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EDITIORIAL POLICY

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Dissemination of Paediatric Nephrology Service- A Demand of Time

Improvement of Paediatric nephrology in Bangladesh is a demand of time. Though Paediatric Nephrology was more or less unknown before 2000 AD to the general people and even to the doctors that Paediatric Nephrology is a separate entity, different from adult Nephrology. But now a days, scenario has been changed but not with entire satisfaction to meet the demand of the Nation as well as Paediatric Renal patients. To provide satisfactory service to the 4-5% paediatric renal patients among our children population, Paediatric Nephrology department should be established in all Government Medical Colleges furnished with qualified paediatric nephrologists, trained nurses, auxiliary staffs and infrastructure facilities of renal replacement therapy. Moreover if applied curriculum on Paediatric Nephrology included in the under graduate curriculum, it will create a dynamic impact of awareness about Paediatric Nephrology among general people. In this context, it may be mentioned that there are created posts of Paediatric Nephrology in different Government Medical colleges, but unfortunately a significant number of posts are occupied by the other specialists, which is jeopardizing proper service to the paediatric renal patients of the country. So it is very much essential to provide need based service to these paediatric renal patients, by paediatric nephrologists who should be posted in the appropriate place for the sake of the country. At present near about thirty five Paediatric Nephrologists are working in different parts of the country without any infrastructure development outside Dhaka city. This number is quite insufficient considering huge number of Paediatric Renal patients throughout the country. As a result, bulk of the patients is being treated by the other speciality people which leads to development of complications in future due to lack of knowledge of Paediatric renal physiology and drugs pharmacology. This problem can be solved by creating awareness about importance of Paediatric Nephrology among mass people and also to state machinery about importance of this subject that these type of renal problems should be managed by the Paediatric Nephrologists and facilities for renal replacement therapy should be established in Government Medical Colleges.

At present, renal replacement therapy only exists in 3/4 hospitals of Dhaka, which is quite insufficient for a country where 170 million people reside. So, it is the demand of time that to disseminate the service of Paediatric Nephrology to the mass people. More specialists’ manpower are badly needed and infrastructure of renal replacement therapies also to be established outside Dhaka city without delay.


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Pattern of Histopathology of Glomerulonephritis in the department of Pediatric Nephrology of A Tertiary Care Hospital: An Experience of Four Years

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Abstract

Background: The study describes histopathological pattern of glomerulonephritis (GN) in department of pediatric nephrology, Chattogram medical college, Chattogram, Bangladesh.

Method: This descriptive study included <15 years old, 48 cases of glomerulonephritis patient who underwent ultrasonography guided percutaneous renal biopsy from January 2014 to December 2017 in department of pediatric nephrology, chattogram medical college which started to serve the nation since December 2013. Biopsy specimens were evaluated histopathologically under light and direct immunofluorescence (DIF) microscopy by an experienced histopathologist.

Results: A total of 48 renal biopsies were performed. Inadequate tissue was obtained in 2 samples. Male were 37.50% and Female were 62.5% with M:F 1:1.66. The youngest child was 11 month old. Majority (64.58%) was between 1 to 10 years old, 33.33% was >10 years old and 2.08% was below 1 year. Among the cases nephrotic syndrome (70.83%) was the major indication of biopsy, lupus nephritis was 16.66%, acute kidney injury was 10.41% and chronic kidney disease was 2.08%. Mesangial proliferative GN(26.06%) appeared most frequently observed histopathology followed by lupus nephritis (LN) of different classes (17.39%), membrano proliferative GN 13.04%, membranous GN 13.04%, IgM nephropathy 8.69%, minimal change disease 6.52%, IgA nephropathy 4.34%, crescentic GN 4.34%, chronic sclerosing GN 2.17%. Among nephrotic Syndrome patients initial attack was the highest, 44.11% followed by steroid dependant nephrotic syndrome (26.47%), steroid resistant nephrotic syndrome (17.46%) and relapse 11.76%. Changing pattern of renal histopathology in nephrotic syndrome was noted in this study. Minimal change disease was nil in 2015 and 2016. Focal segmental glomerulosclerosis was present only in 2017 but overall presence of IgM nephropathy was significant. Mesangial proliferative GN followed by membranous proliferative GN predominantly were prevalent almost in a steady state over the study duration but membranous GN showed rising trend in 2017.

Conclusion: Among all biopsy proven glomerular diseases MesPGN was predominant followed by Lupus Nephritis. Lupus nephritis should be kept in mind even in minimum suspicion without any extra renal manifestation. In our study nephrotic syndrome was the most frequent clinical presentation but MCD was very less. Recent rising trend of other histopathology is a striking feature.

Key words: Glomerulonephritis; Renal Biopsy


Introduction

The pattern of childhood renal disease varies from one geographic region to another even within the same country.¹ This variation is influenced by factors such as genetic predisposition, environmental background, and to a large extent the level of awareness. The causes are different in developing countries as compared to developed ones.² Renal biopsy is a well-established diagnostic modal-ity for the assessment

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of kidney diseases in children. It can provide diagnostic precision and prognostic value and guide in therapeutic options for many renal diseases.

Paediatric nephrology is a new sub specialty in Bangladesh and a few centers are established, almost all centers are in Dhaka city, those are referral centers also. Department of Paediatric Nephrology, Chattogram Medical College, Chattogram, Bangladesh started to serve the nation since December 2013 and till date this is the only Paediatric Nephrology department in Chattogram. First renal biopsy was done in March 2014. Our aim was to maintain biopsy registry and to see the pattern of histopathology of glomerulonephritis (GN).

Materials and Method
This is an on-going descriptive study. A Biopsy register is kept in the Paediatric Nephrology department. This study aims to include children less than 15 years from January 2014 to December 2017 in the department of paediatric nephrology, Chattogram medical college, Chattogram, Bangladesh. A total of 48 renal biopsies were performed after getting written consent from parents or legal guardians. The ultrasound-guided percutaneous renal biopsy specimens were obtained by semi automatic kidney biopsy needle (biopsy gun) 16 gauge in all patients. As the youngest one was 11 month old (close to 1 year) so 16 gauge was used in this patient.

The indications of biopsy were set on nephrotic syndrome (age at onset less than 1 year or more than 10 years, steroid resistant nephrotic syndrome (SRNS), steroid dependent nephrotic syndrome (SDNS) or frequently relapsing nephrotic syndrome (FRNS) before starting any calcineurin inhibitors (CNI), gross or persistent microscopic hematuria, hypertension, hypocomplementemia, persistent renal failure), acute glomerulonephritis with systemic features-fever, rash, joint pain; lack of serological evidence of streptococcal infection, normal C3; Rapidly progressive GN; delayed resolution- 1) oliguria and or azotemia >7 days 2) hypertension and gross hematuria persisting past 3 weeks 3) nephrotic range proteinuria beyond 2 weeks or persistent proteinuria beyond 6 months 4) low C3 levels beyond 12 weeks 5) persistent microscopic hematuria (>18 month), hematuria (Persistent glomerular hematuria with 2+ or more proteinuria, red cell cast, dysmorphic RBC or azotemia; microscopic hematuria of uncertain etiology persisting beyond 2 years), asymptomatic proteinuria (nephrotic range proteinuria; persistent non nephrotic range proteinuria-100 to 1000 mg/m²/day with hematuria), unexplained acute kidney injury (AKI) or suspected drug induced renal failure, chronic kidney disease (CKD) of undetermined etiology with normal sized kidney, inherited nephropathies, systemic diseases (Henoch-Schonlein purpura nephritis, hemolytic uremic syndrome, systemic lupus erythematosus (SLE) etc.)\(^3\,4\,5\,6\)

Nephrotic syndrome defined as proteinuria >40 mg/h/m² or >50 mg/kg/day or protein/creatinine ratio >0.2 g/mmol (>2 g/g) and hypoalbuminemia <25 g/l with or without edema. FRNS was defined by 2 or more relapses within 6 months of initial response or 4 or more relapses within a period of 1 year and SDNS by 2 consecutive relapses during corticosteroid therapy or within 14 days after cessation of therapy. SRNS was defined as failure to achieve remission following 4-week prednisone 60 mg/m² followed by three methylprednisolone pulses.\(^7\) AGN/Acute post streptococcal GN defined by hematuria, proteinuria, acute renal dysfunction, hypertension and fluid retention usually after a latent period of 1-3 weeks after upper respiratory tract infection or 3-5 weeks after pyoderma. Microscopic hematuria defined as >5 RBC per high power field of 10 ml of fresh urine centrifuged at 2000 rpm and resuspended in .5 ml.\(^6\) AKI is defined as any of the following: Increase in SCr by ≥0.3 mg/dl (≥26.5 μmol/l) within 48 hours; or increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume <0.5 ml/kg/h for 6 hours.\(^8\) CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health. Criteria for CKD (either of the following present for >3 months) 1. Markers of kidney damage (one or more) -Albuminuria (AER ≥30 mg/24 hours; ACR ≥30 mg/g [≥3 mg/mmol]), Urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorders, abnormalities detected by histology, structural abnormalities detected by imaging, History of kidney transplantation. 2. Decreased GFR- GFR <60 ml/min/1.73 m² (GFR categories G3a–G5).\(^9\)

Exclusion criteria were age >15 year old, congenital anomaly of kidney disease and urinary tract.

The necessary demographical, clinical and laboratory data at the time of presentation were noted. Two cores of specimen were preserved in formalin and normal saline. Histopathological evaluation of the biopsy specimens by light microscopy (LM) and immunofluorescence (IF) was done by a qualified histopathologist and these were documented in original biopsy forms. IF staining was done with antibodies against IgG, IgM, IgA, C3, C1q. Electron
microscopy was not available. The data was stored and analysed by Microsoft Excel software. An adequate biopsy was defined as one containing a minimum of five glomeruli. Inadequate tissue was found in 2 samples, so histopathology of 46 cases were analysed.

**Results**

Male was 37.50% and Female was 62.5% with M:F ratio 1:1.66. The youngest child was 11 month old. Majority (64.58%) was in 1 to 10 years old, 33.33% in >10 years old and 2.08% below 1 year (Table I).

**Table-I**

<table>
<thead>
<tr>
<th>Sex</th>
<th>No  (48)</th>
<th>M:F</th>
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<tr>
<td>Male</td>
<td>18</td>
<td>37.50%</td>
</tr>
<tr>
<td>Female</td>
<td>30</td>
<td>62.5%</td>
</tr>
<tr>
<td>Age (years)</td>
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<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>1</td>
<td>2.08%</td>
</tr>
<tr>
<td>1-10</td>
<td>31</td>
<td>64.58%</td>
</tr>
<tr>
<td>&gt;10</td>
<td>16</td>
<td>33.33%</td>
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</table>

Among the cases nephrotic syndrome (70.83%) was the major indication. Lupus nephritis (LN) was 16.66%, AKI 10.41% and CKD was 2.08% (Table II).

MesPGN(26.06%) appeared most frequently observed histopathology followed by LN(17.39%) of different class (5 in class-iv, 1 in class- iii and 2 in class- ii), MPGN 13.04%, MGN 13.04%, IgM nephropathy 8.69%, MCD 6.52%, FSGS 4.34%, IgA nephropathy 4.34%, crescentic GN 4.34%, chronic Sclerosing GN 2.17% (Fig 2).

**Table-II**

<table>
<thead>
<tr>
<th>Indications</th>
<th>Number</th>
<th>Percentage</th>
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<tr>
<td>Nephrotic Syndrome</td>
<td>34</td>
<td>70.83%</td>
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<tr>
<td>SLE Nephritis</td>
<td>8</td>
<td>16.66%</td>
</tr>
<tr>
<td>AKI</td>
<td>5</td>
<td>10.41%</td>
</tr>
<tr>
<td>CKD</td>
<td>1</td>
<td>2.08%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>48</td>
<td>100%</td>
</tr>
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</table>

Highest renal biopsy done in 2017. In 2016 biopsy number was least (Fig 1).

**Fig. -2:** Frequency of renal histology in glomerulo-nephritis of 46 biopsy cases with adequate tissue.

MCD: minimal change disease, MesPGN: mesangial proliferative glomerulonephritis, MPGN: membranoproliferative glomerulonephritis, MGN: membranous glomerulopathy, FSGS: focal segmental glomerulosclerosis IgAN: IgA nephropathy, IgMN: IgM nephropathy, Crescentic GN: crescentic glomerulonephritis.
Among nephrotic Syndrome patients initial attack was the highest (44.11%) followed by SDNS (26.47%) and SRNS (17.64%) and relapse 11.76% (Fig 3).

<table>
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<th>Nephrotic Syndrome(n=34)</th>
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<td>Initial attack(15)</td>
</tr>
<tr>
<td>relapse(4)</td>
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<tr>
<td>SDNS(9)</td>
</tr>
<tr>
<td>SRNS(6)</td>
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</tbody>
</table>

Fig.- 3: Pattern of clinical presentation of nephrotic syndrome.

SDNS: steroid-dependent nephrotic syndrome, SRNS: steroid-resistant nephrotic syndrome

Changing pattern of renal histopathology in nephrotic syndrome is noted in this study. MCD was very less in 2014 and 2017 to nil in 2015 and 2016. FSGS was present only in 2017. Presence of IgMN and IgAN was in good proportion.

MesPGN followed by MPGN were predominantly prevalent almost in a steady state over the study duration but MGN showed recent rising trend in 2017 (Fig 4).

Fig.- 4: Changing pattern of histopathology of nephrotic syndrome

Discussion
This is the first systematic study on histopathological pattern of glomerulonephritis conducted in Department of Pediatric Nephrology, Chattogram Medical College, Chattogram, Bangladesh. Female was predominating (62.5%) with M:F 1:1.66 which is dissimilar to study by Miller M et al and Mutalik PP et al.10,11 The youngest child was 11 month old. Majority (64.58%) in 1 to 10 years old and 33.33% in >10 years old which is similar to study done in Cuttack, Odisha, India.11

Highest renal biopsy was done in 2017 which indicate that number of cases and biopsy increasing day by day. The major indication of renal biopsy in Korea by Shin A L et al was asymptomatic urinary abnormality (35.9%); and proteinuria independent of nephrotic syndrome (36%) was in Nottingham University Hospitals, Nottingham, UK and Great Ormond Street Hospital for Children, London, UK.12,13 But in our study nephrotic Syndrome was the major (70.83%) indication similar to study done in Jamaica; Odisha and West Bengal of India.10,11,14 Sinha R found 8% Lupus nephritis which is much less but regarding AKI (7%) and CKD (3%) are almost similar to our study.14

Among all cases MesPGN (26.06%) appeared most frequently observed histopathology followed by Lupus nephritis (LN) of different classes (17.39%), MPGN 13.04% and MGN 13.04% but MCD 6.52% and FSGS 4.34% were insignificant which is in disagreement with study from Pakistan by Moorani KN, India by Mutalik P P and Sinha R where MCD followed by FSGS was the most frequently observed.15,11,14 Henoch Sch’onlein purpura nephritis was predominant in UK by Hussain F et al which was absent in our study.13 IgM nephropathy found 8.69% in this study but it was variable from nil in Jamaican children and 2.54%-14.96% in different centers of Pakistan and India.10,15,16,11,14

The low prevalence (8.69%) of IgAN in our study was due to the low rate of renal biopsies performed in children with urinary abnormality (non-nephrotic proteinuria with or without microhematuria) similar to 6.2% by Kanodia K V et al and 9% in UK.16,13 But The Italian national registry demonstrated that IgA nephropathy was diagnosed in 35% of children undergoing renal biopsy because of isolated hematuria; and 30.4% children with hematuria and non nephrotic proteinuria.17

Frequency of MGN is higher in our study which is low (1.2% -8.47%) in other study.15,12,11,10

Among nephrotic Syndrome patients initial attack was the highest 44.11% followed by SDNS (26.47%)
and SRNS (17.64%). Patients of relapse (infrequent and frequent relapse) found highest by Alam M K et al. SRNS was minimum in Qader A in Bangladesh; more in UK, Nigeria, India. Changing pattern of renal histopathology in Nephrotic Syndrome is noted in this study. MCD was very less in 2014 and 2017; nil in 2015 and 2016 and FSGS was present only in 2017, dissimilar to study done 30 years back by ISKDC where MCD was 76.4%. This decreasing pattern of MCD and FSGS is noted in studies done by Lee SA et al. FSGS was the predominant histopathology and MCD on decreasing trend in the study done by Asinobi A O et al. It is well accepted not to perform renal biopsy in children with a diagnosis of NS without indication. So this is the possible reason of less number of MCD on histopathology among primary nephrotic syndrome cases with typical presentations. MesPGN followed by MPGN predominantly were prevalent almost in a steady state over the study duration. MesPGN found highest by Alam M K. Presence of IgMN was in good proportion but MGN showed recent rising trend in 2017.

Conclusion
This is the biopsy registry of recently established pediatric nephrology department and among all biopsy proven glomerular diseases MesPGN was predominant followed by Lupus Nephritis. Lupus nephritis should be kept in mind even in minimum suspicion without any extra renal manifestation. In our study nephrotic syndrome was the most frequent clinical presentation but MCD was very less. Recent rising trend of other histopathology is a striking feature.

References


Study of Etiological Profile of Children Presented with Hepatomegaly and/or Splenomegaly: An Experience from Pediatric Gastroenterology Department, Bangabandhu Sheikh Mujib Medical University

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Abstracts

**Background:** Childhood gastrointestinal diseases are common and increasing in Bangladesh. Wide variety of diseases present with gastrointestinal symptoms specially hepatomegaly and/or splenomegaly. It is essential to monitor the nature of diseases according to regional area.

**Aim and Objective:** To identify the pattern and etiology of diseases in children presented hepatomegaly with or without splenomegaly at Pediatric Gastroenterology department in Bangabandhu Sheikh Mujib Medical University (BSMMU).

**Methods:** We reviewed retrospectively the data of all children presented with hepatomegaly and/or splenomegaly between 1st July 2017 to 30th June 2018 in the Pediatric Gastroenterology department, Bangabandhu Sheikh Mujib Medical University (BSMMU).

**Result:** A total 390 patients were studied, 26 patients were excluded due to incomplete data, rest 364; among them 222 were males and 142 females. About 39.5% (143) had hepatosplenomegaly and 40% (146) had isolated hepatomegaly. Twenty eight percent (103) diagnosed as neonatal cholestasis, 15.5% (56) chronic liver disease (CLD) other than biliary cirrhosis, 14% (51) extra hepatic portal hypertension, 12% (43) acute hepatitis, 6% (22) storage disease, 6% (22) diagnosed as malignant disease, rest 18% (66) were some common and some rare diseases/syndrome, 3% patients had double pathology at diagnosis.

**Conclusion:** It is observed that neonatal cholestasis was most common followed by chronic liver disease (CLD) and extrahepatic portal hypertension. Double pathology in neonatal cholestasis were common. Malignancies were not uncommon.

