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Original Article

Epidemiology and Risks of Red Urine in Patients in the Pediatric Emergency Department of a Medical Center in Central Taiwan: An 8-Year Study

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Background: Red urine, an uncommon presentation in the pediatric emergency room, can be categorized into pigmenturuia and gross hematuria. Pigmenturia has been associated with a number of conditions, including colored foods and crystals. However, gross hematuria results from different causes and presents different risks in adults than in children. Glomerulopathies, the incomplete clearing of substances from the blood that make their way through the glomerulus to urine, can progress to end-stage renal failure if not detected and treated early. Therefore, this study undertook a retrospective analysis of all pediatric patients who presented red urine at the pediatric emergency department of Changhua Christian Hospital between June 2000 and June 2007 to determine the proportion of red urine, analyze probable etiologies and investigate the factors associated with the development of glomerulonephritis in this population.

Methods: We reviewed and analyzed 180 medical charts of children with red urine and tested our results using two-sample t-test and Pearson product-moment correlation coefficient.

Results: Almost 1/1000 (0.9/1,000) children visiting the pediatric emergency room presented red urine during the study period. Gross hematuria and pigmenturia patients were significantly different in age (6.10 ±3.37SD vs. 3.06 ±3.35SD, respectively; p=<0.001. The most common underlying cause was urinary tract infection (36.7%). Glomerulonephritis occurred in 10.2% of all the patients. There was a significant difference in C-reactive protein concentrations in glomerulonephritis patients and non-glomerulonephritis patients. Cases with recurring red urine and proteinuria were significantly more likely to have glomerulonephritis.

Conclusion: Red urine is relatively uncommon (0.9/1,000) in children visiting the emergency room. Glomerulonephritis was found in 10.2% of patients presenting with red urine. Patients with red urine who had a history of recurrence or proteinuria were a greater risk of glomerulonephritis.

Key words: red urine, gross hematuria, glomerulonephritis, proteinuria, pediatric emergency

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Introduction

Discovering red urine in a child is frightening for both the child and his or her parents. Red urine without red blood cells (RBCs), known as pseudohematuria or pigmenturia, may be caused by various drugs, colored foods, food dyes or crystals

in urine. Gross hematuria, a term for visible bloody urine, on the other hand, is another cause of red urine.

The causes of gross hematuria are complex and it may serve as a warning of more serious conditions for a physician. Gross hematuria is relatively unusual in children, accounting for approximately 1 in 1000 outpatient visits to a pediatrician[1]. Papper reported that only a small quantity of blood (1 mL blood to 1000 mL urine) is necessary to make urine appear red[2]. Gross hematuria in children may be cause by different possible conditions than it is in adults. Although the major causes of gross hematuria in children and young adults are glomerulopathy, urinary tract infection (UTI), hypercalciuria, stones, congenital urologic conditions, and trauma[1, 3, 4], there are a significant number of cases in which the etiology of hematuria remains undetermined in children[3, 5].

Chronic glomerulopathy, a term used to describe a disease affecting the glomeruli of the nephron, can progress to end-stage renal failure. Therefore, it is important for a physician to identify patients who may have glomerulopathies such as glomerulonephritis. Most cases of glomerulonephritis (GN) in children are caused by poststreptococcal glomerulonephritis (PSGN), IgA nephropathy, membranoproliferative glomerulonephritis, Henoch-Schönlein purpura (HSP) nephritis, and systemic lupus erythematosus (SLE) nephritis.

The aim of this epidemiology study was to study children who present with red urine in a pediatric emergency department (PED) to identify risk factors of glomerulopathies in this population. To do this, we conducted a retrospective analysis of epidemiological characteristics of all children visiting the PED of Changhua Christian Hospital (CCH) for red urine between June 2000 and June 2007.

Methods

We reviewed the charts of all patients presenting red urine at our PED between June 2000 and June 2007. Medical records were reviewed for age, sex, associated symptoms, past and present medical history, physical findings, evaluation tests performed, urine analysis, clinical course, and diagnoses. Proteinuria was defined when a dipstick registered ≥1+ (30mg/dl) in a urine sample that had a specific gravity of ≤1.015 or when it registered ≥2+(100mg/dl) in a sample that had a specific gravity of > 1.015. Leukocytosis was defined as the finding of >15,000 white blood cells (WBC) per microliter in a peripheral blood sample, and pyuria was defined as the finding of >5 WBCs per high-power field (HPF) in the urine sample. Hypertension was defined as having an SBP and/or DBP in the > 95th percentile. Anemia was defined based on age-appropriate hemoglobin levels.

