"Clinical, laboratory and etiological profile of children presenting with gross hematuria- experience of a tertiary care centre"

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ABSTRACT:

Background and Objectives: Haematuria or blood in urine is a scary but common medical problem in children. While microscopic hematuria has been well studied and reported, there has been paucity of data regarding the occurrence and profile of macroscopic hematuria in children. This study was conducted to study the prevalence, demographic, clinical, laboratory and etiological profile of macroscopic hematuria in children

Methodology: The present study was conducted in Pediatrics deptt of our tertiary care level teaching hospital over 2 years from January 2020 to December 2021including children between 1-16 years presenting with complaint of reddish, cola coloured or reddish black urine.

Results: 71 children with true macroscopic hematuria were enrolled out of which 41 were males and 30 were females with male: female ratio of 1.4:1. Mean age of the study participants was 6.53 ± 3.1 years and mean weight of the children was 16.7 ± 3.9 kg. Prevalence of macroscopic hematuria was found to be nearly 4.9 per 1000 children visits. Glomerular hematuria was found in 46 or 64.8% of the children while the rest 25 or 35.2% had hematuria of non-glomerular origin. Overall, the most common aetiology of macroscopic hematuria was post-infectious glomerulonephritis (26.8%) followed by HSP (8.5%), HUS (7.1%), renal stones (7.1%) hypercalciuria (5.6%) and bleeding disorders (5.6%). At 1 year follow-up, persistent microscopic hematuria was seen in 5 (7.1%) and 7 (9.9%) children still required antihypertensive therapy.

Conclusion: Gross hematuria is a relatively uncommon condition but its occurrence is most frequently indicator of a serious underlying pathology as glomerular hematuria is the predominant aetiology in children which mandates careful monitoring and long-term follow-up.

Keywords: aetiology, acute glomerulonephritis, children, glomerular, hematuria, macroscopic.

Abbreviations: ASO: antistreptolysin-O;BUN: blood urea nitrogen; CRP: C-reactive protein; C3: complement factor 3; C4:complement factor 4; GBM: glomerular basement membrane; HSP: Henoch Schonlein purpura; HUS: Hemolytic uremic syndrome; S.D: standard deviation;

1. INTRODUCTION:

Haematuria or blood in urine is a scary but common medical problem in children.[1]This condition is considered one of the most important features of kidney or urinary bladder disease. When colour of urine with blood is reddish, brown or dark or cola coloured, the condition is called as macroscopic hematuria. However, blood in urine may not always be visible to the naked eye, when it is called as microscopic hematuria. This condition can be transient, intermittent or persistent and it may be symptomatic or asymptomatic. Hematuria originating from glomerulus is almost never bright red but usually brown, tea coloured or cola coloured. Contrary to this, hematuria originating from the lower urinary tract is usually pink or red in colour.Introduction of chemically labelled dipsticks has enabled rapid and reasonably accurate detection of hematuria and certain other urinary abnormalities like proteinuria, glycosuria etc. When used properly, these dipsticks have been shown to have sensitivity of nearly 99-100% and specificity of 95-99% in detecting hematuria in the range of 1-5 RBCs/HPF, which corresponds to 5-10 RBCs/µL of urine.[2]

Though blood in urine is considered as one of the most important features of genitourinary tract disease, it almost never leads to anaemia since only few drops (less than 1 mL) of blood is sufficient to turn 1 litre of urine into red colour. Nevertheless, considering its prognostic significance, detection of even some amount of blood in a child's urine alarms the patient and/or their parents or even the treating physician so much so that often leads to the conduction of many laboratory studies, not all of which are actually needed. It indeed is the duty of the Paediatrician to ensure thatconditions of clinical importance are not missed, unnecessary and/or expensive tests are not ordered at the outset, the family is properly guided and reassured and wherever necessary additional efforts or timely referral is done if the clinical condition warrants.[3,4]It is prudent to establish the cause and origin of hematuria in each case through proper history, clinical features and investigations including radiological studies and/or percutaneous renal biopsy in some cases.[5,6] But at the same time, it is important that the treating physician is aware what any of such procedures can potentially reveal and underwhich setting the information gathered might be helpful in establishing a proper diagnosis.