**Keywords:** Children, Hepatomegaly, Splenomegaly.


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**Introduction**

Gastrointestinal diseases are common in Bangladesh and increasing day by day.1 Among these a large numbers of patient presented with isolated hepatomegaly with or without splenomegaly. But other than gastrointestinal disease some can present with hepatosplenomegaly. In Pediatric Gastroenterology department, Bangabandhu Sheikh Mujib Medical University (BSMMU) patient admitted with rare diseases and rare presentation and also referred cases from other institute. Wide verity of diagnosis including rare diseases are frequent.

Hepatomegaly and/or splenomegaly is a common finding in infants and children with various etiological factors. Hepatomegaly and/or splenomegaly is a sign seen in various disease processes.2
Hepatomegaly is defined as when the liver span is more than the expected for corresponding age. Similarly, splenomegaly is defined as presence of palpable spleen below left costal margin.3,4

Methods
It was a retrospective observational tertiary care hospital based time bound study. We reviewed Register book (indoor) of the Pediatric Gastroenterology department of BSMMU. Study was done during the period of 1st July 2017 to 30th June 2018. Patients admitted with hepatomegaly and /or splenomegaly, aged up to 18 years into the Pediatric Gastroenterology department of BSMMU included in the study. Patient with incomplete data were excluded from this study.

The following clinical and laboratory information were analyzed from patient case record form (1) demographic characteristics including age and gender, (2) final diagnosis of the patient. Patients were divided into three groups: hepatomegaly group, splenomegaly group and hepatosplenomegaly group. Data were collected from register book of the patient by using data entry preform, which was prepared by the researchers themselves. After collection of relevant information the data were checked, verified, edited manually for consistency, accuracy and to reduce error.

Results
A total 390 patients were studied, 26 were excluded due to incomplete data. Among 364, 222 were males and 142 females (ratio approximately 1.6:1). Mean age 5.57 years with range 24 days to 17 years.

Here 49.5% (180) were in less than 5 years of age than 28% (102) and 22.5% (82) in 5 to 10 years and more than 10 years age group respectively. (Table-1)

About 40% (146) had hepatomegaly, 39.5% (143) had hepatosplenomegaly and 20.5% (75) had splenomegaly.

Here cholestasis was most common cause 28% (103), infectious 17% (61), Wilson disease 8% (30), hemato-oncological 7% (26), storage diseases 6% (22), undiagnosed 4% (14) and miscellaneous were 30% (108). (Fig.-2).

Table 1
Demographic characteristics

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>No of patients</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>222</td>
<td>61</td>
</tr>
<tr>
<td>Female</td>
<td>142</td>
<td>39</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>180</td>
<td>49.5</td>
</tr>
<tr>
<td>5-10</td>
<td>102</td>
<td>28</td>
</tr>
<tr>
<td>&gt;10</td>
<td>82</td>
<td>22.5</td>
</tr>
</tbody>
</table>

Fig 1: Algorithm of data analyzed

Fig 2: Etiological spectrum of patients with hepatomegaly and/or splenomegaly.

Among the 364 analyzed data neonatal cholestasis is the most common and represent 28% (103) of all cases. Chronic liver disease (other than biliary cirrhosis) and extrahepatic portal hypertension are 2nd and 3rd most common cause accordingly. Rest are summarized here in table- II.
**Table-II**  
*Etiology of isolated hepatomegaly, splenomegaly and hepatosplenomegaly*

<table>
<thead>
<tr>
<th>Disease</th>
<th>Hepatomegaly</th>
<th>Splenomegaly</th>
<th>Hepatosplenomegaly</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal Cholestasis</td>
<td>51</td>
<td>0</td>
<td>52</td>
<td>103</td>
</tr>
<tr>
<td>Acute Hepatitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral</td>
<td>33</td>
<td>0</td>
<td>6</td>
<td>39</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Enteric fever with Hepatitis A co-infection</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Acute Liver Failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A virus</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Wilson Disease</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Autoimmune Hepatitis</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Chronic Hepatitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic Hepatitis B</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Chronic Hepatitis C</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Chronic Liver Disease (other than Biliary Cirrhosis)</td>
<td>6</td>
<td>19</td>
<td>31</td>
<td>56</td>
</tr>
<tr>
<td>Extrahepatic Portal Hypertension</td>
<td>0</td>
<td>48</td>
<td>3</td>
<td>51</td>
</tr>
<tr>
<td>Storage Disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycogen Storage Disease</td>
<td>6</td>
<td>0</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Lipid Storage Disease</td>
<td>6</td>
<td>0</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intestinal tuberculosis</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Disseminated tuberculosis</td>
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<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatoblastoma</td>
<td>9</td>
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<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Acute Myeloid Leukemia</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Congenital Hepatic Fibrosis</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Severe Acute Malnutrition</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Thalassemia</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Coeliac Disease</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Budd–Chiari syndrome</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Gilbert’s syndrome</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Crigler-Najjar syndrome</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Dengue fever</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Non-Alcoholic Steatohepatitis</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Caroli Disease</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Juvenile Idiopathic Osteoarthritis</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>AcrodermatitisEnteropathica</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Congenital CMV infection</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Malaria</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Acute Pancreatitis</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Undiagnosed</td>
<td>5</td>
<td>2</td>
<td>7</td>
<td>14</td>
</tr>
</tbody>
</table>
Twenty eight percent patient were neonatal cholestasis and among them 100% patient had hepatomegaly, 50.4% (52) of them had additional splenomegaly. Here biliary atresia was 52.5% (54). In biliary atresia group, 6 number of patient had double pathology. They had biliary atresia with galactosemia 2% (2), biliary atresia with cytomegalovirus (CMV) infection 2% (2), biliary atresia with herpes simplex virus (HSV) with CMV infection 1% (1), and biliary atresia with hypothyroidism 1% (1), also we found progressive familial intrahepatic cholestasis (PFIC) with galactosemia 2% (2).

Idiopathic neonatal hepatitis (INH) 17.5% (18) was 2nd most common cause of neonatal cholestasis, 8% (8) Choledocal cyst, 9% (9) progressive familial intrahepatic cholestasis (PFIC), 7% (7) metabolic cause (Galactosemia, Tyrosinemia). Urinary tract infection (UTI) 3% (3), hypothyroidism 3% (3) not uncommon (table 3).

### Table III

**Etiology of neonatal cholestasis**

<table>
<thead>
<tr>
<th>Neonatal Cholestasis</th>
<th>Number (103)</th>
<th>Percentage (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary Atresia</td>
<td>48</td>
<td>47</td>
</tr>
<tr>
<td>Biliary Atresia with Galactosemia</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Biliary Atresia with CMV infection</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Biliary Atresia with Herpes simplex virus (HSV) with CMV infection</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Biliary Atresia with hypothyroidism</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Idiopathic Neonatal Hepatitis</td>
<td>18</td>
<td>17.5</td>
</tr>
<tr>
<td>Choleodochal cysts</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Progressive Familial Intrahepatic Cholestasis (PFIC)</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>PFIC with Galactosemia</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cytomegalovirus(CMV) infection</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Galactosemia</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Tyrosinemia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Urinary Tract Infection (UTI)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Down Syndrome</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Histiocytosis X</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Alagille syndrome</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Among neonatal cholestasis 18% (18) patients admitted with complication like biliary cirrhosis and/or portal hypertension (table 4). Mean age of presentation of neonatal cholestasis was 4.42 month, early 24 days and late 21 month. Regarding biliary atresia, was presented as early as 37 days and as late as 21 month.

### Table-IV

**Clinical condition of neonatal cholestasis at presentation**

<table>
<thead>
<tr>
<th>Neonatal Cholestasis</th>
<th>Number (103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal Cholestasis without complications</td>
<td>85</td>
</tr>
<tr>
<td>Neonatal Cholestasis with complication</td>
<td></td>
</tr>
<tr>
<td>• Biliary Cirrhosis</td>
<td>11</td>
</tr>
<tr>
<td>• Biliary Cirrhosis with Portal Hypertension</td>
<td>7</td>
</tr>
</tbody>
</table>

After neonatal cholestasis, chronic liver disease (CLD) (74) was the 2nd most common disease, presenting with 17.5% (13) isolated hepatomegaly, 25.5% (19) splenomegaly and 57% (42) hepatosplenomegaly. Wilson disease (40%) most common etiology of CLD followed by biliary cirrhosis (24.5%). Viral cause (HBV, HCV) are less common (table 5).
Table-V
Etiology of CLD

<table>
<thead>
<tr>
<th>Chronic Liver Disease</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson Disease without neurological manifestation</td>
<td>26</td>
<td>35</td>
</tr>
<tr>
<td>Wilson Disease with neurological manifestation</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Autoimmune Hepatitis</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Chronic Hepatitis B</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Chronic Hepatitis C</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Tyrosinemia</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Langerhans cell histiocytosis</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Lipid Storage Disease</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Biliary Cirrhosis</td>
<td>18</td>
<td>24</td>
</tr>
</tbody>
</table>

Portal hypertension was found in 26% (93), among them CLD with portal hypertension 43% (40) and extra hepatic portal hypertension was found in 55% (51) of patients. CLD due to Wilson disease was most common etiology in CLD group 18% (17) (table 6). Extra hepatic portal hypertension also present with hepatosplenomegaly (3).

Table-VI
Etiology of portal hypertension

<table>
<thead>
<tr>
<th>Portal Hypertension</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Liver Disease with Portal Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilson Disease</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Autoimmune Hepatitis</td>
<td>03</td>
<td>3</td>
</tr>
<tr>
<td>Chronic Hepatitis B</td>
<td>01</td>
<td>1</td>
</tr>
<tr>
<td>Lipid Storage Disease</td>
<td>01</td>
<td>1</td>
</tr>
<tr>
<td>Biliary Cirrhosis due to</td>
<td>07</td>
<td>8</td>
</tr>
<tr>
<td>Biliary Atresia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital Hepatic Fibrosis</td>
<td>02</td>
<td>2</td>
</tr>
<tr>
<td>Extrahepatic Portal Hypertension</td>
<td>51</td>
<td>55</td>
</tr>
</tbody>
</table>

Acute hepatitis diagnosed in 12% (43) and all had hepatomegaly (100%), 21% (9) had additional splenomegaly. Hepatitis A 86% (36) being the most common. Both HAV-HEV and enteric fever with HAV co-infection also found in small subset of patients (fig 3).

Fig 3: Etiology of acute hepatitis during study period

Fig 4: Etiology of acute liver failure during study period

Metabolic diseases (other than Wilson disease) found in 8.3% (30), storage disease were most common, glycogen storage disease (GSD) were 30% (9) and lipid storage disease (LSD) 43% (13). (Fig. -5). In GSD (9), 66% had only isolated hepatomegaly and 34% (3) hepatosplenomegaly. In LSD, 53% (7) had splenomegaly and 47% (6) had hepatomegaly. Galactosemia patient 67% (4) had hepatomegaly and 33% (2) had hepatosplenomegaly.

Fig 5: Distribution of metabolic diseases (other than Wilson disease) in study period
Malignant diseases were found 6.5%(23), among them 56%(13) had hepatomegaly and 40% had hepatosplenomegaly. Hepatoblastoma43%(10) were most common then followed by lymphoma13%(6). (Fig.4).

Tests(ALT,AST, gamma-GT, prothrombin time, Albumin), CBC with PBF (to see sepsis), Urine RME and C/S, urine for reducing substance, USG of HBS, TSH, TORCH screening, eye evaluation (for cataract, chorioretinitis, cherry red spot, posterior embryotoxon, hypoplasia / pale optic disc,) hepatobiliary scintigraphy, liver biopsy, MRCP, urine and blood for galactose and tyrosine metabolites. PFIC diagnosed if gamma GT normal and biopsy suggestive.10-18

Here 28%(103) patient were neonatal cholestasis and among them 100% patient had hepatomegaly, 50.4%(52) of them had additional splenomegaly. Here biliary atresia was most common 52.5% (54) .. Idiopathic neonatal hepatitis (INH) 17.5% (18) was 2nd most common cause of neonatal cholestasis, 8% (8) Choledocal cyst, 9% (9)progressive familial intrahepatic cholestasis (PFIC), 7% (7) metabolic cause (Galactosemia, Tyrosinemia). Urinary tract infection (UTI) 3% (3), hypothyroidism 3% (3) not uncommon. Eight (8) patients had double pathology. In study by Mayank et al shows similer result , biliary atresia 41% and INH 18%. Another study by Bazlul karim et al found , biliary atresia (25.8%) and INH (24.2%) are most common two causes of neonatal cholestasis.19,20

Mean age of presentation of neonatal cholestasis was 4.42 month, early 24 days and late 21 month. Regarding biliary atresia, was presented as early as 37 days and as late as 21 month. Study by Mayank et al showed mean age of presentation 2.6 month; range 15 days to 9 months.19

Some investigations were done to find out the cause of CLD, which included, complete blood count(CBC) with peripheral blood film(PBF) (to see hemolysis), liver function tests (ALT,AST, gamma-GT, prothrombin time, Albumin), CBC with PBF (to see sepsis), Urine RME and C/S, urine for reducing substance, USG of HBS, TSH, TORCH screening, eye evaluation (for cataract, chorioretinitis, cherry red spot, posterior embryotoxon, hypoplasia / pale optic disc,) hepatobiliary scintigraphy, liver biopsy, MRCP, urine and blood for galactose and tyrosine metabolites. PFIC diagnosed if gamma GT normal and biopsy suggestive.10-18

Budd-chiari syndrome and Caroli syndrome were common syndromes during study period (fig 5). 

Discussion
Liver is chemical factory of the body.5 Hepatomegaly is present either due to primary disease of liver or as part of systemic disease. Several mechanisms are involved to develop hepatomegaly like inflammation, infiltration, increased size of vascular spaces, increased size of biliary spaces, proliferation of hematopoietic cells, proliferation of kuffer cells, abnormal storage of various metabolites.6-8

Similarly, splenomegaly in infant and children is involved in several pathological condition like increase in its vascular space, inflammation, infiltration, storage disorders etc.9

In our study, common diagnosis are neonatal cholestasis. Diagnosis and etiology are confirmed by fractionated Bilirubin (direct and total), liver function tests (ALT,AST, gamma-GT, prothrombin time, Albumin), CBC with PBF (to see sepsis), Urine RME and C/S, urine for reducing substance, USG of HBS, TSH, TORCH screening, eye evaluation (for cataract, chorioretinitis, cherry red spot, posterior embryotoxon, hypoplasia / pale optic disc,) hepatobiliary scintigraphy, liver biopsy, MRCP, urine and blood for galactose and tyrosine metabolites. PFIC diagnosed if gamma GT normal and biopsy suggestive.10-18

Here 28%(103) patient were neonatal cholestasis and among them 100% patient had hepatomegaly, 50.4%(52) of them had additional splenomegaly. Here biliary atresia was most common 52.5% (54) .. Idiopathic neonatal hepatitis (INH) 17.5% (18) was 2nd most common cause of neonatal cholestasis, 8% (8) Choledocal cyst, 9% (9)progressive familial intrahepatic cholestasis (PFIC), 7% (7) metabolic cause (Galactosemia, Tyrosinemia). Urinary tract infection (UTI) 3% (3), hypothyroidism 3% (3) not uncommon. Eight (8) patients had double pathology. In study by Mayank et al shows similer result , biliary atresia 41% and INH 18%. Another study by Bazlul karim et al found , biliary atresia (25.8%) and INH (24.2%) are most common two causes of neonatal cholestasis.19,20

Mean age of presentation of neonatal cholestasis was 4.42 month, early 24 days and late 21 month. Regarding biliary atresia, was presented as early as 37 days and as late as 21 month. Study by Mayank et al showed mean age of presentation 2.6 month; range 15 days to 9 months.19

Some investigations were done to find out the cause of CLD, which included, complete blood count(CBC) with peripheral blood film(PBF) (to see hemolysis), liver function tests (ALT,AST,PT, albumin, s. bilirubin), USG of hepatobiliary system, Wilson screening; s. ceruloplasmin, 24 hours urinary copper, eye evaluation for K-F ring and sunflower cataract, Penicillamine challenge test, family screening. Autoimmune hepatitis diagnosis by total IgG, ANA,anti LKM1, anti sm antibody, liver biopsy. Viral cause evaluate evaluated by HBs Ag, anti HCV.21-24

In our study, chronic liver disease (CLD) was the 2nd most common disease, presenting with 17.5%(13) isolated hepatomegaly, 25.5%(19) splenomegaly and 57%(42) hepatosplenomegaly. Hepatomegaly is closely correlate with Ganie et al, where hepatomegaly was found 22% correlated. But it differs from Ira shah
et al and Hanif et al, who found hepatomegaly in 71% and 64% respectively; splenomegaly 47.5% and 76% respectively. 

In our study Wilson disease (40%) most common etiology of CLD followed by biliary cirrhosis (24.5%), cryptogenic (16%) and autoimmune (8%). Infectious cause are less frequent; HBV (3%), HCV(1%). This study closely correlate with Behera et al, where Wilson disease was most common 27.5%, chronic hepatitis C was 2.5%. But cryptogenic CLD was not matched which was 52.5%. In present study autoimmune hepatitis was 8%, this finding similar to Yachana et al (4%), Rafeey et al (5.6%).

In our was study, CLD with Portal hypertension 54%, which not matched with Behera et al, where portal hypertension were 35%. 

Endoscopy of upper gastrointestinal tract done to see oesophageal varices, which is a feature of portal hypertension. Extraheptic portal hypertension diagnosed by normal liver function test and color doppler USG (to see any thrombus or cavernous transformation within portal vein) and echocardiography to diagnose Budd-chiari syndrome.

In our study, portal hypertension was found in 26% (93), among them extra hepatic portal hypertension was found in 55% (51) of patients. Here 94% (48) had splenomegaly and 6% (3) had hepatosplenomegaly. Our study differs with Jena su et al, found 14% hepatomegaly. These hepatomegaly due to portal biliopathy.

In our study 12% (43) patient were acute hepatitis, among them 79% had isolated hepatomegaly and 21% hepatosplenomegaly. This study closely correlated with Salahuddin et al and Poddar et al where splenomegaly found 24% and 31%. On etiology, 86% were HAV and 4.7% HEV, 4.7% both HAV-HEV. Among HAV group 11.5% (3) had enteric fever simultaneously. The present study closely correlate with Salahuddin et al, they found HAH 76%, HAV+HEV 4%, HEV 14%. 

In our study 2% (7) were acute liver failure (ALF), among them 57% (4) caused by HAV. This result were similar to Salahuddin et al, 57% cause of ALF was HAV. 

Laboratory findings that are suggestive of glycogen storage disease are CBC, biochemical test includes fasting blood sugar, fasting triglyceride, s.uric acid. Liver biopsy and enzyme assay are confirmatory tests (not available in Bangladesh). For lipid storage disease, eye evaluation for cherry red spot, bone marrow study for foam cell and liver biopsy are done.

