Aetiological and Clinical Profile of Hematuria in Children between 1 month to 12 Years

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Abstract
Objective: To evaluate the clinical and etiological profile of hematuria in children and to describe the course of illness till the end of one year
Methodology: Prospective follow up study of a case series in a tertiary care teaching hospital in Kerala, South India during the period January 2001-2002. Data collection and evaluation were done during initial workup and follow up assessment and relevant investigation were done during subsequent visits.
Results: The study population included 100 children admitted with hematuria during the period of study. Hematuria was found to be a major problem of school going children of age 6-12 years (57%) with slight female preponderance (52%). Highest incidence was occurred in August and December. Majority belong to low socioeconomic status (42%) and were residing around Thiruvananthapuram district. At the time of admission 60% diagnosed as PIGN, 22% as microscopic hematuria of which UTI-9%, infective endocarditis - 1%, Ideopathic (12%) (7 had persistent hematuria on follow up), remaining 18% were contributed by septicemia, snakebite, HSP, HUS, Abdominal mass etc. 75 of them followed up for one year. During follow up among the non biopsied (40) cases PIGN (59%), sepsis-5(12%), UTI-5(12%), Snake bite-3(7%), nephrolithiasis-2(5%), Ideopathic-2(5%) were there. Renal Biopsy was done for 35 cases (46.6%). Among the biopsied cases IGA nephropathy-8(23%)(all between 9-12 years), SLE-6(17%), PIGN-4(11.4%), DPNG-4(11.4%), HUS-3(8.5%), HSP-3(8.5%), FSGS-3(8.5%), Thin basement membrane disease-2 (5.7%), ATN-2(5.7%)
Conclusion: Among the 3.8% total admissions of hematuria PIGN was the leading cause(59% non biopsied cases and 11.4% biopsied cases)followed by IGA Nephropathy(23%) and SLE (17%). 60% of hematuria resolved by one year & there were no deaths due to hematuria till the end of 12 month follo.

Introduction
Normal individual excrete a few red blood cells in their urine and determination of what should be considered abnormal is not absolute. The generally accepted view is that finding of more than 5 red blood cells per High power field in light microscopy of a sample of freshly voided urine sediment constitute further evaluation(1).
Hematuria can be gross or microscopic. Gross hematuria is visible to naked eye, microscopic hematuria detected by dipstick and confirmed by microscopic examination of urine sediment. Gross hematuria may originate from kidney, which is of brown or cola coloured and contain RBC casts. Gross hematuria may originate from lower urinary tract where urine is red to pink and may contain clot. Persistent heavy proteinuria of more than 2+ is virtually diagnostic of glomerular disease.

Hematuria should be differentiated from hemoglobinuria or myoglobinuria which also characterized by dark brown urine but without RBC's. A number of substances including medications can alter the colour of urine and simulate gross hematuria. Examples are Nitrofurantoin, Methyl-dopa, Rifampicin, Alkaptonuria, ingestion of beetroot, prophyrea and by certain food colourings etc. Gross hematuria may be associated with oedema, hypertension and renal insufficiency. This constellation of findings is typical of acute nephritic syndrome and is frequently found in patients with post infectious glomerulonephritis, systemic lupus erythematous, membranoproliferative glomerulonephritis, anaphylactoid purpura and rapidly proliferative glomerulonephritis.

**Table I- Causes of Hematuria**

<table>
<thead>
<tr>
<th>Glomerular diseases</th>
<th>Non-glomerular causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute postinfectious glomerulonephritis</td>
<td>Nephrolithiasis†</td>
</tr>
<tr>
<td>IgA nephropathy†</td>
<td>Hypercalciuria†</td>
</tr>
<tr>
<td>Benign familial hematuria *†</td>
<td>Viral hemorrhagic cystitis</td>
</tr>
<tr>
<td>Systemic infections (malaria, leptospirosis, infective endocarditis)</td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>Membranoproliferative glomerulonephritis</td>
<td>Vascular abnormalities: RVT, RAT, AVM</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>Trauma, Tumors *†, Exercise</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Hematologic</td>
</tr>
<tr>
<td>Hemolytic uremic syndrome†</td>
<td>Hydronephrosis</td>
</tr>
<tr>
<td>Henoch-Schonlein purpura</td>
<td>Renal cystic disease†</td>
</tr>
<tr>
<td>Alport’s syndrome*†</td>
<td>Medications: NSAIDs, anticoagulants, cyclophosphamide, ritonavir, indinavir</td>
</tr>
<tr>
<td>Goodpasture’s disease</td>
<td>Tuberculosis* Munchausenssyndrome/ Munchausen by proxy</td>
</tr>
</tbody>
</table>