While microscopic hematuria has been well studied and reported[7,8], there has been paucity of data regarding theoccurrence and profile of macroscopic hematuria in children.Even researchers who have done considerable research work on acute glomerulonephritis in childrenhave not described clinical features and outcomes from the perspective of gross hematuria which is a common phenomenon.[9,10]Some large prospective studies have shown futility of routine screening for hematuria in otherwise healthy children[11] which further implies that it is more imperative to focus on children presenting with visible or macroscopic

hematuria for a better understanding of the disease process. Based on this background, we intended to conduct this study targeting only those children who presented with macroscopic hematuriaat our tertiary care level teaching hospital.

2.AIM & OBJECTIVES:

1. To study the prevalence of macroscopic hematuria in children.
2. To study the demographic, clinical, laboratory and etiological profile of such children.

3. METHODOLOGY:

Study setting: PaediatricsOPD and I.P.D of Nalanda medical college and hospital, Patna
Study duration: January 2020- December 2021(2 Years).
Study design: hospital basedprospective observational study.
Inclusion criteria:children between 1-16 years presenting to our hospital with complaint of reddish, cola coloured or reddish black urine were assessed for eligibility. True hematuria was confirmed by the presence of >5 red blood cells per high power field on microscopic examination of their freshly voided urine sample. Only such children who had true hematuria were admitted and included in the present study.
Exclusion criteria: Children who suffered from hematuria after surgery of the genitourinary tract, after kidney biopsy, after bladder catheterization, or who had hematuria associated with infection or inflammation of the perineal or genital region were excluded.
Data collection: Children fulfilling the aforesaid criteria were enrolled in this study after obtaining a written informed consent from their parents. Detailed history was taken and focussed clinical examination was done in all cases. Important points from history and clinical examination were recorded in study proforma. Hematuria was sub categorised into glomerular hematuria and non-glomerular hematuria based on certain indicators. Occurrence of cola or smoky coloured urine, edema, oliguria, exanthem, arthritis, history of recent pyoderma or pharyngitis or recurrent hematuria immediately following pharyngitis were considered suggestive of glomerular hematuria. On the other hand, if the patients had frank red blood or clots in their urine, pain in abdomen or loin, fever, pus in urine or a family history of renal stones, it was considered a likely case of non-glomerular hematuria. Similarly, laboratory parameters suggestive of glomerular hematuria included: >20% dysmorphic RBCs in urine microscopy, moderate proteinuria (urine dipstick ≥2+ for protein) with or without casts. Multiple parameters from history, clinical examination and laboratory investigations were carefully analysed to finally label the site of hematuria as glomerular or non-glomerular.Such children were further investigated and managed as per standard protocol. Follow up was intended to be done till 1 year of discharge from our hospital.
Statistical analysis: Important data was compiled, tabulated and entered in Microsoft Excel sheet and then analysed by SPSS version 21 software. Variables were presented as mean, median, percentage, proportion or percentile as appropriate. Unpaired two sample t tests was used to compare the means ofcontinuous variables whereas chi-square test was employed for comparing categorical variables. It was decided to take ‘p’ value less than 5% as significant.

4. OBSERVATION & RESULTS:

Over the 2year study period71 children with true macroscopic hematuria were enrolled in this study out of which 41 were males and 30 were females with male: female ratio of 1.4:1.This sex difference was not statistically significant (p=0.066). Mean age of the study participants was 6.53 ± 3.1 years and mean weight of the children was 16.7 ± 3.9 kg. Prevalence of macroscopic hematuria was found to be nearly 4.9 per 1000 children visiting our department for their various illnesses. Table 1 depicts clinical features at presentation of the study participants. Edema (33.8%), oliguria (32.4%) and hypertension (29.6%) were the most common clinical findings followed by vomiting (21.1%), fever (16.9%), abdominal pain (15.5%), loin pain (11.3%), dysuria (9.9%) and increased frequency of micturition (7.1%). Family history of renal disease was found in 8 (11.3%) of children and the most common renal issue associated with a positive family history was lithiasis.

