A Twist and New Observation in a Case of Persistent Neonatal Hyperuricosuria

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Background

The finding of red or pink spots in the diaper of an infant can be troubling for families, who immediately become concerned about hematuria. However, the differential diagnoses of these spots may include benign and complex causes (Table 1).[1] Using a careful history and focused evaluation, providers can narrow down the possibilities. Perhaps the most common cause of reddish spots in an infant's urine are urate crystals, particularly among breast-fed newborns.[2] Uric acid is a weak organic acid resulting from purine metabolism, and can precipitate as urate crystals. Normal urate levels as well as the affinity to form uric acid stones vary considerably, depending on ethnicity, sex, geographic region, and diet.[3,4] Generally, uric acid levels are higher at birth and wane through adolescence when they stabilize to adult levels.[2] The high amount of protein in breast milk creates very acidic urine in infants, often prompting uric acid crystal formation, manifesting as red-tinged urine.[5] This finding is typically self-limiting in newborns, without requiring further workup or treatment other than maintenance of hydration.[2] Considering the differential diagnosis noted above, we present a case of unusually persistent red-tinged urine in a male infant. This case highlights an atypical presentation of a common condition, which prompted a more detailed evaluation and new clinical observation.

Table 1. Causes of Red-Tinged Urine in an Infant.[1]

Ingestion of red foods (beets, radishes, cranberries, or carrots) or dyes
Medications (eg, cefdinir, rifampin)
Hematuria
Urinary tract abnormalities
Nephrolithiasis
Urate crystal formation
Renal tubular abnormalities
Byproducts from inborn errors of metabolism (eg, Lesch–Nyhan syndrome, HGPRT [hypoxanthine-guanine phosphoribosyltransferase] and APRT [adenine phosphoribosyltransferase] deficiencies)
Serratia species overgrowth
Munchausen's by proxy

Case

A previously healthy 4-month-old boy of Iranian descent presented with parental concerns regarding the appearance of multiple pink spots in his diaper (Figure 1). Parents noted a similar occurrence at 2 months of age with only one small spot in the diaper. Given the likely diagnosis of benign urate crystal formation, the family was provided education and directed to follow up if the symptoms persisted. Three weeks after the initial complaint, the family returned, citing recurrence supplementation with Neosure. There was no unusual odor or gross blood associated with his urine and he had been otherwise healthy and growing well.

Past medical history was notable for a late preterm vaginal delivery and uncomplicated 2-week neonatal intensive care unit stay. His family medical history was remarkable for both his mother and maternal grandmother having a history of nephrolithiasis and his maternal grandfather having gout. Additionally, his mother

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Table 2. Laboratory Evaluation.

Laboratory Test	5 Months of Age	6 Months of Age	12 Months of Age
Glucose	100	108	
BUN (blood urea nitrogen)	6.7	8.3	
Creatinine	0.23	0.22	
Sodium	138	139	
Potassium	4.4	4.0	
Chloride	108	106	
CO_2	21	25	
Anion gap	9	8	
Calcium	11.23	11.12	
Magnesium mg/dL		3.7 (H)	2.5
Phosphorus		6.02	
Uric acid	2.8	4.0	
WBC urinalysis	0-2		
RBC urinalysis	0-2		
Epithelial cell urinalysis	0-2		
Bacteria urinalysis	None seen		
Calcium urine, mg/dL	15.20		
Ratio calcium/creatinine	0.67		
Creatinine urine mg/dL	22.80		
Uric acid urine mg/dL	45		

had α-thalassemia trait and hypothyroidism. Both parents were from Iran, though the patient was born in the United States. His physical and developmental examination was normal. Based on the presentation, age, and family history, a urinalysis was obtained (normal). Given the remote timing from birth for urate crystal appearance, the nephrology service was contacted. Their assessment was that the findings were consistent with benign urate crystals, particularly given that the child was still breast-feeding.