* Causes of recurrent hematuria , RVT - Renal Vein Thrombosis, RAT - Renal Artery Thrombosis, AVM - Arterio Venous Malformation
† Hematuria with familial association

Confirmation of hematuria by microscopic examination of the urine requires the identification of more than 5 RBCs/ hpf. It is done by centrifuging 10 mL of a fresh urine sample at 2000 rpm for 5 min, decanting the supernatant and resuspending the sediment in the remaining 0.5 mL. The sediment is examined by microscopy at high power, counting RBCs in twenty fields and the average is reported. In the absence of gross hematuria, the persistent finding of hematuria in at least two of three urinalyses, performed over 2-3 weeks, warrants further evaluation. A positive dipstick reaction and an absence of RBCs and RBC casts in the urine suggest hemoglobinuria or myoglobinuria. A simple test is to centrifuge a fresh urine sample and evaluate the colour of the supernatant. In hemoglobinuria the supernatant fluid will be clear pink with minimal or no deposits. In hematuria the supernatant will be cloudy red or dark brown with RBC deposit.

**Clinical assessment of child**

The history and examination may reveal important clues to the etiology of hematuria. There may be symptoms suggestive of urinary tract or other infection, multi system disease, bleeding disorder or trauma. A family history of renal diseases, hypertension and deafness should be sought, and details of drug usage, travel, sexual and social experiences were evaluated.
Aim of this study was to evaluate the clinical & etiological profile of hematuria in children attending tertiary care hospital in South India, during Jan 2001-Jan 2002 and to describe the course of illness till one year. This study provides an approach to the evaluation and management of hematuria in children, and the detection of preventable and treatable conditions at the earliest to limit the disease progression, and overall reduction in cost, energy and anxiety.

Methodology
We undertook a prospective follow up study of a case series in a tertiary care teaching hospital in Kerala, South India. Hundred children admitted with hematuria during the period January 2001-Jan 2002 was considered as the population for the conduct of study.

Inclusion criteria: All children between one and twelve years who were presented as hematuria (microscopic or macroscopic) during the fixed time frame were included for the study.

Exclusion criteria: Children whose care taker couldn't provide a reliable history and who were observed to be expired on the same day of admission were excluded. Among the rest, one hundred children were randomly selected for detailed evaluation and follow up.

Data collection- Clinical work up of all selected children were undertaken by the researcher. A preformed and piloted questionnaire was used for data collection. The pilot test was undertaken for ten subjects. After interviewing the mothers for relevant clinical history, the clinical details as well as the detailed investigational workup were entered in the questionnaire. Blood pressure was examined by the investigator by standard technique as per WHO guidelines for measurement. The initial visit was in the ward. Subsequent follow up visits were conducted in the outpatient clinic.

Investigations-All investigations were undertaken in the same in house lab assuring quality control. During the initial visit a detailed medical history was obtained which included family history of kidney diseases, renal failures, history of dialysis for hypercalciuria, deafness or hypertension in any first degree or second degree relatives. Any precipitating factor for hematuria like impetigo, pyoderma, pharyngeal infection, abdominal pain or colic, joint pain, drug ingestion history like anticoagulants were also enquired.

Urine examination was done by dipstick method and also by microscopy. This was to confirm hematuria. A detailed physical examination, general examination, including blood pressure and genitourinary examination was done by the investigator.

Follow up assessment- Follow up assessment was done with repeat urine and blood examination, X-ray chest, urine culture and sensitivity, renal ultrasound, renal function test, etc. Special investigations like MCU, IVU, cystoscopy, CT scan etc were done as and when indicated. Nephrologist in appropriately indicated cases undertook renal biopsy.

Indication for Biopsy
(1) Isolated hematuria (microscopic or macroscopic), persisting beyond 6 months without any clinical or biochemical abnormalities.
(2) Hematuria presenting with clinical and biochemical abnormalities, but etiological diagnosis was not possible by any clinical or lab evidence.
(3) when there are indications of a more serious potentially progressive diseases such as progressive or persistent renal impairment, hypertension, persistent hypocomplimentemia, heavy proteinuria. Biopsy was done by experienced nephrologists, and interpreted by an experienced pathologist.
Results and Analysis
Among the total 14,700 inpatients admitted in our hospital during the year 2001, hematuria was present in 558 (3.8%) children. In the year 2000 it was around 3.2%. Out of 100 cases studied 24 cases were having previous renal disease where as the rest(75) were fresh cases. This indicates a dominance of fresh cases and gives a clue that PSGN could be the major cause for hematuria.