The two-sample t-test and Pearson product-moment correlation coefficient were used to analyze the distributions and correlations of variances among different groups and diagnoses. A $p < 0.05$ was considered significant. All statistical operations were performed using SPSS 14.0 software.

Results

Over an 8-year period, a total of 180 patients (0.9/1000 visits) presented red urine at our PED. No urine samples were obtained from three children (1.7%), so they were excluded from the analysis. Thus, this study represents the analysis of 177 patients. The greatest number of children presenting red urine were seen in 2005 (n = 42), and the fewest were seen in 2003 (n = 8). There was also seasonal variability, with more cases seen during the summer months. Urinalysis showed that 47 (26.6%) had pigmenturia.

As can be seen in Table 1, the sample consisted of 113 boys (63.8%) and 64 girls (36.1%) with a mean age of 5.30±3.61 SD years old. Fifty percent were under five years old, 75% under eight years old and 90% under ten. Only 5 cases (2.8%, 3 boys and 2 girls) were older than twelve years old. The mean age of those with gross hematuria was 6.10± 3.37SD and that of those with pigmenturia 3.06 ± 3.35SD, a significant difference ($p < 0.001$). Over fifty percent of the children with pigmenturia were 2 years old (25, 53.2%). (Table 1)

As can been seen in Figure 1a and 1b,

Table 1. Age-group distribution of red-urine

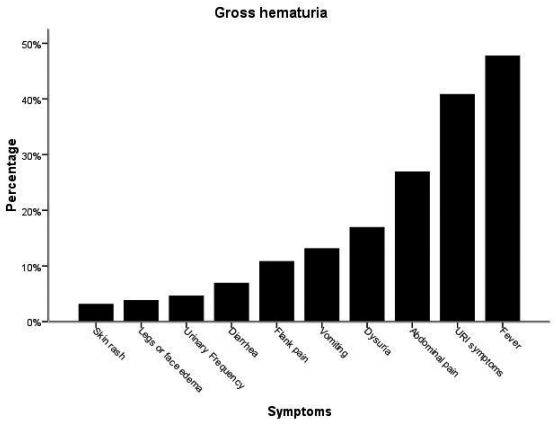
	Hematuria						Pigmenturia					
	Sex						Sex					
	Male n=86			Female n=44			Male n=27			female n=20		
Age	Frequency	%	Cum.%	Frequency	%	Cum.%	Frequency	%	Cum.%	Frequency	%	Cum.%
<1	3	3.5	3.5	0	0.0	0.0	12	44.4	44.4	4	20.0	20.0
1~3	22	25.6	29.1	9	20.5	20.5	6	22.3	66.7	9	45.0	65.0
4~6	22	25.6	54.7	15	34.0	54.5	4	14.8	81.5	2	10.0	75.0
7~9	27	31.3	86.0	14	31.9	86.4	3	11.1	92.6	4	20.0	95.0
>9	12	14.0	100.0	6	13.6	100.0	2	7.4	100.0	1	5.0	100.0

% : Pecent
Cum.% : cumulative percent

summaries of symptoms of in children with gross hematura and pigmentuira, the symptoms most commonly associated with red urine were fever (45.8%) and upper respiratory tract infection (36.7%) such as rhinorrhea, cough, and nasal obstruction. Otherwise, gross hematura and pigmentuira cases had different associated symptoms. Those with gross hematuria most often presented abdominal pain and dysuria, while those with pigmenturia most often presented urinary frequency and diarrhea. Seventeen children (9.6%) had recurrent episodes of red urine (data not shown).

Proteinuria was found in 53 (40%) cases of gross hematuria and in only 2 (4.2%) cases of pigmenturia (Chi-Square test; p <0.0001). Because only 52% of the sample had blood pressure measurements taken, it is more difficult to draw conclusions about blood pressure. However, of that group, only 3 children had hypertension. Those three were also found to have gross hematuria.

