Warm greetings from the Editorial board of Annals of Pediatric Gastroenterology and Hepatology (APGH). PGLJ is now APGH. Pediatric Gut and Liver Journal (PGLJ) laid the foundation in the world of publishing peer-reviewed quality articles exclusively related to pediatric gastroenterology, hepatology and nutrition. We envisage APGH to be the torchbearer for our entry into the international stage. The new name is also symbolic of opening newer horizons for the official journal of ISPGHAN aiming to get indexed in the near future. Do log in to our new website www.apgh.in for more details and subsequent manuscript submissions.

We are excited to announce the dates of the much-awaited 9th Annual meeting of ISPGHAN and 32nd national conference of the Gastroenterology chapter of IAP which will be held in Jaipur on October 8 to 9th 2022 with an enriching pre-conference work shop on October 7th.

In this issue of APGH, the original article is on “Coagulopathy in Celiac disease” where the authors have discussed recommendation of vitamin K to all celiac before endoscopy based on the results.

Sick neonate presenting with cholestasis is a common problem in tertiary referral centers with considerable dilemmas in the management. This issue contains a very practical approach on this topic in our country.

Inflammatory bowel disease is on rise worldwide. MR enterography (MRE) has taken tremendous strides in the last decade and is currently the recommended imaging in children with IBD. A detailed review of this modality in this issue will help us understand and optimally utilize it.

In the drug review series, we have “Commonly used drugs used in pediatric hepatology practice” and it will be a ready reckoner for the practicing physician.

We have a very interesting case of Celiac Disease with Rapunzel Syndrome in the case report section.

The journal watch is the perfect place to keep ourselves abreast with the recent studies and articles in pediatric gastroenterology and hepatology. The column on publication by ISPGHAN members will inspire the rest of us.

The Quiz no 1 in the previous issue generated good response and the editorial board congratulates all the correct respondents. On the lighter side, let us ponder over a lovely poem on GI bleed and rake our brains to answer the image Quiz no 2.

Happy reading for insightful thinking!

Editor in Chief APGH 2022-23
Dr Lalit Bharadia

Associate Editors APGH 2022-23
Dr Moinak Sen Sarma, Dr Rajiv Khanna, Dr Jaya Agarwal, Dr Rimjhim Srivastava, Dr Prasanth K.S., Dr Aathira Ravindranath
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- Proposed Workshops on:
  - Basic Endoscopy
  - Advanced Diagnostic & Therapeutic Modalities
  - Nutrition in GI and Liver Disease
- Oration
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REGISTRATION FEES

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- Account Number: 222121441208925
- Bank Name: AU SMALL FINANCE BANK LTD.
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- IFS Code: AUBL0002214
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Dr Neelam Mohan
President, ISPGHAN
drneelam@yahoo.com

Dr R K Gupta
Organizing Chairman
M. : +91 94140 54040

Dr Shrish Bhatnagar
Secretary, ISPGHAN
drsrishbhatnagar@gmail.com

Dr Lalit Bharadwaj
Organizing Secretary
M. : +91 98291 24065

Dr Vishnu Biradar
Treasurer, ISPGHAN
vishnubiradar@gmail.com

Dr Natwar Parwal
Co-Organizer, Secretary & Treasurer
M. : +91 96109 51425

Conference Secretariat
Arthart Hospitality
Mr. Rupesh Lohadia
Mobile: +91 9413975000
Email: ispghancon2022@gmail.com

Dr. R K Gupta
Organizing Chairman ISPGHANCON 2022
3-3, Gangrai Park, Near JK Loin Hospital,
JLN Marg, Jaipur-302004 (Rajasthan)
Mobile : +91 9414054040, +91 9829124065, +91 9610961425
Email: ispghancon2022@gmail.com
Coagulopathy and its Correction by Vitamin K in Children with Celiac Disease

Sanjay Kumar¹, Shyam Sundar Sharma², Lalit Bharadia³, Deepak Shivpuri⁴

ABSTRACT

Background: 25% of children with Celiac disease (CD) have coagulopathy at the time of presentation. Diagnosis of CD involves endoscopy and multiple duodenal biopsies. Risk of bleeding with endoscopy and biopsy is more if there is underlying coagulopathy.

Objective: to study the correlation of coagulopathy with grade of histology in CD and to assess the response of a single dose of vitamin K on coagulopathy in children undergoing upper GI endoscopy and duodenal biopsy for CD.

Study design: Non-randomized interventional study.

Method: Children (<18 years) suspected to have CD referred for duodenal biopsies were prospectively recruited in study. During the first 6 months (Group A) Prothrombin time (PT) was tested prior to endoscopy. During the next 6 months (Group B) children were given one dose of Vitamin K (5 mg IM in <10 years and 10 mg IM in >10 years) 24 hour prior to endoscopy and PT was tested prior to endoscopy as in group A. A cut off of INR of >1.4 was labeled as abnormal (coagulopathy). Subsequently PT/INR was compared in both the groups and correlated with severity of histology.

Results: Of 133 recruited children, 100 had confirmed CD by histology and were analyzed subsequently. Both groups (A and B) had 50 subjects in each. The male female ratio in CD was 1.6:1 and the mean age was 5 years and 4 months. Group A and B were identical in terms of degree of demography and histological abnormality. Coagulopathy was seen in 32% of children in group A and 14% of children in group B and the difference was statistically significant. More than 50% of subjects with coagulopathy had advanced (Marsh grade IIIc) histology in both the groups which was significantly higher than those who had no coagulopathy. None had any significant bleeding during the endoscopic procedure in the study population.

Conclusion: CD with coagulopathy at presentation predicts advanced histological Marsh grade on duodenal biopsy. Coagulopathy can be significantly improved by single dose of parenteral vitamin K administration a day prior to endoscopy.

Keywords: Celiac disease, Coagulation, Children, vitamin K

INTRODUCTION

Celiac disease (CD) is an autoimmune disorder of the small intestine elicited by gluten and related prolamins in genetically predisposed people of all ages from middle infancy onward. CD is characterized by malabsorption of multiple nutrients, vitamin K being one of them. Vitamin K deficiency leads to deranged coagulation and bleeding manifestations.

¹Former resident, Centre for Advanced Pediatrics, Fortis Escorts Hospital, Jaipur
E-mail: Sanjaymed006@gmail.com
²Department of Neonatology, Fortis Escorts Hospital, Jaipur
E-mail: dshyam12346@gmail.com
³Division of Pediatric Gastroenterology, Santokba Durlabhji Memorial Hospital, Jaipur
E-mail: lalitbharadia@gmail.com
⁴Centre for Advanced Pediatrics, Surya hospital, Jaipur
E-mail: d_shivpuri@yahoo.com
CD has a prevalence of 0.8% to 2.67% in the western world [1-3]. In one of the large population studies in India, CD was prevalent in 1.54% by serology and 1.04% by histology [4-6]. CD is characterized by coagulopathy in 27% of children in a recent study from our institute [5]. Considering the most probable cause of coagulopathy to be vitamin K deficiency, we planned to see the improvement in coagulopathy by giving a single dose of vitamin K to children with CD 24 hours prior to endoscopic biopsy in a large cohort.

Vitamin K injection at birth to all newborns is standard practice all over the world [5]. This is to prevent Hemorrhagic disease of newborn (HDN) which has an incidence of 0.25–1.7% [7,8] in absence of prophylactic vitamin K. On the other hand, 27% children with CD have coagulopathy. Celiacs need duodenal biopsy for confirmation of diagnosis. Endoscopy and biopsy in coagulopathic state has more chance of bleeding. If our study shows a significant reduction in coagulopathy by giving one dose of inj. vitamin K, we would be able to recommend the administration of vitamin K to all celiac children before duodenal biopsy.

We took up this study to know the effect of vitamin K in correcting coagulopathy during endoscopic biopsy in children with celiac disease.

**METHODS**

**Study Design**

Non-randomized interventional study.

**Sample size**

In our study, sample size calculation was done by using Epi Info statistical software version 7. The sample size was calculated at 80% study power and 5% alpha error assuming 35% reduction in coagulopathy with vitamin K administration (Group B) as compared to without vitamin K administration (Group A). With these parameters a sample size of 50 patients in each group was required.

- Sample correlation coefficient: 0.9
- Population correlation coefficient: 0.8
- Power (1-beta)%: 80
- Alpha error (%): 5
- One or two sided: 2
- Required sample size (each group): 50

**Time frame**

Study was done over 10–month period. (June 2015 to March 2016)

**Inclusion Criteria**

1. Children aged 6 months to 18 years with suspected CD referred to Fortis Escorts Hospital for duodenal biopsy.
2. Children aged 6 months to 18 years were admitted in Pediatric ward and were seropositive for CD.
3. Those who gave written consent.

**Group allocation and intervention**

Study was designed as non-randomized interventional study. Patients were recruited in two groups (A and B) following study protocol inclusion criteria.

For convenience initial group A recruitment was done followed by group B.

During the first half of the study, Group A was assigned to the 50 consecutive children of confirmed CD and these were tested for PT at the time of duodenal biopsy without any prior vitamin K administration.

During the second half of study, Group B was assigned to the 50 consecutive children of confirmed CD who received a single IM dose of inj. vitamin K 24 hours prior to duodenal biopsy and PT was tested at the time of duodenal biopsy.

**Sample Technique**

Blood Sample (PT/INR) was taken during cannulation for IV sedation before biopsy. This tested at SRL laboratory at Fortis Escorts Hospital, Jaipur which is an NABL accredited laboratory. The test was funded by the Research Department of the hospital.

Group B patients received a single dose of vitamin K (5mg IM in children <10 years and 10mg IM in those >10 years). Name-Kenadion, Company-Samarth Life sciences Pvt Ltd. Strength of 10 mg/ml, use for IV/IM.

Before collection of samples, parents were counselled regarding participation in the study and oral and written consent was obtained.

**STATISTICAL ANALYSIS**

Data was analysed using software, STATA version 12. All the qualitative data was described as simple frequency with relative percentage. Quantitative data was expressed using descriptive statistics as mean, SD or percentages for categorical data. Statistical significant between different groups was evaluated by using appropriate statistical test. Intergroup difference among different group was evaluated by using independent t test for continuous variables while chi-square test was performed to differentiate categorical variables. A p-value ≤ 0.05 was taken as statistically significant. 95% confidence interval (CI) was estimated to understand the variability which can help to develop predictive models to estimate the risk of subsequent events in both group in concern to entitled problem.

**RESULTS**

We recruited 133 cases. Among them 100 had confirmed CD by histology and were analysed subsequently (figure 1). Both groups (A and B) had 50 subjects in each. The male female ratio in CD was 1.6:1 and the mean age was 5 years and 4 months (Table 1). Group A and B were identical in terms of degree of demography and histological abnormality. Coagulopathy was seen in 32% of children in group A and 14% of children in group B and the difference was statistically significant. More than 50% of subjects with coagulopathy had advanced (Marsh grade IIIc) histology in both the groups which was significantly higher than those who had no coagulopathy. None had any significant bleeding during the endoscopic procedure in the study population.

**Description of various histological grades in the two groups of children with deranged PT/INR**

We considered normal PT as 13–15 sec. and INR as <1.4 [10]. In group A 16 children (32%) had deranged PT/INR (>1.40). We observed that of the 16 children with deranged PT, 9 had...
Coagulopathy and its Correction by Vitamin K in Children with Celiac Disease

Marsh grade 3c histology (56.25 %) and 5 had Marsh grade 3b histology (31.25%).

In group B 7 (14%) had deranged PT/INR (>1.40). Among the 7 children, 4 had marsh grade 3c histology (57.14%) and 3 had Marsh grade 3b histology (42.85%).