Table-2 Distribution of Age and Sex

<table>
<thead>
<tr>
<th>Age(yr)</th>
<th>Male (%)</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>1-6</td>
<td>14</td>
<td>24</td>
<td>38</td>
</tr>
<tr>
<td>6-12</td>
<td>27</td>
<td>30</td>
<td>57</td>
</tr>
</tbody>
</table>

The time distribution showed that, a uniform occurrence in all months with slight peaking in August and December (10 - 12%).

Socioeconomic status
It is observed that majority of children are coming from poor socio economic status. This may be because low income groups are coming to our hospital. However in the setting as a public hospital, poor people are expected to come for medical colleges and hence this cannot be conclusively studied.

Table-3 Age and Sex distribution in general population of patients admitted in ward

<table>
<thead>
<tr>
<th>Age(yr)</th>
<th>Total (%)</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>200 (20)</td>
<td>130</td>
<td>70</td>
</tr>
<tr>
<td>1-6</td>
<td>590(59)</td>
<td>250</td>
<td>340</td>
</tr>
<tr>
<td>6-12</td>
<td>210(21)</td>
<td>90</td>
<td>120</td>
</tr>
</tbody>
</table>

Among 100 cases, 5 were infants (5%) 38 children belonged to age 1- 6 years (38%) and 57 children belonged to age 6-12 years (57%). 43 out of 100 were males and 57 were females. When we compared our observations with general population of patients admitted in our ward, female dominance in older children is found to be significant. Between 1-6 years 25% of patients in general population belongs to females. Of this 24% found to have hematuria. Similarly between 6-12 years among the 9% females 30% were having hematuria. Comparison with other hundred cases shows that hematuria is a problem among 6-12 year age group than infant.
Place of distribution - Majority were around Trivandrum city (70%). Rest from Kollam (24%) & Kottayam (6%). The referred cases from Kottayam might have been with specific aetiology and referred for renal biopsy facility which is available in our centre.

Table 4 Presenting clinical features

<table>
<thead>
<tr>
<th>Hematuria</th>
<th>Oedema</th>
<th>Oliguria</th>
<th>Pyoderma</th>
<th>Hypertension</th>
<th>dysurea</th>
</tr>
</thead>
<tbody>
<tr>
<td>59</td>
<td>12</td>
<td>12</td>
<td>40</td>
<td>44</td>
<td>10</td>
</tr>
</tbody>
</table>

Etiological pattern -at the time of admission
Among the hundred patients we studied, in 60% patients, diagnosis at time of admission was acute post infectious glomerulonephritis, because they all presented with hematuria, oedema, oliguria, 30 of them presented with typical history of pyoderma and upper respiratory infection with a latent period of 1-3 weeks. 22 cases were present as asymptomatic microscopic hematuria only. One case of Infective endocarditis, 9 cases of urinary tract infection and remaining cases were diagnosed as idiopathic microscopic hematuria. Among these 12 idiopathic cases, who were under strict follow up, 7 of them persistently had hematuria over 1 year and 4 of them later became macroscopic within one year. They all underwent biopsy. Rest 18 cases we evaluated with further investigations and they present with other diagnosis like, Septicemia, Snake bite, Henochschonleinpurpura, Haemolytic uremic syndrome, abdominal mass etc

Table 5 Distribution of Non Biopsy Cases

<table>
<thead>
<tr>
<th>PIGN</th>
<th>Sepsis</th>
<th>UTI</th>
<th>Snakebite</th>
<th>Nephrolithiasis</th>
<th>Ideopathic</th>
</tr>
</thead>
<tbody>
<tr>
<td>59</td>
<td>12</td>
<td>12</td>
<td>7</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

Figure 2

Etiological pattern during follow up and before biopsy - It was said that our initial working diagnosis in majority (60%) was post infectious glomerulonephritis. They were followed up over one year. But 25 of them lost to follow up. They might have cleared of hematuria after the first episode. That could be the reason for their non compliance. Rest 35 patients were followed up, and 25 cases diagnosed as post streptococcal glomerulonephritis. They were not undergone biopsy. They all of age between 2-12 years and with female predominance. Preceding skin infection was present in 70%, upper respiratory infection 30%. Latent interval was found to be 1-3 weeks. Hypo complementemia which was present in 30 cases which normalized in 25 cases after 8 weeks Microscopic hematuria was present in 100% patients, proteinuria in 80%, Leucocyturia 60%. Their clinical presentation was gross hematuria (80%) oedema (60%) hypertension (60%). Thus we followed up 75 patients. Among the 40 cases where we have not done biopsy, 25 cases were of post infectious glomerulonephritis (59%), sepsis 5 (12%) (UTI) 5(12%) and snake bite 3(7%), Nephrolithiasis 2(5%) idiopathic 2(5%). We have done ca-creatinine ratio for all needed patients, according to protocol, but hypercalciuria noticed only in two patients in our study. Also we got two cases of renal stones one with hyperuressemia and other with hypercalciuria. A 7 year old boy was investigated after an episode of gross hematuria of non glomerular origin and was found to have idiopathic hypercalciuria.
Aetiological profile in biopsied cases