Etiology could not be identified in 67 patients (37.9%). Overall, UTI was the most common cause (36.7%). Table 2, a summary of causes of non-



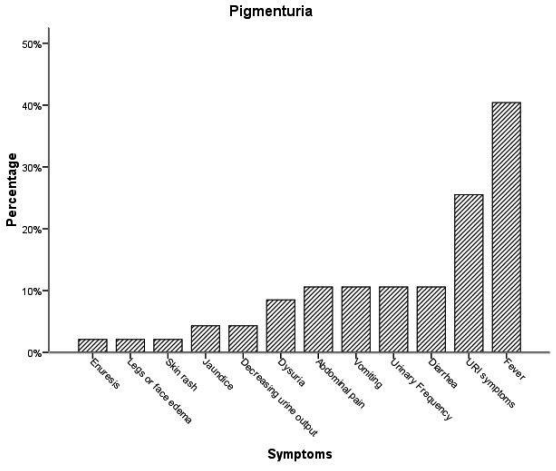


Fig. 1a. Associated symptoms of gross hematuria patients
Fig. 1b. Associated symptoms of pigmenturia patients

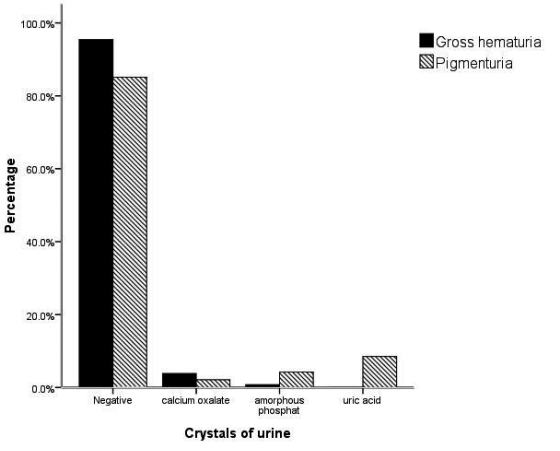


Fig. 2. The Crystals of urine between patients of gross hematuria and pigmenturia

Table 2. Etiology of red -urine without hematuria patients

Male		Female	
Etiology	n = 27	Etiology	n=20
Unknown	10	Unknown	11
Urinary tract infection	8	Urinary tract infection	3
Hypogammaglobulinemia	1	Lupus nephritis	1
Hyperbilirubinemia	1	Vaginal bleeding	1
Colored food	1	Nephrotic syndrome	1
Rhabdomyolysis	1	Salmonella gastrocolitis	1
Vasculitis	1	Choledochal cystitis	1
Uric acid crystalluria	4	G6PD deficiency	1

G6PD: Glucose-6-phosphate dehydrogenase

hemaria cases, shows that except for UTI, the etiology of pigmenturia could not be identified. However, because the pigmenturia mostly happened in younger-aged children, whose urine was more acidized (pH 6.26±0.94 vs. 6.32±0.77, p=0.07), uric acid crystals of urine could be found in 8.5% of the pigmenturia cases. (Fig. 2)

Table 3 shows the causes of gross hematuria analyzed by sex. In both genders, the most frequent causes of gross hematuria were UTI (boys 46.5% vs. girls 31.8%), acute GN (9.3.0% vs. 9.1%) (such as is found in PSGN, IgA nephropathy and lupus nephritis) and trauma (7.0% vs. 6.8%). Gross hematuria was caused by trauma in nine patients (6 boys and 3 girls). In one case (0.6%), it was caused by sexual assault of a girl older than 12 years. Seventy-five (57.7%) of the children with gross hematuria patients were admitted to pediatric wards for further evaluation and treatment.

Of the seventeen patients with the recurrent red urine, nine had no apparent etiology, two were diagnosed as having IgA nephropathy, two with Alport syndrome, one with hypercalciuria, one with hypogammaglobulinemia, one with nephrotic syndrome, and the other with UTI.

Eighteen patients (10.2%) had glomerulonephritis (GN). Fifteen of them had hematuria. The underlying causes of GN were undefined acute glomerulonephritis (n = 2), lupus nephritis (3), PSGN (5), HSP (1), hypogammaglobulinemia (1), nephrotic syndrome (1), Alport syndrome (2), and IgA nephropathy (3).