We observed that in both groups, advanced histological picture (higher Marsh grade) was associated with greater number of children with deranged PT/INR.

The difference of deranged PT/INR in both the groups was statistical significant (p value 0.032) (Table II)

Description of degree of derangement of INR in different Marsh grades in group A & B

Derangement of INR was categorized as mild (1.40–2.50), moderate (2.51–5.00) and severe (>5.00). In group A 16 children (32%) had deranged PT/INR (INR>1.40), 15(30.0 %) children had mildly deranged PT/INR while 1 (2.0%) had moderately deranged PT/INR.

Figure 1: Study Flow Diagram

Figure 2: Bar diagram illustrating the decrement in the numbers of children with deranged PT/INR after injecting vitamin K

TABLE 1. Demographic characteristics of CD children in Group A and B

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=50)</th>
<th>Group B (n=50)</th>
<th>Total (n=100)(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Place of patient recruitment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPD</td>
<td>50</td>
<td>49</td>
<td>99(98.5%)</td>
</tr>
<tr>
<td>IPD</td>
<td>0</td>
<td>01</td>
<td>01(1.5%)</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>50</td>
<td>100(100%)</td>
</tr>
<tr>
<td>Mean age at presentation (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.9 ± 3.0 years (59.8 ± 36.2 months) (49.51–70.10)</td>
<td>5.8 ± 4.6 years (69.8 ± 55.9 months) (53.94–85.73)</td>
<td>P value 0.29</td>
<td></td>
</tr>
<tr>
<td>Range (month)</td>
<td>13–192</td>
<td>12–192</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>31</td>
<td>29</td>
<td>60 (60%)</td>
</tr>
<tr>
<td>Female</td>
<td>19</td>
<td>21</td>
<td>40 (40%)</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>Male to Female ratio</td>
<td>1.6:1</td>
<td>1.4:1</td>
<td></td>
</tr>
</tbody>
</table>

(ODP- out patient department, IPD- in patient department)

TABLE 2. Comparison of PT / INR in CD children between Groups A & B

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=50)</th>
<th>Group B (n=50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR&lt;1.4</td>
<td>34</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>INR&gt;1.4</td>
<td>16</td>
<td>7</td>
<td>0.032</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>50</td>
<td></td>
</tr>
</tbody>
</table>

INR- international normalised ratio

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In group B, 7(14%) had deranged INR (INR>1.40) (figure 2)
All had mildly deranged INR while none had moderate and severe deranged INR. In both the groups, most children with deranged INR were with Marsh grade 3c hence the more severe the Marsh grading on histology, the more chances of coagulation abnormality. There wasstatistically significant difference between the two groups in term of number of children with mildly deranged PT/INR (p value 0.04).

Clinical features and lab parameters of CD in different histological grades
We defined low degree villous atrophy as marsh grade 2 and 3a, while high degree villous atrophy included marsh grade 3b and 3c. Among 100 total children with CD, children presented with pallor (74.0%), failure to thrive (73.0%), abdominal distention (64.0%), short stature (62.0%), chronic diarrhea (43.0 %) and abdominal pain (36.0%). Frontal bossing, dry skin and hepatomegaly was found in 6 %, 14 % and 11% respectively. No case of sibling celiac, IDDM, pedal edema, purpura and petechiae was seen. Deranged PT/INR was observed in 50 % children. We observed that clinical features and deranged lab parameters (PT/INR) were more pronounced in high degree villous atrophy grades. (Table III).

DISCUSSION
CD is a chronic inflammatory disorder of the small bowel that results in malabsorption of nutrients. Because vitamin K is a fat soluble vitamin absorbed from the small bowel, malabsorption leads to vitamin K deficiency, coagulative deficit of the vitamin K dependent factors resulting in prolonged PT.

The previous study from same centre demonstrated that deranged coagulation profile (INR≥1.40) is seen in 27% of children with CD[10]. There is a significant correlation between progression of Marsh Grade and number of children with deranged PT/INR as well as severity of coagulopathy.
We observed that of 50 CD children in group A 16 (32%) had deranged PT/INR. Of 50 CD children in group B 7 (14%) had deranged PT/INR. The difference between the two groups was significant (p value 0.03).

We also observed that of 16 children with deranged PT/INR in group A 15 children had mild coagulopathy and 1 child had moderate coagulopathy. In group B all 7 children had mild coagulopathy. There was significant difference between the two groups in term of number of children with mildly deranged PT/INR (p value 0.04).
As two groups were comparable in terms of demography, serology, histology and anthropometry the significant improvement in coagulopathy can be attributed to vitamin K therapy.

Battaro G et al[13] studied the effect of the therapy with vitamin K on coagulation factors in CD in Italian children. The Authors carried out a study on 37 untreated celiac children to investigate the behavior of K-dependent factors after vitamin K administration. They demonstrated that vitamin K administration resulted in a rapid increase in clotting activity of all K-dependent factors after 24 hours.

Mitterstieler Get al[16] studied 4 children with hemorrhagic diathesis in CD. In all 4 cases the hemorrhagic diathesis could be explained by a low prothrombin complex. After the administration of vitamin K1 there was an immediate rise in the prothrombin complex and bleeding quickly stopped.

Djuric Z et al[11] described a 4 years old girl with CD with diffuse cutaneous bleed due to vitamin K deficiency. Test showed considerably prolonged PT and aPTT. A coagulation profile showed a decrease in clotting factors II, VII, IX, and X. The patient was given intravenous vitamin K 5 mg daily for 3 days. All coagulation tests were normalized and bruising started to disappear.

Cavallaro et al[12] carried out a cross sectional analysis on 390 adults with untreated CD. Of 390 untreated CD 72 (18.5%) had prolonged PT (INR ≥1.4). 5 of them (7%) had an INR ≥ 5, 15(21%) had an INR between 4.9 and 2.5, and 52 (72%) had an INR between 2.4 and 1.4. Parenteral vitamin K was required in those who had INR ≥ 2.4.

Chen CS et al[15] presented a case with coagulopathy due to CD presenting as non traumatic intramuscular hemorrhage associated with prolongation of both PT and aPTT. He was treated with 5 mg oral vitamin K, FFP and cryoprecipitate which resulted in resolution of bleeding. Coagulopathy was attributed to vitamin K deficiency due to malabsorption.

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Low degree villous atrophy (%)</th>
<th>High degree villous atrophy (%)</th>
<th>Total (%)</th>
<th>p value</th>
</tr>
</thead>
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<tr>
<td>Chronic diarrhea</td>
<td>7(16)</td>
<td>36(84)</td>
<td>43(100)</td>
<td>0.27</td>
</tr>
<tr>
<td>Abdomen distension</td>
<td>9(14)</td>
<td>55(86)</td>
<td>64(100)</td>
<td>0.11</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>12(16.6)</td>
<td>61(83.6)</td>
<td>73(100)</td>
<td>0.13</td>
</tr>
<tr>
<td>Short stature</td>
<td>11(17.7)</td>
<td>51(82.3)</td>
<td>62(100)</td>
<td>0.48</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>9(25)</td>
<td>27(75)</td>
<td>36(100)</td>
<td>0.30</td>
</tr>
<tr>
<td>Pallor</td>
<td>14(19)</td>
<td>60(81)</td>
<td>74(100)</td>
<td>0.79</td>
</tr>
<tr>
<td>Cheilitis</td>
<td>1(13)</td>
<td>2(67)</td>
<td>3(100)</td>
<td>0.72</td>
</tr>
<tr>
<td>Frontal bossing</td>
<td>1(16.6)</td>
<td>5(83.4)</td>
<td>6(100)</td>
<td>0.61</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>0(0)</td>
<td>11(100)</td>
<td>11(100)</td>
<td>0.18</td>
</tr>
<tr>
<td>Deranged PT/INR</td>
<td>12(24)</td>
<td>28(76)</td>
<td>50(100)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

(Low degree villous atrophy - Marsh grade 2 and 3a, High degree villous atrophy- Marsh grade 3b and 3c)
FO Hosnut et al[13] stated that children with CD are predisposed to coagulopathy secondary to vitamin K deficiency. Correction of coagulopathy with vitamin K is necessary before endoscopic biopsy in patients with suspected CD. However, since vitamin K causes hemolysis in G6PD deficiency, possibility of hemolysis following vitamin K administration should be kept in mind.


CONCLUSIONS

- CD with coagulopathy at presentation predicts advanced histological Marsh grade on duodenal biopsy.
- As two groups were comparable in terms of demography, serology, histology and anthropometry the significant difference in coagulopathy can be attributed to only vitamin K therapy

LIMITATIONS

- We have compared the effect of vitamin K on PT/INR by comparing PT/INR in groups who had received vitamin K (group B) and who had not (group A). It would have been better to compare PT/INR in same subject pre and post vitamin K to see the effect of vitamin K on each child.
- This was a study with a small sample size. A well designed RCT with a large sample size is recommended.

WHAT IS ALREADY KNOWN

- Endoscopic biopsy in children with underlying coagulopathy increases risk of bleeding complications.
- Children with seropositive CD had elevated PT/INR at the time of endoscopic duodenal biopsy.

WHAT THIS STUDY ADDS

- CD with coagulopathy at presentation predicts advanced histological Marsh grade on duodenal biopsy.
- Coagulopathy can be significantly improved by single dose of parenteral vitamin K administration a day prior to endoscopy.

Authors’ contributions:

- SKLB, DS: Contributed to conception and design of the study, drafting and critically reviewed the content.
- SSS: Contributed in collecting data, analysis, interpretation of data and drafting the manuscript.

Acknowledgements: Dr Sanjoy Choudhary, Consultant Pediatrician, Fortis Escorts Hospital, Jaipur for guiding and helping in manuscript writing.

Ethical clearance: study was approved by Institutional ethics committee.

Conflict of Interest: No

Funding: None; competing interest: none

REFERENCES

Approach to a Sick Neonate with Cholestasis in India

Chiranjit Gope¹, Moinak Sen Sarma²

INTRODUCTION
Sick neonate presenting with cholestasis is a common problem in tertiary referral centers with considerable dilemmas in the management. There are limitations at multiple steps with poor clarity in some areas. The aim of this review is to provide a step by step simplified approach to a sick neonate with cholestasis. We will focus only on the common etiologies and those that are treatable presently in India. Uncommon etiologies and their discussions are beyond the scope of the authors. The approach is based on authors’ personal experiences.

What is neonatal cholestasis?
Presence of direct bilirubin >1 mg/dL confirms presence of cholestasis¹⁰. For practical purposes, any infant (irrespective of referral age) with onset of cholestasis starting in the neonatal period is neonatal cholestasis (NC).

How to identify a sick neonate with cholestasis at presentation?
In the authors opinion, sick NC is any cholestasis with one or more of the following urgencies: a) poor feeding or lethargy, b) hypoglycemia, c) seizure, d) uncorrectable coagulopathy or mucocutaneous bleeding, e) ascites, f) anemia, g) respiratory distress, h) shock, i) family h/o recurrent sibling death, abortions or stillbirths, j) preterm or low birth weight, g) features of sepsis²⁹.

What are the setbacks or issues in India?
Poor referral systems, low resource settings, unreliability of labs, cost-prohibitive genetic analysis and unavailability of various life saving drugs and feeding formulas are major limitations in the diagnosis and therapy of various etiologies. TORCH infection titres (especially cytomegalovirus which is an innocuous bystander) are often positive in any NC setting. When these are unnecessarily prioritised for therapy, the underlying disease is often missed or delayed.

