 (63.8)	—
Diabetes mellitus			.08
Yes	5 (12.2)	3 (3.8)	—
No	36 (87.8)	77 (96.3)	—
Dehydration			.02
Yes	18 (43.9)	19 (23.8)	—
No	23 (56.1)	61 (76.3)	—
Wheelchair-bound ^a			.26
Yes	26 (74.3)	47 (63.5)	—
No	9 (25.7)	27 (36.5)	—
Medications/supplements			
Topiramate use			$< .01$
Yes	16 (39.0)	10 (12.5)	—
No	25 (61.0)	70 (87.5)	—
Non-thiazide diuretic use			.11
Yes	7 (17.1)	6 (7.5)	—
No	34 (82.9)	74 (92.5)	—
Multivitamin			.14
Yes	20 (48.8)	28 (35.0)	—
No	21 (51.2)	52 (65.0)	—
Calcium supplementation			.09
Yes	12 (29.3)	13 (16.3)	—
No	29 (70.7)	67 (83.8)	—
Vitamin D supplementation			.02
Yes	9 (22.0)	6 (7.5)	—
No	32 (78.0)	74 (92.5)	—
Nutritional parameters			
Tube feed protein type			.39
Intact	25 (61.0)	55 (68.8)	—
Elemental/Semielemental	16 (39.0)	25 (31.3)	—
High protein or ketogenic formulation			.71
Yes	5 (12.2)	8 (10.0)	—
No	36 (87.8)	72 (90.0)	—
Feeding schedule			.54
Continuous	13 (32.5)	24 (30.0)	—
Bolus	14 (35.0)	36 (45.0)	—
Combination	13 (32.5)	20 (25.0)	—

TABLE 2 Continued

	Cases (Stones) (N = 41)	Controls (No Stones) (N = 80)	P
Duration with G-tube			.01
<2 y	13 (31.7)	10 (12.5)	—
≥2 y	28 (68.3)	70 (87.5)	—
PO intake in addition to tube feeding			.79
Yes	20 (48.8)	37 (46.3)	—
No	21 (51.2)	43 (53.8)	—
Nutrition consult within 2 y of stone			.57
Yes	25 (60.1)	53 (66.3)	—
No	16 (39.9)	27 (33.8)	—
Goal free water documented within 2 y of stone			<.01
Yes	19 (46.3)	17 (21.3)	—
No	22 (53.7)	63 (78.8)	—
Free deficit >10% + no additional PO intake			.13
Yes	9 (22.0)	28 (35.4)	—
No	32 (78.0)	51 (64.6)	—

^a Excludes 12 patients under age 3.

TABLE 3 Matched Logistic Regression of Factors Associated With Stone Formation in GTF Patients

	Unadjusted OR	95% CI	P	Adjusted OR	95% CI	P
White race	2.67	0.94–7.58	.06	1.93	0.62–6.02	.26
UTI	3.84	1.31–11.27	.01	7.70	1.59–37.17	.01
Topiramate	5.90	1.92–18.10	<.01	6.58	1.76–24.59	<.01
Malabsorption	2.23	1.03–4.84	.04	1.75	0.63–4.89	.29
Tube duration >2 y	5.71	1.56–20.83	<.01	8.78	1.27–62.50	.03

case. Of the 10 patients with both a UTI and a stone, only 2 (20%) had UTI as their indication for imaging.

Stone Characteristics

The stone characteristics for the patients with urolithiasis are illustrated in Table 4. Median stone size was 0.6 cm (range, 0.2–1.3 cm), 18 patients (45%) had bilateral disease, and 26/39 patients (67%) with imaging studies available had 2 or more stones identified. Nearly half of patients presented symptomatically, with pain, infection, and hematuria all being common. If we defined “clinically significant” stones as symptomatic presentation, stone size >3 mm, and/or surgical intervention being necessary, 33/41 (83%) of patients fell within this category.

Only 7 patients (17%) underwent surgical therapy for treatment of their stones. Chemical stone analysis was available for 8 patients (20%). Of these, 7 (87.5%) had calcium phosphate as

a primary or secondary component of their stone, and only 2 (25%) had a struvite component.