Table 3. Etiology and admission rate of red -urine with hematuria

		Sex			
		male		Female	
Etilogy		No.	%	No.	%
Unknown		28	32.60%	21	47.70%
UTI	Cystitis	8	46.50%	2	31.80%
	Urethritis	1	0		
	APN	0	1		
	Undefined part of urinary tract system	31	11		
Acute GN	PSGN	4	9.30%	1	9.09%
	IgA nephropathy	3	0		
	Lupus nephritis	1	1		
	Undefined GN	0	2		
Trauma	6	7.00%	3	6.80%	
Hypercalciuria	4	4.70%	2	4.50%	
Alport syndrome	2	2.30%			
Renal Stone	1	1.20%			
HSP	1	1.20%	1	2.30%	

UTI: Urinary tract infection, PSGN: Post -streptococcal glomerulonephritis, HSP: Henoch-Schönlein purpura
APN: Acute pyelonephritis, GN: Glomerulonephritis

More boys than girls had GN (12 vs. 6). Of these 18 patients, only two (1.1%) children presented acute nephritic syndrome (tea or cola-colored urine, facial/body edema, hypertension, and oliguria).

A t-test or Pearson product-moment correlation coefficient was used to examine the correlations between glomerulonephritis and all potential factors, including age, sex, symptoms, blood, and urine. In blood, only the level of C-reactive protein (CRP) had a trend for significance in the difference ($p = 0.051$) between GN and non-GN patients. No significant association was found between GN and peripheral blood leukocytosis, anemia, or mean cell volume of RBCs. In urine, only the presence of proteinuria was significantly correlated with GN ($p = 0.030$; $R = 0.22$). There were also no significant correlations between GN and hematuria, pyuria, specific gravity of urine, or urinary glucose levels.

We found no relationship between age, sex, and symptoms and the prevalence of glomerulonephritis. However, based on our results, there was a significant correlation between the history of recurrence of red urine and GN ($p < 0.001$, $R = 0.27$).

A logistic regression model was constructed to determine the two significant predictive factors. From the model, "recurrent red urine" had an odds ratio of 5.44 (95% CI: 1.635–18.103) and "proteinuria" had an odds ratio of 4.342 (95% CI: 1.332–14.154).

Discussion

This study found red urine to be relatively uncommon (0.9/1,000) in children visiting the emergency room, urinary tract infection to be the largest single cause (36.7%), and 10.2% of patient with red urine to have glomerulonephritis. Recurrent red urine and proteinuria were associated with glomerulonephritis.

Our study found a smaller frequency of red urine presented in our PED than Ingelfinger (0.9/1000 vs. 1.4/1000)[6]. Generally, urine analysis can be used to divide patients with red urine into those having gross hematuria or pigmenturia. We found UTI was the most common cause of red urine, and glomerulonephritis to be the cause in 10.2%, the latter a higher percentage than that reported by Ingelfinger et al. (4%)[1]. We also found gender difference in the prevalence of UTI being the cause of red urine. At the elementary school age, the rate of UTI decreased in boys but increased in girls. In addition,73.6% of the cases of UTI were accompanied by either pyuria on urinalysis.

The excretion of uric acid in urine is especially high during early infancy and falls during childhood. The high protein content of breast milk favors acid urine, so sometimes the reddish stain in the diaper is caused by uric acid crystals. The problem is self-limited and no treatment is usually necessary. This phenomenon can explain partially the of reason for the greater prevalence of pigmenturia in younger aged children. Although urinalysis did not recognize hermaturia in 47 (26.6%) of the 177 patients, 51.1% of those 47 cases with red urine were still found to be caused by hematuria (Table 2). In Taiwan, school children need to receive two sequential urine screenings to confirm the abnormal results during mass urinary screening[6, 7]. Likewise, in order to avoid missing GN, we suggest that when patients presenting red urine at a PED have normal urinalysis findings, they should be scheduled to receive a repeat urinalysis two week later.

Greenfield reported of predominance of boys (4:1) having gross hematuria8. We also found a larger proportion of boys (2:1) to have this disorder. In our study, 62.3% of the cases of gross hematuria resulted from UTI or other identifiable causes. As in another study, we did not identify a cause for red urine in an a large subset of children[5].

