

Etiology, Clinical Spectrum and Outcome of Metabolic Liver Diseases in Children

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ABSTRACT

Objective: To determine the etiology, clinical spectrum and outcome of metabolic liver diseases (MLD) in children admitted in a tertiary care hospital of Eastern India.

Study Design: An observational study.

Place and Duration of Study: Paediatric Liver Clinic and Paediatrics Inpatient Department of Nilratan Sircar Medical College and Hospital, Kolkata, Eastern India, from April 2009 to March 2011.

Methodology: All children aged 0 – 12 years having characteristic clinical features along with diagnostic hallmark of any MLDs were included in this study and data were collected on a pre-designed proforma. After appropriate management and discharge, all patients were followed-up for next 6 months.

Results: Fifty one children with mean age 4.34 ± 3.78 years (range 2 days – 12 years), male: female ratio 1.55:1, were studied. The etiologies were Wilson's disease (33.33%, n = 17); glycogen storage disorder (23.53%, n = 12); galactosemia (19.61%, n = 10); non-alcoholic fatty liver disease (11.76%, n = 6); Gaucher disease (5.88%, n = 3); mucopolysaccharidoses (3.92%, n = 2) and familial hyperlipoproteinemia type-I (1.96%, n = 1). Jaundice (n = 24) and hepatomegaly (n = 47), was the commonest symptom and sign respectively. Of the 17 non-responders, most were Wilson's disease (n = 7) cases. There was statistical difference in outcome with respect to INR > 1.3 at diagnosis (p = 0.026).

Conclusion: High index of suspicion, early detection and screening, simple dietary modification and cost effective drugs along with good compliance are sufficient to treat and even prevent evolution of most causes of the MLDs.

Key words: Metabolism. Liver diseases. Wilson's disease.

INTRODUCTION

Metabolic liver diseases (MLD), an inborn error of metabolism, is caused by defect of single enzyme or transport protein resulting into abnormality in synthesis or catabolism of carbohydrate, protein and fat.¹ It accounts for upto 40% of all chronic liver diseases (CLD) admitted to large medical centres in India.² With raised awareness for MLDs like Wilson's disease (WD) and increasing recognition of relatively newer entities like Non-Alcoholic Fatty Liver Disease (NAFLD), there is a considerable change in the spectrum of epidemioclinical profile of MLDs in India.³

Studies on childhood MLDs have been conducted in India and abroad.^{1,2} But in view of the changing epidemio-

clinical profile, no similar study on MLDs has been done in Eastern India. So, the purpose of this study was to determine the etiology, clinical spectrum and outcome of MLDs in children in this part of the country.

METHODOLOGY

This observational study was conducted on children aged 0 – 12 years, who either attended the Paediatric Liver Clinic in the Outpatient Department or were admitted directly in the Paediatric Inpatient Department of Nilratan Sircar Medical College and Hospital, between April 2009 and March 2011 with symptoms/signs of any form of liver disease.

Those patients, who had characteristic clinical features along with diagnostic hallmark of any MLDs, were included. The exclusion criteria were presence of any infective markers, including those of the hepatotropic virus and all confirmed cases of extra-hepatic portal hypertension.

A pre-designed proforma collected information including detailed history, general survey including anthropometry, gastrointestinal examination, neurological examination, ocular examination and relevant systemic examination. All patients underwent specific diagnostic investigations, as and when felt necessary. The children were given supportive as well as specific management, when needed. Follow-up was done for the next 6 months.

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Screening tests included urine for non-glucose reducing substance and uronic acid for galactosemia and mucopolysaccharidoses (MPS) respectively. Wilson's disease was diagnosed on the presence of liver disease with 2 or more of (i) serum ceruloplasmin < 20 mg/dL, (ii) urinary copper excretion > 100 µg/day, (iii) urinary copper excretion > 1600 µg/day after penicillamine challenge and (iv) presence of the Kayser - Fleischer (KF) ring.⁴ The special investigations done to confirm diagnosis were: Galactosemia panel test which included estimation of galactose-1-phosphate uridyl transferase, galactokinase, uridine diphosphate galactose-4-epimerase for galactosemia; glucose-6-phosphatase and glucose-6-phosphatase translocase for Glycogen storage diseases (GSD) Type-Ia and Ib respectively; estimation of enzymes of subtypes of MPS wherever feasible and bone marrow / trephine biopsy for Gaucher cells in Gaucher disease. Characteristic liver biopsy findings were documented for GSD and NAFLD. MRI brain was done in cases of WD with neurological manifestations.