Metabolic diseases (other than Wilson disease) found in 8.3% (30), storage disease were most common 6% (22). This study correlate with Bricks et al with 8% storage disease.

In our study malignancy were 6%, which also correlate with Bricks et al, 6% malignant disease.

Galactosemia diagnosed by eye evaluation for cataract, urine for non-glucose reducing substance, blood and urine for galactose metabolites. Tyrosinemia diagnosed by exclusion of other cause, elevated alfa fetoprotein, blood and urine for tyrosine metabolites.

In our study all galactosemia (6) patient had hepatomegaly and 33% had also splenomegaly, which is similar of Hasan et al.

**Limitation**

Small sample size, only diagnoses cases considered, enzyme assay in metabolic diseases were not done.

**Conclusion**

Hepatomegaly and/or splenomegaly is important clinical findings and it can give clue for diagnosis of gastrointestinal diseases as well as non-gastrointestinal disease like malignant diseases. Our study found neonatal cholestasis was most common. CLD, portal hypertension, metabolic and malignant diseases were common accordingly. Also found that double pathology in several cases of neonatal cholestasis and mean age at hospitalization of neonatal cholestasis was delayed.

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Study of etiological profile of children presented with hepatomegaly and/or splenomegaly

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Estimation of Serum IgG level in Nephrotic Children with Infection

Saima Easin¹, Fareha Jesmin Rabbi², Shireen Afroz³, Md. Anwar Hossain Khan⁴

Abstract:
100 nephrotic children were studied in the Microbiology Department of Dhaka Medical College, Dhaka, from January to December 2004. The mean age was 5.4 years (range 1-15 yrs.), 68 were male and the rest 32 were female. All children were diagnosed case of nephrotic syndrome having International Study of Kidney Diseases in Children (ISKDC) criteria with normal renal functions. The patients were monitored clinically presented with any infections as a complication of nephrotic syndrome and investigations were carried out accordingly. Serum IgG levels were estimated in the immunology department of National Institute of Kidney Diseases and Urology (NIKDU) by immunoturbidimetry method. This study was done to find out a relation between culture positive nephrotic syndrome cases with lower levels of serum immunoglobulin G (IgG) with an aim to predict the rate of relapse in these cases. Significant lowering of mean values of serum IgG level was seen in culture positive cases than that of culture negative cases. In comparison, lower serum IgG level seen in nephrotic syndrome cases with history of relapse than history of first attack. Low serum IgG level at onset is an important feature of nephrotic syndrome, but this level revert back to normal level at the period of remission after treatment with steroid. During remission, low level of serum IgG level acts as an indicator for relapse of nephrotic syndrome.

Key words: Nephrotic syndrome, Infections, Serum IgG, Relapse.

Introduction:
Nephrotic syndrome is an immune mediated disorder of kidney associated with T cell dysfunction and secondary disturbance of B cell with changes in the levels of immunoglobulins, which is characterized by massive proteinuria, hypoalbuminaemia, hyperlipidaemia and generalized oedema. According to International Study of Kidney Diseases in Children (ISKDC), nephrotic proteinuria is defined as urinary protein excretion exceeds 2.5 gm. in 24 hours (>1 gm./m²/24 hours) and serum albumin drops below 2.5 gm/dl. In developing countries, bacterial infection is an important complication of nephrotic children resulting significant morbidity and may also be responsible for a poor response to steroid therapy or induce relapse in children who has already attained remission. Recent reports suggest that UTI is the commonest infection in nephrotic children. The probable factors associated with the occurrence of bacterial infections in nephrotic children are decreased immunoglobulins (Igs) concentration, protein deficiency, decreased bactericidal activity of the leukocytes, immunosuppressive therapy, loss of complement factors in urine (properdin, factor B) that opsonize certain bacteria. Nephrotic children may develop bacterial infection not only due to urinary losses of immunoglobulins but also due to impaired synthesis of immunoglobulins especially immunoglobulin G (IgG). Nephrotic children have the altered serum immunoglobulin levels i.e. decreased concentration of serum IgG and IgA and elevated level of serum IgM. Serum IgG and IgA levels usually increase after treatment of nephrotic syndrome with corticosteroids but mean values remain low. The nephrotic patients are unable to convert serum IgM to IgG and IgA synthesis due to failure of B cells to switch from IgM to IgG. But persistent low level of serum IgG may be an important factor responsible for frequent relapse in those patients. There may be a relation that nephrotic children with lower level serum IgG may predispose to bacterial infection and also causes relapse after remission.

Materials and methods:
Study population, Inclusion criteria: Total 100 clinically diagnosed nephrotic syndrome patients (based on massive proteinuria, hypoalbuminaemia,
generalized oedema, hyperlipidaemia) were included. Samples were collected from patients admitted in the Pediatric department of Dhaka Medical College Hospital (DMCH), Dhaka, Pediatric Nephrology department of National Institute of Kidney diseases and urology (NIKDU), Dhaka and of Bangobondhu Sheikh Mujib Medical University (BSMMU), Dhaka.

**Place and duration of the Study:** This study was carried out in the Department of Microbiology, Dhaka Medical College (DMC), Dhaka, and in the Department of Immunology, National Institute of Kidney Diseases and Urology (NIKDU), Dhaka, Bangladesh, for a period of one year, from January to December/2004.

**Methodology:**
Test tube containing two ml of blood was allowed to clot and then tubes were centrifuged at 1500 rpm for 15 minutes. Serum was separated and transferred to a sterile eppendorf tubes. After labeling, the serum was stored in a refrigerator for up to 7 days and serum IgG estimation was done within this period. The test was performed in NIKDU by turbidimetric immunoassay and was based on the principle of agglutination reaction. The test specimen was mixed with the Activation buffer (R1) and then with Anti-human IgG reagent (R2) and allowed to react. Presence of IgG in the test specimen resulted in the formation of insoluble complex, producing a turbidity, which was measured at wavelength 340 nm by spectrophotometer. The extent of turbidity corresponds to the concentration of IgG in the test specimen. At first, sample was 10 times diluted with normal saline (Sw) (i.e. 90 µl normal saline + 10 µl serum). 500 µl of reagent (R1) was mixed with 5 µl of Sw, and then it was incubated for 5 minutes. Then 50 µl of reagent (R2) was added, gently mixed and reading was taken exactly five (5) min. later and multiplied by 10 to obtain the final result.

Reference value: 700-1600 mg/dl.

**Results:**

### Table-I

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Culture positive cases (n=59)</th>
<th>Culture negative cases (n=41)</th>
<th>Mean age</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 6</td>
<td>48 (81.4)</td>
<td>29 (70.47)</td>
<td>5.4</td>
</tr>
<tr>
<td>&gt;6-15</td>
<td>11 (18.6)</td>
<td>12 (29.53)</td>
<td></td>
</tr>
<tr>
<td>Total (n=100)</td>
<td>59 (100)</td>
<td>41 (100)</td>
<td></td>
</tr>
</tbody>
</table>

P value (Z test): P < 0.001

### Table-II

<table>
<thead>
<tr>
<th>Sex</th>
<th>Culture positive cases (n=59)</th>
<th>Culture negative cases (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>68</td>
<td>43 (72.9)</td>
</tr>
<tr>
<td>Female</td>
<td>32</td>
<td>16 (27.1)</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>59 (100)</td>
</tr>
</tbody>
</table>
Table-III
Organisms isolated from different samples of culture positive nephrotic cases (n=59).

<table>
<thead>
<tr>
<th>Types of infection</th>
<th>Material used for culture</th>
<th>n</th>
<th>E.coli n (%)</th>
<th>Pseudomonas n (%)</th>
<th>Klebsiella n (%)</th>
<th>Proteus n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UTI</td>
<td>Urine</td>
<td>50</td>
<td>37 (74)</td>
<td>7 (14)</td>
<td>4 (8.0)</td>
<td>2 (4.0)</td>
</tr>
<tr>
<td>Cellulitis/skin infection</td>
<td>Pus/cellular exudates</td>
<td>5</td>
<td>1 (20)</td>
<td>2 (40)</td>
<td>0 (00)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>Septicemia</td>
<td>Blood</td>
<td>2</td>
<td>1 (50)</td>
<td>1 (50)</td>
<td>0 (00)</td>
<td>0 (00)</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>Peritoneal fluid</td>
<td>2</td>
<td>1 (50)</td>
<td>0 (00)</td>
<td>1 (50)</td>
<td>0 (00)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>59</td>
<td>40</td>
<td>10</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

Table-IV
Serum IgG level (≤700 mg/dl and >700 mg/dl) in culture positive and culture negative cases (n=100)

<table>
<thead>
<tr>
<th>Cases</th>
<th>Serum IgG level ≤700 (mg/dl)</th>
<th>No (%)</th>
<th>Serum IgG level &gt;700 (mg/dl)</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture positive</td>
<td>23 (82.1)</td>
<td>36 (50.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culture negative</td>
<td>5 (17.9)</td>
<td>36 (50.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>28 (100)</td>
<td>72 (100)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P value (Z test): P < 0.001

Table-V
Serum IgG level in culture positive and culture negative nephrotic syndrome cases (n=100)

<table>
<thead>
<tr>
<th>Group</th>
<th>n=100</th>
<th>Serum IgG (mg/dl)</th>
<th>Serum IgG (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture positive</td>
<td>59</td>
<td>510-1120</td>
<td>732.20±116.15</td>
</tr>
<tr>
<td>Culture negative</td>
<td>41</td>
<td>740-1380</td>
<td>1064.63±193.77</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>59 (100)</td>
<td>41 (100)</td>
</tr>
</tbody>
</table>

P value (Z test): P <0.001

Table-IV
Serum IgG level in nephrotic children with history of first attack and relapse of culture positive cases (n=59)

<table>
<thead>
<tr>
<th>Attack</th>
<th>n=100</th>
<th>Serum IgG (mg/dl)</th>
<th>Serum IgG (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of first attack</td>
<td>50</td>
<td>510-1120</td>
<td>747.00 ± 120.73</td>
</tr>
<tr>
<td>History of Relapse</td>
<td>9</td>
<td>510-740</td>
<td>650.00 ± 94.21</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>59 (100)</td>
<td>41 (100)</td>
</tr>
</tbody>
</table>

P value (Z test): P <0.05

Discussion:
Nephrotic syndrome is primarily a pediatric disorder, which is characterized by massive proteinuria, hypalbuminaemia, hyperlipidaemia and generalized oedema. Male children are predominantly affected and most commonly appears between 2-6 years of age. In this study of 100 nephrotic cases, 77 cases were up to 6 years of age and 23 cases were between 6-15 years of age. Among 59 culture positive cases, 48 (81.40 %) cases were up to six years and the rest 11
Estimation of Serum IgG level in Nephrotic Children with Infection

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(18.6 %) were between > 6-15 years of age (p <0.001). In this study, the ratio of male and female was 2:1. Among 59 culture positive cases, male children were significantly more than female (p <0.001). The ratio between male and female were 2.5:1 and 3:1 reported in different studies. In this study, UTI was the commonest infection with a prevalence of 50 %. It was found that UTI was the commonest infection among nephrotic children. Childhood nephrotic syndrome is common between 2-6 years of age and become more immunodeficient during active disease and become more susceptible to bacterial infections. There may be a relation that nephrotic children with hypoalbuminaemia and lower level of serum IgG may predispose to bacterial infection. This study showed significant lowering of serum IgG in culture positive cases than in culture negative cases. In this study, serum IgG level was below the normal lower limit (700 mg/dl; range 700-1600 mg/dl) in 28 cases of which 82.1 % (n=23) were culture positive and 17.9 % (n=5) were culture negative which was statistically significant (p<0.001). Serum IgG level was > 700 mg/dl in the rest 72 cases of which 50 % (n=36) were culture positive and 50% (n=36) were culture negative. In this study, the upper limit of serum IgG in culture negative cases was also below the normal reference level (700-1600 mg/dl) (p<0.001). The results showed that patients with lower serum IgG level were more prone to develop bacterial infection, which was similar with study of Srivastava et al (India 1987). They observed that nephrotic children having lower serum IgG level were more susceptible to infection, responsible to treatment failure and resulting in relapse of nephrotic syndrome.

Among 59 culture positive cases of this study, 50 patients had history of first attack with relatively higher serum IgG level (range 510-1120; mean±SD, 747±120.73 mg/dl). Nine patients with history of relapse had lower level of serum IgG level than those with history of first attack (range 510-740; mean±SD, 650±94.21 mg/dl), which was statistically significant (P <0.05). Several studies have shown that in patients who turned out to be frequent relapsers, serum IgG levels remain in the lower range during remission. So, persistent low level of serum IgG at onset of disease and during remission may be an important factor responsible for frequent relapse in those patients. Sanjeev (Bangladesh 2005) observed that nephrotic children in remission with lower serum IgG level turned out to be frequent relapsers within one year. He concluded that lower level of serum IgG during remission could probably indicate the possibility of frequent relapses in nephrotic syndrome cases. In their study, it is also stated that lower level of serum IgG at the onset of disease act as a marker for early identification of relapse cases of nephrotic syndrome. It has been postulated that the low level of serum IgG is due to impaired synthesis of IgG in nephrotic children. This impaired synthesis of serum IgG is due to defective T-cell function resulting in increased synthesis of serum IgM and decreased synthesis of serum IgG. Studies on T cell subpopulation in nephrotic children show not only decreased levels of T helper and suppressive cells but also functional impairment of T helper cell activity that may contribute to the failure of B cell to class switch from IgM to IgG synthesis. It is possible that children with frequently relapsing nephrotic syndrome cases are in a state of either constant impaired T cell activity or greater suppressor cell function resulting in low levels of serum IgG observed in those patients. Very low levels of serum IgG at the onset observed in study may serve as a marker for early identification of frequent relapse.

Effects of low serum IgG in nephrotic children:
Low serum IgG > Infection > Steroid non-response > Relapse

Limitation
This study included a minimal number of subjects (n=100) with shorter study period. After measurement of serum IgG at onset, follow-up study could not be done in these patients during remission to sort out the relapse cases. Because after treatment with corticosteroid, during the period of remission persistent low level of serum IgG acts as a marker of relapse of nephrotic syndrome in those cases.

Conclusion
It can be concluded that culture positive cases of this study having lower levels of serum IgG (<700 mg/dl) were in the risk of developing relapse. Detailed studies on the predisposing factors of infections in nephrotic children should be carried out involving a larger number of cases for a longer period of time.

References
IgA Nephropathy: A Review
Sabina Sultana¹, Afroza Begum²

Abstract:
IgA Nephropathy or Berger disease is a primary glomerulonephritis which is prevalent worldwide, with greatest frequency in Asians. It has a familial tendency and it is not a benign condition. Nearly 40% adult population develops CKD due to Ig A Nephropathy. Primary Ig A Nephropathy is characterized by deposition of Ig A antibody in the glomerulus. Henoch Schölein purpura (HSP) is a Ig A Nephropathy with systemic manifestation. Current data indicate an abnormal mucosal immune response resulting in production of galactose deficient Ig A Nephropathy, is the main cause of Ig A Nephropathy. The Classic presentation is recurrent gross haematuria within a day or two of a non-specific upper respiratory tract infection (RTI). Nephrotic range proteinuria and hypertension bears poor prognosis. Some patients with Ig A Nephropathy goes spontaneous remission. Non aggressive diseases can be managed with non-immuno suppressive measure but patients with severe or rapidly progressive disease needs immuno suppressive therapy. Glucocorticoids & ACE inhibition remains mainstay of therapy.

Whatever treatment receives, each and every patient should remain on long term follow up to detect early markers of CKD.

Key words: IgA, Nephritis, CKD.


Introduction/Background:
Immunoglobulin A (IgA) nephropathy (IgA N) or Berger disease, is first described by Berger and Hinglaisin 1968,¹ based on the findings of predominant IgA deposition in the mesangium with a mesangial proliferation.

It is one of the primary glomerulonephritis which is higher in frequency worldwide than any other primary glomerulopathy.² Initially it was thought that this clinical entity is benign in nature but with a long term follow up of patients now it is found that 20 to 50 % of adult would ultimately progress to end stage renal failure.² So, its favorable prognosis in case of children are now questionable in light of some recent studies.³⁻⁸

The clinical spectrum varies from asymptomatic microscopichematuria to rapidly progressive glomerulonephritis. Most of the cases are characterized by recurrent episode of gross hematuria associated with upper respiratory tract or other mucosal infection or by asymptomatic microscopic hematuria with or without proteinuria.⁹

Spontaneous remission has been reported in children and adults.

Secondary IgA nephropathy is also associated with various underlying disease processes. Advanced age, hypertension, proteinuria and impaired renal function at presentation are poor prognostic factors.⁹,¹⁰

Epidemiology:
Its prevalence is worldwide but it varies from country to country. IgA nephropathy occurs with greatest frequency in Asians and whites and it is relatively rare in black. In a Chinese study, IgA nephropathy constituted 45% of all cases of primary glomerulonephritis.¹¹

The explanation for this variability in incidence is uncertain, but it may be due to racial differences or to differences in biopsy selection practices¹². Genetic factors and environmental influences could
contribute to geographic differences in prevalence. But in Australia\textsuperscript{13} where the population is heterogeneous including migrant from many countries all racial group seem to be equally affected. Although it can present at any time, the peak incidence of disease is in the second and third decades of life. A male to female ratio of 2:1 is observed in north America and western European populations, although this difference is not observed among population in the Pacific.

Etiology and pathogenesis:
The pathogenesis of IgAN is not fully understood or uncovered. It is generally considered to be an immune complex mediated or aggregated (polymerized) IgA mediated glomerulonephritis. Because IgA is the main immunoglobulin directed against antigen (viral and bacteria) and because it’s frequent association between upper respiratory or gastrointestinal tract infection with onset on microscopic hematuria.

Many studies done to find out true specificity for antigen and for antibody for mesangial IgA but there are limited success.

Predisposing genetic factors:
It has been suggested that genetic factor has an important role in the development of IgAN\textsuperscript{14} and it not only determine susceptibility to glomerulonephritis but also influence the pathological severity and natural course of IgAN.\textsuperscript{15,16} Schena et al\textsuperscript{17} reported that familial IgAN had a poorer prognosis than sporadic IgAN. So, genetic factor might play an important role.

Current data indicate that at least 4 processes contribute to development of IgA nephropathy\textsuperscript{18}.

a) Patients with IgA nephropathy often have a genetically determined increase in circulating levels of IgA1, with galactose deficient O-glycans in the hinge region.

b and c): this glycosylation aberrancy is, however, not sufficient to induce renal injury, synthesis and binding of antibodies directed against galactose-deficient IgA1 are required for the formation of immune complexes that accumulate in the glomerular mesangium.

d) This immune complexes activate mesangial cells, inducing proliferation and secretion of extracellular matrix, cytokines, and chemokines, which result in renal injury.

An abnormal mucosal immune response resulting in production of galactose deficient IgA\textsubscript{1} in IgA nephropathy patients is supported by several observations\textsuperscript{19}.