What are the common etiologies pertinent to Indian settings?
By and large, biliary atresia (BA) forms 30–50% of all NC referrals and approximately 90% of all extrahepatic causes (authors’ experience). Most are referred in a stable state. However advanced cases or those with concomitant cardiac anomalies are predisposed to community-acquired infections and become sick. Of all the extrahepatic causes, choledochal cyst (CC) is an etiology in <5%. Neonatal CC can develop cholangitis due to an obstructed system. In a given case with cyst at porta on sonology, absent or rudimentary gall bladder and presence of triangular cord sign reliably distinguishes BA from CC. Sick NC with intrahepatic causes are usually due to genetic-metabolic causes and rarely infections. In the authors experience, of all sick NC, biliary atresia with superimposed infections and galactosemia are the predominant etiologies.

Table 1 shows the common etiologies of sick NC in India. FAOD and respiratory chain defects are collectively termed as mitochondrial hepatopathies since the aberration is at the level of mitochondria. Features of these two disease considerably overlap as there is significant energy depletion. Among the FAOD, long chain, very long chain the carnitine pathway

### Table 1. Common Causes of sick neonatal cholestasis

<table>
<thead>
<tr>
<th>Extrahepatic</th>
<th>Intrahepatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Biliary atresia with superimposed infections</td>
<td>- Galactosemia</td>
</tr>
<tr>
<td>- Choledochal cyst with cholangitis</td>
<td>- Tyrosinemia</td>
</tr>
<tr>
<td>- Gestational alloimmune disorder (GALD)</td>
<td>- Mitochondrial hepatopathies (MH)</td>
</tr>
<tr>
<td>- Herpes simplex virus infection (HSV)</td>
<td>- Hereditary fructose intolerance (HFI)</td>
</tr>
<tr>
<td>- Hemophagocytic lymphohistiocytosis (HLH)</td>
<td>- Niemann–Pick disease (type C)</td>
</tr>
<tr>
<td>- Progressive familial intrahepatic cholestasis (especially types 2 and 5)</td>
<td>- Bile acid synthetic defects</td>
</tr>
</tbody>
</table>

¹ Senior Resident, Department of Pediatric Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow 226014, India. Email: cgope123@gmail.com
² Associate Professor, Department of Pediatric Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow 226014, India. Email: moinaksen@yahoo.com
defects are known to cause NC. POLG1, DGUOK, MPV-17 and TWINKLE are mutations that cause mitochondrial DNA depletion and often associated with liver failure[16,4].

Contrary to the popular belief that TORCH is a major cause of neonatal cholestasis, it is now clear that positive TORCH titers are a red herring in the workup of a neonate with cholestasis. Except for acquired HSV infection which has rapid deterioration, the rest of the TORCH infections rarely cause jaundice. Acquired cytomegalovirus (CMV) causing neonatal hepatitis is rare and most often self-resolving. CMV titres in blood or urine or antibodies to CMV are not sufficient criteria for therapy. It is mandatory to demonstrate CMV DNA by the polymerase chain reaction (PCR) or culture in liver tissue or document histological changes (inclusion bodies in vascular endothelium of the liver). Congenital CMV hepatitis should be treated only if the infection is proven in a setting of deteriorating liver functions or coagulopathy where no other alternative cause is found[16].

Other causes of sick NC that have been reported as isolated case reports or series are congenital disease of glycosylation (CDG) type 1, Coombs positive hemolytic anemia with giant cell hepatitis, congenital portosystemic shunts, Zellweger syndrome, Wolman disease, transaldolase deficiency, citrin deficiency, arthrogryposis renal dysfunction cholestasis (ARC) syndrome, urea cycle disorder (ornithine transcarbamylase deficiency), congenital leukemia, large hepatic hemangioma, metastatic neuroblastoma, panhypopituitarism (septo-optic dysplasia), neonatal lupus and congenital cardiomyopathies[6,7].

What are the common presentations?

Presence of pigmented stools makes biliary atresia unlikely and mostly suggests intrahepatic causes. Acholic stools could be consistent with both intrahepatic (with significant cholestasis) and extrahepatic causes. Sick intrahepatic NC can present as neonatal liver failure (NLF), congenital ascites or hydrops (explained below). Significant family history is pertinent in genetic-metabolic causes and absent in biliary atresia. Hypoglycemia may suggest consequences of liver failure or glycopenia due to blocks in metabolic pathway (galactosemia, fatty acid oxidation defects, HFI). Seizures suggest hypoglycemia (due to above reasons), dyselectrolytemia, intracranial bleed (coagulopathy), infection (Herpes simplex virus encephalitis) or intoxication (mitochondrial diseases). Sites of bleeding can be oral, pulmonary, gastrointestinal intracranial, from umbilical stump and musculocutaneous. They are often spontaneous or secondarily due to intramuscular injections. Most often bleeding is due to coagulopathy. In rare cases, it may be compounded by thrombocytopenia (sepsis, HLH, transaldolase deficiency). Significant anemia may be secondary to bleeding, intravascular hemolysis, aplasia (parvovirus infection), hemolysis (Coombs negative in galactosemia, transaldolase deficiency and Coombs positive in associated giant cell hepatitis) or marrow infiltration (HLH). Clinical clues are shown in table 2.

What is neonatal liver failure?

The proposed definition of NLF is a sick baby with neonatal cholestasis (up to 2 months age) with international normalized ratio (INR) >3.0. The definition does not include encephalopathy as it is difficult to assess in newborns. INR up to 2.0 may be normal in premature newborns[6,8]. The common causes are gestational alloimmune liver disease (GALD), herpes simplex virus (HSV) infection, metabolic diseases (galactosemia, fatty acid oxidation defect, tyrosinemia type 1, and Niemann-Pick disease), hemophagocytosis lymphohistiocytosis (HLH), PFIC-2 and PFIC-5 and bile acid synthetic defects (BASD) [9,10,11,12]. Rarely HFI (infants on formula feeds), UCD, leucine-tRNA synthetase (LARS), transaldolase deficiency, glycogen storage disease type 4 and enterovirus infection (from mother) have been reported[11,13]. Fulminant Hepatitis B in an infant has also been reported in mothers who have Hepatitis B (pre-core mutant, e-antigen negative, e-antibody positive and DNA negative). This occurs due to an exaggeration in cytotoxic T-cell response[14]. GALD should be strongly suspected in a case of NLF with significant ascites but absence of splenomegaly. In this condition, the ductus venosus remains patent and prevents the development of splenomegaly[15]. The main differentiating features of some of the conditions are given in Table 3.

What is the significance of ascites?

Presence of ascites early in the neonatal or infancy period indicates that cirrhosis or liver failure has set in. In the presence of early onset (<4 months age) ascites, metabolic causes of NC must be considered, top most priority being galactosemia. Since biliary cirrhosis causes have delayed decompensation, the ascites in biliary atresia occurs after 3–6 months of age. Diagnostic tap is required to detect ascitic fluid infection (absolute neutrophil count >250/mm² and/or fluid culture positivity). Presence of coagulopathy and thrombocytopenia are not contraindications for an ultrasound guided diagnostic tap. Congenital ascites indicates that the cirrhosis has already started in utero and is classically seen in GALD. This condition is usually associated with shrunken liver. Hydrops is an even more severe form where the neonate is born with anasarca. Of the many mechanisms and diverse etiologies of hydrops, one of the mechanisms is liver failure and organ infiltration where the disease has started in the intrauterine period. Niemann Pick disease Type C (NPD-C), transaldolase deficiency and various other rare lysosomal storage disorders can be associated with hydrops. Hydrops has a universally poor outcome. Placental tissue analysis in the proband is recommended for subsequent pregnancies[16,17].

How to interpret LFT in a sick NC?

LFT per say is not discriminatory for any particular NC. However some assumptions can be made based on the LFT profile. Disproportionate derangement of INR as compared to total bilirubin and liver enzymes is usually found in tyrosinemia and GALD. These conditions also have mildly deranged enzymes as compared to other causes. ALP is usually raised tyrosinemia due to hypophosphatemic rickets and in NPD-C due to infiltration. Gamma glutamyl transpeptidase (GGT) is low in all PFIC (except PFIC-3) and BASD. CDG type 1 has hypoproteinemia due to protein losing enteropathy. HSV induced liver failure causes transaminases to be in thousands (U/L). Rising bilirubin, progressively worsening international normalised ratio (INR) and fall in albumin indicate that the trend of the patient is towards worsening of the disease and is a possible indication for liver transplantation LT referral. Though worsening INR has poor prognostic value, an improving INR is a good indicator of recovery. Even during recovery, albumin may take 3–4 weeks to normalise due to its half-life of 21 days.
What is the role of tissue biopsy in a sick NC?

The role of liver biopsy is gradually being limited due to the increasing availability of genetic confirmation in many conditions. In the authors’ opinion, if the workup is favouring the diagnosis of biliary atresia, then a liver biopsy is necessary for confirmation. However, many a times due to delayed referral, there is inadequate window between recovery of the infection and a timely surgery (<90 days of life). In such dire situations, the child may be taken up for POC without the liver biopsy. In GALD, a definitive diagnosis is obtained from documenting iron staining from salivary glands. For this a lip biopsy is necessary which may often be daunting in a child with profound coagulopathy. Diagnosis of HLH is made with a set of criteria which fulfil the same. In the absence of genetic confirmation, a bone marrow examination is required to document hemophagocytosis. Similarly in the absence of enzyme or genetic analysis, Niemann-Pick disease type C can be diagnosed by typical foamy histiocytes on bone marrow or liver. However the yield for the same is 40–60%.[18] Progressive liver disease due to CMV is extremely rare. Definitive diagnosis of CMV hepatitis is by documenting inclusion bodies in liver parenchyma. In the presence of genetic analysis, electron microscopy of liver and muscle have become near obsolete in MH. Immunohistochemistry of the liver is an optional but recommended workup in PFIC.[4,9] Other genetic-metabolic conditions do not require liver biopsy.

What is the role of genetic testing in a sick NC?

Clinical or whole exome sequencing, recently available in India has changed the understanding of neonatal cholestasis where etiologies were previously unascertained. The turnaround

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**TABLE 2. Clinical Evaluation of Intrahepatic Causes of Neonatal Cholestasis**

| Onset of jaundice | • At birth or soon after (days): GALD, HSV
| • Few weeks after birth: PFIC, galactosemia
| • Delayed-onset (after 1 month): Tyrosinemia, PFIC
| • Any point of time: MH, HLH
| Affected sib or sib death | • Galactosemia, tyrosinemia, MH, HLH, PFIC, GALD
| Seizures | • Hypoglycemia: Galactosemia, MH, HFI, panhypopituitarism
| • Intracranial bleed: All conditions
| • CNS infection: HSV
| • Intoxication: MH, CPSS, UCD
| Maternal clues | • Genital vesicles: HSV
| • Oligoamnios, megaplacenta: GALD
| • Antenatal pruritus (3rd trimester) with similar history in maternal sisters or grandmother: PFIC
| • Pruritus on oral contraceptives: PFIC
| • Acute fatty liver of pregnancy: FAOD (long and very long chain disease)
| • Hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome: FAOD (long chain disease)
| • Recent diarrheal or respiratory illness: Enterovirus
| Early-onset ascites | • Galactosemia, tyrosinemia, GALD, MH, HLH
| Shrunken liver | • HLH, Niemann–Pick disease type C
| Splenohepatomegaly | • Scalp vesicles: HSV
| • Cataract: galactosemia
| • Cabbage odor urine: tyrosinemia
| • Rickets (cranioalbas): tyrosinemia
| • Hypotonia: MH, Niemann–Pick disease type C
| • Hypertonia: CPSS, UCD
| • Chubby cheeks: Citrin deficiency
| • Micropenis: Panhypopituitarism
| • Vision fixation issues: Septo-optic dysplasia
| • Nystagmus, gaze palsy: NPD-C, Gauchers
| • Dysmorphism: Zellweger syndrome, transaldolase deficiency
| • Hirsutism, hypertrichosis and cuts laxa: transaldolase deficiency
| Ultrasound-Doppler finding | • Gall stone: PFIC-2
| • Anomalous vascular anatomy: Abernathy malformations (CPSS)
| • Nephehromegaly: Tyrosinemia, HFI
| • Adrenal calcifications: Wolman disease
| • SOL in liver, adrenals: hemangiomas, metastatic neuroblastoma