Outcome of treatment were termed as 'responders' comprising of cases who had clinical improvement and were discharged in favourable condition along with sustained remission (lasting greater than 6 months). Non-responders comprised all who had unchanged clinical condition or non-persistent remission of symptoms, clinical deterioration or had died or had to be referred from the study setting.

The study had necessary approval from the Institutional Ethical Committee and informed consent was taken from the parents/guardians of the subjects. Statistical analysis was done with the help of statistics calculators of Graph Pad Quickcalcs software with p-value < 0.05 taken as significant. Qualitative variables were presented as frequency and percentages whereas quantitative variables were presented as mean and standard deviation. Chi-square test/ Fisher's exact test were used to compute the difference with respect to various parameters.

RESULTS

Fifty one children were enrolled with a mean age 4.34 ± 3.78 years, ranging from 2 days to 12 years. Males (60.78%, n = 31) outnumbered the females (39.22%, n = 20). Most of the subjects (84.31%, n = 43) were from in and around southern Bengal, which is the catchment area of the study centre.

The presentations were diverse depending on etiology and age group concerned. Jaundice (47.06%, n = 24), poor growth (35.29%, n = 18), abdominal distension (23.53%, n = 12) and hematemesis/malena (9.80%, n = 5) were the most common presenting complaints. On examination, the most frequent signs elicited during hospital stay were hepatomegaly (92.16%, n = 47),

splenomegaly (64.7%, n = 33), icterus (62.75%, n = 32), short stature (50.98%, n = 26) and ascites (25.49%, n = 13, Table I).

The commonest detected etiology was Wilson's disease (33.33%, n = 17), followed by GSD (23.53%, n = 12) and Galactosemia (19.61%, n = 10). NAFLD, Gaucher disease, MPS, familial hyperlipoproteinemia Type 1 contributed the rest (Table II).

Haemoglobin was < 10 gm/dL in 14 cases (27.45%). Abnormal liver function test was characterized by conjugated hyperbilirubinemia (62.75%, n = 32), alanine aminotransaminase (ALT) > 50 IU/L (86.27%, n = 44), aspartate aminotransferase (AST) > 50 IU/L (90.19%, n = 46) and albumin < 3 gm/dL (23.53%, n = 12). INR > 1.3 was found in 14 cases (27.45%).

Ophthalmological examination showed variable features. All cases of WD with neurological manifestations revealed KF ring. Sunflower cataract was found in 2 cases of WD and oil droplet cataract in one case of Galactosemia. Ophthalmoplegia, optic atrophy and oculogyric crisis (OGC) were seen in all 3 cases of Gaucher disease. Lipemia retinalis was detected in the familial hyperlipoproteinemia Type-I case.

Table I: Initial modes of presentation with metabolic liver diseases.

| Initial modes of presentation | Number of cases (%) |
|--|---------------------|
| A. Symptoms | |
| Jaundice | 24 (47.06) |
| Poor growth | 18 (35.29) |
| Abdominal distension | 12 (23.53) |
| Hematemesis/malena | 5 (9.80) |
| Voracious appetite | 4 (7.84) |
| Pain abdomen | 3 (5.88) |
| Progressive pallor | 3 (5.88) |
| Developmental delay | 2 (3.92) |
| Excessive vomiting | 1 (1.96) |
| Intractable pruritus | 1 (1.96) |
| Hematuria | 1 (1.96) |
| B. Symptoms | |
| Hepatomegaly | 47 (92.16) |
| Splenomegaly | 33 (64.70) |
| Icterus | 32 (62.75) |
| Short stature (height \leq 5 th centile)* | 26 (50.98) |
| Ascites | 13 (25.49) |
| Obesity (Body mass index \geq 30 kg/m ²) | 6 (11.76) |
| Extrapyramidal signs, dystonia, tremor, athetosis | 6 (11.76) |

* Height percentile as per Centres for Disease Control and Prevention growth chart

Table II: Aetiological profile of metabolic liver diseases.