The child returned at 5 months of age, noting the red-orange spots were now occurring nearly every void. The parents, concerned about dehydration, were feeding the patient 3 to 4 oz every 2 to 3 hours following nursing. The patient had no acute illnesses or signs of underlying chronic disease. The family denied antibiotic intake or maternal ingestion of foods known to cause urine discoloration. Given this increasing frequency, further workup was initiated. Laboratory evaluation (Table 2) demonstrated high normal serum calcium with an otherwise normal metabolic panel, serum uric acid, and urinalysis. A urine calcium/creatinine (Ca/Cr) ratio of 0.67 and urine uric acid/creatinine (UA/Cr) ratio of 1.97 were obtained. There are varying reports on the normal range of urine UA/Cr ratio in infants around 6 months of age, and the patient's ratio appeared to suggest hyperexcretion of uric acid beyond what would normally be expected.[4]

A renal ultrasound was obtained as screening for nephrolithiasis. The ultrasound demonstrated no evidence of renal stones; however, a distended left upper pole renal calyx was noted. A voiding cystourethrogam was recommended to exclude vesicouretral reflux (as a cause of urinary stasis and elevated urinary urate) but was declined by the parents. Over the following week, he continued to have red spots in the diaper every 1 to 2 days. The parents remained concerned about dehydration and increased his intake to approximately 32 oz a day. He was switched from Neosure formula to Similac Advance to decrease his protein intake as a possible source of the discolored urine. During this interval, his mother's milk supply began to decline. The orange urine's appearance subsequently decreased to about 1 time a week.

At 6 months of age, the patient had a formal outpatient evaluation by nephrology. A complete blood count, a basic metabolic panel, phosphate, and uric acid were all normal. Specific testing for hypoxanthine-guanine phosphoribosyltransferase (HGPRT) and adenine phosphoribosyltransferase (APRT) deficiencies was obtained. Both of these disorders can present with red-tinged urine and lead to renal stones; both studies returned normal. The only abnormal finding was an elevated magnesium level (3.7 mg/dL; normal range 1.7-2.3 mg/dL), with a repeat still elevated (2.7 mg/dL). There was no common cause for the elevated magnesium value, including evidence of visible hemolysis or a history of exogenous magnesium supplementation. A repeat magnesium level the following week remained elevated (2.9 mg/dL). Additional causes of hypermagnesemia were considered, including intrinsic renal disease, hypercalcemia, thyroid disease, and hypoparathyroidism.

As medication can commonly increase magnesium levels, the family was questioned again regarding supplements or foods consumed by the mother as she was breast-feeding. She had started taking fenugreek (*Trigonella foenum-graecum*) tablets to increase her lactation 10 days prior to first magnesium level being drawn. She stopped, however, after the repeat magnesium level was elevated, as the family was concerned that fenugreek had been reported in the lay press as a treatment for hypomagnesemia. A magnesium and fractional excretion (FE) of magnesium were done to see if the patient was excreting additional magnesium given his high levels. The magnesium level was 2.7 mg/dL, with a FE of magnesium of 3.9% (upper end of normal range). The patient continued to do clinically well and by the time the results of the FE magnesium returned, he had ceased having red-tinged urine in his diaper.

The family followed up for a 12-month well-visit and the patient had not had a red-tinged diaper for 5 months. A repeat magnesium level (obtained not breast-feeding or on fenugreek) was 2.5 mg/dL. Given the disappearance of the red-tinged urine and otherwise normal

growth and development, it was decided that no additional evaluation was required. His final diagnosis was benign, prolonged urinary urate crystallization without stone formation, predisposed by his ethnicity, diet, and family medical history.