**PFIC:** Progressive familial intrahepatic cholestasis; **GALD:** gestational alloimmune disease; **HSV:** Herpes simplex virus; **MH:** Mitochondrial hepatopathies; **HLH:** Hemophagocytic lymphohistiocytosis; **FAOD:** Fatty acid oxidation defects; **CPSS:** congenital portosystemic shunting; **UCD:** urea cycle defect, **HFI:** hereditary fructose intolerance, **SOL:** space occupying lesions, **GB:** gall bladder, **NPC-D:** Niemann-Pick disease type C
time is approximately 4–6 weeks and must be sent with discretion of cost and time. “Variants of unknown significance” must be interpreted with caution in any clinical setting. Based on clinical suspicion, empirical management must be instituted while awaiting genetic results. Genetic studies are useful in the following scenarios of sick NC:

- Presentation of babies with pruritus or steatorrhea (PFIC, bile acid synthetic defects)
- Low GGT cholestasis (PFIC, bile acid synthetic defects)
- Suspected galactosemia where enzyme assay is fallacious due to hemolysis or blood transfusion
- Suspected tyrosinemia where urinary succinyl acetone cannot be done and the suspicion is strong
- Neonatal liver failure where infectious causes have been ruled out
- Predominant extrahepatic manifestations (PFIC-1, bile acid synthetic defects, mitochondrial hepatopathy)
- Strong family or sibling history
- Significant clues on mass spectroscopy or gas chromatography

Genetic analysis has no role in diagnosis in GALD. Hence the absence of genetic yield during the workup of a proband with NLF should alert physician for subsequent pregnancies.

What are the special precautions during testing or caveats in interpretation?

- Urine NGRS, though a non-specific test, should be done while the child is on the incriminating feed. It is recommended to perform at least 3 samples. Patients on soy formulations and sucrose-free formula will have negative reports in galactosemia and HFI.
- GAL-1-PUT level assessment should be deferred in the presence of hemolysis or recent (<12 weeks) blood transfusion as the levels will be erroneously normal.
- Urine or blood succinyl acetone is a volatile compound and hence best collected at the lab or transported within 30 minutes.
- Urine or blood ketones should be documented at the time of hypoglycemia. Once resuscitated into a euglycemic state, the ketones are negative.
- Ursodeoxycholic acid should be stopped for 7 days prior to assessment of bile acid levels
- Ferritin may be high as acute phase reactant in an overtly sick child. Repeating values after stabilisation may be required.

### TABLE 3. Differentiating features of neonatal liver failure

<table>
<thead>
<tr>
<th></th>
<th>Neonatal hemo-chromatosis</th>
<th>HSV infection</th>
<th>Hemophagocytic lymphohistiocytosis (HLH)</th>
<th>Mitochondrial hepatopathy</th>
<th>Galactosemia type 1</th>
<th>Tyrosinemia type 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at presentation</td>
<td>Usually at birth</td>
<td>5–14 days of life</td>
<td>Variable</td>
<td>Variable</td>
<td>Usually from second week of life onwards</td>
<td>Variable</td>
</tr>
<tr>
<td>Premature birth/IUGR</td>
<td>70–90%</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Sibling death</td>
<td>Common</td>
<td>None</td>
<td>Possible</td>
<td>25%</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Amniotic fluid</td>
<td>Oligoamnios</td>
<td>Normal</td>
<td>Normal</td>
<td>Polyamnios</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Ascites at birth</td>
<td>Common</td>
<td>Rare</td>
<td>Rare</td>
<td>No. Occurs later</td>
<td>No. Occurs later</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>Shrunken (in-utero cirrhosis)</td>
<td>Enlarged</td>
<td>Enlarged</td>
<td>Multisystemic commonly cardio-myopathy, Skeletal myopathy (hypotonia)</td>
<td>Cataract in 50–60% Renal tubular acidosis</td>
<td>Rickets</td>
</tr>
<tr>
<td>Extrahepatic involvement</td>
<td>Renal tubular dysplasia</td>
<td>Meningitis Scalp vesicles</td>
<td>Bone marrow depression</td>
<td>Cataract in 50–60% Renal tubular acidosis</td>
<td>Cataract in 50–60% Renal tubular acidosis</td>
<td>Hypohosphatemia</td>
</tr>
<tr>
<td>Acidosis at presentation</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>+</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>Profound (+++)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Profound (+++)</td>
</tr>
<tr>
<td>Alanine transaminase (U/L)</td>
<td>Low normal (&lt;100)</td>
<td>High (&gt;1000)</td>
<td>High (&gt;1000)</td>
<td>Moderate (100–500)</td>
<td>Moderate (100–500)</td>
<td>Low normal (&lt;100)</td>
</tr>
<tr>
<td>Ferritin (ng/mL)</td>
<td>800–7000</td>
<td>&gt;20,000</td>
<td>&gt;20,000</td>
<td>Variable</td>
<td>normal</td>
<td>normal</td>
</tr>
<tr>
<td>Alpha fetoprotein (ng/mL)</td>
<td>80,000–300,000</td>
<td>&lt;80,000</td>
<td>&lt;80,000</td>
<td>Variable</td>
<td>normal</td>
<td>Variable but usually in thousands to lakhs</td>
</tr>
<tr>
<td>Definitive test</td>
<td>Lip biopsy MRI pancreas Complement C5b–9 complex</td>
<td>HSV-PCR</td>
<td>Perforin levels Genetics</td>
<td>Urine GCMS, Blood TMS Genetics</td>
<td>GAL-1-PUT enzyme assay Genetics</td>
<td>Urine or blood succinyl acetone Genetics</td>
</tr>
</tbody>
</table>

HSV: herpes simplex virus, PCR: polymerase chain reaction, GCMS: gas chromatography and mass spectroscopy; TMS: tandem mass spectroscopy; GAL-1-PUT: galactose-1-phosphate undiy transferase; MRI: magnetic resonance imaging; IUGR: intrauterine growth retardation.
**Table 4: Investigations and therapy in the common etiologies of sick NC**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Tier 1 investigations (screening or definitive)</th>
<th>Tier 2 investigations (confirmatory or invasive)</th>
<th>Specific therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galactosemia</td>
<td>GAL-1-PUT levels (low)</td>
<td>Genetics (if hemolysis, blood transfusion or ambiguity in GAL-1-PUT levels)</td>
<td>Lactose-free diet</td>
</tr>
<tr>
<td>Tyrosinemia</td>
<td>Alpha fetoprotein (high)</td>
<td>Genetics (if Ur. SA is not available)</td>
<td>Tye/Phe free diet</td>
</tr>
<tr>
<td>Mitochondrial hepatopathies and urea cycle defects</td>
<td>CPK (high), ABG (acidosis), lactate (high), ketones (positive), blood sugar (low)</td>
<td>Genetics</td>
<td>None except: Anti-ammonia measures in Urea cycle defects</td>
</tr>
<tr>
<td></td>
<td>Urine GCMS/ Blood TMS (for abnormal metabolites)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLH</td>
<td>Ferritin (high), triglycerides (high), fibrinogen (low), NK cell activity (low/absent) Perforn levels (low)</td>
<td>Bone marrow examination Genetics</td>
<td>HLH protocol therapy</td>
</tr>
<tr>
<td>GALT</td>
<td>Ferritin (high)</td>
<td>Lip biopsy</td>
<td>IVIG</td>
</tr>
<tr>
<td></td>
<td>Alpha fetoprotein (high)</td>
<td>MRI pancreas</td>
<td>DVET</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Liver biopsy for CSb–9 complex staining</td>
<td></td>
</tr>
<tr>
<td>PFIC</td>
<td>GGT (low)</td>
<td>Liver biopsy with IHC</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Bile acid levels (high)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BASD</td>
<td>GGT (low)</td>
<td>Genetics</td>
<td>Cholic acid and chenodeoxycholic acid (not marketed presently in India)</td>
</tr>
<tr>
<td></td>
<td>Bile acid levels (low)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stool fat (steatorrhea)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niemann-Pick disease Type C</td>
<td>Chitotriadose (high)</td>
<td>Bone marrow examination Genetics</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Acid sphingomyelinas (normal)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSV</td>
<td>HSV PCR (body fluids)</td>
<td></td>
<td>Acyclovir</td>
</tr>
</tbody>
</table>

**GAL-1-PUT:** galactose-1-uridylyl phosphatase enzyme; **GALT:** gestational alloimmune disease; **Ur. SA:** urinary succinyl acetone; **Tye/Phe:** tyrosine/phenylalanine; **ABG:** gamma glutamyl transeptidase; **HLH:** Hemophagocytic lymphohistiocytosis; **MH:** mitochondrial hepatopathies; **CPK:** creatinine phosphokinase; **ABG:** arterial blood gas; **NK:** natural killer; **IVIG:** intravenous immunoglobulin; **DVET:** double volume exchange transfusion; **NGRS:** non-glucose reducing substances; **SBP:** spontaneous bacterial peritonitis; **UGC:** ultrasonography; **PFIC:** Progressive familial intrahepatic cholestasis; **BASD:** bile acid synthetic defects; **PCR:** polymerase chain reaction; **HSV:** Herpes simplex virus; **MRI:** magnetic resonance imaging

- Urine for gas chromatography and blood for tandem mass spectroscopy yield better in a decompensated state than in a resuscitated state.
- If a genetic-metabolic cause is suspected, it is suggested to store a blood sample of the proband a part of future genetic counselling.
- Non-contractile gall bladder on ultrasonography may not necessarily be due to biliary atresia. A sick NC with sepsis may transiently have an adynamic gall bladder. Repeat scans are recommended before proceeding for liver biopsy.
- Before MRI is performed in GALT, it should be carefully discussed with the radiologist for usage of appropriate software to detect iron overload in the extrahepatic tissue.

**What diseases are treatable in India?**

Galactosemia has an excellent liver outcome on lactose-free diet. In tyrosinemia, though the specific dietary formulations are available, the drug, nitisinone is not presently marketed in India. MH (esp. long and very long chain FAOD) are difficult to salvage with supportive therapy; LT is contraindicated if there are overt systemic features. GALT may survive with intravenous immunoglobulin therapy (IVIG) and double volume exchange transfusion (DVET) but most will require LT. Primary HLH should be given a trial of the HLH protocol before referring for bone marrow transplant. HSV is curable with acyclovir. Plecanaril is used on compassionate grounds for enterovirus infections in the West but unavailable in India. Enterovirus infections are not routinely tested for in India. Cholic acid (in pharmaceutical form) and chenodeoxycholic acid are not yet marketed in India and are possibly in the pipeline. CMV may be treated with ganciclovir in desperate measures.