Recurrence of IgA nephropathy has been reported in allograft, and rapid disappearance of IgA deposits is observed when kidneys with IgA deposits are transplanted in a patient without IgA nephropathy.

In the next few years, it is hope that advances of understanding of pathogenesis of IgA Nephropathy which will give clear picture of classification of patient not only with clinical and morphological criteria but also on pathogenesis basis.

Pathology

Immunohistologic findings:
Deposition of IgA in the glomerular mesangium as the sole or predominant IgA Immunoglobulin G and/or IgM may also deposits but in a lesser intensity and frequency. Ig A deposits are associated with IgG and IgM in 32% and 11% respectively\textsuperscript{20} and C\textsubscript{3} deposits may preset in 64% cases.

Light Microscopic Findings
Most characteristic abnormality is ,mesangial enlargement caused by various combinations of hpercellularity and increase in matrix.

According to amount and proliferation of mesangial cell, biopsy is graded by the world health organization\textsuperscript{21}

a) Minimal glomerular lesion

b) Focal mesangial proliferation, upto 80% of glomeruli show moderate or severe mesangial cell proliferation.

c) Glomerulonephritis show moderate or severe mesangial proliferation.

Four types of mesangial changes are identified in children with IgAN\textsuperscript{22}

a) Messangialhypercellularity is more prominent than the increase in matrix

b) The degrees of mesangial hypercellularity and matrix increase are similar.
c) The increase in matrix is more prominent than the mesangial cellularity, and
d) Progression of IgA N is associated with the development of global glomerulosclerosis accompanied by reactive cell invasion.

**Electron microscopy**

Electron microscopic abnormalities are mainly observed in the mesangium which is enlarged by increased cytoplasm and matrix. Electron-dense deposits in the mesangium are the most constant and prominent features and are seen in all of the patients.

**Oxford classification of IgA nephropathy**

A Working group of the international IgA nephropathy network and renal pathology society have developed a consensus on the pathologic classification of IgA nephropathy. The goal of the new classification was to identify specific pathological features that more accurately predict risk of progression of renal disease in IgA nephropathy.

Several pathologists identified histological variables by repeated analysis of biopsies that were consistently interpreted with a high degree of reproducibility.

The following variables were identified that correlated with renal outcomes.

- Mesangial hypercellularity
- Segmental glomerulosclerosis
- Endocapillary hypercellularity
- Tubular atrophy/interstitial fibrosis

Based on these data, the committee developed the numerical scores on the presence or absence of these variables. The suggested scoring system is as below:

Mesangial cells are counted per mesangial area and a score of 0-3 is assigned for each glomerulus. A score of 0 indicates that fewer than 4 mesangial cells are present per mesangial area; a score of 1 indicates that 4-5 mesangial cells are present per mesangial area; a score of 2 indicates that 6-7 mesangial cells are present per mesangial area; and a score of 3 indicates that greater than 8 mesangial cells are present per mesangial area. Scores obtained for all glomeruli are averaged, and the resulting assigned hypercellularity score is either M0 if the mean score is less than 0.5 or M1 if the mean score is greater than 0.5.

Segmental glomerulosclerosis is defined as present (S1) if any part of the glomerular tuft is involved in sclerosis or absent (S1) if no segmental glomerulosclerosis is present.

Endocapillary hypercellularity is defined as present (E1) if hypercellularity is present within the glomerular capillary lumina and results in narrowing of the lumina or absent (E0) if no hypercellularity is present within lumina.

The percentage of the cortical area involved by tubular atrophy or interstitial fibrosis is quantitated. A score of T0, T1, or T2 is given if the percentage of involved cortical area is 0-25%, 26-50%, or more than 50%, respectively.

Biopsies with fewer than 8 glomeruli should be considered of uncertain value for prognosis.

Differences between childhood and adult patients with IgAN:

There are several difference of IgAN between children and adult like

a) Glomerular hypercellularity in mesangial area is prominent in children then adult
b) Glomeruler matrix expansion, cresenet formation, and interstitial damage are more severe in adult
c) Glomerular hypercellularity correlated with proteinuria in children and in case of adult it is related to matrix.

**Relationship between IgAN and HSP:**

The relationship between IgAN and HSP is complex and seems to have a close relationship. The morphologic and immunopathologic features are similar in the two conditions. The two disorders have been reported to coexist in different member of same family. It has been suggested that the two conditions are variants of the same process and that IgAN is HSP without the rash.

**Presentation/ Clinical features:**

Primary IgA nephropathy

Although the clinical presentation of IgA nephropathy varies from asymptomatic urinary abnormalities to acute renal failure, 5 different clinical syndromes are generally recognized.

The most common presentation (approximately 60-80%) of IgA nephropathy is asymptomatic microscopic urinary abnormalities with one or more
episodes of intermittent gross hematuria. The recurrent macroscopic hematuria often associated with upper respiratory infection (viral pharyngitis) is traditionally regarded as the hallmark of childhood IgA nephropathy, compared with poststreptococcal glomerulonephritis (PSGN), in which hematuria usually occurs 1-2 weeks after infection. The hematuria is usually painless, but loin pain has been reported. Blood pressure may be within the reference range or elevated. Renal clearance function is within the reference range or reduced.

The second most common presentation (approximately 26%) is asymptomatic microscopic hematuria with or without mild proteinuria, hypertension, or reduced renal clearance function.

Acute nephritic presentation (approximately 12%) with heavy proteinuria, normal or low clearance function, and normal or high blood pressure is the third most common presentation.

Nephrotic syndrome may be the initial presentation in as many as 10% of patients.

Rarely, IgA nephropathy may present as an acute crescentic glomerulonephritis with oliguria, edema, and hypertension.

Secondary IgA nephropathy
When renal mesangial IgA deposition occurs because of another specific clinical condition (secondary IgA nephropathy), the history of that disease or signs and symptoms related to the primary condition may be present.

Physical
In the early stages of primary IgA nephropathy, no physical signs may be observed. However, early diagnosis might be suggested by a urinalysis that reveals microscopic hematuria with or without proteinuria.

Hypertension is infrequent, is mild to moderate, and is usually a late presentation of disease.

Edema due to nephrosis is reported in approximately 10% of patients.

If renal function is compromised at presentation, the patients may have signs of uremic syndrome, anemia, pallor, and lethargy.

If IgA nephropathy is secondary to underlying disease, such Henoch-Schönlein purpura (HSP) or systemic lupus erythematosus (SLE), the signs and symptoms of that specific primary disease may be apparent.

Workup

Laboratory Studies
The diagnosis of IgA nephropathy is based on clinical history and laboratory data, but it can only be confirmed by kidney biopsy. The IgA deposits within mesangium visualized by immunofluorescence or immunoperoxidase studies confirm the IgA nephropathy.

Although circulating autoantibodies, including antiendothelin antibodies, have been reported in IgA nephropathy, none appears to be disease specific.

The following studies are used to identify immunoglobulin A (IgA) nephropathy and to rule out other causes of nephropathy:

- Urinalysis (UA) usually reveals hematuria, proteinuria, and leukocytes. Microscopic examination shows dysmorphic RBCs and RBC casts suggestive of glomerular origin of RBC but not specific for IgA nephropathy
- CBC count with differential to identify anemia, leukocytosis, and thrombocytopenia help exclude other underlying causes for nephritis
- A 24-hour urine collection estimates creatinine clearance (CrCl) and protein excretion; proteinuria is associated with histologic lesions and a risk for progression; proteinuria also helps determine therapeutic course.
- The ratio of urine calcium (Ca) to creatinine (Cr) measures hypercalciuria (normal is < 0.2), a common cause for microhematuria
- Serum electrolyte levels; Na, K⁺, Cl, and HCO₃ could help detect early abnormalities
- BUN and Cr levels estimate renal function and help in further management decisions
- Serum C3 and C4 levels are usually normal; C3 is routinely measured to eliminate the diagnosis of postinfectious glomerulonephritis (PSAGN) or membranoproliferative glomerulonephritis (MPGN); low C3 and C4 suggest lupus nephritis
- Anti streptolysin-O (ASO) titer or streptozyme tests help exclude PSAGN
- Serum Ig A levels are increased in 30 to 50% of adult patients but in only 8 – 16% in children.
Plasma polymeric IgA1 levels are elevated in 30-50% of cases, but this suggestive finding is not sufficiently specific to establish the diagnosis; measurement of the proportion of poorly galactosylated IgA1 O-glycoforms in the serum with or without measurement of poorly galactosylated IgA1-specific IgG has been proposed as a clinically useful diagnostic test but this test are insufficient for the replace of the kidney biopsy as diagnostic standard.

Imaging Studies
Renal ultrasonography is an excellent diagnostic tool to detect structural abnormalities leading to hematuria, such as renal stone, neoplasm, cystic lesion, hydronephrosis, dilated urinary tract, and bladder abnormalities. However, it cannot be used to confirm, support, or reject the diagnosis of IgA nephropathy.

Procedures
Percutaneous renal biopsy is essential for the confirmation of IgA nephropathy. The diagnosis of IgA nephropathy is based on the presence of IgA in the glomerular mesangium. The indications for biopsy include the following:

- Macroscopic (gross) hematuria
- Microscopic hematuria with significant proteinuria (>2 mg/kg/d)
- Acute nephritic syndrome (hematuria with hypertension or renal insufficiency)
- Nephrotic syndrome

A skin biopsy, looking for IgA deposition in the dermal capillaries, has not proven to be sufficiently predictive in IgA nephropathy.

Natural History and progress
The long term prognosis of the 169 Japanese children with IgAN, followed more than 10 years, developed chronic renal failure in 9% of the patient by 15 years. In adult series, the incidence of renal insufficiency varies from less than 10% to as high as 45% in patient followed more than one year.

The prognostic features in case of children in several studies have shown that, the degree of proteinuria correlates with the severity of morphologic glomerular lesion. Heavy proteinuria predicts a poor outcome. Male gender has also been considered as a less favorable outcome by some Author. Acute renal failure at onset is usually transient.

The pathologic features which is associated with poor prognosis are:

a) Diffuse mesangial proliferation
b) A high proportion of glomeruli showing sclerosis, crescents or capsular adhesion
c) The presence of moderate or severe tubulo interstitial changes
d) The presence of sub epithelial electron dense deposits and lysis of glomerular basement membrane by electron microscopy

Levy and associates found that mesangial proliferative glomerulonephritis with crescents was associated with poor prognosis in children.

Some patients with IgAN goes spontaneous remission without any treatment. The rate of spontaneous remission in a study as high as 59.4%.

That’s why physician should consider the potential for spontaneous remission and should not treat aggressively patient with minor glomerular abnormalities or focal mesangial proliferation.

Treatment/Management
The most appropriate treatment for patients with IgAN is still a matter of controversy and a therapeutic challenge.

At present there is no curative therapy for IgAN. However available evidence for treatment is partially, clearly different between children and adults. Generally, the evidence for treatments of IgAN in adults supports relatively passive treatments, whereas that in children supports relatively active treatment.

The slow progression of renal disease [ie, glomerular filtration rate (GFR) loss of 1-3 mL/min/y] hampers the ability to perform adequate studies. The 2 primary approaches to therapy for primary IgA nephropathy are non-immunosuppressive interventions and immunosuppressive therapy.

Non-immunosuppressive interventions to slow progression that are not specific to IgA nephropathy, include blood pressure control and, in patients with proteinuria, angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs). In addition, statin therapy may be beneficial in
patients with chronic kidney disease and serum low-density lipoprotein (LDL) cholesterol concentrations above goal values. Fish oil (omega-3 fatty acid) may be effective in selected patients.

Immunosuppressive therapy to treat the underlying inflammatory disease includes glucocorticoids with or without other immunosuppressive agents (e.g., cyclophosphamide, cyclosporine, mycophenolate).

Not all patients need immunosuppressives; the selection of patients for therapy is based, in part, on the perceived risk of progressive kidney disease: (1) patients with isolated hematuria, (2) patients with persistent proteinuria, and (3) patients with more severe or rapidly progressive disease.

Patients with isolated haematuria, no or minimal proteinuria (< 500 mg/d), and a normal GFR typically are not treated and do not undergo biopsy and, therefore, are identified as having IgA nephropathy. However, these patients should be periodically monitored at 6- to 12-month intervals since they have an appreciable risk of progressive disease as manifested by increases in proteinuria, blood pressure, and serum creatinine.

Patients with persistent proteinuria (>500 mg/d), a normal or only slightly reduced GFR that is not declining rapidly, and only mild-to-moderate histologic abnormalities on renal biopsy are managed with non-immunosuppressive therapies to slow progression and, perhaps, with fish oil.

Patients with more severe or rapidly progressive disease (nephrotic-range proteinuria or proteinuria persisting despite ACE inhibitor/ARB therapy, rising serum creatinine, and/or renal biopsy with more severe histologic abnormalities, but with no significant chronic changes) may benefit from immunosuppressive therapy in addition to non-immunosuppressive interventions to slow disease progression.

The Oxford histologic classification system may assist to select patients with the worst prognosis at the time of renal biopsy.

Non-immunosuppressive therapies

The 3 non-immunosuppressive therapies in IgA nephropathy are (1) ACE inhibitors and/or, which are used blood pressure and/or proteinuria control to slow the rate of progression of the renal disease; (2) statin therapy, which is for lipid lowering in selected patients (with elevated LDL cholesterol) to lower cardiovascular risk, although no evidence is available to show that such therapy slows the rate of progression of renal disease; and (3) fish oil (omega-3 fatty acids at prescription strength and quality), but its role is less clear.

Immunosuppressive therapy

Indications for immunosuppressive therapy

Indications for the use of glucocorticoids alone or in combination with other immunosuppressive agents in patients with IgA nephropathy are not well defined, and one must take into account the potential toxicity of these drugs. Most nephrologists do not treat mild, stable, or very slowly progressive IgA nephropathy with glucocorticoids or other immunosuppressive therapies. 43

Immunosuppressive therapy should be considered only in patients with clinical features (e.g., hematuria with an elevated or increasing serum creatinine value and/or protein excretion >1 g/day despite maximum antiproteinuric therapy) and histologic features (e.g., active inflammation with necrotizing glomerular lesions) suggesting an adverse renal prognosis.

Patients with an acute onset of nephrotic syndrome and diffuse foot process fusion on renal biopsy are treated as if they have minimal change disease.

Glucocorticoids plus angiotensin inhibitors

Simultaneous treatment with glucocorticoids plus an angiotensin inhibitor is preferred to glucocorticoids alone and may be superior to angiotensin inhibitors alone. 44

Monitoring disease activity

Hematuria

Persistent hematuria is generally a marker of persistent immunologic activity, but not necessarily of progressive disease.

Proteinuria

Protein excretion above 1 g/day is a marker of more severe disease and is a major risk factor for disease progression.

Serum creatinine

Serum creatinine concentration, unless it is rapidly rising, permits an estimation of the GFR. Most patients with chronic IgA nephropathy have stable or slowly progressive disease. The rate of loss of GFR
is often as low as 1-3 mL/min per year, a change that may not raise the serum creatinine level to above normal values for a number of years.

Conclusion:
IgA Nephropathy is one of the most common kidney disease. Though recurrent gross haematuria is a typical presentation, it can be silent for years or decades. Proteinuria and hypertension are the most important prognostic factor. There is no curative treatment for IgAN. Early detection and supportive measures are the main stay of treatment. Aggressive disease are treated with combination immunosuppressive therapy with varied results.

References:


Review Article

Recombinant Erythropoietin Therapy in Children With Renal Anaemia: A Review

Azmeri Sultana¹, Ranjit Ranjan Roy², Golam Muinuddin², Md. Habibur Rahman²

Abstract:
Erythropoietin (Epo), an important hormone that regulates erythropoiesis, which is produced by kidneys in response to hypoxia. Recombinant human Epo (rHuEpo) is considered as an advanced treatment for various types of anemias.

The addition of rHuEpo to the therapeutic regimen for children with CKD is one of the most important improvements care in the last 20 years. Anemia is a universal problem among children with chronic kidney disease (CKD). Erythropoietin deficiency is most important contributory cause of renal anaemia, other contributory are iron and folate deficiency, shortened red cell survival, mineral bone disease with hyperparathyroidism. Lower levels of glomerular filtration rate (GFR) are associated with lower levels of hemoglobin, and in adults the anaemia is most pronounced when the GFR falls below 60 mL/min per 1.73 m². In children, the relationship between GFR and anemia is less clear. However, treatment of anemia in both adults and children has improved dramatically with the advent of regular erythropoietin (EPO) and iron therapy, and it has become possible to avoid routine transfusions to maintain a patient’s hemoglobin. As well, the many studies performed in adults and relatively fewer studies carried out in children have demonstrated that improved hemoglobin levels are associated with benefits in quality of life, cognitive function, exercise capacity and cardiovascular function. This article will review the use of rHuEPO in infants and children.

Key Words: Recombinant erythropoietin, renal anaemia

Introduction:
Erythropoietin is a 30-kDa glycoprotein, upregulated by hypoxia, and known primarily for its actions as an inducer of erythropoiesis.¹ Other functions of erythropoietin are being defined, however, including neuroprotection ² and promotion of angiogenesis. Erythropoietin has been shown to contribute to angiogenesis in response to ischemia through upregulation of VEGF/VEGFR and in promoting recruitment of endothelial progenitor cells.

Recombinant human erythropoietin (rHuEPO), has Food and Drug Administration (FDA) approval for the treatment of anemia in pediatric patients with chronic renal failure (CRF) requiring dialysis. It is generally well tolerated and may offer the benefit of reducing the need for blood transfusions in these pediatric populations.¹ Mechanism of Action e/rythropoietin is a glycoprotein which is essential in the production of red blood cells. It is produced in the kidney and stimulates the division and differentiation of erythroid progenitors in the bone marrow. Hypoxia and anemia increase the production of erythropoietin.² rHuEPO is recombinant human erythropoietin, it has the same biological effects as endogenous erythropoietin.³ Use in Chronic Renal Failure There are many clinical studies describing the efficacy of rHuEPO in adult patients with anemia pre-dialysis, during hemodialysis (HD) or peritoneal dialysis (PD), and after transplant. The body of literature in pediatrics is smaller, but supportive.⁴⁻⁻⁵ The major cause of anemia in patients with CKD is lack of EPO synthesis in the diseased kidneys.⁶⁻⁻⁷ EPO is a 30.4-kDa glycoprotein containing 40% carbohydrate that is encoded by a gene identified and cloned in 1985.⁸⁻⁻⁹ The liver is the primary source of

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EPO production in the fetus, but after birth, a group of peritubular interstitial cells in the kidney take over this function, becoming the major sites of EPO production. In response to reduced oxygen supply, EPO production is increased by a hypoxia-inducible factor transcription factor that controls the EPO gene. In renal failure the control of EPO is dearranged, becoming the single largest factor contributing to the anemia of chronic renal disease. In 1987, therapy with recombinant human EPO was shown to correct the anemia resulting from chronic renal failure in dialysis patients.

