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Clinical profile of children with metabolic liver diseases presenting in a tertiary care hospital of Eastern India

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ABSTRACT

Background: Metabolic liver diseases (MLDs) in children can present with a wide range of clinical features. **Aims and Objectives:** This study aims to increase the high index of suspicion among physicians and awareness among caregivers regarding early diagnosis of MLD. **Materials and Methods:** This hospital-based prospective observational study has been conducted in the Paediatric Outpatient Department and Inpatient Department of RG Kar Medical College, Kolkata, over 2 years from 2021 to 2023. A total of 47 children aged up to 12 years were diagnosed as various MLDs who fulfilled inclusion and exclusion criteria were included in the study. Template was generated and analysis was done on SPSS software. **Results:** The study sample was 47 children with MLDs. Mean age was 4.21 ± 3.81 years. Males: female ratio was approximately 2.35:1. History of consanguinity among parents was present in 23.40% cases which affirmed the autosomal recessive mode of inheritance in most of the MLD. History of sibling deaths was there in 10 cases. The most common symptom was yellowish discoloration 21 (44.68%) followed by abdominal distension 12 (25.53%). There were diverse modes of presentations. The most common presentations were hepatomegaly 47 (100%) and splenomegaly 30 (63.83%). Of 47 MLDs, Wilson disease cases were maximum (27.66%) followed by glycogen storage disease (23.40%). **Conclusion:** High index of suspicion should be prevalent among physicians for early diagnosis of cases to reduce disease mortality and morbidity.

Key words: Galactosemia; Jaundice; Metabolic liver disease; Wilson disease

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INTRODUCTION

In this era of modern medicine, metabolic liver diseases (MLDs) are no longer any unfamiliar term. For the past three decades, MLDs have emerged to be an important cause of hepatobiliary diseases and chronic liver diseases. The liver being the major organ for metabolism gets affected primarily or secondarily. Any form of liver disease in children should evoke the possibility for MLD.

Their average incidence of metabolic liver disease in children is 1 in 1,00,000. However, due to huge number of enzymatic derangements, they are collectively common with overall incidence of 1 in 800 to 1 in 2500. They are one of the major contributors to chronic diseases in childhood.[1]

Formation of abnormal products in propionic aciduria formed because of accumulated Propionyl coA, participating in reactions normally using acetyl coA.[2]

Frequently manifested symptoms which suggest that inborn errors of metabolism may fall into several categories including hypoxia, seizures, lethargy, vomiting, poor feeding, and other changes that may often cause death if not promptly intervened.[3]

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MLD can present with wide varieties of clinical features starting with mere increased appetite to fulminant liver failure and death. It is not curable, but definitely its progress is preventable with simple dietary modifications and some essential drugs. Hence, approach to the child should be done starting from meticulous history to extensive clinical examination because even a family history of neonatal deaths can be due to MLD and consanguinity increase the risk of autosomal recessive disorders.

Proper diagnosis requires the use of biochemical markers, and the diagnosed cases may require lifelong therapy, so it imposes a substantial burden on the patient's family which includes the cost if diagnosis and treatment.[4]

Aims and objectives

This study aims to increase the high index of suspicion among physicians and awareness among caregivers regarding early diagnosis of MLD.

MATERIALS AND METHODS

Study design

This is a hospital-based prospective observational study. This study was conducted in the Paediatric Outpatient Department and Inpatient Department of RG Kar Medical College, Kolkata, over 2 years from 2021 to 2023 after acceptance of the synopsis.

This study was conducted among children aged up to 12 years who were diagnosed as various MLDs who fulfilled inclusion and exclusion criteria attending the Paediatric Outpatient Department and Inpatient Department of RG Kar Medical College, Kolkata.

Study population

Final sample size was 47 children aged up to 12 years, who were diagnosed as various MLDs.