**What are the difficulties with diet in NLF?**

Etiologies presenting as NLF often have overlapping features and not clearly distinguishable at presentation. Yet an empirical diet need to be prescribed that can encompass all the possible diseases. The challenge is the choice of the same. The is no consensus over this aspect and it is individualised as per the physician’s experience. Since galactosemia is a major etiology and empirical dietary restrictions are required, many physicians choose soy formulations on compassionate grounds due to financial constraints. It is to be noted that soy formulations contain high amounts of tyrosine and phenylalanine that may make tyrosinemia worsen. Since some soy formulations also contain sucrose, HFI may worsen. Fatty acid oxidation defects (FAOD) ideally need a ketogenic diet. All NC need high medium chain triglycerides (MCT) in their diet. In the authors’ opinion, an initiation with amino acid formula enriched with MCT is possibly safest bet in India. The diet may be modified as the etiology becomes clearer.
Figure 1: Approach to a sick NC without extrahepatic cause

Algorithm of management of sick NC

Sick NC is a dire emergency. Despite supportive management, the underlying metabolic or infectious processes quickly decompensate and progress rapidly. If not intervened on time, they are universally lethal. Hence swift and empirical management is required while simultaneously working them up for the underlying etiology. In this regard, a brief bedside algorithm of management of sick NC without an extrahepatic cause is suggested in Fig 1 with an accompanying table (table 4). Individual etiologies will need further reading.

CONCLUSIONS:

Sick children presenting as neonatal cholestasis have diverse etiologies with overlapping presentations. If an extrahepatic cause has been ruled out, galactosemia workup should be prioritised in India as this is a rewarding disease to treat. Every effort should be made to salvage the rest of the metabolic disorders though setbacks in management are likely in India. The initial part of the management is largely presumptive and empirical for salvage. The algorithm of management is largely on the clinical wisdom of the physician. Genetic testing of the proband provides closure for the physician and enables genetic counselling for the family.
FURTHER READING:


MR Enteroigraphy in Pediatric Inflammatory Bowel Disease- Where do we Stand?

Guntaka Srujana¹, Devarapalli Venkata Umesh Reddy²

INTRODUCTION

Nearly, 10–25% of inflammatory bowel disease (IBD) is diagnosed in children. There is a surge in the pediatric inflammatory bowel disease (PIBD) cases diagnosed in the last decade.¹ Srivastava et al. in a multicentric study from India have shown Crohn disease (CD) as the most common type, occurring in two thirds of the overall PIBD patients. It is well known that adolescents form a large proportion of the PIBD, with >50% of the cases occurring in the 10–18 years age group.² Imaging of the bowel is required as a part of small bowel evaluation at diagnosis in all IBD patients except typical ulcerative colitis (UC). Similarly during the management course, imaging is commonly required to diagnose complications and assist therapeutic decisions. Various imaging modalities have been traditionally used like gastro-intestinal contrast series (e.g., barium meal follow through, barium enema) and later CT enterography (CTE). MR enterography (MRE) has taken tremendous strides in the last decade and is currently the recommended imaging in children with IBD.³ There is a sense of under utilization of pediatric MR enterography with most centers preferring CT, which may not be the right choice always. We discuss the role of MR enterography in PIBD, highlighting its diagnostic performance and comparison with CT enterography.

MR Enteroigraphy

MR enterography allows for evaluation of the bowel lumen and wall, adjacent mesentery and soft tissues, as well as a variety of extraintestinal abdominopelvic IBD manifestations while sparing the patient any risks associated with ionizing radiation. MR enterography can be used to initially support the diagnosis of IBD, particularly small bowel Crohn’s disease, while also proving useful in identifying a variety of disease-related complications, including strictures, fistulae, and abscesses. The procedure may be performed in an awake state as in a cooperative older child or using general anesthesia (GA) in younger children. Mollard et al. showed that in children less than 10 years of age, >90% of MR enterographic examinations were performed under GA.⁴ However, this constituted only 20% of the total pediatric MR enterographic examinations performed in their high volume center.⁵ Limiting the motion artifacts and breath holding is required to allow certain sequences which are necessary for interpreting the study. Biphasic oral contrast like polyethylene glycol, lactulose, barium etc. are commonly used for bowel distension. Small volume lactulose protocol using only 150ml of total fluid (50ml of lactulose in 100ml of water) 1 hour prior to the scheduled scan (followed by advice to drink water freely before imaging) has shown to be useful with good compliance.⁶ Gadolinium based intravenous contrast is used in those not contraindicated. Intravenous glucagon is used as a spasmolytic agent for improved visualization of the small and large bowel. Commonly used pulse sequences include T2-Weighted single-shot fast spin echo (FSE)/ single-shot turbo spin echo, FIESTA (Fast imaging employing steady-state acquisition), balanced steady state free precession (SSFP), diffusion-weighted imaging (DWI), and precontrast and postcontrast T1-weighted fat saturated (most often two-dimensional or 3D GRE). Unlike CT enterography, MR enterography also allows for cine imaging and for imaging that highlights multiple determinants of image contrast (e.g., T1 and T2 relaxivity, diffusion-weighted imaging [DWI], pre- and postcontrast imaging etc.). MR enterography gives excellent details of the lumen, bowel wall and perienteric abnormalities.⁷ Imaging findings commonly found include those of active inflammation like bowel wall thickening with hyperenhancement, edema, restricted diffusion in DWI, mesenteric hypervascularity (comb’s sign), fat stranding, fibrofatty proliferation or complications like stricture, fistula, abscesses, perianal disease (Figures 1a, 1b, 2a, 2b). Imaging findings associated with active inflammation, strictureing and penetrating crohn’s disease are presented in table 1.

¹ Former Senior Resident, Department of Radiology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow.
² Assistant Professor, Department of Pediatric Gastroenterology, Postgraduate Institute of Child Health Hospital, Noida.
Email: srujanaguntaka@gmail.com; umeshreddyd@gmail.com
Table 1: Imaging findings associated with Crohn’s disease

<table>
<thead>
<tr>
<th>1) Active inflammation:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bowel wall features</strong></td>
</tr>
<tr>
<td>- Mural hyperenhancement</td>
</tr>
<tr>
<td>- Wall thickening with mural hyperenhancement</td>
</tr>
<tr>
<td>- Intramural edema</td>
</tr>
<tr>
<td>- Restricted diffusion</td>
</tr>
<tr>
<td>- Featureless ahastral (lead pipe) appearance of colon (more common with UC)</td>
</tr>
<tr>
<td><strong>Mesentery</strong></td>
</tr>
<tr>
<td>- Perienteric edema</td>
</tr>
<tr>
<td>- Engorged vasa recta (comb sign)</td>
</tr>
<tr>
<td>- Fibrofatty proliferation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2) Stricture disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Stricture with signs of active inflammation</td>
</tr>
<tr>
<td>- Stricture without signs of active inflammation</td>
</tr>
<tr>
<td>- Stricture with upstream bowel dilatation (upstream bowel segment dilatation &gt; 3cm)</td>
</tr>
<tr>
<td>- Stricture with no upstream bowel dilatation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3) Penetrating disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Sinus tract</td>
</tr>
<tr>
<td>- Fistula (simple or complex)</td>
</tr>
<tr>
<td>- Abscess</td>
</tr>
<tr>
<td>- Inflammatory mass</td>
</tr>
<tr>
<td>- Free perforation</td>
</tr>
</tbody>
</table>
Role in PIBD

1. Determination of the disease extent, particularly involvement of small bowel in a child with suspected or newly diagnosed PIBD (other than typical UC) at presentation. In our country, a common differential diagnosis for Crohn's disease is intestinal tuberculosis, where CT is preferred for simultaneous evaluation of necrotic lymph nodes, ascites, peritoneal involvement and possibly combining it with a HRCT of chest in the same session. For afore mentioned reasons and familiarity of the procedure, in countries with high prevalence of tuberculosis, CT is usually preferred for this indication. However, head to head studies comparing CTE and MRE in differentiating microbiologically confirmed abdominal tuberculosis in children are lacking.

2. Evaluation of worsening clinical status or suspected disease-related complications (both CD and UC). In children with intestinal obstruction due to strictureing disease, MR enterography is indicated for assessing the presence of fibrosis, active inflammation or both. This has considerable bearing on whether the child would benefit from medical management or requires surgery. Although comparable in detecting active inflammation, Quencer et al. showed MR enterography to be significantly superior to CT in detecting mural fibrosis using histology as the reference standard. Ream et al. showed increasing bowel wall restricted diffusion as lower apparent diffusion coefficient (ADC) values is associated with multiple MRI findings that are commonly seen with active inflammation in pediatric small bowel Crohn's disease. Serial ADC values may help in assessing the severity of inflammation in respective segments of the bowel wall over time. Radhakrishnan et al. showed strong positive correlation between MRE scores and PCDAI, predicting disease activity non-invasively akin to fecal calprotectin.

4. Differentiation of CD from UC in the setting of indeterminate colitis
5. Evaluation of J-pouch complications following proctocolectomy
6. Evaluation of the extent and severity of perianal disease. By defining the exact course of the fistula tract (combining with fistulography) and establishing whether it involves the ischioanal or ischiorectal fossae or extends through the pelvic floor musculature, MR imaging can guide surgical management and provide prognostic information.

7. Evaluation of extraintestinal IBD manifestations like sclerosing cholangitis (combining with high resolution T2 MR cholangiopancreatography sequences) and sacroiliitis.
8. Cine imaging provides functional information about bowel motility and can be used to evaluate strictures, adhesions. However, pediatric experience for this is limited.

Diagnostic performance and comparison with CT enterography

In a systematic review by Yoon et al. pediatric MR enterography demonstrated a high diagnostic performance (specificity and specificity of 86% and 91% respectively) in the detection of active inflammation in children with known or suspected inflammatory bowel disease. Although statistically not significant, Quencer et al. showed diagnostic accuracy of 83.6% for MRE against 81.9% for CTE in detecting active disease compared to the histologic gold standard. Contrastingly, Gale et al. in their comparative study between CT and MR enterography showed mural features (wall thickening>3 mm, mural hyperenhancement) were diagnosed with similar accuracy, but perienteric features (mesenteric hypervascularity, edema, fibrofatty proliferation and lymphadenopathy) were picked up better on CT enterography. For detection of mural fibrosis, MR was significantly better than CT enterography. Comparison of important merits and demerits of both the imaging procedures is shown in the table 2.

MR enterography severity scores

Severity of disease in MRE was evaluated using different validated scores like MR enterography global score (MEGS) and CD MRI index. Clinical disease activity in pediatric Crohn's disease is assessed by the pediatric Crohn's disease activity index (PCDAI). Radhakrishnan et al. showed MEGS had a strong positive correlation with PCDAI compared to CD MRI index score. MEGS may provide an alternative to endoscopy in disease monitoring, showing

Table 2: Comparing merits and demerits of CT and MR enterography

<table>
<thead>
<tr>
<th>Clinical utility</th>
<th>MR enterography</th>
<th>CT enterography</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td>Safe (no use of ionizing radiation)</td>
<td>Easier to perform, less costly</td>
</tr>
<tr>
<td></td>
<td>Best to differentiate mural inflammation from fibrosis</td>
<td>Emergency situations (eg: suspected intestinal perforation)</td>
</tr>
<tr>
<td></td>
<td>Can guide management (especially surgical) in perianal disease and its complications</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Potential role in the monitoring of active inflammation (using serial ADC values)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>For extra-intestinal IBD manifestations like sclerosing cholangitis, sacroiliitis</td>
<td></td>
</tr>
<tr>
<td><strong>Limitations</strong></td>
<td>May require general anesthesia</td>
<td>Ionizing radiation (Effective radiation dose for a single standard CT enterography=12–20mSv; equivalent to 4 to 7 years of cumulative natural radiation exposure)</td>
</tr>
<tr>
<td></td>
<td>Long examination time</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lack of appropriate state of the art imaging protocol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lack of experience reviewing and interpreting in children</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Contraindicated in presence of certain implantable devices</td>
<td></td>
</tr>
</tbody>
</table>
good positive correlation with fecal calprotectin.\(^{(13)}\) Components of MEGS are shown in table 3. For the purpose of calculating the MEGS score the bowel is divided into eight anatomical segments: jejunum; ileum; terminal ileum; ascending, transverse, descending, and sigmoid colon; and rectum. The total length of disease (irrespective of mural scores) within each segment is measured to provide a multiplication factor (ranging from 1 to 2) for each segmental score. Individual segmental scores are summed and then 5 points added if lymph nodes ≥1 cm (short axis diameter), comb sign, fistulae (entero-enteric, entero-cutaneous or entero-vesical) or abscesses are present. The final summed score constitutes MEGS.\(^{(14)}\)