The relationship between anemia and hypoxia/atmospheric pressure was perceived around the 16th century, predicted experimentally by Carnot and Deflandre, and then the tentative name erythropoietin (EPO) was proposed independently by Komiya and by Bonsdorff and Jalavisto. Reissmann and Erslev confirmed the humoral activity in the blood. Jacobson and colleagues found that the kidney primarily produced EPO. The human EPO protein was finally purified directly from approximately 2,550 liters of human urine of patients with aplastic anemia. The subsequent molecular cloning of cDNA and genomic DNA of human EPO was accomplished concurrently by two research groups in 1985.

**Diagnosis of Anaemia in CKD:**
Anemia is a major consequence of chronic kidney disease. When severe, it is associated with cardiovascular dysfunction, cardiomyopathy, and death. According to the classical definition of anemia reduction of the red blood cell volume or hemoglobin below the range of values for healthy persons. However, a great deal of controversy surrounds the definition of normal values of hemoglobin in children with CKD. Normal values adopted for children with CKD are based on observations of values in healthy children, the ranges of which are 120 g/L (range: 95-145 g/L) in 3-month-old children, 120 g/L (range: 105-140 g/L) in 6-month-old to 6-year-old children and 130 g/L (range: 110-160 g/L) in children aged 7-12 years. Some studies also cite the World Health Organization definition of anemia where children aged 6 months to 6 years are anemic if the hemoglobin count is less than 11 g/L and children aged 6-14 years are considered anemic if it is less than 12 g/L. The new NKF-KDOQI clinical practice guidelines use NHANES-III reference data to cite normative values in children.

Hemoglobin concentration for the diagnosis of anemia in children with CKD.

<table>
<thead>
<tr>
<th>Age</th>
<th>Hb(g/dl)</th>
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<tbody>
<tr>
<td>6months -5 years</td>
<td>&lt;11.0</td>
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<tr>
<td>5-12 years</td>
<td>&lt;11.5</td>
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<tr>
<td>12-15 years</td>
<td>&lt;12.0</td>
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<tr>
<td>&gt;15 years</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>&lt;13.0</td>
</tr>
<tr>
<td>Females</td>
<td>&lt;12.0</td>
</tr>
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**Types of Recombinant Erythropoietin & It’s Uses:**

1. **Intravenous rhEPO-alfa**
   Recommended for patients on hemodialysis
   Starting dose: 50-70 IU/kg/ three times a week, monitoring Hb 2 weekly until target Hb achieved. Increase to maximum of 240 IU/kg/dose. Then maintenance dose 100-300 IU/kg/week.
   rhEpo-alfa should not be used in subcutaneous route due to risk of pure red cell aplasia.

2. **rhEPO-beta**
   Recommended for pre dialysis patient and those on peritoneal dialysis.
   Used as subcutaneous route.
   Starting dose: 75-150 IU/kg/week, increase dose by 25-50IU/kg/week monthly to a maximum of 240 IU/kg/week. Once target Hb has been reached dose should be reduced by 25-50 % in order to maintain Hb at that level. If required further dose reduction may be needed to ensure Hb level does not exceed 13gm/dl. If Hb rises >2gm/dl in 4 weeks dose should be reduced by 25-50%. Half life is longer in subcutaneous route than intravenous route.
   The first reports of EPO use in children described five patients on continuous cycling peritoneal dialysis (CCPD) who received 150 U/kg three times per week; this resulted in the successful treatment of anemia, although hypertension was exacerbated in three of the patients. Once the target hemoglobin level was achieved, these researchers reported that the treatment of anemia could be maintained with a dosage once weekly. A larger patient group of 14...
children on CCPD were described in a subsequent study in Germany. These patients received an initial EPO dose of 300 U/kg once weekly, which was adjusted downwards to a maintenance dose of approximately 100 U/kg once per week. Again, the only side effect reported was hypertension. Following publication of these studies, EPO became the standard treatment for renal anemia in childhood and was prescribed at a dose of approximately 150 U/kg per week in clinical practice, divided into three doses per week. More recently, Provenzano et al. reported that for pre-dialysis adult patients, hemoglobin >110 g/L could be maintained by 90% of patients dosed every 1 or 2 weeks, and by three-quarters of patients dosed every 3 or 4 weeks. Observational data from the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) 2004 registry report shows that younger children tend to require higher doses of EPO. Infants were shown to require the highest dose, ranging from 275 to 350 U/kg per week, while children older than 6 years of age required between 200 and 250 U/kg per week. These apparent differences in the dosing of EPO among children of different age groups may be related to an increased presence of non-hematopoietic binding sites of EPO in younger children that may lead to increased clearance. The requirement for EPO dosing also varies with modality of dialysis. PD patients tend to require less EPO (200–250 U/kg per week) than HD patients, who require 250–300 U/kg per week. The differences between dosing according to dialysis modality seem to dissipate at 30 months of follow-up. Most PD patients are reported to have received subcutaneous administration, whereas most HD patients received EPO via the IV route. Dosing adjustments for EPO should be made cautiously using best clinical experience, always taking into consideration the duration of action of the EPO product prescribed. A dose increase or decrease of approximately 20% may be instituted in an attempt to maintain the hemoglobin at the target recommendations.

3. Darbepoeitin-alpha

In 1999, MacDougall described the pharmacokinetics of darbepoeitin alfa, Novel recombinant erythropoiesis stimulating protein (analogue of rhEPO) with extra oligosaccharides chains resulting in a more prolong effect, requiring less frequent dosing than rhEPO. Half life for intravenous administration is 21 hours. In subcutaneous route half life is 32 hours. A subsequent randomized controlled trial demonstrated that darbepoeitin alfa administered IV once weekly was equally effective for controlling anemia in HD patients as I/V EPO administered three times per week. Similarly, in a multicenter randomized open label study of predialysis patients, darbepoeitin, administered once weekly was again shown to be as effective as EPO administered twice weekly.

Starting dose is sc or iv 0.45mcg/kg/week. Dose titration is done by checking Hb. If Hb does not increase by 1 g/dl within 4 weeks dose should be increased by 25%. Further increases may be done at 4 week interval until desired response is obtained. If Hb increases more than 2.5 g/dl within 4 weeks the dose should be decreased by 25-50%. If Hb >13g/dl discontinue darbepoetin-alpha until Hb <12g/dl, then restart at a dose 25% below the previous dose.

The first report of darbepoeitin use in pediatric endstage renal disease described seven children, aged 11.5 ± 3 years who received darbepoeitin at a mean starting dose of 1.6 μg/kg IV once weekly. The dose of darbepoeitin reached a mean steady state value of 0.5 μg/kg per week by 3 months, with satisfactory hemoglobin values of 118 g/L. One patient had persistent thrombocytosis, while hypertension was seen in two patients when the hemoglobin was greater than 130 g/L. Our own subsequent experience in 33 children, including pre-dialysis, HD, and PD populations, confirmed the efficacy of darbepoeitin. A mean hemoglobin level of 114 g/L was recorded between 20 and 28 weeks, and 91% of the patients had a hemoglobin value of greater than 100g/L during the same time interval. Another study found that an exacerbation of hypertension associated with hemoglobin values greater than 130 g/L and an occasional thrombocytosis were the only complications. This study did not restrict patients to once weekly dosing, and almost 90% of our patients were prescribed darbepoeitin less often than once weekly by week 28 of the study. However, two problems were noted with darbepoeitin: (1) eight of the 14 patients who were asked to describe the pain of darbepoeitin injection reported that it was worse than what they had previously experienced with EPO; (2) because darbepoeitin comes in pre-filled unidose syringes at 10-ìg increments, dosing is not convenient for small infants, and the administration of a partial syringe is not recommended because of potential
inconsistent mixing of the active ingredient within the syringe. Based on these results, researchers experienced in six infants weighing <8 kg. The drug was administered after partial withdrawal of the pre-filled syringe into a calibrated 1-ml syringe prior to injection. Three medically stable infants responded very well to darbepoetin at a dose of only 0.25 IUg/kg per week. In three infants who were medically unstable and continually hospitalized for various invasive procedures, it was difficult to determine the efficacy of darbepoetin.

2. Methoxy polyethylene glycol-epoetin beta (MICERA)
It is a newer class of third generation erythropoietic stimulating agent. It is structurally similar to the previous synthetic EPOs except that it is connected to polyethylene glycol that gives longer half life (6 times longer than darbepoetin-alpha and 20 times longer than epoietin).

Following iv administration the half life for Micera is almost 5.6 days and following subcutaneous it is approximately 5.8 days.

Starting dose is 0.6 mcg/kg once in every 2 week IV or SC to increase Hb level ≥11gm/dl. once Hb ≥11 reached dose should be continued as once in monthly. Dose should be titrated by monitoring, Hb monthly.

Initiation Of rhEPO therapy:
1. Before starting treatment with rhEPO some factors must be addressed.
   - Maintain adequate nutrition
   - Do iron profile and give iron folate and VitB12
   - Correction of severe hyperparathyroidism.
   - Treatment of chronic infection or inflammation prior to rhEPO therapy.

2. Consider starting treatment with rhEPO
   - In case of Children: Hb ≤10gm/dl
   - In case of adult: Hb ≤9-10 gm/dl
   - If patient is symptomatic despite of Hb >10gm/dl, starting rhEPO may improve quality of life.

3. Dose adjustment:
   - Based on concentration of patient’s Hb concentration, rate of change of Hb, ongoing rhEPO dose and clinical condition.
   - Target rate of increase Hb >0.5g/dl per week
   - If Hb is higher than desired, withhold rhEPO dose or decreasing the dose may be done.

4. Monitoring:
   - CBC 1-2 weekly with reticulocyte count may be required until target is reached. Once target is achieved and patient is stable on therapy monitor CBC monthly with serum ferritin and TIBC level.

5. Recommended Hb level during rhEPO therapy:
   - For children target Hb level 11-12g/dl
   - Hb level shouldn’t ≥13gm/dl, study showed greater risk for death, cardio vascular risk and stroke.
   - Hb targets for maintenance rhEPO therapy can be individualized with patient

NKF-KDOQI clinical practice guidelines for anemia in children with CKD recommend that the target hemoglobin level should be 11.0 g/dL or greater. In contrast to the benefits achieved by maintaining hemoglobin above a minimum target level, there is insufficient evidence to support an upper limit of hemoglobin for therapy in children. Besarab et al. published a randomized prospective open-label trial in which they compared the effects of normal (42%) and lower (30%) hematocrit values in patients with clinically evident congestive heart failure or ischemic heart disease on HD. The risk ratio for the normal hematocrit group compared to lower hematocrit group was 1.3 (95% confidence interval: 0.9–1.9).

Benefits of rhEPO therapy
Anemia is associated with significant morbidity and mortality in children with CKD. Complications related to anemia include kidney disease progression, cardiovascular disease, hospitalization, mortality, and an impaired quality of life.

Progression of kidney disease
Irrespective of the underlying cause, the progression of kidney disease leads to obsolete or sclerotic glomeruli, tubular atrophy and interstitial fibrosis. Anemia and subsequent tissue hypoxia may contribute to this progression to end stage kidney disease. Therefore, the correction of anemia may lead to increased oxygen delivery to tubular cells, decrease tubular damage and protect against nephron loss induced by tubular injury.
Cardiovascular disease
Ongoing chronic anemia will manifest clinically as tachycardia and shortness of breath on exertion, possibly progressing over time to cardiac dilatation, left ventricular hypertrophy or congestive heart failure. Mitsnefes et al. reported that pediatric patients with left ventricular hypertrophy had significantly lower hemoglobin values than those without left ventricular hypertrophy (hemoglobin: 9.5±1.8 vs. 10.9±2.3 g/dL).32

Hospitalization and mortality
Warady and Ho studied the NAPRTCS database to assess the association between anemia at 30 days post-initiation of dialysis and patient mortality. They demonstrated that anemia 30 days post-initiation of dialysis was associated with a relative risk of death of 1.52 (95% confidence interval: 1.03–2.26) and that the presence of anemia was also related to an increased risk of hospitalization.33

Quality of life:
In children with CKD, the correction of anemia has been associated with an improvement in exercise capacity and quality of life. Morris et al. completed a single blind, placebo controlled crossover study in 11 children with end stage kidney disease to assess the clinical benefits of anemia correction. An increase in hemoglobin level was associated with an improvement in exercise tolerance, physical performance and school attendance.3 They found that anemic patients had a lower quality of life across all stages of CKD and that there was a strong dose response relationship between hemoglobin level and quality of life as measured using this particular questionnaire.33

Adverse effect associated with rhEPO Therapy:
- Hypertension
- Seizures
- Hyperkalaemia
- Thrombosis
- rhEPO hypo responsiveness
- Antibody mediated pure red cell aplasia.

A report was published on the occurrence of pure red cell aplasia and anti-EPO antibodies in patients treated with EPO.34 Most of these patients received Eprex, an epoetin alfa product marketed outside of the United States.35 In a review of 170 of 200 patients for whom there was follow-up information on PRCA for at least 3 months, 37% recovered hematologically, although the vast majority of these patients required immunosuppressive therapy.36-37

The epidemiologic data confirmed that PRCA was much more likely with subcutaneous administration of EPO than with IV administration, with the majority of cases occurring with EPO alfa produced by Ortho Biotech, although 11 cases were also reported following the use of EPO-Beta, manufactured by Roche and eight cases following the use of EPO Alfa produced by Amgen and marketed in the United States.38 Finally, two cases of antibody-mediated PRCA have also been reported with darbepoetin use. The overall incidence of PRCA following the administration of Eprex has dropped greatly since 2004, when the method by which Eprex is stored and reconstituted was changed.39-40

The incidence of thrombosis of the vascular access sites was higher in the higher hematocrit group. These results should be viewed with caution in that they may not be generalizable to the pediatric population, as many CKD patients may not have clinically evident cardiovascular disease.41

Conclusion:
Anemia continues to be a very prevalent problem among pediatric CKD patients. Recombinant EPO therapy have revolutionized the treatment of anemia in children. Thus complications related to anemia include kidney disease progression, cardiovascular disease; hospitalization, mortality, and an impaired quality of life can be prevented by recombinant EPO therapy.

References
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Nephrocalcinosis in Children: A Review
Farhana Rahman¹, Sharmin Akter Luna¹, Tahmina Jesmin², Ranjit Ranjan Roy³

Abstract
Nephrocalcinosis (NC) is more frequent in children than currently anticipated, but still remain under- or misdiagnosed in a significant proportion of patients, since symptoms and signs may be subtle or misleading. Definite incidence rates are not available for children, which can appear as a single entity or together with urolithiasis. In contrast to the adult patient, where environmental factors are the main cause, genetic and/or metabolic disorders are the main reason for childhood nephrocalcinosis. Common causes such as hypercalciuria, several metabolic disorders such as hypocitraturia or hyperoxaluria, as well as a variety of renal tubular diseases, e.g., Dent’s disease or renal tubular acidosis, have to be ruled out by urine and/or blood analysis. Preterm infants are a special risk population with a high incidence of nephrocalcinosis arising from immature kidney, medication and hypocitraturia. Early treatment with increasing fluid intake, low calcium & oxalate diet, crystallization inhibitors and disease specific medication are mandatory to prevent progression of nephrocalcinosis and subsequently deterioration of renal function.

Keywords: Childhood, Nephrocalcinosis, Diagnosis, Management.


Introduction
Nephrocalcinosis (NC) is defined as deposition of calcium in the tubules, the tubular epithelium, and/or the interstitial tissue of the kidney.¹ Where as Urolithiasis describes stones formed in the kidney but localized anywhere in the urinary tract, as well as primary bladder stones and nephrolithiasis refers to stones residing in the kidney. Nephrocalcinosis is less common than urinary tract calculi and it can appear as a single entity or together with urolithiasis. Definite incidence rates are, however, not available for nephrocalcinosis (NC) in children. The increase of nephrocalcinosis in adults was most likely related to (changing) environmental factors such as dietary habits, fluid intake, and obesity, all subsumed in the metabolic syndrome. Although this will clearly also gain importance in the pediatric population, genetic and anatomical causes are still the main determinants. Studies related to nephrocalcinosis are very limited. Nephrocalcinosis is the sign of a disease but not the disease itself. The condition can progress to chronic kidney disease (CKD), and the renal prognosis is determined by its underlying cause, so a through and early diagnostic evaluation in all children with nephrocalcinosis to determine its causes and preserve kidney function is mandatory.

Epidemiology
Incidence
Different incidence rates and aetiological factors are reported in children with urolithiasis or nephrocalcinosis, reflecting differences in geographic, genetic and socioeconomic background as well as the source of the series and the study design.² While the exact rates for nephrocalcinosis are unknown, the incidence of urolithiasis in childhood is considered to be approximately 10% of that in adults, which is around 5% in industrialized
countries. An incidental discovery occurs in 15–40% of children due to high proportion of unspecific symptoms, the real incidence in childhood is likely to be underestimated. Caucasian children are 5.6 times more likely to have kidney stones compared with African-American children.

Sex and Age
Nephrocalcinosis affects children of all ages. Nephrocalcinosis seems to primarily appear in the first years of life, which might be due to the fact that it is frequently based on tubulopathies or inborn errors of metabolism (Table 2). Sound data on sex and age distribution are, however, only known for Urolithiasis.

Classification
Nephrocalcinosis can be classified according to the anatomic area involved. Medullary nephrocalcinosis, subdivided into three subtypes according to the degree of echogenicity, is distinguished from cortical (e.g., in acute cortical necrosis) and diffuse nephrocalcinosis. Focal deposition of calcium ( dystrophic calcification) may be seen in an area of previously damaged parenchyma, but diffuse nephrocalcinosis usually results from a metabolic disorder.

Risk Factor
Risk factors for nephrocalcinosis include genetic abnormalities in epithelial transport, metabolic disturbances, anatomical abnormalities, and urinary tract infections in the majority of pediatric patients. Environmental factors such as dietary habit, fluid intake, obesity, immobilization contributed more to the increasing incidence in adults, but may gain importance in the pediatric population in the near future, expressed by the increasing numbers of children with obesity or the metabolic syndrome.

Etiology
Metabolic disorders are more likely to occur in children in comparison to adult and subsequently increase risk of progression of nephrocalcinosis. Common causes include hypercalciuria, renal tubular acidosis and hyperoxaluria. Hyperparathyroidism is not a common cause in children, though important in adults. Nephrocalcinosis may be seen in very low birth weight infants receiving therapy with frusemide or acetazolamide. Causes of Nephrocalcinosis are listed in Table-1.