| Etiology | Number of cases (%) |
|--------------------------------------|---------------------|
| Wilson's disease | 17 (33.33) |
| Glycogen storage diseases | 12 (23.53) |
| Galactosemia | 10 (19.61) |
| Non-alcoholic fatty liver disease | 6 (11.76) |
| Gaucher disease | 3 (5.88) |
| Mucopolysaccharidoses | 2 (3.92) |
| Familial hyperlipoproteinemia Type-1 | 1 (1.96) |

Ultrasonography of hepatobiliary system showed coarse echotexture of liver in 14 (27.45%) and fatty liver in 15 (29.41%). Biliary sludge was detected in 2 (3.92%). One case (1.96%) of GSD revealed enlarged kidneys. Seven (13.73%) had dilated portal vein and in 5 (9.80%) of them, grade-II esophageal varices were detected by upper GI endoscopy. MRI brain T2 weighted images revealed bilateral basal ganglia and thalami hyperintensity in all cases of WD with neurological manifestations.

Liver biopsy was done in 31 cases (60.78%). Fatty change was detected in GSD and NAFLD cases.

Table III: Outcome of treatment among children with metabolic liver diseases.

| Outcome | No (%) | Total No (%) |
|------------------------------------|------------|--------------|
| Responders | | 34 (66.67) |
| Improved | 30 (58.82) | |
| Discharged in favourable condition | 4 (7.84) | |
| Non-responders | | 17 (33.33) |
| Died | 5 (9.8) | |
| Lost in follow-up | 2 (3.92) | |
| Unchanged clinical condition | 6 (11.76) | |
| Persistent disabilities | 4 (7.84) | |
| Total | 51 (100) | 51 (100) |

Table IV: The difference in outcomes in respect to various variables of metabolic liver disease.

| Parameters | Outcome | | p-value** |
|--------------------|--|--|----------------|
| | Responders to therapy (n = 34) No (%) | Non-responders to therapy (n = 17) No (%) | |
| Gender | | | p = 0.417 (ns) |
| Male | 22 (70.97) | 9 (29.03) | |
| Female | 12 (60.00) | 8 (40.00) | |
| Height percentile* | | | p = 0.075 (ns) |
| < 5 | 14 (53.85) | 12 (46.15) | |
| ≥ 5 | 20 (80.00) | 5 (20.00) | |
| Icterus | | | p = 0.543 (ns) |
| Present | 20 (62.50) | 12 (37.50) | |
| Absent | 14 (73.68) | 5 (26.32) | |
| Ascites | | | p = 0.069 (ns) |
| Present | 6 (46.15) | 7 (53.85) | |
| Absent | 28 (73.68) | 10 (26.32) | |
| ALT | | | p = 0.673 (ns) |
| ≤ 50 IU/L | 4 (57.14) | 3 (42.86) | |
| > 50 IU/L | 30 (68.18) | 14 (31.82) | |
| AST | | | p = 0.318 (ns) |
| ≤ 50 IU/L | 2 (40.00) | 3 (60.00) | |
| > 50 IU/L | 32 (69.57) | 14 (30.43) | |
| INR | | | p = 0.026 (s) |
| ≤ 1.3 | 28 (75.68) | 9 (24.32) | |
| > 1.3 | 6 (42.86) | 8 (57.14) | |
| Albumin | | | p = 0.161 (ns) |
| < 3 gm/dL | 6 (50.00) | 6 (50.00) | |
| ≥ 3 gm/dL | 28 (71.79) | 11 (28.21) | |

* Height percentile as per CDC growth chart, ALT=Alanine aminotransaminase; AST= Aspartate Aminotransferase; INR = International Normalized Ratio; s = significant; ns = non-significant
** Chi-square test / Fisher's exact test are applied to calculate p-value.

Deposition of glycogen in hepatocytes with plant like appearance and PAS positivity was found in all cases of GSD (23.53%). Type-I was diastase sensitive and Type-IV was diastase resistant. Gaucher cells in liver biopsy and bone marrow biopsy were detected in all cases of Gaucher disease.

Overall, 34 (66.67%) patients responded to management. Among the responders, regression of hepatomegaly, decrease/absence of icterus, normalization/near normalization of growth pattern, decrease/absence of ascites have been noted in 35, 25, 15 and 7 respectively in follow-up of 6 months. Of the 17 non-responders, most were due to WD (n = 7). Five of them died in hepatic encephalopathy and rest had persistent neuromuscular disabilities. One GSD Type-IV case died in renal impairment from renal tubular acidosis (RTA) Type-II. Septicemia caused death in 2 cases of galactosemia. MPS and Gaucher disease cases were referred to higher centres (Table III).