Table 1: Clinical features at presentation:

Variables	Number	Percentage
Fever	12	16.9
Abdominal pain	11	15.5
Loin pain	8	11.3
Vomiting	15	21.1
Dysuria	7	9.9
Increased frequency of urination	5	7.1
Diarrhoea	4	5.6
Joint pain	2	2.8
Bleeding from other sites	4	5.6
History of recent URI	8	11.3
History of recent pyoderma	6	8.5
Oedema	24	33.8
Hypertension	21	29.6
Oliguria	23	32.4

Pertinent laboratory parameters were studied in all affected children as shown in table 2 below. In light microscopic examination, 28 (39.4%) of the patients had isomorphic, 27 (38%) had >80% dysmorphic and 16 (22.5%) had mixed types of RBCs in their urine. Pyuria was found in 11 (15.5%) of cases. Non-nephrotic range proteinuria was found in 23 (32.4%) children and 1 child (1.4%) had even nephrotic range proteinuria. Raised urinary calcium to creatinine ratio was seen in 9 patients (9.9%) and raised urinary uric acid to creatinine ratio was found in 1 (1.4 %) patient.

Table 2: Laboratory parameters of the study population:

Parameter	Number	Percentage
Anemia	11	15.5
Thrombocytopenia	5	7.1
Elevated serum Creatinine level	25	35.2
Elevated BUN level	27	38
Elevated CRP	24	33.8
Hypoalbuminemia	8	11.3

Prolonged PT	3	4.2
Prolonged aPTT	2	2.8
Low C3	22	31
Low C4	6	8.5
Elevated ASO titre	18	25.4
Positive urine culture	4	5.6
Positive Throat swab culture	7	9.9

An abdominal ultrasonography was performed in all study participants and found abnormality in 45.1% of such children as shown in table 3 below. The most common pathological finding was increase in echogenicity in 15.5% children followed by hydronephrosis in 8.5%, urolithiasis in 7.1% and features of cystitis, reduced size and microlithiasis in 4.2% each. However, USG findings were normal in a whopping 54.9% of children with hematuria.

Table 3: USG findings of the study population:

Findings	**Number**	**Percentage**
Normal USG scan	39	**54.9**
Hydronephrosis	6	8.5
Increased echogenicity	11	15.5
Decreased size	3	4.2
Microlithiasis	3	4.2
Urolithiasis	5	7.1
Cystitis	3	4.2
Cystic disease	1	1.4
Congenital malformation	1	1.4
Malignancy	2	2.8

Based on history, clinical features and standard laboratory investigations aetiological characterisation of the subjects was carried out as shown in table 4 below. Glomerular hematuria was found in 46 or 64.8% of the children while the rest 25 or 35.2% had hematuria of non-glomerular origin. Overall, the most common aetiology of macroscopic hematuria was post-infectious glomerulonephritis (26.8% of total cases) followed by HSP (8.5%), HUS (7.1%), renal stones (7.1%) hypercalciuria (5.6%) and bleeding disorders (5.6%). Unfortunately, the aetiology of hematuria couldn't be found in 8 or 11.3% of total cases owing to refusal of parents for further diagnostic work-ups.

Table 4: Aetiology of hematuria

Aetiology	**Number**	**Percentage**
Glomerular hematuria (n=46)		
Post-infectious glomerulonephritis	19	26.8
Henoch Schonlein purpura	6	8.5
Hemolytic uremic syndrome	5	7.1
IgA nephropathy	3	4.2

C3 glomerulonephritis	3	4.2
Mesangioproliferative glomerulonephritis	3	4.2
Anti-GBM disease	1	1.4
Undiagnosed	6	8.5
Non- Glomerular hematuria (25)		
Hypercalciuria	4	5.6
Renal stones	5	7.1
Urinary tract infection	4	5.6
Chronic kidney disease	3	4.2
Bleeding diathesis	4	5.6
Malignancy	2	2.8
Menstruation	1	1.4
Undiagnosed	2	2.8