Table -1
Causes of nephrocalcinosis:

<table>
<thead>
<tr>
<th>Causes of Medullary Nephrocalcinosis</th>
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<tbody>
<tr>
<td>Adrenal insufficiency</td>
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<tr>
<td>Bartter syndrome</td>
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<tr>
<td>Familial hypomagnesaemia-hypercalciuria</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>Hyper and hypothyroidism</td>
</tr>
<tr>
<td>Idiopathic hypercalciuria</td>
</tr>
<tr>
<td>Lesch-Nyhan syndrome</td>
</tr>
<tr>
<td>Lowes syndrome</td>
</tr>
<tr>
<td>Medications - frusemide, dexamethasone</td>
</tr>
<tr>
<td>Medullary sponge kidney</td>
</tr>
<tr>
<td>Prematurity</td>
</tr>
<tr>
<td>Tyrosinaemia</td>
</tr>
<tr>
<td>Williams syndrome</td>
</tr>
<tr>
<td>Wilsons disease</td>
</tr>
<tr>
<td>Enamel - renal syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Causes of Cortical Nephrocalcinosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical necrosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Causes of both Cortical and Medullary Nephrocalcinosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperoxaluria-</td>
</tr>
<tr>
<td>Primary types 1,2,3</td>
</tr>
<tr>
<td>Enteric</td>
</tr>
<tr>
<td>Idiopathic</td>
</tr>
<tr>
<td>Hypercalcaemia</td>
</tr>
<tr>
<td>Lipoid (fat) necrosis</td>
</tr>
<tr>
<td>Sickle cell disease</td>
</tr>
</tbody>
</table>

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Table - II

**Genetic Diseases with Nephrocalcinosis:**

(MIM Mendelian inheritance in man (catalogue no.), HPRT hypoxanthine-guanine-phosphoribosyl transferase, APRT adenine phosphoribosyltransferase, dRTA distal renal tubular acidosis, AD autosomal dominant, AR autosomal recessive, XLR, X linked recessive, LMW low molecular weight, CRF chronic renal failure)

<table>
<thead>
<tr>
<th>Disease Description</th>
<th>MIM</th>
<th>Locus, gene</th>
<th>Inheritance</th>
<th>Gene product</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercalciuria-induced urolithiasis/nephrocalcinosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autosomal dominant hypercalciuria</td>
<td>146200, 601199</td>
<td>3q13.3-q21, CASR</td>
<td>AD</td>
<td>CASR</td>
<td>Hypercalciuria</td>
</tr>
<tr>
<td>Hypercalciuria and nephrocalcinosis (FHNCC)</td>
<td>248250, 603959</td>
<td>3p7.1, 1p34.2, CLDN16, CLDN 19</td>
<td>AR</td>
<td>Paracelcin 1, Claudin 16, 19</td>
<td>Hypercalciuria, nephrocalcinosis, renal phosphate leak (variable), LMW proteinuria, hypophosphatemia (variable)</td>
</tr>
<tr>
<td>Dent's disease, (Dent 1)</td>
<td>310009, 310468; 300008</td>
<td>Xp11.22, CLCN5</td>
<td>XLR</td>
<td>CLC-5</td>
<td>Hypercalciuria, renal phosphate leak (variable), LMW proteinuria, hypophosphatemia (variable)</td>
</tr>
<tr>
<td>Lowe syndrome, (Dent 2)</td>
<td>309000</td>
<td>Xq25.26, OCR1</td>
<td>XLR</td>
<td>OCR1 protein</td>
<td>Hypercalciuria, megalin deficiency, phosphate leak, Fanconi syndrome</td>
</tr>
<tr>
<td>Bartter's syndrome type 1</td>
<td>600839</td>
<td>15q13-q21.1, NKCC2</td>
<td>AR</td>
<td>SLC12A1</td>
<td>Salt wasting, hypokalemic metabolic alkalosis, and hypercalciuria, nephrocalcinosis</td>
</tr>
<tr>
<td>Bartter's syndrome type 2</td>
<td>600359</td>
<td>11q24, ROMK</td>
<td>AR</td>
<td>KCNJ1</td>
<td>Salt wasting, hypokalemic metabolic alkalosis, and hypercalciuria, nephrocalcinosis</td>
</tr>
<tr>
<td>Infantile Bartter's syndrome with sensorineural deafness</td>
<td>602522, 604642; 602024, 602023</td>
<td>1p31, 1p36, BSND</td>
<td>AR</td>
<td></td>
<td>Salt wasting, hypokalemic metabolic alkalosis, and hypercalciuria, nephrocalcinosis</td>
</tr>
<tr>
<td>Williams–Beuren syndrome</td>
<td>194050; 130160; 601329; 600404</td>
<td>Contiguous gene deletion syndrome 7q11.23, ELN, LIMK1, RFC2</td>
<td>AD</td>
<td>Elastin, LIM-kinase 1</td>
<td>Hypocalciuria, hypercalciuria, mental retardation, &quot;happy face manner&quot;, ectopic stenosis, &quot;Elfin-foaco&quot;, nephrocalcinosis</td>
</tr>
<tr>
<td>Nephrolithiasis and osteoporosis associated with hypophosphatemia due to mutation in the type 2 sodium phosphate co-transporter</td>
<td>182389</td>
<td>5q35</td>
<td>Unknown</td>
<td>NPT2a</td>
<td>Renal phosphate leak, hypercalciuria, osteoporosis, ↑1,25 dihydroxy-vitamin D</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease Description</th>
<th>MIM</th>
<th>Locus, gene</th>
<th>Inheritance</th>
<th>Gene product</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperoxaluria-induced urolithiasis/nephrocalcinosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary hyperoxaluria, type I</td>
<td>259900, 604285</td>
<td>2q37.3, ASGTX</td>
<td>AR</td>
<td>AGT</td>
<td>Hyperoxaluria, hyperglycemic aciduria, CRF, systemic encephalopathy</td>
</tr>
<tr>
<td>Primary hyperoxaluria, type II</td>
<td>260000, 604296</td>
<td>9q11, GRHPR</td>
<td>AR</td>
<td>GRHPR</td>
<td>Hyperoxaluria, 1,3-glyceric aciduria, CRF</td>
</tr>
<tr>
<td>Cystinuria and urolithiasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystinuria type A</td>
<td>104614</td>
<td>2p q16.3, SLC3A1</td>
<td>AR</td>
<td>r BAT</td>
<td>Elevated urinary excretion of cystine (and other dibasic amino acids)</td>
</tr>
<tr>
<td>Cystinuria type B</td>
<td>604144</td>
<td>19 q13.1, SLC7A9</td>
<td>Inc AR</td>
<td>B β &quot; AT</td>
<td>Elevated urinary excretion of cystine (and other dibasic amino acids)</td>
</tr>
<tr>
<td>Cystinuria type A/B</td>
<td>220100</td>
<td>SLC3A1/SLC7A1</td>
<td>AR</td>
<td></td>
<td>Urine microscopy: hexagonal cystine crystals, recurrent urolithiasis, (CRF)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease Description</th>
<th>MIM</th>
<th>Locus, gene</th>
<th>Inheritance</th>
<th>Gene product</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purine/pyrimidine-induced urolithiasis/nephrocalcinosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesch-Nyhan syndrome</td>
<td>300322</td>
<td>Xq26, HPRT</td>
<td>XLR</td>
<td>HPRT</td>
<td>Hyperinsulinemia, gout, automatistation, recurrent urolithiasis</td>
</tr>
<tr>
<td>Partial HPRT deficiency</td>
<td>308000</td>
<td>Xq26-27.2, HPRT</td>
<td>XLR</td>
<td>HPRT</td>
<td>Hyperinsulinemia, gout, automatistation, recurrent urolithiasis</td>
</tr>
<tr>
<td>Glycogenosis type 1a</td>
<td>232200</td>
<td>17q21.1, G6PC</td>
<td>AR</td>
<td>Glucose-6-phosphatase</td>
<td>Hyperinsulinemia</td>
</tr>
<tr>
<td>Glycogenosis type 1b</td>
<td>232220</td>
<td>11q23.3, SLC3A7A</td>
<td>AR</td>
<td>Transporter</td>
<td>Hyperinsulinemia</td>
</tr>
<tr>
<td>Phosphoribosylpyrophosphate synthetase 1 superactivity</td>
<td>310130</td>
<td>Xq21, PRPS1</td>
<td>XL</td>
<td></td>
<td>Hyperinsulinemia</td>
</tr>
<tr>
<td>APRT deficiency</td>
<td>102600</td>
<td>16q24.3, APRT</td>
<td>AR</td>
<td>APRT</td>
<td>2,3 Dihydroxy-adipinurin, recurrent crystalluria (round + brown), urolithiasis (radiolucent), rarely renal failure from crystal nephropathy</td>
</tr>
<tr>
<td>Xanthinuria (classical)</td>
<td>278300</td>
<td>2p22, XDH</td>
<td>AR</td>
<td>Xanthine oxidoreductase or dehydrogenase</td>
<td>Xanthinuria, hyperuricemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease Description</th>
<th>MIM</th>
<th>Locus, gene</th>
<th>Inheritance</th>
<th>Gene product</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal renal tubular acidosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal tubular acidosis autosomal dominant</td>
<td>179800, 109270</td>
<td>17q21-q22, SLC4A1, A1</td>
<td>AD</td>
<td>A1</td>
<td>Hypocitruric aciduria, hypercalciuria, hyperkalemia, osteomalacia</td>
</tr>
<tr>
<td>Autosomal recessive dRTA with hearing loss</td>
<td>267300; 192132</td>
<td>2em-q13, ATP6B1</td>
<td>AR</td>
<td>B1</td>
<td>Hypercalciuria, hypocalciuric aciduria, hyperkalemia, rickets, hearing loss</td>
</tr>
<tr>
<td>Autosomal recessive dRTA</td>
<td>602722, 605239</td>
<td>7q33-34, SLC4A1</td>
<td>AR</td>
<td>A4</td>
<td>Hypercalciuria, hypocalciuric aciduria, hyperkalemia</td>
</tr>
</tbody>
</table>
Pathophysiology of NC:
There is no common denominator that can be assigned an etiologic role in all cases.

Physiologic mechanism:
When physical and biochemical conditions disturb a delicate balance between stone-forming and inhibiting factors lead to crystal formation in renal tubules (Fig 1).

<table>
<thead>
<tr>
<th>Promotes stone formation</th>
<th>Inhibits stone formation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less Volume More</td>
<td>Less pH / Citrate Higher</td>
</tr>
<tr>
<td>Lower Motion More mobile</td>
<td>Lower Sterile Concentrated</td>
</tr>
<tr>
<td>More static Stone Forming ions Dilute</td>
<td></td>
</tr>
</tbody>
</table>

*Struvite stones are an exception, requiring an alkaline pH to form

Widespread renal parenchymal injury can cause local deposition of calcium without systemic changes.

Pathological factors:
Hypercalciuria: Most frequent risk factor of NC as well as UL.\textsuperscript{18,19,20} Idiopathic hypercalciuria is considered as a multifactorial disease, which can be divided into renal and absorptive subtypes, distinguished by an elevated fasting urinary calcium excretion (> 0.2 mmol/kg/day) in renal subtype.\textsuperscript{21} Several studies revealed, upto 50% of patients have a positive family history\textsuperscript{22,23}. In that case interestingly, calcium excretion correlates positively between parents and their offspring and between siblings, but not between spouses.\textsuperscript{14}

Distal renal tubular acidosis: Several factors can contribute to form nephrocalcinosis. Acidemia promotes increased calcium phosphate release from bone during bone buffering and direct reduction in the tubular reabsorption of these ions. The degree of hypercalciuria is roughly proportional to the severity of the acidemia. Two other factors contribute to stone formation in this disorder: the persistently high urine pH, which favors the precipitation of calcium phosphate and reduced citrate excretion, as acidemia enhances proximal citrate reabsorption.

X-linked hypercalciuric nephropathy, Dent’s disease\textsuperscript{1} is a rare but severe renal disease, in which early progressive NC, nephrolithiasis and progressive renal failure occur.\textsuperscript{12,24} This disease caused by mutations in the CLCN5 located on chromosome Xp11.22. Inactivation of CIC-5 is associated with a severe trafficking defect in PT cells, with loss of megalin and cubilin at the brush border, resulting in decreased reabsorption of the vitamin D-binding protein, the 25(OH)-vitamin D3 and parathyroid hormone (PTH) that are ultrafiltrated by the glomerulus.\textsuperscript{25,26,27}

Secondary hypercalciuria: Several clinical entities lead to hypercalcinemia with secondary hypercalcuria and risk of developing NC. Primary hyperparathyroidism is a rare cause in children consists of tetralogy of hypercalciuria, hyperphosphaturia, hypophosphatemia and hypercalcemia.\textsuperscript{28,29} NC occurs in this disorder for exceeding the solubility product of
calcium phosphate and calcium carbonate either in blood flowing through kidney, urine or in fluids of renal tissue. Renal insufficiency resulting in hyperphosphatemia would make precipitation even more likely. Hypervitaminosis D diagnosed in patients with hypercalcemia (Ca level >11 mg/dL), high blood levels of 25(OH) Vitamin D (>90 ng/mL), with hypercalciuria and history of excess Vitamin D intake in the doses of vitamin D 900 000–4 000 000 U over a period of 2–8 weeks from uses of multivitamin, milk preparation, also from vitamin D prophylaxis in preterm infants. An excessive daily intake of vitamin A > 10,000 units, may also lead to hypercalcemia and hypercalciuria. Apart from vitamin excess short-term immobilization reduces bone mass of about 15-20% accompanied by hypercalciuria. Long term administration of furosemide causes inhibition by furosemide of the Na+ K+ 2Cl" carrier in the apical membrane leads to a parallel reduction in the reabsorption, by alteration of gradient created by sodium chloride (NaCl) transport.

Glucocorticoids: high doses of glucocorticoids relates to an imbalance between resorption and formation of bone. Some syndromes like Barter’s syndrome causes NC due to defect in the normal function of the thick ascending loop of Henles relevant to Na+, K+, and Cl", which impairs Ca++ reabsorption in passive process in coupled to Na+ reabsorption. Hyper and hypothyroidism: the postulated mechanism is that the intact mitochondria can accumulate calcium against concentration gradient as an active process, in proximal or distal renal tubular cell. In hypothyroidism, leading to high intracytoplasmic calcium concentrations predisposing to nephrocalcinosis. Studies have shown that supplementation of thyroxine increases serum calcium and 1,25-dihydroxyvitamin D levels. This further predisposes to nephrolithiasis.

Chronic pyelonephritis: In chronic renal infection, a urea-splitting organism growing in the tubules or interstitial tissue of the kidney liberates ammonia, resulting in local alkaline environment, permits precipitation of calcium salts which may be facilitated by necrosis of renal tissue due to bacterial invasion.

Hyperoxaluria: Oxalate nephropathy is a rare cause of end stage renal disease (ESRD). Hyperoxaluria can be of primary or secondary causes. Primary hyperoxaluria (PH) types I, II, III are rare AR disorder of glyoxylate metabolism due to specific hepatic enzyme deficiencies. Type I PH is the most frequent subtype and it occurs due to low or absent activity of liver-specific peroxisomal: glyoxylate amino-transferase (AGT), leads to elevated urinary excretion of oxalate and L-glyceric acid due to defect of D- glycerate dehydrogenase and hydroxypyruvate reductase (GRHPR). It is generally more benign and ESRD occurs less frequently in children. The pathogenic basis of type III is little known. It so far has no documented case of ESRD. But initial presentation in infancy with massive uni- or bilateral nephrolithiasis eventually complicated by urinary tract infections can be quite severe.

Secondary hyperoxaluria results of 1) excessive intake (nutritional intake contributes only 10%) of oxalate precursors (ethylene glycol, ascorbic acid, methoxyflurane), 2) increased absorption of oxalate (inflammatory bowel disease, malabsorption syndrome e.g., Cystic fibrosis, celiac disease; extensive bowel resection), or 3) deficiency of cofactors in oxalate metabolism (pyridoxine deficiency), lead to systemic oxalosis as calcium oxalate, which precipitates in multiple organs and joints. In patients with enteric hyperoxaluria, calcium instead binds to fatty acids instead of binding oxalate to form insoluble calcium oxalate, and thus more soluble oxalate is available for absorption. On the other hand, intestinal oxalate-degrading bacteria, e.g., Oxalobacter formigenes, are often not found in patients with frequent antibiotic treatment, e.g., in cystic fibrosis. Enteric oxaluria may lead to severe NC and/or recurrent UL, even with progression to ESRD.
Dignostic Evaluation

NC is only the symptom of underlying disease but not the disease itself.¹ Systematic diagnostic approach as below.

Medical history
Family history of renal stone, hematuria and renal failure, metabolic diseases; prematurity, nutrition or specific diets, fluid intake (dehydration), medications (vitamin D/A, steroid, diuretics, etc.), any mineral supplementation, immobilization, children with chronic bowel disease, neurologic disorders (anti-convulsant drugs, low fluid intake), anomalies of urinary tract.

Clinical findings
Infants and young children
NC is mostly asymptomatic, incidentally noted on an imaging study performed for other reasons, during evaluation of UTI. The first clinical symptoms, if any, are very frequent gross or microscopic hematuria and/or sterile leukocyturia.
Older children may present with flank or abdominal pain.

2nd step
For metabolic disorder:
24-hour urine collection for evaluating creatinine, sodium, calcium, phosphorus, magnesium, oxalate, citrate, cysteine, uric acid and urine volume OR Spot (Table III).

Imaging
Plain X-ray KUB region, renal high resolution US, CT scan, renal histology (Table 5).

Investigation
1st step
Urinalysis
Specific gravity (marker of urine concentration and fluid intake), urine pH, hematuria, pyuria, crystalluria, glucosuria, proteinuria.
Others:
Evaluation of renal function-electrolyte levels including potassium, sodium, magnesium, calcium, phosphorus, PTH.