DISCUSSION

In this study, we aimed to identify clinical differences between stone-forming and nonstone-forming children who are primarily GTF, with the ultimate goal of determining modifiable factors associated with increased risk of urolithiasis in this population. For our patients, we identified 3 predictors of stone formation: topiramate administration, UTI, and shorter length of time with the G-tube. We found no association between the presence of stones and specific tube feed formulation or mobility status. The majority of our patients appeared to have clinically important stone disease. However, a small minority received surgical treatment, suggesting that many of these complicated patients are managed conservatively.

Our study findings highlight an important association between topiramate usage and stone development and confirm the results of several previous studies. Topiramate has previously been associated with an increased risk for nephrolithiasis in patients with refractory epilepsy, both as an isolated factor^{9–11} and when examined in combination with ketogenic diets.¹² Neurologically impaired, nonambulatory children appear to be at particularly high risk for kidney stone development when taking topiramate, with 1 study demonstrating a 54% incidence of urolithiasis among a group of 24 such patients.¹³ Topiramate is a weak carbonic anhydrase inhibitor that is thought to induce stone formation through the development of hypocitraturia as well as potentially a defect in distal tubular urinary acidification.⁹ Treatment with topiramate has been shown to cause metabolic acidosis, markedly lower urinary citrate excretion, and increased urinary pH, all putting patients at risk for calcium-based urolithiasis.¹⁰ Interestingly, calcium phosphate was the primary stone component for both cases with available stone analysis data who were on topiramate. Taken in context of previous related studies, our data suggest that strong consideration should be given to using alternative antiepileptic agents in GTF children whenever possible. Additionally, one could also consider administering potassium citrate prophylaxis in patients who must stay on topiramate; this strategy has shown to be effective in patients on the ketogenic diet for seizure control.^{14,15}

We also observed a strong association between a documented UTI and the presence of stones in our population. Despite this, only 2/8 (25%) of patients with a stone analysis had struvite as a stone component, and a higher proportion of controls (60%) versus cases (30%) had evidence of infection

TABLE 4 Clinical Characteristics for GTF Patients With Stones

	Median [Range] or N (%)
Maximum stone size	0.6 [0.2–1.3]
Stone number	
1	13 (33.3)
2	6 (15.4)
3	8 (20.5)
4	2 (5.1)
5 or more	10 (25.6)
Type of presentation	
Hematuria	5 (12.2)
Pain	7 (17.1)
Infection	7 (17.1)
Other symptom	1 (2.4)
Incidental	21 (51.2)
Family history	
First degree relative	2 (4.9)
Other relative	8 (19.5)
Any family history	9 (22.0)
Clinically significant stone ^a	
Yes	33 (80.5)
No	8 (19.5)
Primary component	
Calcium oxalate	3 (37.5)
Calcium phosphate	4 (50.0)
Brushite	1 (12.5)
Secondary component	
Calcium oxalate	1 (16.7)
Calcium phosphate	3 (50.0)
Struvite	2 (33.3)
Stone side	
Right	6 (15.8)
Left	14 (36.8)
Bilateral	18 (47.4)
Treatment type	
Observation	33 (80.5)
Medical	2 (4.88)
Extracorporeal shock wave lithotripsy	5 (12.2)
Ureteroscopy	1 (2.44)

^a Symptomatic presentation, stone size >3 mm, and/or surgical intervention necessary.

with a urea splitting organism. Previous studies of pediatric patients with urolithiasis in endemic regions have demonstrated a high rate of UTIs in patients with stones, ranging from 45.9% to 70%.^{16–18} However, these investigations have noted varying rates of struvite stones (10%–44.8%).^{16,19} Although we only have stone analysis results available on 8 patients, it is unlikely that the remainder of our patients had a significant struvite component, given the lack of staghorn calculi.^{20,21}

Our 24.4% rate of UTIs among stone forming patients is similar to the 30%

UTI rate found in a contemporary British series of pediatric stone patients.²² Causality in our sample is difficult to determine; based on the available stone analyses, most of the stones were noninfectious. UTIs diagnosed before the discovery of the stone did not necessarily cause, or even temporally precede, formation of the stone. Regardless of causality, this relationship between UTI and stones appears to be an important marker for clinicians to be aware of in patients who are GTF.

Although the associations between UTI and stones and topiramate and stones were strong, the relationship between hydration status and the development of stone disease was less clear. These complex patients are often managed at multiple facilities and we found documentation of nutrition assessments and free water goals to be less reliable when compared with other, more defined clinical parameters, such as length of time with a G-tube. On bivariate analysis, we found that documentation of goal free water intake was positively associated with stone disease, whereas longer duration of G-tube was negatively associated with stone disease; goal free water documentation and length of time with a G-tube were also negatively related to one another. Given this, coupled with our concern about reliability of the documentation variables, we included only length of time with a G-tube in the final regression model.