**Radiology report impression statements**

Checklist of the radiology report impression statements in children with a suspected or diagnosed Crohn's disease is given in table 4.\(^{(15)}\)

### Table 3: MEGS scoring: Scoring method for Small Bowel and Colonic Segments and Extra-Mural Features. Score Per Segment: Jejunum, Ileum, Terminal Ileum, Caecum, Ascending, Transverse, Descending, Sigmoid colon and Rectum \((\text{Jejunal Score} \times \text{Factor for Jejunum Involved Length}) + \text{(Proximal Ileum Score} \times \text{Factor for Proximal Ileum Length}) + \text{(Terminal Ileum Score} \times \text{Factor for Terminal Ileum Length}) + \text{(Caecum Score} \times \text{Factor for Caecum Length}) + \text{(Ascending Score} \times \text{Factor for Ascending Length}) + \text{(Transverse Score} \times \text{Factor for Transverse Length}) + \text{(Descending Score} \times \text{Factor for Descending Length}) + \text{(Sigmoid Score} \times \text{Factor for Sigmoid Length}) + \text{(Rectum Score} \times \text{Factor for Rectum Length}) + \text{Score for Abscess} + \text{Score for Fistula} + \text{Score for Adenopathy} + \text{Score for Comb Sign} + \text{MRI Score} = \text{Total Possible Score 296} \)

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mural Thickness*</td>
<td>&lt;3mm</td>
<td>3–5mm</td>
<td>6–7mm</td>
<td>&gt;7mm</td>
</tr>
<tr>
<td>Mural T2 signal**</td>
<td>Equivalent to normal bowel wall</td>
<td>Minor increase in signal: bowel wall appears dark grey on fat-saturated images</td>
<td>Moderate increase in signal: bowel wall appears light grey on fat-saturated images</td>
<td>Marked increase in signal: bowel wall contains areas of white high signal approaching that of luminal content</td>
</tr>
<tr>
<td>Peri-mural T2 signal (mesenteric edema)</td>
<td>Equivalent to normal mesentery</td>
<td>Increase in mesenteric signal but no fluid</td>
<td>Small fluid rim (≤ 2mm)</td>
<td>Large fluid rim (≥ 2mm)</td>
</tr>
<tr>
<td>T1 Enhancement***</td>
<td>Equivalent to normal bowel wall</td>
<td>Minor enhancement: bowel wall signal greater than normal small bowel but significantly less than nearby vascular structures</td>
<td>Moderate enhancement: bowel wall signal increased but somewhat less than nearby vascular structures</td>
<td>Marked enhancement: bowel wall signal approaches that of nearby vascular structures</td>
</tr>
<tr>
<td>Mural enhancement pattern</td>
<td>N/A or homogeneous</td>
<td>Mucosal</td>
<td>Layered</td>
<td></td>
</tr>
<tr>
<td>Haustral loss (colon only)</td>
<td>None</td>
<td>&lt;1/3 segment</td>
<td>1/3 to 2/3 segment</td>
<td>&gt;2/3 segment</td>
</tr>
</tbody>
</table>

*Measured using electronic callipers; ** compared with normal small bowel; *** compared with nearest vessel

### Additional score for extramural features

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph nodes (≥1cm measured in shortest diameter)</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Comb sign</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Abscess</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Fistulae</td>
<td>Absent</td>
<td>Present</td>
</tr>
</tbody>
</table>

### Table 4: Radiology report impression statements for suspected or diagnosed Crohn’s disease at MR enterography

**Inflammation impression statements**
- No imaging signs of active inflammation
- Non-specific signs of bowel inflammation*
- Active inflammatory small bowel Crohn’s disease without luminal narrowing
- Active inflammatory small bowel Crohn’s disease with luminal narrowing
- Crohn’s disease with no imaging signs of active inflammation

**Stricture impression statements**
- Stricture with imaging findings of active inflammation
- Stricture without imaging findings of active inflammation
CONCLUSION

MR enterography has its own advantages over CT and has been recommended as the imaging of choice, however it is often under-utilised owing to the costs, requirement of general anaesthesia and inability to perform breath holding sequences. Although CTE will continue to have its own place as in emergency situations or where MR is contraindicated, otherwise for most situations MRE should be the preferred modality. Increasing use of MRE will help in reducing the burden of ionizing radiation especially knowing repeated imaging procedures are often necessary in these children. MR enterography severity scores like MEGS may reduce the need for repeated endoscopies and supplement fecal calprotectin in disease monitoring. We believe that each center should have a state of the art MR enterography protocol with regular inter-disciplinary consultations between the pediatric gastroenterologist and the radiologist to enhance its utility where clinically indicated.

FURTHER READING:


In a busy day to day OPD/practice of a pediatric gastroenterologist/pediatric hepatologist, keeping a list of the common drugs with their doses will be handy for easy reference. Below section describes the drugs with their doses for the commonly encountered diseases in our practice.

We would like to highlight that most of the conditions discussed below like Wilson’s disease, Autoimmune hepatitis etc. needs specialized care and should be managed by specialists in the subject.

<table>
<thead>
<tr>
<th>Disease/Symptom</th>
<th>Medications</th>
<th>Dose</th>
</tr>
</thead>
</table>
| 1) Neonatal cholestasis | Vitamin supplements, Calcium, Medium chain triglycerides (MCT), Ursodeoxy cholic acid (UDCA) | • Vitamin K dose: 5 mg weekly  
• Vitamin D dose: 1000 IU/day  
• Vitamin E dose: 100–200 IU/day  
• Vitamin A dose: 5000–25000 IU/day  
• Water soluble vitamins dose: Twice RDA  
• MCT dose: 20% of total calorie intake as MCT  
• UDCA dose: 15–20 mg/kg/day |
| 2) Cholangitis prophylaxis | Antibiotics | • Septran for prophylaxis (Trimethoprim dose): 4 mg/kg/days BD  
• Cefixime: dose for prophylaxis is not well studied, therapeutic dose-8 mg/kg/day BD |
| 3) Pruritus | • UDCA  
• Rifampicin  
• Cholestyamine | • UDCA dose: 15–20 mg/kg/days BD  
• Rifampicin dose: 10 mg/kg/days BD  
(studies used upto 20 mg/kg/day)  
• Cholestyamine dose: 240 mg/kg/day  
(along with food as TDS; max 8 gm/day) |
| 4) Bile acid synthetic defect | -Bile acids  
(Cholic acid) | • Cholic acid dose: 7–15 mg/kg/day |
| 5) Budd-chiari syndrome | • Warfarin | • Warfarin dose: At outset as 0.2 mg/kg/day OD  
(then to titrate based on the INR; dose is adjusted by cumulative weekly dose) |
| 6) Autoimmune hepatitis | • Steroids  
• Azathioprine  
• MMF  
• Cyclosporine  
• Tacrolimus | • Prednisolone dose: 1–2 mg/kg/day (at onset) OD  
• Azathioprine dose: 1–2 mg/kg/day OD  
• MMF dose: 20 to 40 mg/kg/day BD. Upper limit of MMF dose: 1500 mg/day in pediatric studies; 3 g/day in adult studies  
• Cyclosporine dose: 3–8 mg/kg/day BD  
• Tacrolimus dose: 0.05–0.1 mg/kg/day BD |
| 7) Wilson’s disease | Chelating agents, Zinc | • D-pencillamine dose: 10–20 mg/kg/day (max 1500 mg/day, 1 hour before or two hours after meal)  
• Trientine dose: 20 mg/kg/day (max 1500 mg/day, 1 hour before or three hours after meal) |

1 Assistant Professor, Department of Pediatric Gastroenterology, Postgraduate Institute of Child Health Hospital, Noida. Email: umeshreddyd@gmail.com
2 Assistant Professor, Department of Pediatric Gastroenterology, Postgraduate Institute of Child Health Hospital, Noida. Email: doctorviki16@gmail.com
### Commonly used Drugs with their Doses in Pediatric Hepatologist’s Practice

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosage and Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Zinc</strong></td>
<td>Age &gt;16 years and body weight &gt;50 kg: 150 mg/day TDS</td>
</tr>
<tr>
<td><strong>Hepatitis B Antivirals, Peg-Interferon (as indicated)</strong></td>
<td>Entecavir dose (&gt; 2 yrs): 0.015 mg/kg/day (max 0.5 mg) OD</td>
</tr>
<tr>
<td></td>
<td>Tenofovir (disoproxilfumarate, TDF) dose: &gt;12 yr 300 mg OD</td>
</tr>
<tr>
<td></td>
<td>Tenofovir (alafenamide, TAF) dose: &gt;12 yr 25 mg OD</td>
</tr>
<tr>
<td></td>
<td>Lamivudine dose: &gt;3 yr 3 mg/kg (max 100 mg) OD/BD</td>
</tr>
<tr>
<td></td>
<td>Peg-IFN dose: &gt;3 yr 180 mcg/1.73 m² once a week</td>
</tr>
<tr>
<td><strong>Hepatitis C Antivirals (Directly acting antivirals)</strong></td>
<td>Drug combinations (EASL—irrespective of genotype)</td>
</tr>
<tr>
<td></td>
<td>Sofosbuvir-Velpatasvir (&gt;3 yr) Dose: &gt;12 yr: 400/100 mg; between 3–11 yrs with &lt;17 kg: 150/37.5 mg and &gt;17kg: 200/50 mg OD for 12 weeks</td>
</tr>
<tr>
<td></td>
<td>Glecaprevir-pibrentasvir (&gt;3 yr) 12–19 kg: 150/60 mg 20–29 kg: 200/80 mg 30–44 kg: 250/100 mg OD for 12 weeks</td>
</tr>
<tr>
<td><strong>Variceal bleed</strong></td>
<td>Octreotide during acute bleed dose: Loading with 1 mcg/kg followed by 1–5 mcg/kg/hr</td>
</tr>
<tr>
<td></td>
<td>Propranolol dose: 0.5–3 mg/kg/day (usual range 1–2 mg/kg/day; up to 8 mg/kg/day max)</td>
</tr>
<tr>
<td></td>
<td>Carvedilol dose: 0.05–0.3 mg/kg/day BD, adult doses used in most studies: 6.25 mg/day to 12.5 mg/day</td>
</tr>
<tr>
<td><strong>Ascites</strong></td>
<td>Spironolactone dose: 2–6 mg/kg/day (max 400 mg/day)</td>
</tr>
<tr>
<td></td>
<td>Furosemide–spironolactone combination (1:2.5 ratio)</td>
</tr>
<tr>
<td></td>
<td>Furosemide dose: 1–4 mg/kg/day (max 160 mg/day)</td>
</tr>
<tr>
<td></td>
<td>Albumin infusions dose: 1 gm/kg over 6–8 hours</td>
</tr>
<tr>
<td><strong>SBP prophylaxis</strong></td>
<td>Norfloxacin dose: 5–7.5 mg/kg/day OD</td>
</tr>
</tbody>
</table>

### REFERENCES

Celiac Disease with Rapunzel Syndrome: A Rare Clinical Presentation

Tibin Johny¹, Rahul Diwedi¹, Ravi Sharma¹, Lalit Bharadia², Sunita Ojha³

ABSTRACT

10-year-old girl was brought with complaints of intermittent abdominal pain and fullness in upper abdomen for 1 year along with features of malnutrition such as wasting and poor growth velocity. On investigation, celiac serology was positive along with mild fullness in upper abdomen. Endoscopy showed trichobezoar in stomach, extended to duodenum which was managed surgically along with celiac diet and psychotherapy. During postoperative period she improved with psychotherapy and celiac diet.