Table 3 | Normal values for lithogenic and stone-inhibitory parameters in spot urine (related to creatinine excretion) and 24-h urine collection (tubes or container need to be preserved with either thymol 5% in isopropanol, or 2 N HCl before collection starts)

<table>
<thead>
<tr>
<th>Calcium/creatinine</th>
<th>Citrate/creatinine</th>
<th>Cystine/creatinine</th>
<th>Oxalate/creatinine</th>
<th>Urate/creatinine</th>
</tr>
</thead>
<tbody>
<tr>
<td>mol/mol g/g</td>
<td>mol/mol g/g</td>
<td>mmol/mol mg/g</td>
<td>mol/mol g/g</td>
<td>mol/mol g/g</td>
</tr>
<tr>
<td>Soluble/creatinine ratio (spot urine samples)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
< 12 Months | < 2.2 | < 0.8 | < 0.12 to 0.25 | < 0.2 to 0.42 | < 1 Month | < 85 | < 180 |
1-3 Years | < 3.5 | < 5/3 | > 0.8 to 1.5 | > 0.14 to 0.25 | 0-6 Months | < 325 to 360 | < 260 to 380 |
| 3-5 Years | < 1.1 | < 0.4 | > 0.8 to 1.5 | > 0.14 to 0.25 | 1-6 Months | < 53 | < 112 |
5-7 Years | < 0.8 | < 0.3 | > 0.8 to 1.5 | > 0.14 to 0.25 | 5-10 Years | < 70 to 82 | < 60 to 81 |
> 7 Years | < 0.6 | < 0.2 | > 0.8 to 1.5 | > 0.14 to 0.25 | > 10 Years | < 40 | < 32 |

Urine excretion of soluble in 24-h urine samples

<table>
<thead>
<tr>
<th>Calcium excretion</th>
<th>Citrate excretion</th>
<th>Cystine excretion</th>
<th>Oxalate excretion</th>
<th>Urate excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>All age groups</td>
<td>&lt; 0.1 mmol/kg per 24h</td>
<td>&lt; 4 mg/kg per 24h</td>
<td>&lt; 55 mmol/1.73 m² per 24h</td>
<td>&lt; 10 Years</td>
</tr>
<tr>
<td>Boys: &gt; 1.9 mmol/1.73 m² per 24h</td>
<td>365 mg/1.73 m² per 24h</td>
<td>6.6 mg/1.73 m² per 24h</td>
<td>200 mmol/1.73 m² per 24h</td>
<td>24h</td>
</tr>
<tr>
<td>Girls: &gt; 1.6 mmol/1.73 m² per 24h</td>
<td>&gt; 310 mg/1.73 m² per 24h</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Repeat collection after stone passage or removal, as stones in situ may diminish lithogenic excretion parameters. Check 24-h urine volume and creatinine excretion (2 mg/kg ± 0.8 mg) to ensure adequate collection.
Several studies documented that still, renal US is the first diagnostic imaging option in infants and children with suspected stones or nephrocalcinosis and an optimal imaging method for monitoring of nephrocalcinosis (Fig. 2).

![Fig. 2: a) normal, still hyperechoic kidney of a preterm infant; b) Tamm–Horsfall kidney; c) medullary nephrocalcinosis (NC) grade I (mild increase of echogenicity around the pyramidal border); d) medullary NC grade II (mild increase of echogenicity at whole pyramid); e) medullary NC grade III (more severe hyperechogenicity of entire pyramid); f) diffuse corticomedullary NC.](image)

Renal US of neonates has some pitfalls, especially in preterm infants, have to be noted: Tamm–Horsfall protein (THP) deposits within the renal calyces may look like nephrocalcinosis (Fig. 1). THP deposition, disappears usually within 1–2 weeks, and follow-up will show completely normal kidneys. Hence detection of cortical nephrocalcinosis may become evident only some weeks later when a rim of cortical calcification becomes visible. However, in patients with suspected primary hyperoxaluria, diffuse cortical nephrocalcinosis may be detectable shortly after birth and it is directly visible both by US and X-ray. The association of hyperechoic pyramids with a posterior acoustic shadow is a clear sign of nephrocalcinosis, hence gross calcifications are thus required before nephrocalcinosis can be diagnosed from conventional radiographs (Diag exa p 408). A pediatric study indicated that sensitivity and specificity of USG compared with CT was 76% and 100%, respectively [43, 44, 45] (Moudi p 533, 36, 57).

### Table V

**Histological findings in nephrocalcinotic kidneys.**

<table>
<thead>
<tr>
<th>Usual findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcification in basement membrane, collecting tubules</td>
</tr>
<tr>
<td>Calcification in medullary interstitial tissue</td>
</tr>
<tr>
<td>Parenchymal destruction in fibrosis of the medulla</td>
</tr>
<tr>
<td>Intracellular calcification, collecting tubules</td>
</tr>
<tr>
<td>Fibrosis, cortical interstitial tissue</td>
</tr>
<tr>
<td>Lymphocytic infiltration, medullary interstitial tissue</td>
</tr>
<tr>
<td>Lymphocytic infiltration, cortical interstitial tissue</td>
</tr>
<tr>
<td>Dilatation, convoluted tubules</td>
</tr>
</tbody>
</table>

### Management

Patients with nephrocalcinosis usually do not present with acute symptom, so chronic management is the mainstay of treatment.

**Chronic management:** Prevention is main and the most important therapeutic goal! Management of children with NC is mainly based on the reduction of the solute concentration in the urine. Independently of the underlying disorder, a high fluid intake (> 1.5 to 2 l/1.73m² body surface area per day) is the precondition of treatment. The benefit of high fluid intake is to distribute over the whole body and provide a stable urinary excretion rate by avoiding a peak of high concentration levels of the lithogenic substances. A low calcium diet in calcium stone formers should be avoided. Furthermore, low sodium diet and high potassium intake can be advised.

Crystallization inhibitors mainly citrate and magnesium are an effective treatment. Urinary calcium excretion can be reduced by 30% with adequate alkali citrate treatment, reduce progression of NC. The recommended daily dosage of alkali citrate (sodium potassium or, best preparation is potassium citrate) is 0.1–0.2 g/kg (0.3–0.6mmol/kg). In case of distal RTA, the dosage has to be adapted to the serum pH and can be given completely as
potassium-based solution. Alkalinization of urine increases the solubility of cystine, uric acid, and calcium oxalate. However, urinary pH should be monitored, as very high pH levels carry the risk of calcium phosphate precipitation.

Children with severe hypercalciuria, with reduced bone mass should be treated with thiazides, which reduce renal calcium excretion by increasing calcium uptake in the distal tubule and stimulate calcium reabsorption in the proximal tubule via volume control and it may improve bone density. A daily dose is 0.5–1 mg/kg (hydrochlorothiazide) b.i.d., but side effects such as hypokalemia and hypotension have to be considered. In such cases amiloride (calcium-lowering but potassium-sparing agent) should be added.48

In PH I treatment of choice is pyridoxal phosphate (cofactor of the defective enzyme). Two pilot trials shows future treatment options in patients with all types of PH might include oral administration of intestinal oxalate degrading bacteria, e.g., Oxalobacter formigenes.49 Patients with PH and ESRD should be transplanted as early as possible, as no renal replacement therapy is capable of removing sufficient amounts of oxalate. Combined liver--kidney transplantation is the choice in PH I to cure the liver-specific enzyme defect. Isolated kidney transplantation is to be performed in PH II (the defective enzyme is ubiquitous).

Low oxalate diet in those patients with secondary hyperoxaluria to avoid disturbances of the intestinal interplay of ions resulting in increased intestinal calcium absorption. Also high ascorbic acid levels should be avoided in patients at risk for calcium oxalate stone formation. It can increase the endogenous oxalate production and hence urinary oxalate excretion. The oral administration of oxalate-degrading enzymes might help reduce the dietary oxalate burden.

Patients with cystinuria, a methionine-restricted diet (protein-rich food) may be recommended but, strict protein restriction is not recommended in children.50 Urine alkalinization (pH > 8) is the main goal of pharmacotherapy in addition to chelating agents (cleave the disulfide bond of cystine to cysteine, a homodimer of cystine, which is 50 times more soluble). D-penicillamine and a-mercaptopropionyl-glycine are equally effective. But Side effects (rash, arthralgia, exantheme, thrombocytopenia, polymyositis, and nephritic syndrome) limit treatment with these agents.51

Patients with purine stones (uric acid, 2, 8-dihydroxyadenine, xanthine), high fluid intake and urine alkalinization to maintain a urinary pH above 6.5 are the main goals. Protein excess has to be avoided to reduce purine intake. In refractory hyperuricosuria, allopurinol (inhibitor of the xanthine-oxidase) can be given. Careful dosing regimens are necessary, as allopurinol treatment may lead to significant xanthinuria. In contrast to uric acid, xanthine solubility does not increase in alkalinized urine, so citrate is of no effect and fluid intake is the main means of therapy.52

Conclusion

Nephrocalcinosis in children is not as rare as generally believed. Through and early diagnostic examination is mandatory for every child with nephrocalcinosis. Children should not be treated like adults. They have to be prescribed a proper preventive treatment. Following this advice progression of Nephrocalcinosis can be prevented and consequently deterioration of renal function.

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Aerophagia in Children: Report of a Rare Functional Gastrointestinal Disorder with Literature Review

Wahiduzzaman Majumder¹, Afsana Yasmin², Zannatul Ferdous Sonia², Fahmida Begum², Rubaiyat Alam³, Md. Rukunuzzaman¹, ASM Bazlul Karim⁴

Abstract
Aerophagia is a functional gastrointestinal disorder characterized by excessive air swallowing, abdominal distension, belching and flatulence. Pathologic aerophagia is a condition caused by the swallowing of excessive volumes of air with associated various gastrointestinal symptoms, such as burping, abdominal cramps, flatulence and a reduced appetite. It is a clinical entity that can simulate pediatric gastrointestinal motility disorders, such as gastroparesis, megacolon and intestinal pseudo-obstruction, and presents more frequently in children with mental retardation. Early recognition and diagnosis of functional aerophagia or pathologic aerophagia is required to avoid unnecessary, expensive diagnostic investigations or serious clinical complications. Functional aerophagia is frequent in the adult population, but rarely discussed in the pediatric literature. We present a pediatric clinical case with a history of excessive swallowed air, excessive belching, nausea, gaseous abdominal distension are the most important symptoms. Mechanical intestinal obstruction, chronic intestinal pseudo-obstruction, malabsorption and congenital aganglionic megacolon were ruled out. Extensive gaseous abdominal distension was due to aerophagia, and managed the patient by psychotherapy, behavioral therapy, clonazepam, lactulose and simethicone.

Key Words: Aerophagia, Belching, Functional gastrointestinal disorders.

Introduction
Aerophagia involves excessive air swallowing causing progressive abdominal distension. Children with aerophagia usually complaints with a nondistended abdomen in the morning, progressive abdominal distension during daytime, visible, often audible, air swallowing, and excessive flatus may present. Resolution of the abdominal distension occurs during the night by absorption of gas and by flatulence. Although aerophagia is a common disorder seen by adult gastroenterologists, but it is rarely occurred in children discussed in the literature.¹-⁵

Case Report
A 9 years old boy presented with history of excessive belching, mild anxiety, nausea and occasional vomiting for last two months. Mother also noticed abdominal distention which occurred at evening and symptoms aggravated. He had no history of abdominal pain, fever, growth failure or developmental delay.

Physical examination showed temperature normal, respiratory rate 24 breaths/minutes, pulse 85 beats/minutes, blood pressure 90/50 mm hg and dehydration absent. Anthropometrically he was normal. His abdominal girth was 45 cm at morning and 52 cm at evening. We also observed excessive swallowing of air during feeding which is audible. The abdomen was distended and moved with respiration. There was no area of tenderness. There was no palpable mass and bowel sounds were normal.

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Plain abdominal radiograph showed gaseous distension of the small and large intestines without any features of obstruction (Figure 1). Serum TSH, FT4, barium follow through and barium enema reports all are normal. Neuropsychiatric consultation pointed out a mild anxiety and considered aerophagia as a stereotype symptom. A diagnosis of FA was made with indication of a cognitive-behavioral approach and associated therapy with oral simethicone, lactulose and benzodiazepine.

Fig.-1: a) photo of the child b) plain abdominal radiography showed gaseous distension of small and large bowel loops

Table-I
Diagnostic criteria for diagnosis of aerophagia

Must include all of the following:
1. Excessive air swallowing
2. Abdominal distention due to intraluminal air which increases during the day
3. Repetitive belching and/or increased flatus
4. After appropriate evaluation, the symptoms cannot be fully explained by another medical condition.

Criteria must be fulfilled for at least 2 months before diagnosis

Discussion
Aerophagia involves excessive air swallowing causing progressive abdominal distension. The symptoms in children are non-distended abdomen in the morning, progressive abdominal distension during the day, visible, often audible, air swallowing and excessive flatus. Resolution of the abdominal distension occurs during the night by absorption of gas and by flatulence. In a large US population study using Rome III criteria, Van Tilburg MAL showed prevalence of aerophagia was found in 4.2% of children by parental report of symptoms. ROME IV Diagnostic Criteria for diagnosis of Aerophagia showed in table 1. When air swallowing is excessive, gas fills the gastrointestinal lumen, resulting in excessive belching, abdominal distention, flatus, and pain, presumably as a consequence of luminal distention. A subgroup of children seems unable to belch and, in those patients, symptoms of distention and pain may be more severe. A higher percentage of children with aerophagia were found to be exposed to stressful events compared with controls and anxiety can be a cause for excessive air swallowing. FA in healthy patients implies a diagnosis on the basis of the presence of diagnostic clinical criteria combined with a normal physical examination. A careful history and a minimal number of diagnostic studies can exclude organic disease, such as malabsorption or intestinal obstruction. Supplementary investigations should be performed based on case history and physical examination [10]. There are no controlled studies in children to guide therapy, which remains largely supportive and may include behavioral therapy, psychotherapy, and benzodiazepines.

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Systemic Lupus Erythematosus Presenting as Steroid Resistant Nephrotic Syndrome – A Rare Event

Jahanara Arju¹, Rummana Tazia¹, Tahmina Jesmin², Ranjit Ranjan Roy³

Abstract:
Systemic lupus erythematosus (SLE) is an autoimmune disease involving multiple system of the body. Renal involvement occur in 60-80% patient and about 55% present with nephrotic syndrome. Induction therapy of lupus nephritis (LN) usually done by corticosteroid and immunosuppressive agent, mainly cyclophosphamide or mycophenolate mofetil (MMF). But, despite aggressive induction therapy, up to 20% of patients with LN are resistant to initial therapy and up to 44% suffer a renal relapse.¹ However, there is no consensus on an appropriate therapeutic regimen for refractory LN. Here, we are reporting a 10 years old girl presented to us with steroid resistant nephrotic syndrome whose serology for lupus nephritis were positive without any other clinical features of SLE. We initially treated her with oral prednisolone followed by I/V methylprednisolone but she failed to respond and turned to SRNS. Thereafter I/V cyclophosphamide (IVCY), MMF failed to improve her condition. Finally, she responded to oral CyclosporineA (CsA). So, we conclude that, steroid resistant nephrotic syndrome can be only presentation of SLE and CsA may be an effective treatment option in patients of SLE presented with steroid resistant nephrotic syndrome.

Keywords: Lupus Nephritis, Steroid resistant nephrotic syndrome, Cyclosporine A.

Case Report

Introduction:
Systemic lupus erythematosus (SLE) is a chronic inflammatory disease with highly diverse clinical manifestations and the presence of a variety of auto antibodies in the serum reacting with different cell components.² Pediatric SLE patient may present with nephritis in 60 to 80% cases which is an important prognostic determinants.³ Nephrotic syndrome is a common presentation of Lupus Nephritis and common histological findings of nephrotic syndrome with SLE are diffuse proliferative lupus nephritis and membranous lupus nephritis.⁴ Patients with SLE who present with NS, may become SRNS during the initial course of treatment; although it is rare. About 20% patients with LN may be resistant to initial therapy.¹ Due to the unfavourable prognosis of SRNS, numerous therapies have been utilized in an attempt to achieve remission, including I/V cyclophosphamide (IVCY), mycophenolate mofetil (MMF), Calcineurin inhibitors [CyclosporineA (CsA) or tacrolimus] and rituximab.⁵

Here, we report a case of 10yrs old girl who developed SRNS at the onset of SLE and who underwent successful clinical remission following treatment with CsA.

Case Summary:
A 10-years-old girl, 2nd issue of her non-consanguineous parents admitted at pediatric nephrology department of Bangabandhu Sheikh Mujib Medical University with the complaints of swelling of whole body, scanty micturition and passage of red coloured urine for 10 days; high grade intermittent fever for last 7 days. Fever was not associated with chills and rigor. Swelling first appeared on face, then gradually became generalized. She had no history of sore throat, skin infection, cough, respiratory distress, headache, convulsion, photosensitivity, skin rash, oral ulcer, joint pain, burning sensation during micturition, no family

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history of such type of illness, but she was a known case of beta-thalassaemia trait.

She was mildly pale, febrile (temperature 102F), normotensive (110/70mmHg) initially, pulse 82 b/min, R/R 22 br/min., she was grossly oedematous evidenced by puffy face, bipedal oedema and ascites. Ear-nose-throat were normal and oral cavity was healthy. skin survey - normal, anthropometrically well thrived. Bed side urine albumin (BSUA) ++++. Initially she had gross hematuria which resolved spontaneously a few days later. Laboratory studies showed: Complete blood count – hemoglobin % 6.5 gm/dl, ESR 67 mm in 1st hr, white blood cell count 4,500/mm3 (neutrophil 68%, lymphocyte 25%), platelet count 1,60,000/mm3; Peripheral blood film – normocytic normochromic anemia.

Urinalysis showed proteinuria (3+), no red blood cell, no cast, pus cell 5—7/HPF, Urine culture and sensitivity revealed no growth, 24hrs Urinay total protein 4.48 gm/m2/day. S. Albumin – hypoalbuminaemia (26 gm/L). Serological exam revealed low C3 (<0.169 gm/L) and C4 (<0.065 gm/L); Anti-nuclear antibody positive (32.8 U/ml); Anti double stranded – DNA (ELISA) positive (153.3 U/ml). Her anti-cardiolipin Ab and anti-phospholipid Ab were negative. Prothrombin time, Activated partial thromboplastin time were normal. HBsAg was negative. Coomb’s test (both direct and indirect) was positive. Serum creatinine was within normal limit (0.56 mg/dl). Serum electrolytes, random blood sugar level and liver function test were normal, but S. calcium was low (6.6mg/dl). USG of KUB region revealed bilateral renal parenchymal change. Chest X-Ray was normal. Renal biopsy revealed no renal tissue, section showed only skeletal muscle. We planned for repeat renal biopsy.

Patient was initially treated with salt, fat and fluid restricted diet, calcium, injection Ampicillin, hydroxychloroquine at a dose of 5 mg/kg/day and oral prednisolone 60mg/m2/day for 2weeks. we couldn’t wait because of massive proteinuria, anasarca and cost of albumin. 2 weeks later, she was treated with IV methyl prednisolone (IVMP)- 25mg/kg for 6 consecutive days as per expertise opinion. But her condition didn’t improve; rather she developed hypertension during IVMP therapy which was controlled with several anti-hypertensive drugs like angiotensin converting enzyme inhibitor (ACEI), calcium channel blocker, alfa – blocker, alfa – methyldopa, clonidine and hydralazine. During hospital stay, once she developed hypertensive encephalopathy and managed with nifedipine sublingual gel and Inj. Phenobarbitone.

After IVMP therapy, she got one dose of I/V Cyclophosphamide. Still she failed to achieve remission, then MMF was added (675mg/m2) and got MMF for 2 weeks, then discontinued, as her condition didn’t improve. Lastly, Cyclosporine was added after taking permission from clinical review board at a dose of 5mg/kg/day. After 17 days, patient underwent clinical and serological remission. Her BSUA became nil for the first time and Disease activity index (DAI) became negative. She also got 2 units of packed RBC, albumin infusion and several units of fresh frozen plasma as per her condition. Gradually she became improved, oedema subsided. While on diuretic phase, anti-hypertensives were withdrawn except calcium – channel blocker, ACEI and clonidine. Patient was discharged with appropriate advice on day 45 of hospital stay. She was prescribed with oral corticosteroid, hydroxy – chloroquine, cyclosporine, iron, calcium and folic acid and above mentioned anti-hypertensives. Our further plan was to repeat renal biopsy and follow up the patient carefully.