Outcome:6 children died within 1 week of admission, 2 had bleeding disorder, 2 had end stage renal disease, 1 had RPGN and the aetiology couldn't be established in 1. Post hospital discharge, mean duration of persistence of macroscopic hematuria was significantly higher in glomerular group as compared to non- glomerular group (3.8 ± 1.7 months versus 1.5 ± 0.6 months, p <0.001). Similarly, the mean duration of persistence of microscopic hematuria was significantly higher in glomerular group as compared to non-glomerular group (5.9 ± 2.5 months versus 2.3.5 ± 1.2.6, p <0.001). However, this didn't significantly affect survival at 1 year of follow up. 8 (11.3%) children were lost to follow up by 1 year of discharge from hospital. At the end of this 1 year follow-up, microscopic hematuria was persisting in 4 children with glomerular aetiology and 1 child with non-glomerular aetiology. Similarly, 7 (9.9%) children still required antihypertensive therapy, all of them had glomerular aetiology.

5. DISCUSSION:

The present study enrolled 71 children with gross hematuria and followed them up till next 1 year. Detailed history and a meticulous examination can provide vital information related to the aetiology of hematuria. For example, history of vigorous physical exercise or recent urogenital trauma or coexisting coagulopathies if known are unlikely to be missed by a focussed history taking. Similarly, history of recent upper respiratory tract infection (URTI) or pyoderma may suggest a glomerulopathy. Accordingly, we could detect recent URTIand pyoderma as precipitating factor of glomerular hematuria in 11.3% and 8.5% cases respectively. Comparable rates of pyoderma and URTI was reported by a recent Turkish study of Ari ME et al.[12]Family history of renal disease should also be asked for as nephrolithiasis, hereditary nephropathies, polycystic kidney disease etc tend to run in families. Surprisingly, we found a positive family history in 11.3% of cases.

Light microscopy is a valuable initial investigation as it confirms and characterises the type of erythrocytes in a freshly voided urine sample. It has been shown that if more than 80% erythrocytes are dysmorphic, a glomerular cause is highly likely.[13]In the present study we found non-dysmorphic erythrocytes in less than 40% of patients in

proportion to the occurrence of non-glomerular hematuria. Ultrasonography of the reno-urogenital tract is the preferred imaging modality and has now virtually replaced plain radiographs due to its availability and utility in the evaluation of a child with hematuria.[14] In the present study a USG was performed on all cases irrespective of the origin of hematuria which was able to detect one or more pathology in 45.1% cases. Similar but a bit lower diagnostic yield of USG was reported byElbouaeshi A et al in Libya.[15]

Glomerular aetiology was found in more than half of the children with gross hematuria which is similar to the findings of Mishra K et al[16] but against the findings ofYounet al[17] and Bergstein et al[18] where the non-glomerular causes predominated. This can be attributed to differences in geography and ethnicity or due to referral bias where more sick children (glomerular diseases) werebrought to our tertiary care centre more often.Furthermore, this study also showed that the most common cause of glomerular hematuria was post infectious glomerulonephritis (PIGN), whereas earlier studies have shown IgA nephropathy to be the commonest cause.[19]We admit that some cases of IgA nephropathy could be potentially missed among children with undiagnosed aetiology, still the number of PIGN would clearly outweigh those with IgA nephropathy. It is being established now that occurrence of PIGN has drastically decreased in developed countries in parallel to their socioeconomic scenario, yet it remains the major disease in developing countries.[20]In our study less than 10% children with gross hematuria had RPGN which is similar to the findings of Moreno et al.[21] At 1 year follow-up, persistent microscopic hematuria was seen in 4 children with glomerular aetiology and 1 child with non-glomerular aetiology. Similarly, 7 (9.9%) children still required antihypertensive therapy, all of them had glomerular aetiology. Other researchers have reported variable rate of persistent microscopic hematuria and hypertension ranging from 5-30%.[22,23]

6. Conclusion:Gross hematuria is a relatively uncommon condition but its occurrence is most frequently indicator of a serious underlying pathology. All such children deserve proper work-up and risk stratification as glomerular hematuria is the predominant aetiology in children, especially indeveloping countries like ours.

7. Limitations:First limitation is that the present study is a single centre study. Second, it is a hospital-based study and so the findings may not be representative of the general community. Third, aetiology of hematuria couldn't be estableshed in nearly 10% of cases.

8. Conflict of interest: None to declare.

9. Financial disclosure: The authors hereby declare that this study has not been conducted under any financial assistance.

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