RESEARCH PAPER

Clinico-Etiologic Profile of Macroscopic Hematuria in Children: A Single Center Experience

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Objective: To study the demographic, clinical and etiological profile of macroscopic hematuria in children presenting to a tertiary care hospital. **Methods:** This prospective observational study, conducted between January, 2018 and December, 2019, enrolled children aged 3 months to 12 years, presenting with gross hematuria. **Results:** Of the 62 children (44 males) enrolled, (mean (SD) age of 7.3 (2.6) years), glomerular hematuria was seen in 59.7%. Post-infectious glomerulonephritis was the commonest etiology of glomerular hematuria; hypercalciuria and renal calculi predominated among non-glomerular hematuria. After a median (IQR) follow up of 8 (6,14.2) months, microscopic hematuria persisted in 10 (7, glomerular hematuria) children. The median time to resolution of gross as well as microscopic hematuria tended to be longer in glomerular etiologies. **Conclusion:** Majority of children with gross hematuria had glomerular etiologies, thus requiring monitoring and follow-up.

Key words: *Glomerular hematuria, Outcome, Post-infectious glomerulonephritis.*

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Evaluation of a child with gross or macroscopic hematuria should essentially rule out serious underlying renal disease having grave prognosis. While prevalence of microscopic hematuria has been well-described [1,2], the incidence and profile of macroscopic hematuria in children is hardly reported [3]. Authors describing acute glomerulonephritis (AGN) in children [4-6] have not reported facts from the perspective of gross hematuria. Since the lack of utility of routine screening for microscopic hematuria in healthy children has been well-established in large follow-up studies [2], it is worthwhile to focus on children having visible hematuria and understand their profile. Hence, this study aimed to determine the demographic, clinical and etiological profile of gross hematuria in children presenting to a tertiary care hospital.

METHODS

This prospective, observational study, conducted between January, 2018 and December, 2019, enrolled children aged 3 months to 12 years presenting with gross hematuria. Children with hematuria following surgery of the kidney/urinary tract, post-renal biopsy, post- catheterization, or associated with perineal/genital inflammation were excluded. Ethics approval was taken from institutional ethics committee. Children with gross hematuria (confirmed by the presence of > 5 red blood cells (RBC)/high power field (hpf) on microscopic examination), were enrolled after informed consent.

Clinical features considered indicative of glomerular etiology included cola-colored/smoky urine, oliguria, edema, rash, arthritis, with or without history of pyoderma/ sore throat or recurrent synpharyngitic episodes. Children with fresh blood/clots in urine, urine sediment, pus, associated pain abdomen/loin or painful micturition, voiding symptoms, fever, or family history of renal stones, were considered likely to be having non-glomerular hematuria.

Microscopic urine examination showing >5 RBC/hpf with >20% dysmorphic RBC, along with moderate proteinuria (dipstick ≥2+) with or without casts was considered to be glomerular hematuria [7]. Final categorization in to glomerular and non-glomerular hematuria was made based on findings in history, clinical examination and urinalysis. Further work-up to elicit the etiology and management was as per departmental protocol, based on standard guidelines [7].

Statistical analyses: We used SPSS 21.0 software for analyses. Continuous variables were compared by independent *t* test/Mann-Whitney *U* test, and categorical variables were compared by chi-square test. Time to event was compared by Cox-regression survival analysis. $P<0.05$ was considered significant.

RESULTS

A total of 62 children (48 males) with a mean (SD) age of 7.3 (2.6) years were evaluated for gross hematuria. Concomitant or past upper respiratory tract infection and pyoderma were seen in two patients each, while voiding symptoms were found in three children. Edema, hypertension and oliguria were seen in 25 (40.3%), 22 (35.5%) and 19 (30.6%) children, respectively. Twenty-three (39.7%) children had deranged renal functions, two of whom had chronic kidney disease (CKD), the rest having acute kidney injury (AKI).

Based on urinalysis, clinical, biochemical and imaging parameters, 37 (59.7%) children were diagnosed to have glomerular hematuria, 21 (33.8%) had non-glomerular hematuria and four had hematuria of uncertain origin (**Table I**).

Infection-related glomerulonephritis (IRGN), was the commonest cause of glomerular hematuria, seen in 17 (45.9%) children, with 10 of these children (58.8%) having raised anti-streptolysin O (ASO) antibody titres. Ten children with glomerular hematuria presented as rapidly progressive glomerulonephritis (RPGN). The mean (SD) C3 in children with glomerular hematuria was 88 (56.5) mg/dL. Sixteen children underwent renal biopsy (9 RPGN, 3 Henoch-Schonlein purpura (HSP) nephritis, 7 glomerular hematuria with normal serological tests). Biopsies from the children with RPGN showed diffuse proliferative glomer-ulonephritis in 3, C3 glomerulonephritis in 4, anti-glomerular-basement membrane disease and mesangio-proliferative GN in one child each. Two of them had no crescents, one showed 100% crescents, while the rest showed 13-77% crescents. Three children biopsied for HSP nephritis showed mesangioproliferative glomerulo-nephritis with IgA and C3 deposits, all having Oxford score of M0E0S0T0 with C1 in 2 children. Both the children having IgA nephropathy had scores M0E0S0T0C0.