Discussion:

Systemic lupus erythematosus is a classic example of multisystem autoimmune disease that is caused by failure of recognition of self-proteins by the body’s own defense mechanism and subsequent production of auto antibodies against a wide range of body proteins. The clinical presentation of juvenile SLE is more severe than adult onset SLE with multiple organ involvement, particularly the kidney and central nervous system. About 50% of patients may develop renal involvement, 40-80 % of which involve during 1st year of disease. Renal involvement are variable, from asymptomatic proteinuria to overt nephrotic syndrome or even renal failure. About 55% of lupus nephritis may present with nephrotic syndrome, and our reported patient present with isolated steroid resistant nephrotic syndrome with positive serology for lupus nephritis without any other manifestation of SLE.

Most common histologic findings of nephrotic patients with SLE are diffuse proliferative lupus nephritis (ISN class IV) and membranous lupus nephritis (ISN class V). However, previous reports also showed SLE patients presenting with NS whose
renal histologic findings demonstrated far milder form of lupus nephritis, i.e. class I (absence of glomerular pathological characteristics by light microscopy), class II (mild to moderate mesangial proliferation), or no evidence of lupus nephritis. In our patient, we could not know histological classification as biopsy reveal no renal tissue and parents refused to do re- biopsy. Literature review states, inadvertent biopsy specimen can be obtained in 1-3% of cases. Aggressive immunosuppressive therapy such as IV Methylprednisolone (MP) and IVCY pulse therapy, has been reported to be effective for the treatment of lupus nephritis and of the available option IVCY has been reported to be the most effective for initial treatment of active lupus. Boletis el al. reported that, 80% patients with active lupus nephritis showed satisfactory response to 6 monthly IVCY, with a reduction in the number of unexpected severe exacerbations. MMF is also used for induction and maintenance of lupus nephritis with equal efficacy like cyclophosphamide but has less side effect. However, it is reported that, despite aggressive induction therapy about20% patient of LN fails to respond initial therapy. Patients who did not respond to 1st line therapies, namely prednisolone and CY or MMF are termed as refractory lupus nephritis. There have been several reports on the efficacy of CsA in cases of refractory SLE and persistent proteinuria is a risk for long term deterioration of renal function. Initial favorable response is the best predictor of good long term outcome of lupus nephritis and to disease modifying anti- rheumatic drugs in rheumatoid arthritis. Interestingly, Lee el al [26] reported that a proportion of patient with SLE have a silent mutation in codon 766 of the glucocorticoid receptor gene which may attribute to variable response to steroid in SLE patient. It has been reported that the major adverse effect of CsA is nephrotoxicity. However, Ferratio et al reported on the efficacy of CsA in patient with lupus nephritis without significant adverse effect. Our patient did not have any definite toxicity till date. Conclusion: It can be concluded, resistant nephrotic syndrome may be the only presentation of SLE. CsA may be an effective treatment option for selected patients of lupus nephritis presented with SRNS.

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Bowing of Leg and Gynaecomastia as an Atypical Presentation of Wilson Disease: A Case Report

Md. Benzamin¹, ASM Bazlul Karim², Afsana Yasmin³, Abdullahel Amaan⁴, Rubaiyat Alam⁵, Bijoy Talukder⁶

Abstract

Wilson disease is an autosomal-recessive disorder of chronic copper toxicosis due to mutation in the ATP7B gene which causes impaired biliary copper excretion resulting in hepatic copper accumulation & toxicity and subsequent multisystem disease involving the liver, brain, cornea, skeleton and rarely the heart. The disease typically begins with an asymptomatic period with subclinical hepatitis and progresses to liver cirrhosis and neuropsychiatric symptoms. It may present with some unusual features which sometimes confuses clinicians and makes a diagnostic dilemma. Here we present an 15 years old boy presenting with Bowing of leg and gynaecomastia diagnosed as Wilson disease.

Keywords: Wilson disease, Bowing of leg, gynaecomastia.


Introduction:

Wilson disease (WD) is a rare autosomal recessive disorder of copper metabolism. It was first described in 1912 by Kinnear Wilson as “progressive lenticular degeneration,” a familial, lethal neurological disease accompanied by chronic liver disease leading to cirrhosis.¹

It affects 1 in 30,000 people with a gene frequency of 0.56% & a carrier frequency of 1 in 90.² In some populations living in socio-culturally isolated communities with a high rate of consanguinity, the frequency of the disease is higher and may increase up to 1:1130.³

Wilson disease (WD) is a disease of copper metabolism caused by mutations within the ATP7B gene which causes impaired biliary copper excretion resulting in hepatic copper accumulation & toxicity and subsequent multisystem disease involving the liver, brain, cornea, skeleton and rarely the heart.⁴

Case Report

15 year old boy,¹st issue of non-consanguineous parents presented with the history of bowing of leg & difficulty in walking for last 2 years, enlargement of breast for last 1 year & slurring of speech for last 6 months. Bowing of both leg initially was mild which gradually increasing associated with progressive walking difficulty.

Mother noticed gradual enlargement of his breast like female. For last 6 month he developed dysarthria in the form of slurring & is progressive. Mother also noticed abnormal body movement for last 6 month. Mother give history of deterioration of school performance for last 3 years & fracture of shaft of tibia (right) following minor trauma 1 year back. He had no history of jaundice, joint pain & convulsion. He had family history of death due to liver disease; others member are healthy. He had no H/O immunization against Hepatitis B. He received inj. testosterone for gynaecomastia. On examination, he has smiling face, afebrile, moderately pale, anicteric and vitally stable. Wasting of thenar & hypothenar muscle, true gynaecomastia present, no pubic hair or axillary hair. His height was 149 cm & weight 33 kg -within centile. On gastrointestinal sytem examination, just palpable liver, splenomegaly 3 cm & ascites present evidence by shifting dullness. On neurological examination incoordination of movement, dysarthria & brisk knee jerk present. On locomotor examination, joint normal & intercondyler distance 10 cm.

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Complete blood count shows moderate anemia, thrombocytopenia, serum albumin low, SGPT high, 25-OH vit-D low, s.creatinine, s.uric acid normal, prothrombin time with INR-high, USG of HBS shows coarse hepatic parenchyma with splenomegaly with ascites (Table I). After evaluating the clinical data, physical findings and investigations results, the case was provisionally diagnosed Chronic liver disease due to Wilson disease with Rickets. As patient is not immunized against HBV we had a differential diagnosis - Chronic liver disease due to chronic Hepatitis B with Rickets. After evaluating the patient’s presenting features, physical findings and the laboratory tests results, s.ceruloplasmin (6mg/dl), 24 hour urinary copper (374 micro gm/dl) , eye evaluation for K-F ring (+ve) was done which all goes in favour of Wilson disease.

HBsAg & anti HCV was negative which exclude viral cause of CLD. We also did esophago-gastroduodenoscopy which shows esophageal varices.

For bowing of leg we gone for xray lower limb & there was no feature suggestive of rickets except generalized osteopenia ,S.Vitamine D was low( insufficient) but S.Ca++, Alkaline phosphatase, S.PTH was normal. Dexa bone scan for bone marrow density was done & shows reduced bone mineral density .MRI of brain suggestive of Wilson disease.

<table>
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<th>Table-I</th>
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<tr>
<td><strong>Laboratory investigation</strong></td>
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<tr>
<td>Investigations</td>
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<td>Hemoglobin</td>
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<td>White cell count</td>
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<td>Neutrophil</td>
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<td>Eosinophil</td>
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<td>S.Albumin</td>
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<td>Prothrombin time</td>
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<td>SGPT</td>
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<td>25-OH vit-D</td>
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<td>Urine R/M/E</td>
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<td>S.creatinine</td>
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<td>S.electrolytes</td>
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<td>S.uric acid</td>
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<td>Doppler USG of HBS</td>
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Fig: a. Smiling face with bowing of leg b. Generalized osteopenia c. Hyperintense signal changes in lentiform nucleus.
We also done family screening, younger brother of case shows low ceruloplasmin 6, normal ALT, significant urinary copper(259 mic gm/day) & K-F ring on both eye. But as he was asymptomatic. According to the history, physical examination, investigation, it was the case of Chronic liver disease due to Wilson disease with neurological involvement with osteomalacia with portal hypertension. Wilson disease is an autosomal-recessive disorder of chronic copper toxicosis. It is caused by mutation in the \( \text{ATP7B} \) gene, which is located within 13q14-q21 on chromosome 13. It results in the impairment of biliary excretion of copper and subsequent accumulation of it in various tissues, initially in the liver.\(^{5,6}\) Subsequently, when hepatic storage capacity for copper becomes saturated, circulatory ‘free copper’ level is increased and deposited in various organs, notably the brain, kidneys, and cornea.\(^7\)

The clinical manifestations of Wilson disease usually are related to the hepatic or CNS involvement. The presenting features are variable, and clinical disease is rarely present before 5 years of age. In the series of Scheinberg and Sternlib (1984), the initial clinical manifestations were hepatic in 42% of patients, neurologic in 34%, psychiatric in 10%, hematologic or endocrinological in 12% and renal in 1%.\(^8\) In children the disease usually presents after 3 years of age with either incidental discovery of abnormal liver function tests or as chronic liver disease and rarely as acute hepatic failure.\(^9\) Our patient having the feature of both hepatic, neurological and endocrine involvement like stigmata of chronic liver disease, hepatosplenomegaly, dysarthria, deterioration of school performance, smiling face, gynecomastia and delayed puberty. Various other presentations may be there in Wilson Disease, including- neuropsychiatric disorder, Coombs negative hemolytic anemia, gall stone formation, cardiac involvement, ovarian dysfunction, hypoparathyroidism, renal tubular lesion and subsequent renal calculi. Some osseomuscular defect with bony deformity, spontaneous fracture and arthropathy are also seen. KF rings are found in 50-60% cases without neurological symptoms.\(^10\)

Occasionally these patients develop some atypical features, which produces diagnostic dilemmas.\(^5,6\)

In addition, several authors have noted its association with musculoskeletal impairments, and among the various impairments described, demineralization is found to be the most principle involvement.\(^11-13\) The prevalence of osteopenia and osteoporosis in children with WD was found as 22.6% and 67.7%, respectively. BMD and BMC levels were higher in children with neurologic involvement.\(^14\)

Our patient presented with musculoskeletal feature that is bowing of leg and walking difficulty. This bowing of leg due to steomlacia supported by X-ray and bone mineral density (BMD) \(Z\) score.

### Table-II

*Laboratory investigations*

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Patient’s value</th>
<th>Reference value</th>
</tr>
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<tbody>
<tr>
<td>S.ceruloplasmin</td>
<td>6 mg/dl</td>
<td>20-60 mg/dl</td>
</tr>
<tr>
<td>24 hours urinary copper</td>
<td>374 micro gm/d</td>
<td>less than 60 micro gm/d</td>
</tr>
<tr>
<td>Eye evaluations for K-F ring</td>
<td>Present</td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>Negative</td>
<td></td>
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<tr>
<td>Anti HCV</td>
<td>Negative</td>
<td></td>
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<tr>
<td>Endoscopy of UGIT</td>
<td>Grade III Oesophageal varices</td>
<td></td>
</tr>
<tr>
<td>Xray both leg (fig b)</td>
<td>Generalized osteopenia; no features of rickets</td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>210 U/L</td>
<td>30-120 U/L</td>
</tr>
<tr>
<td>S.Ca++</td>
<td>9 mg/dl</td>
<td></td>
</tr>
<tr>
<td>S.PTH</td>
<td>17.15 pg/ml</td>
<td>9.0-80 pg/ml</td>
</tr>
<tr>
<td>BMD (by DXA)Z score above -2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI of brain(fig-c)</td>
<td>Bilateral symmetrical T2WI &amp;FLAIR hyperintense signal changes in lentiform nucleus ,also in paraventricular &amp; sub cortical white matter -suggestive of metabolic liver disease ,most likely Wilson disease</td>
<td></td>
</tr>
</tbody>
</table>

We also done family screening, younger brother of case shows low ceruloplasmin 6, normal ALT, significant urinary copper(259 mic gm/day) & K-F ring on both eye. But as he was asymptomatic. According to the history, physical examination, investigation, it was the case of Chronic liver disease due to Wilson disease with neurological involvement with osteomalacia with portal hypertension. Wilson disease is an autosomal-recessive disorder of chronic copper toxicosis. It is caused by mutation in the \( \text{ATP7B} \) gene, which is located within 13q14-q21 on chromosome 13. It results in the impairment of biliary excretion of copper and subsequent accumulation of it in various tissues, initially in the liver.\(^5,6\) Subsequently, when hepatic storage capacity for copper becomes saturated, circulatory ‘free copper’ level is increased and deposited in various organs, notably the brain, kidneys, and cornea.\(^7\)

The clinical manifestations of Wilson disease usually are related to the hepatic or CNS involvement. The presenting features are variable, and clinical disease is rarely present before 5 years of age. In the series of Scheinberg and Sternlib (1984), the initial clinical manifestations were hepatic in 42% of patients, neurologic in 34%, psychiatric in 10%, hematologic or endocrinological in 12% and renal in 1%.\(^8\) In children the disease usually presents after 3 years of age with either incidental discovery of abnormal liver function tests or as chronic liver disease and rarely as acute hepatic failure.\(^9\) Our patient having the feature of both hepatic, neurological and endocrine involvement like stigmata of chronic liver disease, hepatosplenomegaly, dysarthria, deterioration of school performance, smiling face, gynecomastia and delayed puberty. Various other presentations may be there in Wilson Disease, including- neuropsychiatric disorder, Coombs negative hemolytic anemia, gall stone formation, cardiac involvement, ovarian dysfunction, hypoparathyroidism, renal tubular lesion and subsequent renal calculi. Some osseomuscular defect with bony deformity, spontaneous fracture and arthropathy are also seen. KF rings are found in 50-60% cases without neurological symptoms.\(^10\)

Occasionally these patients develop some atypical features, which produces diagnostic dilemmas.\(^5,6\)

In addition, several authors have noted its association with musculoskeletal impairments, and among the various impairments described, demineralization is found to be the most principle involvement.\(^11-13\) The prevalence of osteopenia and osteoporosis in children with WD was found as 22.6% and 67.7%, respectively. BMD and BMC levels were higher in children with neurologic involvement.\(^14\)

Our patient presented with musculoskeletal feature that is bowing of leg and walking difficulty. This bowing of leg due to steomlacia supported by X-ray and bone mineral density (BMD) \(Z\) score.
Due to difficulty in diagnosing Wilson disease, a scoring system was created and promoted by the 8th International meeting on Wilson disease which is based on seven criteria, including the presence of Kayser-Flesicher rings; typical neurological symptoms; decreased serum ceruloplasmin concentration; Coombs’ negative hemolytic anemia; elevated urinary copper excretion; high liver copper value in the absence of cholestasis and mutational findings. Like all other laboratory testing, this scoring system tends to be more reliable in patients with advanced disease. A score e” 4 indicates that disease is highly likely; a score of 2 or 3 indicates that disease is probable and further investigations are needed, and a score of 0 or 1 indicates that disease is unlikely. 

Our patient’s Leipzig score was 7 that is Serum ceruloplasmin < 10mg/dl, Daily urinary copper excretion >2 times of upper limit, K-F ring present, mild neuropsychiatric symptoms suggestive of WD and typical brain magnetic resonance imaging.

Treatment of Wilson disease is copper diet and copper chelator. In 1951, Denny-Brown and Porter and Cumings introduced dimercaprol (BAL) as an effective treatment of Wilson disease. But the daily painful intramuscular injections made BAL impractical. In 1956, D-penicillamine was first used as an effective alternative treatment for Wilson’s disease. other’s treatment include Trientine, Zinc, Tetrathiomolybdate, Liver transplantation, Genetic therapy and hepatocyte transplantation.

Our patient were treated with copper free diet, zinc, D-penicillamine and propranolol. D-penicillamine can cause worsening of neurologic Wilson disease in 10%-50% cases. In a recent series, neurologic worsening occurred on all three treatments used for Wilson’s disease (D-penicillamine, trientine, zinc), but mainly with D-penicillamine, where 13.8% were adversely affected. Trientine is not available in our country. That’s why D-penicillamine given with proper monitoring.

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**Table III**

<table>
<thead>
<tr>
<th>Biochemistry</th>
<th>Score</th>
<th>Clinical symptoms and signs</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver copper content (in the absence of cholestasis)</td>
<td></td>
<td>KF rings</td>
<td></td>
</tr>
<tr>
<td>Normal (&lt;50 µg/g of dry weight)</td>
<td>-1</td>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>&lt;5 times ULN (50-250 µg/g of dry weight)</td>
<td>+1</td>
<td>Present</td>
<td>+2</td>
</tr>
<tr>
<td>&gt;5 times ULN (&gt;250 µg/g of dry weight)</td>
<td>+2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhodanine stain</td>
<td></td>
<td>Coomb’s negative hemolytic anemia</td>
<td></td>
</tr>
<tr>
<td>absent</td>
<td>0</td>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>present</td>
<td>+1</td>
<td>Present</td>
<td>+1</td>
</tr>
<tr>
<td>Serum ceruloplasmin</td>
<td></td>
<td>Neuropsychiatric symptoms suggestive of WD and/or typical brain magnetic resonance imaging</td>
<td></td>
</tr>
<tr>
<td>Normal (&gt;20 mg/dL)</td>
<td>0</td>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td>10-20 mg/dL</td>
<td>+1</td>
<td>Mild</td>
<td>+1</td>
</tr>
<tr>
<td>&lt;10 mg/dL</td>
<td>+2</td>
<td>Severe</td>
<td>+2</td>
</tr>
<tr>
<td>Daily urinary copper excretion</td>
<td></td>
<td>ATP7B genetic analysis</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
<td>No mutation found</td>
<td>0</td>
</tr>
<tr>
<td>1-2 times ULN</td>
<td>+1</td>
<td>Mutation on one chromosome</td>
<td>+1</td>
</tr>
<tr>
<td>&gt;2 times ULN</td>
<td>+2</td>
<td>Mutations on both chromosomes</td>
<td>+4</td>
</tr>
<tr>
<td>Normal but &gt;5 times ULN after PCT</td>
<td>+2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Authors ???
Conclusion

Wilson disease is a multisystem involving disease and it has a variable clinical presentation. It may present as asymptomatic elevated ALT to liver cirrhosis, neurological and neuropsychiatric manifestation. Atypical feature like musculoskeletal and endocrine symptoms may give a clue for Wilson disease. Early diagnosis and treatment is an important factor for better prognosis.

References
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