Ingelfinger et al. reported UTI to be the most common cause of gross hematuria, followed by irritation of the perineum, meatal stenosis with ulceration, trauma, and the receipt of recent surgical procedure[1]. The frequency of trauma in our results was the same as that found by Ingelfinger (7%)[1]. Less common causes of hematuria that have been reported include malignancy, angiomatous malformations of the collecting system, the nutcracker syndrome, autosomal dominant polycystic kidney disease, hyperoxaluria, idiopathic thrombocytopenic purpura, etc[3, 8-15]. There were no findings of

malignancy in our study, although malignancy was found in Ingelfinger's large series[1]. Child abuse or sexual assault should be suspected in a child presenting unexplained bruising and hematuria, although the incidence was quite low in our results.

Several articles have discussed the steps for determining the etiology of gross hematuria[16, 17]. In addition to urinalysis, a careful family history, a physical examination and the recording of symptoms are important in assessing the causes of hematuria. Ultrasonography has been shown in the past to reliably identify bladder transitional cell carcinoma in children[18]. A cystoscopy can be reserved for the evaluation of unusual causes of gross hematuria[13, 15], such as angiomatous malformations of the collecting system. Three patients (2.3%) in our series had cystoscopies, though we could not identify their etiologies.

Quigley reported that children with combined hematuria and proteinuria had a higher prevalence of significant kidney disease19. According to our analysis, in addition to proteinuria, the history of recurrent episodes of red urine may be a more important reason than a single case of hematuria of red urine to cause a PED physician to suspect glomerulonephropathy. The recurrence of red urine resulting from gross hematuria suggests the possibility of IgA nephropathy, Alport syndrome, thin glomerular basement membrane disease, hypercalciuria, or urolithiasis.

This study has two obvious limitations. First, it is a retrospective study, so there is some degree of unreliability associated with data gleaned from medical charts filled out by different physicians in the PED. Second, gross hematuria may cause a false-positive result of proteinuria and affect the analysis. Future studies on this topic should involve a greater number of patients, standardize the way physicians record their findings in medical charts in advance and make their diagnoses.

In conclusion, red urine was relatively uncommon (0.9/1,000) in children visiting our emergency room. Urinary tract infection was the largest single cause (36.7%). Glomerulonephritis was found in 10.2%. Recurrent episodes of red urine and proteinuria were associated with glomerulonephritis. Our results suggest that PED physicians consider hospitalizing children with red urine when cases are combined with either of these two factors or combined with symptoms of acute nephritis. Otherwise, children with asymptomatic hematuria lasting longer than 1 year or a family history of renal disease, such as polycystic kidney disease or hereditary nephritis, should be referred to a pediatric nephrologist for the prevention of chronic kidney disease (CKD)[20].

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Original Article

兒科急診中赤尿患者的流行病學和風險：中台灣一所醫學中心的8年的研究

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背景：紅色尿在兒科急診室的病童中是一項少見的主訴，赤尿的原因可分成血尿及非血尿。造成非血尿的赤尿有許多的原因且兒童血尿的成因不同於成年的患者。腎絲球的病變若沒有即早發現或治療可能會造成腎衰竭的情形，因此為了研究有關兒童赤尿患者的流行病學和腎絲球腎炎的風險，我們進行了一個回顧性研究，分析了從2000年6月至2007年6月間以紅色尿液為主訴來到彰化基督教醫院兒童急診求診的病患。

方法：以描述性統計、two- sample t test和Pearson product-moment correlation coefficient回顧分析了180份相關病歷。

結果：兒童急診求診的病患中，紅色尿的盛行率為 0.9 / 1,000。血尿和非血尿病童的年齡在統計上有顯著差異 (6.10±3.37SD vs. 3.06±3.35SD)。泌尿道感染是最常見的原因（36.7%）。約有10.2%的病童有腎絲球腎炎。赤尿的兒童中，腎絲球腎炎患者的血中C-reactive 蛋白較非腎絲球腎炎患者高且接近統計上有意義的差異。而反覆赤尿的病史與蛋白尿則與腎絲球腎炎有顯著的相關性。

結論：赤尿為主訴的患者在兒童急診是不常見的狀況 (0.9/1000)。約有10.2%的赤尿兒童有腎絲球腎炎。病史中有反覆赤尿或是蛋白尿的患者有較高的腎病風險。

關鍵詞：紅尿，血尿，腎絲球腎炎，蛋白尿，兒童急診

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