Comparison of results in relation to responders and non-responders showed that there was statistically significant poor outcome with respect to INR > 1.3 at diagnosis (p = 0.026, Table IV).

DISCUSSION

The clinical presentation of MLD in the study reflects the referral pattern in a specialised tertiary centre. This series showed a higher frequency of disease in males than in females.

In this series, Wilson's disease was the top most cause of MLDs (33.33%), a finding similar to what was documented by Yachha *et al.*,⁴ however, GSD (23.53%) and galactosemia (19.61%) were more in number than in the above mentioned study. Combined data of 8 medical centres in India showed that galactosemia was a significant cause of neonatal cholestasis which has also been corroborated here (2%).⁵

WD has an estimated occurrence of one in 500,000 to one in 100,000 in Western countries.⁶ But studies in Indian subcontinent showed that the prevalence is much higher (approximately one in 30,000 – 50,000) in South East Asia and it is a leading cause of metabolic and chronic liver disease in children.⁷⁻¹⁰

Most cases with WD (n = 10) had manifestations of chronic liver disease, 4 had associated Coombs negative hemolytic anaemia. Of these subjects, 5 had past history of jaundice and 2 had multiple episodes of the same. Four children presented with acute hepatitis like manifestations, 2 of them were relapsed cases. One relapsed patient had a protracted course with jaundice lasting greater than 12 weeks. Three children presented with acute liver failure, and all of them succumbed, inspite of vigorous supportive management. Although it has been mentioned in the Western literature that neurologic feature of Wilson's disease to appear after

the first decade of life,¹¹ neurologic manifestations were found well within the first decade of life. The features were dystonia, regression of milestones, protruded tongue, drooling of saliva, slurring of speech, tremor and athetosis. All neurologic cases had KF ring. One patient had complicated sunflower cataract from copper deposition in lens. MRI revealed signal hyper intensity in basal ganglia bilateral.

In the present series, 76.47% of patients had low ceruloplasmin level. The urinary copper excretion was the only test that was 100% sensitive in this study. A complete KF ring is the best sign for diagnosis of WD but uncommon in the paediatric series; it was absent in 71% of the children in the present series.¹² Among the 6 patients of WD in older age group (> 9 years) 5 were non-responders, which only emphasizes the need of early diagnosis.

GSD was the second most common disease entity in this study (23.53%). Clinical and laboratory work-up revealed that 9 of them were suffering from Type-Ia or Von Gierke disease, one had Type-Ib and the other two had Type-IV or Anderson disease. The mean age of presentation was 2.55 ± 2.29 years with male: female ratio of 7:5. The most common presentation was abdominal distension (n = 11). Voracious appetite and craving for food on waking-up were complained in 9 of these children. One asymptomatic child with normal growth curves was referred only because of enlarged liver found on routine checkup. Doll-like rounded facies, hepatomegaly, failure to thrive and hypotonia were noted in 11, 10, 7 and 3 children respectively. The patient with Type-Ib GSD had features of recurrent skin infections and mucosal ulcers. The subjects with Anderson disease presented with features of decompensated chronic liver disease. Complication of GSD like seizure and clavicular fracture from osteoporosis were separately present in 2 cases. All cases of GSD Type-I showed fasting hypoglycemia (< 54 mg/dL) and hypertriglyceridemia (≥ 125 mg/dL). However, hyperuricemia (> 5 mg/dL) was documented in 5 children only. Upper GI endoscopy done in both cases of Anderson disease revealed grade-II oesophageal varix.

GSD should be suspected in a child with failure to thrive associated with moderate to massive un-explained hepatomegaly. Typical doll-like face may not be always present as we have found in this series. Any case of asymptomatic hepatomegaly should also be screened. Case reports describing an association between GSD and RTA Type-II have been described but death attributing to the renal condition which occurred in one of these cases is quite uncommon.¹³

Among 10 cases of galactosemia, 5 were neonates with low birth weight as well as small for gestational age. Two cases presented beyond neonatal period, one at