We did biopsy for 35 cases and was done by an experienced nephrologist. Majority found to have IgA nephropathy (IgA) 8 (23%), Systemic Lupus erythematosis (SLE) 6(17%), Post Infectious Glomerulonephritis (PIGN) 4(11.4%) , Diffuse proliferative glomerulonephritis4 (DPGN) (11.4%), Hemolytic uremic syndrome (HUS) 3(8.5%), HenochSchonleinpurpura (HSP) 3 (8.5%), Focal segmental glomerulosclerosis (FSGS) 3 (8.5%), Normal 2 (5.7%), Acute Tubular Necrosis (ATN) 2(5.7%).

Those patients who were diagnosed as IgA nephropathy after biopsy were already diagnosed so by their clinical presentation of recurrent / gross hematuria, or persistent microscopic hematuria. All of them between 9-12 years. Recurrent gross hematuria and protienuria present in 4 patients (50%) persistent hematuria more than 3 months in 3 patients. The glomerular involvement was similar in 3 patients with history of Henoch Schonleinpurpura and in rest of the patients no such history. End stage renal disease developed in one patient with massive protienuria and biopsy shows more crescents. We got 6 cases of systemic Lupus erythematosis. ANA and dsDNA was positive in all six cases. Four of them had protienuria WHO class II (2), Class III(1), class IV (3). None of them were not normal at the end of one year follow up. All of them were females between 5-15 years. Biopsy diagnosis of post infectious glomerulonephritis was in 4 cases, all between 2-12 years and 3 of them with hypocomplimentemia and renal function impairment was present in all. Biopsy done for these patients because of atypical features like persistent hematuria and hypocomplimentemia. 3 cases of HUS on biopsy was found. They all presented to us with atypical features and chronic renal impairment without any history of diarrhoea.

Discussion

In this study an attempt was made to identify the clinical profile & aetiology of hematuria in children and their outcome and prognosis at the end of 12 months.

Prevalence of hematuria- The prevalence of hematuria in our hospital was 3.2%&3.8% in the year 2000 &2001 respectively. In the study by Denvir(1) the prevalence of hematuria was 4-6% in children between 6-12 years.

Age & Sex Pattern- Our study showed that hematuria is more prevalent in females of school going age (6-12yr). Similar observations was made by other studies(1,10,11). After complete evaluation of all cases, SLE was found to be in
girls and in age group b/w 5-15 years. Similar finding was seen in other studies also\(^{(12,13)}\). Those with IgA nephropathy sex ratio ratio was found to be equal and age group were more than 8 years. Some other studies also showed the same pattern\(^{(14)}\). But the study by Kher et al\(^{(15)}\) showed that no definite prediction for any age group but majority were older than 6 years. Rirnediotti MJ et al\(^{(16)}\) studied 62 children with glomerulonephritis and hematuria. There found to have a male dominance (M/F = 1.5/1). In our study we got female predominance (M/F = 1:1.5.) Age distribution of MPGN was found to be between 5-15 years with female predominance. Similar observations seen in many studies\(^{(17)}\). Age distribution of PSGN was between 2-12 years.

**Seasonality** showed a steady pattern in all months with slight, peaking in August and December (10-12%). Similar trends were observed by Parekh DJ\(^{(18)}\).

**Etiological pattern during follow up and before biopsy** - In our study though initial diagnosis of PSGN was made in 60% cases finally 25 cases diagnosed without biopsy evidence. Clinical diagnosis was made with supportive evidence of preceding skin infection (70%), upper respiratory infection (30%), Hypo complementemia (30%). Similar observation were found in other studies\(^{(19)}\). Wierzchowska 1997\(^{(11)}\) diagnosed microscopic hematuria in 102 children and he observed that the most common reason of microscopic hematuria was infections of urinary system and found in 34 (33%) but in our study we got only 12.5%. His another important observation was that isolated microscopic hematuria observed in 38% of cases, similar to our study which is 30%. But more than half of these children (59%) the threat of urolithiasis was recognized in his study in contrast to our study which was only 5%. Idiopathic hypercalciuria is believed to be the cause of a variety of urinary tract complaints in clinical pediatrics. In children noncalculus manifestation of idiopathic hypercalciuria are reportedly more common than urolithiasis\(^{(18)}\).