Discussion

For pediatricians, red-appearing urine in an infant's diaper is not unusual. However, the persistence of this finding beyond the immediate neonatal period is rather uncommon and should prompt consideration of underlying metabolic abnormalities, structural anomalies that encourage urinary stasis, or genetic disorders (Table 1). This case was atypical given the prolonged time course and persistence of the red-tinged urine. Likely causes were the patient's ethnicity (as both parents were from Iran, a country well-described to have a higher incidence of urinary urate deposition) and diet. As uric acid solubility is very much affected by urinary pH, low urine pH can be reflective of excessive amounts of acid-forming foods (eg, protein, particularly with breast milk).[3]

A traditional way to prevent uric acid crystallization is to increase the urinary solubility by increasing urinary volume. Reducing protein intake will also improve solubility and increase urinary pH. For this patient, as his parents felt that the red-tinged urine was a sign of dehydration and inadequate breast-feeding, they increased his total fluid volume of 22 kcal/oz infant formula, which subsequently increased his protein load and likely contributed further to his urinary urate deposition. Despite persistent hyperuricosuria and the patient's risk factors as described above, no stones were formed. This may have been due to several factors. It was recommended to his parents to change to standard 20 kcal/oz infant formula, particularly given the patient's robust growth. This decreased his total protein load and likely raised his urinary pH. Additionally, having an elevated level of magnesium may have been protective against renal stone formation. Magnesium inhibits urinary calcium oxalate supersaturation, causing patients with hypomagnesemia to be at a greater risk of renal stones.[4]

Fenugreek has been used as a galactogogue and as an aid to indigestion.[6] Reported side effects include abdominal pain, diarrhea, and a maple syrup like odor to milk, sweat, and urine.[7,8] Although no studies suggest that fenugreek increases maternal magnesium production, known side effects include diarrhea and abdominal pain, which coincide with common symptoms associated with hypermagnesemia. It is possible that this patient's mother's use of fenugreek as a galactogogue may have resulted in his elevated magnesium level and subsequently may have been protective against urate stone formation as well. Interestingly, the patient's magnesium level declined following the cessation of oral fenugreek by the mother. It is unclear how much of an effect fenugreek and some transient hypermagnesemia may have played on his hyperuricosuria.

Though a common cause of transient red-tinged urine in the neonate, persistent uric acid crystallization beyond 6 months of age should prompt additional consideration of underlying metabolic disease, structural abnormalities, or renal tubular dysfunction, particularly among populations more predisposed to hyperuricosuria and nephrolithiasis.

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References

1. Pan C, Avner E. Clinical evaluation of the child with hematuria. In: Kliegman R, Stanton B, St. Geme J, Schor N, Behrman R, eds. *Nelson Textbook of Pediatrics*. 19th ed. Philadelphia, PA: Elsevier; 2011:1779.
2. Robson WLM, Leung AKC. Reddish urine stain in the diaper of a 3-week-old boy. *Consultant Pediatr*. 2006;5(4). http://www.pediatricsconsultant360.com/content/pediatric-urology-clinics-reddish-urine-stain-diaper-3-week-old-boy. Accessed June 30, 2014.
3. Halabe A, Sperling O. Uric acid nephrolithiasis. *Miner Electrolyte Metab*. 1994;20:424-431.
4. Naseri M, Varasteh AR, Alamdaran SA. Metabolic factors associated with urinary calculi in children. *Iran J Kidney Dis*. 2010;4:32-38.
5. Baldree LA, Stapleton FB. Uric acid metabolism in children. *Pediatr Clin North Am*. 1990;37:391-418.
6. Forinash AB, Yancey AM, Barnes KN, Myles TD. The use of galactogogues in the breastfeeding mother. *Ann Pharmacother*. 2012;46:1392-1404.
7. Budzynska K, Gardner ZE, Low Dog T, Gardiner P. Complementary, holistic, and integrative medicine: advice for clinicians on herbs and breastfeeding. *Pediatr Rev*. 2013;34:343-352.
8. Zuppa AA, Sindico P, Orchi C, Carducci C, Cardiello V, Romagnoli C. Safety and efficacy of galactogogues: substances that induce, maintain and increase breast milk production. *J Pharm Pharm Sci*. 2010;13:162-174.