6 weeks and the other at 8 weeks. All presented with jaundice or neonatal/infantile cholestasis. Five cases had sepsis and organisms isolated in blood culture were *Pseudomonas aeruginosa* (n = 2), *Citrobacter* (n = 1), *Enterobacter* (n = 1) and *Klebsiella pneumoniae* (n = 1). This is in contrast to Western studies where *Escherichia coli* is the commonest aetiology of neonatal sepsis in galactosemia. One neonate had bilateral cataract and the enzyme deficient in that case was galactokinase.^{14,15} Reduced levels of galactose-1-phosphatase uridyl transferase were documented in 6 babies and UDP galactose epimerase deficiency in the rest 3. Since routine neonatal metabolic screening is not practiced in this region, whenever neonatal/infantile cholestasis is encountered, especially in the background of sepsis, urine should be screened for galactosemia.

Six patients in this study presented with NAFLD. The mean age of presentation was around pre-pubertal period (7.9 ± 1.4 years). Interestingly, all the children were from upper middle (n = 4) and upper (n = 2) socioeconomic strata of modified Kuppuswamy scale.¹⁶ Dietary intakes of calories were greater than 120% of recommended daily allowance in 4 children. All the subjects had hepatomegaly and elevated liver enzymes. Four patients were obese (body mass index [BMI] > 95th percentile), and rest 2 overweight (BMI > 85th percentile). Pre-hypertension and stage-I hypertension was present in 2 and one case each. Dyslipidemia either in the form of hypercholesterolemia (≥ 200 mg/dL) and or hypertriglyceridemia (≥ 125 mg/dL) was documented in all. In 3 cases, fasting blood sugar level was high (> 126 mg/dL). Altered echotexture and fatty liver in abdominal USG was present universally.

In view of the epidemic obesity in childhood in the affluent society and its consequences, early diagnosis of NAFLD is crucial.¹⁷ Since noninvasive tests like serum transaminases and abdominal imaging are indirect diagnostic pointers and simple lifestyle modifications can lead to dramatic improvement, it is of utmost necessity to be aware of this entity.¹⁸ Though our understanding of NAFLD in terms of epidemiology and risk factors has improved considerably but significantly more investigation is required to unravel its pathophysiology and identify novel therapeutic targets.¹⁹

Non-neuronopathic form of Gaucher disease commonly manifests in childhood and affects many ethnic groups, as found in this series.²⁰ Of the 3 cases of Gaucher disease detected, 2 were of Type-I (non-neuronopathic) and one of Type-II (neuronopathic) types. All of them presented within the first 2 years of life (range 7 – 17 months). All of the cases had splenohepatomegaly, pallor and delayed developmental milestones. The child with neuronopathic form had optic atrophy and characteristic ophthalmoplegia (oculogyric crisis). With specific treatment, all clinical and biological symptoms

dramatically improved but some specific organic damages were irreversible. The patients were referred to higher centres for enzyme replacement therapy.

MPS was diagnosed in 2 children, both being males. The cases presented with developmental delay, failure to thrive, dysmorphic face, large head, hepatosplenomegaly and clear cornea. In addition to liver function test report suggestive of chronic liver disease and presence of urinary mucopolysaccharides, characteristic skeletal survey X-ray revealed dysostosis multiplex. Both of them were managed conservatively and referred to higher centres.

The initial presenting features of the five-months old female child with familial hyperlipoproteinemia Type-I was recurrent cough and cold, excessive vomiting, hepatomegaly and whitish plaque over face and arm. Fundoscopic examination showed lipemia retinalis. Lipid profile was grossly deranged with hypertriglyceridemia (1855 mg/dL) and hypercholesterolemia (280 mg/dL). There was fasting hyperglycemia (188 mg/dL) and elevated pancreatic enzymes (serum amylase 350 IU/L, serum lipase 216 IU/L). Both parents were also hyperlipidemic. Dietary fat restriction with medium chain triglyceride supplementation reversed all biochemical parameters and normalised the growth curves.

CONCLUSION

The frequency of diagnosis non-viral chronic liver damage, especially metabolic liver disease in children is increasing in recent years, probably because of technical improvements. High index of suspicion, early detection and screening, dietary modification and cost effective drugs along with good compliance are sufficient to treat and even prevent evolution of most causes of the MLDs in India. Timely picking-up of asymptomatic potential cases and genetic counselling of parents describing the mode of inheritance of the disease before pregnancy and early detection of cases by chorionic villus sampling or amniocentesis can prevent the rise in disease prevalence.

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