This study evaluated 288 patients over 8 years with spot calcium: creatinine ratio and found that 28% had idiopathic hypercalciuria with gross hematuria, 30% hypercalciuria and microscopic hematuria. But our study had only 2 cases of hypercalciuria.

**Aetiologal profile in biopsied cases** - In this study we got 8 cases (23%) IgA nephropathy All of them between 9-12 years. Recurrent gross hematuria and protienuria present in 4 patients (50%) persistent hematuria more than 3 months in 3 patients. Henoch Schonleinpurpura and in rest of the patients no such history. End stage renal disease developed in one patient with massive protienuria and biopsy shows more crescents. Kern et al\(^{(15)}\) retrospectively evaluated 25 children with mesangial IgA deposits. 19 patients (73%) had recurrent macroscopic hematuria, chronic protienuria in 5 cases and there also glomerular involvement was similar in six patients with history of Henoch Schonleinpurpura. Also he demonstrated mesangeal IgA deposits in idiopathic nephrotic syndrome. Giane et al\(^{(20)}\) who followed up 53 children with IgA nephropathy over 6.2 years. He staged them in to A, B, C, D, Stage A-no urinary anomalies for 1 year (18.2%), Stage B- microscopic hematuria with protienuria<1 g/m2/day (63.6%), Stage C-Protienuria>1g/m2/day (11.4%), Stage D-Chronic renal insufficiency (6.8%) Gross or microscopic hematuria at onset, correlated with stage A or B disease at the end of follow up, where as presence of protienuria or nephritic syndrome correlate with stage C or D disease. In our study all patients had gross/microscopic hematuria at onset and histology also suggestive of stage A or B disease. No renal failures or end stage renal disease reported till the end of follow up. Besides mesangial deposits of IgA in all patient, c3 deposits in 4 patients, IgG in 3 patients and IgM in 2 patients and mesangeal hyper cellularity in 4 patients also were observed.

Among the 6 (17%) cases of SLE 4(66.7%) had proteinuria, WHO class II-2(33%), Class III-1(16.7%), class IV-3(50%) cases. All cases were
females between 5-15 years & were not normal at the end of one year follow up. Ernre et al (12) followed up 43 children with biopsy proven lupus nephritis. Mean age of children was 12.0 ± 2.8 years. All of them (21) were having hematuria and 53.5% had protienuria at admission. class IV (diffuse proliferative glomerulonephritis) was observed in 29 patients as the most frequent histopathology [67.45%]. The patients with class IV nephritis had a tendency to develop nephrotic syndrome, heavy protienuria, increased creatinine level and persistent hypertension at initial evaluation. Diffuse proliferative glomerulonephritis was found in 4 (11.4%) patients in this study. All were having clinical picture suggestive of nephritic onset nephrotic syndrome. The observation found in study by Takahashi (21) (Table-10) also showed similar biopsy results. His study concluded in children under three year. They have done biopsy for 13 cases all under 3 years and they found that, 4 cases of FSGS (33%), DPGN 3 cases (25%), thin basement membrane disease 2[16%], minor glomerular abnormalities in 4 cases. Here the reason for difference in aetiology was because they have done biopsy for small children below 3 years. In our study age group of IgA nephropathy was 9-12 years and PSGN between 2-12 years, SLE between 9-12 years.

Limitations of Present Study
Our follow up period is too short. Long term outlook can be projected only by following these children into adult hood. Moreover our sample size was very small & biopsy was limited to specially indicated cases, hence the diagnosis made mainly clinically lacking definitive diagnosis.

Conclusions
During the year studied, 3.8% of total hospital admissions in our hospital was due to hematuria. Acute post infectious glomerulonephritis is most common cause of hematuria that constitute about 59% of total non biopsied and 11.4% of biopsied cases. IgA nephropathy (23%) Systemic lupus erythematosus (17%) were found to be the next common causes.60% of hematuria was found to be resolved completely in the course of 1 year. There were no deaths due to hematuria even in significant renal lesions till the end of our 12 month follow up. Thus the outcome was observed to be more promising.

Bibliography
6. Indian Pediatric Nephrology Group, Indian Academy of Pediatrics Consensus statement on Evaluation Hematuri Indian Pediatrics 2006; 43:965-973