Table I Diagnosis in Children With Gross Hematuria (*N*=58)

Diagnosis	*No. (%)*
Glomerular origin (n=37)	
Post-infectious glomerulonephritis	17 (45.9)
Henoch Schonlein purpura	4 (10.8)
Hemolytic uremic syndrome	2 (5.4)
Miscellaneous[a]	2 (5.4)
C3 glomerulonephritis	4 (10.8)
Mesangioproliferative glomerulonephritis	3 (8.1)
IgA nephropathy	2 (5.4)
Unknown	3 (8.1)
Non-glomerular origin (n=21)	
Hypercalciuria	7 (33.3)
Renal calculus	5 (23.8)
Urinary tract infection	3 (14.3)
Chronic kidney disease	2 (9.5)
Unknown	4 (19.0)

[a]*One child each had idiopathic nephrotic syndrome and anti-GBM disease.*

Hypertension and AKI were each seen in 21 (56.7%) children with glomerular hematuria. Eight out of the 21 children (38%) with AKI (6 RPGN and 2 Hemolytic Uremic Syndrome) required dialysis, 5 of whom recovered, one died, one got transferred to another hospital, and one progressed to CKD requiring regular hemodialysis. Thus renal functions recovered in 18 (85.7%) of those with AKI.

In children with non-glomerular hematuria, hyper-calciuria (7; 33%) and renal calculi (5; 23.8%) constituted the most common causes. The mean (SD) 24-hour calcium excretion of six of the children with hypercalciuria was 6.26 (1.54) mg/kg/day and one child had spot urine calcium/ creatinine ratio of 0.2 with calcium oxalate crystals in urinalysis. On ultrasonography, five children had renal calculi, one had bilateral hydro-ureteronephrosis and one had bilateral small kidneys, the latter two children having deranged renal functions, as a part of CKD. Three children died; one child had RPGN (C3GN) and the other two had end stage renal disease at presentation.

Comparison of parameters showed age and gender of children to be comparable between glomerular and non-glomerular groups, while hypertension and deranged renal functions were significantly more in glomerular hematuria. Though the median (IQR) time to resolution of gross hematuria [9 (3,15) months and 3 (2,10) months in glomerular versus non-glomerular hematuria, respectively)] as well as of microscopic hematuria [4 (1,12) months and 1 (0.2,2) in glomerular versus non-glomerular hematuria, respectively] tended to be longer in glomerular etiologies, survival analysis failed to show statistical significance.

Barring four children who had a follow-up of <1 month, the rest had a median (IQR) follow-up of 8 (6,14.2) months. At the last follow up, microscopic hematuria was persisting in 10 children, 7 of whom had glomerular etiologies, 83.8% being free of any hematuria; 9 children were having hypertension, all with glomerular hematuria.

DISCUSSION

We prospectively enrolled and studied 62 children with macroscopic hematuria over two years and found glomerular causes to be more common and persistence of hematuria in one-sixth of the patients.

More than half of the children with gross hematuria were due to glomerular origin, unlike the profile observed by others, where the non-glomerular causes predominated [8,9]. The latter studies belong to a geographical and ethnic background different from ours. It is possible that in a

WHAT THIS STUDY ADDS?

- Glomerular etiologies predominated in children with macroscopic hematuria seeking medical care, with post-infectious glomerulonephritis being more common than IgA nephropathy.

developing country, there may be a delay in presentation or a referral bias to a speciality centre. Further, the present study showed that IRGN was the leading diagnosis in children with gross hematuria of glomerular origin, a finding which contradicts existing reports where IgA nephropathy has been the commonest glomerular etiology of macroscopic hematuria [8-11]. Even considering that some cases of IgA nephropathy may have been missed among the cases with unproven etiology in our study; still, the figure of IRGN clearly surpasses the number of IgA nephropathy. It should be acknowledged that though the incidence of IRGN has abated in industrialized countries, it is still one of the most common renal disorders in children in developing countries [12,13] and therefore, accounts for the major proportion of macroscopic hematuria.

Nearly one-third of the children in this study presented as RPGN, higher than that reported in previous pediatric studies [6-9]. While long-term follow-up studies, describing crescentic GN have shown a plethora of etiologies of RPGN [4,14], our study of over two years, found diffuse proliferative and C3 dominant GN as the commonest findings in RPGN. Though nearly 35% of children with AKI in our study required dialysis support, the recovery rate (over 85%) was higher, compared to existing literature [15].

While 16% children were not free of RBC in their urine, at the last follow-up, nearly a quarter of the children with gross hematuria had persistent hypertension. Studies dealing only with glomerulonephritis report 0-35% children having persistent urinary abnormalities and hypertension at follow-up [4,11,13].

Children presenting with gross hematuria need thorough evaluation and risk stratification, because glomerular causes could account for a major proportion, especially in developing countries.

Ethics clearance: Institutional Ethics Committee, MAMC; No. F.1/IEC/MAMC/58/03/2017/No. 33, dated August 23, 2017.
Contributors: KM conceived and planned the study with critical inputs from MK.AP and KDZ helped in collection of data under supervision of KM. LS was involved in supervising laboratory related investigations. KM analyzed the data and wrote the primary draft. All authors approved the final manuscript.
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