The finding that a shorter duration of GTF is associated with a higher rate of stone disease nevertheless leads us to question whether these patients with complex chronic conditions (CCCs) had been experiencing significant, but clinically underappreciated, chronic dehydration before GT placement, as presumably inability to meet all nutrition and hydration needs via oral ingestion had been a primary indication

for receiving a GT. A state of chronic dehydration could put GTF children at risk for urolithiasis (and other dehydration-related issues), especially as the initial post-GT placement period may involve a very different feeding regimen from that which children were receiving before tube placement. Although further studies are necessary to clarify the relationship between stones and hydration in patients with CCCs, previous authors have demonstrated that these patients are at significant risk for dehydration. For example, 1 investigation of nutritional parameters in nonambulatory GTF children revealed that increased urine osmolality is a common issue in patients with CCCs, and that concentrated tube feed formulation appears to be a risk factor for this marker of dehydration.²³ Additionally, nutritional guidelines for patients with CCCs have traditionally focused on nutrient content and total caloric intake, and make only passing mention of free water needs.^{24,25} Early, routine nutrition consultation with a protocol that includes universal assessment of whether free water needs are being met via total fluid intake could benefit all patients with CCCs, particularly those who are GTF.

Our findings expand upon clinical details regarding GTF patients with stones and help to answer some of the questions posed by Smith et al.⁷ Akin to patients in their investigation, we found a high proportion of calcium phosphate stones, supporting a metabolic explanation for the increased risk of stones in GTF children. Smith et al.⁷ reported similar rates of hypercalciuria in GTF patients with stones, and otherwise healthy children with stones, and suggest that hypercalcemia due to immobility was not a key factor in stone promotion. Similarly, we found no association between mobility status and urolithiasis in GTF children with and without stones.

Our study has several important limitations. We relied upon billing data to identify our patient population, and may have missed potential cases or controls if appropriate billing codes were not applied. Also, GTF children represent a heterogeneous group with a constellation of underlying diagnoses; our particular sample of GTF children may not be generalizable to other institutions or regions, and these results may not apply to similar patients elsewhere, regardless of G-tube status. In addition, we cannot be certain that control patients did not have undetected stones or that they will not develop stones in the future. Finally, our study may be underpowered for detection of certain differences in stone risk, particularly those related to nutritional parameters. For example, only 13/121 (10.7%) of patients overall were on a high-risk (high protein or ketogenic) formulation.

While the case-control nature of this study allowed us to examine potential risk factors for stone formation in this population, its retrospective nature limited the level of clinical details available. For example, we were unable to reliably assess specific functional measures other than wheelchair status when evaluating mobility. Additionally, assessment of 24-hour urinary parameters was only available for 1 of our

stone patients, so we were unable to evaluate urinary risk factors for stone disease. Perhaps the most important consideration is that we found hydration status to be difficult to assess accurately, and proxy data such as serum urea nitrogen and urinary specific gravity were too heterogeneously detailed in clinical records for us to report accurately. An additional challenge was encountered in the assessment of hydration status for patients who take in fluids orally and via G-tube, as there appeared to be no standardized documentation of clinical goals for free water intake in this population.

Despite these limitations, we believe our study provides important insight into the clinical differences between GTF children who form stones and those who do not. Taken together, our findings provide a preliminary risk profile for GTF patients at the highest risk of urolithiasis, which can help guide the evaluation of these complex patients. We also identified several areas for further consideration, specifically the use of topiramate and the unclear relationship between free water intake and stones in GTF patients. Potential targets for further investigation include the following: (1) determining if potassium citrate is an appropriate prophylactic strategy for patients on topiramate and (2) prospectively establishing the relationship between free

water intake and urolithiasis in patients with CCCs.

CONCLUSIONS

Our findings provide a preliminary risk profile for the development of urolithiasis in GTF children. We found important associations of stone formation to include topiramate administration, UTI, and shorter duration with a G-tube, which we postulate may be a marker for chronic dehydration. Of the relationships observed, topiramate usage appears to have the strongest plausibility for a causal relationship with stone development. Areas identified for further investigation include strategies for targeted risk reduction and clarifying the relationship between free water intake and stone risk in this challenging population.

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