INTRODUCTION

Celiac disease is an immune mediated systemic disorder elicited by gluten and related prolamins in genetically susceptible individuals and characterized by the presence of a variable combination of gluten-dependent clinical manifestations, CD-specific antibodies, a human leukocyte antigen (HLA)-DQ2 or HLA-DQ8 haplotype, and enteropathy. The classical presentation of CD is characterized by steatorrhea, abdominal distension, and oedema, but constitutional symptoms, such as lethargy, poor appetite, depression, and emotional disorders, are frequently present. It has been associated with behavioural disorder such as trichotillomania and trichophagia.[1]

A trichobezoar is a mass of hair found in the stomach[2] or, less commonly when it extends to the small bowel it is called Rapunzel syndrome.[3] This rare condition is nearly exclusively observed in young females. The continuous ingestion of hair together with mucus and food can cause impaction, leading to the formation of a trichobezoar.[4]

CASE REPORT

A ten-year-old girl was brought to Pediatric Gastroenterology OPD with history of intermittent abdominal pain since 1 year. She had few episodes of vomiting and decreased appetite for the last 2 days prior to hospital visit. Poor weight gain and growth was also noticed by parents during the last one year. She had no history of constipation, diarrhoea, fever, rashes, or dysuria.

On examination, the vitals were stable. There was no pallor on general examination. Systemic examination showed mild fullness of abdomen.

At the time of admission, laboratory investigations showed a normal haemoglobin concentration of 11.7 g/dL [normal range: 10.7–14.8 g/dL], a normal red cell count and haematocrit (73.1 fL, NR 77–95 fL), thrombocytosis 742 × 10³/uL lakh and a normal white cell. Anti-tissue transglutaminase antibody (IgA tTg) levels were tested and found to be greater than 100 Au/ml (normal range <100 Au/ml). An abdominal x-ray was done which showed multiple air fluid levels noted, which likely indicate sub-acute intestinal obstruction. The patient was subsequently sent for upper GI endoscopy study for further evaluation and duodenal biopsy for celiac confirmation.

On endoscopy, the stomach was filled with a large trichobezoar occupying around 50% of the gastric lumen (Figure 1) and was extending through the pylorus into the duodenum and beyond. The removal of the hair shafts was attempted endoscopically but was not successful. The duodenal biopsy (gold standard for diagnosing celiac disease) revealed fragments of duodenal mucosa (Figure 2) showing total villous atrophy with crypt hyperplasia and marked infiltration of lymphoplasmacytic cells in lamina propria. Increased intraepithelial lymphocytes (>40 lymphocytes/100 enterocytes) were also seen. No granuloma or parasites were seen. This histology was consistent with celiac disease - Marsh grade 3c classification.

In view of large trichobezoar extending distally into the small intestine, the patient was posted for laparotomy. An upper midline incision was made and gastrotomy was done. Large trichobezoar involving stomach, duodenum, and up to mid-ileum was removed (Figure 3, length was 97 cm). Post-operatively psychiatric evaluation was done, which revealed

¹Department of Pediatrics and Pediatric Intensive Care, SDM Hospital, Jaipur, India
²Division of Pediatric Gastroenterology, SDM Hospital, Jaipur, India
³Department of Pediatric Surgery, SDM Hospital, Jaipur, India
*Corresponding author: Tibin Johny, Santokbha Durlabhji Memorial Hospital, Jaipur, Rajasthan
E-mail: tjj4jlb@gmail.com

Context: Rapunzel syndrome is a rare form of gastric trichobezoar that develops through outstretching of the bezoar from stomach to the intestine.
trichophagia and mixed anxiety depression. The patient was subsequently started on sertraline and etizolam along with celiac diet and nutritional support.

**DISCUSSION**

Celiac disease is found to have associated with cognitive emotional and neurodegenerative disorders and atypical symptoms such as trichotillomania, trichophagia and depression, other than its usual symptoms such as growth failure, anaemia etc.

Trichotillomania is the morbid craving to pull out hair from the scalp or other parts of body and is frequently associated with trichophagia, the compulsion to eat hair. This habit is more often observed in girls during the first two decades of life. The two have been associated with mental disorders in children and may lead to the formation of a gastric trichobezoar, a concretion built from the continuous deposition of hair on the stomach lining. In rare cases, trichobezoars may extend into the duodenum in a condition known as Rapunzel syndrome. It is usually presented with abdominal pain, vomiting, abdominal fullness and bowel obstruction. The treatment of choice is the removal of the concretion via laparotomy, in some cases also involving the resection of portions of the bowel.

Patients with celiac disease must be examined and interviewed thoroughly to enable the identification of supplementary investigation needs. Familial predisposition to mental illness, in addition to stress and socialization factors, must be considered in the detection of symptoms of depression or anxiety.

**CONCLUSION**

In a child with long-standing GI symptoms and malabsorption, coeliac disease should be suspected and screened for. Upper GI endoscopy and duodenal biopsy can help confirm the diagnosis especially if the child is resistant to gluten free diet. Although psychiatric symptoms are not an uncommon association with coeliac disease, the presence of specific conditions like trichobezoar is rare. Large bezoars especially those having extensions into small bowel are difficult to manage endoscopically and often require laparotomy. Appropriate psychiatric management is also an essential part of the management.

**REFERENCES**

1. The Use of Fecal Calprotectin Testing in Paediatric Disorders: A Position Paper of the European Society for Paediatric Gastroenterology and Nutrition Gastroenterology Committee


The role of fecal calprotectin (FC) in the clinical practice to get clues about inflammatory bowel disease (IBD) or functional gastrointestinal disorders (FGD) is well known. Calprotectin, a complex protein, is present in tissues and fluids which are abundant in neutrophils and monocytes. In inflammatory conditions there is influx of inflammatory cells mainly neutrophils and monocytes. Activation followed by death of aggregated inflammatory cells release large amount of calprotectin which can be measured in faeces. Various conditions as Crohn disease (CD), ulcerative colitis (UC), cystic fibrosis, rheumatoid arthritis, bacterial infections etc. demonstrate high fecal calprotectin. This position paper reviews the evidence through a literature search in PubMed and Cochrane databases, determining the value of FC in different gastrointestinal disorders and formulate a recommendation. A stool weight of 50-100 gm preferably early morning sample is sufficient for the test. Most of the literature suggest that the sample can be kept at room temperature for 3-7 days but most analysis methods recommend to keep faecal samples for up to 2 to 3 days at room temperature, 5 to 7 days in a fridge or frozen if long-term storage is required. False positive results may be seen in samples collected from diaper, after bowel enema, post colonoscopy and in blood mixed stool. Commonly used drugs as nonsteroidal anti-inflammatory drugs and proton pump inhibitors can also lead to falsely high levels of FC. The normal range of FC is stated as less than 50µg/g of faeces and a cut-off of more than 100 µg/g of faeces has better diagnostic value for IBD. FC levels are higher in children as compared to adults however specific ranges for various age groups have not been established. Preterm and younger children may have higher levels. High FC levels are indicators of IBD and can help decide whether a colonoscopy is required or not. However, levels of FC cannot be used to differentiate between IBD and non IBD conditions. FC may be used to confirm remission or diagnose relapse in view of clinical symptoms and should be measured every six monthly during follow up. FC can be used to differentiate FGD from organic ones. In irritable bowel syndrome FC levels are observed to be higher than healthy children but lower than that seen in children with IBD. Children with constipation have normal FC levels whether functional or organic. FC levels show a great range of variability in food allergies, cow’s milk protein allergy and celiac disease, so it cannot be used as a diagnostic or prognostic marker in these conditions. There is no evidence which correlates FC levels and clinical or laboratory findings of enteropathy, so FC levels should be used with caution in conditions with enteropathy as cystic fibrosis. Similarly, it has low utility in acute gastroenteritis and appendicitis. It is helpful in predicting the risk of necrotising enterocolitis (NEC) if there are rising levels in serial FC estimations. It is also useful in monitoring patients with NEC. Juvenile polyps are associated with high FC but a normal level doesn’t rule out polyp. FC levels should always be analysed based on the clinical presentations.

2. The Value of Obtaining Colonic Mucosal Biopsies of Grossly Normal Tissue in Pediatric Patients


Endoscopic mucosal biopsy plays an important role in the diagnosis of a number of gastrointestinal conditions. However, there is no guideline regarding the necessity and yield of mucosal biopsy from grossly normal colonic mucosa. This paper describes a retrospective study with an aim to assess the value of mucosal biopsy from grossly normal tissue. In this study the agreement between the endoscopist and the histopathologist was examined whether they both reported normal or abnormal tissue. After exclusion 237 endoscopies were analysed. The predictive value of agreement between the endoscopist and pathologist was 81%. Abnormal histology was observed in 46 out of 237 patients (19.4%) with normal appearing colonic mucosa on endoscopy. Out of 46, 17 patients were known case of IBD, 11 had histological evidence of inflammation and rest had non-specific or clinically non-significant histological findings. These findings proposed that colonic mucosal biopsies may not be required from patients with grossly normal mucosa on colonoscopy. Biopsy should be obtained from patients with significant clinical or laboratory features.

3. Diagnostic Value of Persistently Low Positive TGA-IgA Titers in Symptomatic Children With Suspected Celiac Disease

The role of high titers of serum tissue transglutaminase 2 IgA (TGA-IgA) is undisputable in the screening of celiac disease in symptomatic as well as asymptomatic children. But the diagnostic value of persistently low positive titers in children with suspected CD is not known. This retrospective study in 281 children tries to find the answer and describes the diagnostic outcome of suspected CD children with persistently low positive anti-TGA IgA who underwent upper gastrointestinal endoscopy and duodenal biopsy. All of the patients had one or more gastrointestinal or extra-gastrointestinal manifestations of CD. Three groups were made: Group A (Low positive) with TGA levels more than ULN but less than 5ULN; Group B (moderate positive) with TGA levels more than 5ULN but less than 10ULN; Group C (TGA negative) as controls. Out of 281 patients a repeat test showed positive TTG in 224 whereas 57 had negative reports. Mucosal changes compatible with CD was observed in 204 children out of 224, who had positive TTG and the median level of TTG was 3ULN. In group A 87% (n=142) were diagnosed as CD. Endomysial antibody (EMA) was performed in 138 in group A and was found to be negative in 21% (n=29). Almost 80% had mucosal changes in second part of duodenum and beyond. Only 15% exhibited changes in the duodenal bulb. Out of 20 with normal mucosal findings, 14 were designated as potential CD on the basis of symptoms, positive TTG and EMA, and HLA predisposition. In group B all were diagnosed as CD on the basis of biopsy and only 3% had isolated duodenal bulb changes and EMA was positive in only 3%. The study concluded that a mean value of TTG 1.7ULN may be considered as threshold for duodenal biopsy.

4. Noninvasive biomarkers for the diagnosis and management of autoimmune hepatitis


The diagnosis and management of autoimmune hepatitis (AIH) still continues to intrigue gastroenterologists. Lack of predictors for response to the treatment and identification of high-risk individuals for relapse adds to the struggle. This review based on PubMed literature search tries to look for biomarkers that can help predict the clinical course and early relapse in patients with AIH. Currently the biomarkers used to speculate the response and relapse are aminotransferases (AST and ALT); IgG and total immunoglobulins, and 6-thioguanine (6-TG). ALT levels less than half the upper limit of normal (ULN) and IgG level less than 1200 mg/dL when sustained for 2 years, decreases the risk of relapse by almost 40% after cessation of treatment and improves the histology in terms of disappearance of interface hepatitis. Liver enzymes are good predictors of biochemical remission but not histological remission. In the preclinical stage, DRB1*03:01, SH2B3, and CARD10 can be of help in screening children with other autoimmune features. The frequency of T cells secreting IL-17 and TNF-α increases significantly in active AIH and correlates with liver injury, and the levels of Th1 and Th17 cells significantly decreased after immunosuppression withdraw. These markers may have utility in detection of the disease before serological changes are evident and can also keep a track of the disease activity. High levels of adenosine deaminase, serum TGF-β1, vitamin 25(OH)-D and ferritin have been found to match up with interface hepatitis and active histological process in children with AIH. High levels of Treg cells and serum DNAse1 have been shown to corroborate with histological remission. For relapse prediction anti-asialoglycoprotein receptor (ASGPR) titers may be helpful as their levels increase prior to elevation of liver enzymes thus it can predict relapse after withdrawal of immunosuppression.

Compiled by Dr Rimjhim Shrivastava
The shear wave elastography (SWE) values of the spleen in healthy children using Elastography Point Quantification (ElastPQ). SWE values were recorded in upper pole, mid pole, and lower pole of the spleen in 146 children and compared across the age groups ≤ 5 years, > 5-10 years and > 10-15 years. Authors have concluded that SWE values of the spleen in healthy children do not correlate with age, and no significant difference is there in the SWE values for boys and girls. There was a statistically significant difference in the SWE values of the spleen while comparing the groups based on the median splenic length.

MAY 2022


In this systematic review and meta-analysis authors have aimed to analyze the outcomes of endoscopic drainage with or without endoscopic ultrasonography (EUS) guidance in children with pancreatic fluid collections (PFCs). Fourteen studies (187 children, 70.3% male) were included in this review. The subtypes of fluid collection included pseudocysts (60.3%) and walled-off necrosis (39.7%). The pooled technical success rates in studies where drainage of PFCs were performed with and without EUS guidance were 95.3% and 93.9% respectively. The pooled clinical success rates in studies where drainage of PFCs were performed with and without EUS guidance were 88.7% and 92.3%, respectively. The pooled technical success rate of recurrent PFCs after endoscopic drainage was 10.4%. They have concluded that endoscopic drainage is safe and effective in children with PFCs and added that future studies are required to compare endoscopic and EUS-guided drainage of PFCs in children.


In this case report authors have reported on a child who presented with recurrent anasarca who was diagnosed to have congenital disorder of glycosylation harbouring a novel mutation. Through this case report authors emphasize that protein losing enteropathy should be suspected in children with chronic diarrhoea and peripheral oedema and worked up for definitive etiology.

In this brief report authors have presented a first series of preliminary post-liver transplant [LT] outcomes in progressive familial intrahepatic cholestasis [PFIC] type IV. Previously undescribed, certain interesting findings unique to this disease were noted in this series of 4 cases and have been highlighted. One of the four patients had a high-GGT cholestasis; one of the patients, developed recurrent pneumothorax observed on the 5th post-LT day and one of four patients had an incidental HCC on the explant liver. On a median follow-up of 18.5 months (range 5-58 months), all the recipients remained well with a normal graft function. Severely stunted growth was a striking feature of all patients except one, all of them had a remarkable improvement in their Z scores following LT. None of the patients developed any extrahepatic manifestations or disease recurrence.

MISSED INADVERTENTLY IN PREVIOUS ISSUES

2021


In this minireview authors have described the pathogenesis and clinical features of the newer variants of progressive familial intrahepatic cholestasis [PFIC]. PFIC manifests with a varying spectrum of clinical features, with some variants progressing rapidly into end stage liver disease. Recently, newer variants of PFIC have been described including PFIC 4 due to tight junction protein 2 (TJP2) mutation, PFIC 5 due to NR1H4 mutation and MYO5B related cholestasis also sometimes known as PFIC 6. TJP2 related PFIC has variable clinical presentations and carries risk for development of hepatocellular carcinoma. PFIC-5 patients usually have rapidly progressive liver disease with early onset coagulopathy, high alpha-fetoprotein and ultimately require a liver transplant. Subjects with MYO5 B-related disease can present with isolated cholestasis or cholestasis with intractable diarrhea resulting from microvillus inclusion disease [MVID]. These children are at risk of worsening cholestasis post intestinal transplant (IT) for MVID, hence combined intestinal and liver transplant or IT with biliary diversion is preferred.

2022


A national consultative group (NCG) was constituted by the Indian Academy of Pediatrics (IAP), consisting of subjects experts including representation from ISPGHAN fraternity to develop a guideline for the use of probiotics in children with diarrhea. The NCG suggested Lactobacillus GG as a conditional recommendation with low-to-moderate level evidence or Saccharomyces boulardii as a conditional recommendation with very low-to-low level evidence as adjuvant therapy in acute diarrhea. The NCG also recommended the use of combination probiotics in neonatal necrotizing enterocolitis (NEC), as these reduce the risk of NEC stage II and above, late-onset sepsis, mortality and also time to achieve full feeds. The NCG did not recommend the use of any kind of probiotics in the therapy of acute dysentery, persistent diarrhea, Clostridium difficile diarrhea and chronic diarrheal conditions such as celiac disease, diarrhea-predominant irritable bowel syndrome and inflammatory bowel disease in children. The NCG recommended probiotics only in special situations of AAD. L. rhamnoses GG or S. boulardii may be used for the prevention of AAD. VSL#3, a combination probiotic, may be used as an adjuvant in active pouchitis, prevention of recurrences and maintenance of remission in pouchitis.

Compiled by Dr. Prasanth K.S
Associate Professor, Division of Pediatric Gastroenterology, Dept. of Pediatrics, Sree Avittom Thirunal (SAT) Hospital, Govt. Medical College, Thiruvananthapuram-695011, Kerala
Email ID – drprasanthksobhan@gmail.com

ISPGHAN Members are kindly requested to mail a copy of their published articles in PUBMED indexed journals to pglj.ispghan@gmail.com
A 14 year old girl presented with progressively enlarging lump and pain in right hypochondrium with intermittent fever for last 3 years. Complete blood picture and liver function tests were largely unremarkable. A contrast enhanced computerised tomography was performed.

What is the diagnosis and possible modalities of management (in brief)?

1. Diagnosis: Water lily sign, Hydatid cyst of liver.

2. Possible treatment modalities:
   a) Long term albendazole,
   b) Percutaneous puncture, aspiration, injection, re-aspiration (PAIR),
   c) Excision surgery

Congratulations to the Winners of Quiz 1 APGH

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A 1.5 month old baby was brought to the emergency with recurrent non-bilious vomiting and failure to gain weight. Complete blood picture and liver function tests were largely unremarkable. Abdominal sonology showed normal pyloric channel. A barium study was performed.

What is the diagnosis and the possible modality of management?

Answers will be revealed in the next issue | Winners will receive an e-certificate

Send in your answers to pglj.ispghan@gmail.com by 15/07/2022 with your name, designation, affiliation and email id.
BEYOND GUT SENSE

GI Bleed-What Crosses the Mind!

Dr. D V Umesh Reddy

Little ones puke or purge on the bed
Frightening the colour is black or red
Whats inside as the cause
Makes you plan with a pause
Oh varices, do they look angry
Carefully scope and band merry
Caves which spurt is it the ulcer
Lowering the acid is wiser
A beautiful stalk not a berry but a polyp
Hidden behind the fold there is no gossip
As giant as it may grow
Cut and smear not throw
Acute with fever and pain
Few pills and all to gain
Is it in the milk sounds allergic
Simply stop and awe the magic
Hard and painful movements that’s a fissure
Softening the stools keeps her happier
Pray for no signs of inflammation
Or tortuous path may be an undermined summation
Prick to look for coagulopathy
Ruling out is always worthy
Entire bowel is scoped and navigated
Nothing abnormal makes you flabbergasted
Have you ever wondered is it just spurious
Afterall the doctor is curious!

Thank you

Assistant Professor, Department of Pediatric Gastroenterology, Postgraduate Institute of Child Health Hospital, Noida.
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Congress Secretariat
KonferenceX Event Solution
Neudimension, B-5-8
Plaza Mont Kiara, 50480
Kuala Lumpur, Malaysia
secretariat@appspghan2022.org
ASSOCIATE EDITORS

Dr. Rajeev Khanna,
Associate Professor (Pediatric Hepatology),
Institute of Liver & Biliary Sciences,
New Delhi
Email: drrajeev_khanna@rediffmail.com

Dr. Moinak Sen Sarma
Associate professor
Department of Pediatric Gastroenterology
Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow
Email: moinaksen@yahoo.com

Dr. Rimjhim Shrivastava,
Consultant, Pediatric Gastroenterology and Hepatology
Ekta Institute of Child Health, Raipur
Swapnil Nursing Home, Raipur
Petals Children Hospital, Raipur
Email: docrimjhim@gmail.com

Dr. Jaya Agarwal,
Consultant, Pediatric Gastroenterology
Regency health Kanpur
Email: drjaya.agarwal@gmail.com

Dr. Prasanth K. S.,
Associate Professor, Division of Pediatric Gastroenterology
Dept. of Pediatrics, SAT Hospital, Govt. Medical College, Thiruvananthapuram - 695011, Kerala
Email: drprasanthksobhan@gmail.com

Dr. Aathira Ravindranath,
Consultant, Pediatric Gastroenterology
Apollo BGS hospital
Mysore
Email: aathira.r@gmail.com
Details of Office Bearers for ISPGHAN 2022-23

Dr. Neelam Mohan
President
ISPGHAN membership Number: ISPGHAN2014LM10002
Email id: drneelam@yahoo.com

Dr. Shrish Bhatnagar
Secretary
Membership No: ISPGHAN 2015 LM 10043
Email id : drshrishbhatnagar@gmail.com

Dr. Vishnu Biradar
Treasurer
ISPGHAN membership Number: ISPGHAN2015LM00071
Email id: vishnubiradar@gmail.com

Jagadeesh Menon V R
Joint treasurer
Membership number : ISPGHAN2015LM10047
jagadeeshmenonv@gmail.com

Dr. R. K. Gupta
Executive Member (West)
ISPGHAN membership Number: ISPGHAN2014LM10009
Email: rkguptadr@hotmail.com

Dr. Aathira Ravindranath
EB member South
ISPGHAN membership:
ISPGHAN2016/LM/10133
Email: aathira.r@gmail.com

Dr. Bikrant Bihari Lal
EB Member (North)
ISPGHAN membership:
ISPGHAN2016LM10109
Email: bikrant18may@gmail.com

Dr. Sumit Kumar Singh
Executive Member (Central)
ISPGHAN membership Number:
ISPGHAN2014LM10037
Email: drsumitkgmu@gmail.com

Dr. Rimjhim Shrivastava
EB Member, East
Membership no: ISPGHAN 2016 LM 10104
Email: docrimjhim@gmail.com

Executive Members

Dr. Dr. Shrish Bhatnagar
Secretary
Membership No: ISPGHAN 2015 LM 10043
Email id : drshrishbhatnagar@gmail.com

Dr. Vishnu Biradar
Treasurer
ISPGHAN membership Number: ISPGHAN2015LM00071
Email id: vishnubiradar@gmail.com

Jagadeesh Menon V R
Joint treasurer
Membership number : ISPGHAN2015LM10047
jagadeeshmenonv@gmail.com
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