Inclusion criteria

Children between 1 month and 12 years attending the Paediatric Outpatient Department and Inpatient Department of RG Kar Medical College, Kolkata, and cases with diagnostic hallmarks of MLD were included in the study.

Exclusion criteria

Exclusion criteria were hepatic infections including viral hepatitis and extra-hepatic portal hypertension.

Tools used for data collection

All A pre-structured and tested pro forma was used to record the detailed clinical history, family history, clinical features, and complications.

Data collection and processing

The cases were mostly referred from other districts. Initial screening criteria were symptoms/signs of any form of liver disease. Specific diagnosis and management were done for all patients.

Statistical analysis

Data were analyzed using SPSS V21 for Windows. Categorical variables are expressed as frequency and percentages.

Ethical clearance

The study was conducted only after obtaining written approval from the Institutional Ethics Committee of RG Kar Medical College, Kolkata (RGKMC/EC/042, January 2021). Written informed consent was taken from logical representative of every study patient.

RESULTS

The study sample was 47 children with MLDs. Mean age was 4.21±3.81 years. Male: female ratio was approximately 2.35:1.

History of consanguinity among parents was present in 23.40% cases which affirmed the autosomal recessive mode of inheritance in most of the MLD. History of sibling deaths was there in 10 cases (Table 1).

The most common symptom was yellowish discoloration 21 (44.68%) followed by abdominal distension 12 (25.53%), voracious appetite 4 (8.51%), and pain abdomen 3 (6.38%) (Table 2).

There were diverse modes of presentations. The most common presentations were hepatomegaly 47 (100%), splenomegaly 30 (63.83%), short stature and jaundice 25 (53.19%) each, failure to thrive 18 (38.30%), ascites 8 (17.02%), extrapyramidal signs, dystonia, tremor, athetosis, and obesity 6 (12.77%), and developmental delay 2 (4.26%). Diagnosis was done after a thorough history clinical examination and laboratory investigations (Table 3).

Of 47 MLDs, Wilson disease (WD) cases were maximum (27.66%) followed by glycogen storage disease (GSD) (23.40%). Galactosemia was most common in neonates. Non-alcoholic fatty liver diseases (NAFLDs) were also of significant prevalence (Table 4).

Characteristic facies were found in WD, GSD, and mucopolysaccharidosis (Table 5).

Approximately 30% cases presented with various eye changes. Complicated cataracts were found in WD and galactosemia. Kayser–Fleischer rings (K-F rings)

Table 1: Consanguinity among parents and sibling deaths – percentage distribution

Family history	Present	Absent	Total
Consanguinity No. (%)	11 (23.40)	36 (76.60)	47 (100)
Sibling deaths No. (%)	10 (21.28)	37 (78.72)	

Table 2: Presenting symptoms of MLDs

Symptoms	No (%)
Yellowish discoloration	21 (44.68)
Abdominal distension	12 (25.53)
Voracious appetite	4 (8.51)
Pain abdomen	3 (6.38)
Hematuria	1 (2.13)
Excessive vomiting	1 (2.13)
Intractable pruritus	1 (2.13)

Table 3: Presenting signs of MLDs

Signs	No (%)
Hepatomegaly	47 (100)
Splenomegaly	30 (63.83)
Short stature (height≤5th centile)	25 (53.19)
Jaundice	25 (53.19)
Failure to thrive	18 (38.30)
Ascites	8 (17.02)
Extrapyramidal signs, dystonia, tremor, athetosis	6 (12.77)
Obesity (Body mass index >30 kg/m^2)	6 (12.77)
Developmental delay	2 (4.26)

Table 4: Percentage distribution of MLDs

Provisional diagnosis	No (%)
Wilson disease	13 (27.66)
Glycogen storage disease	11 (23.40)
Galactosemia	10 (21.28)
Non-alcoholic fatty liver disease	6 (12.77)
Gaucher disease	3 (6.38)
Mucopolysaccharidosis	2 (4.26)
Familial hyperlipoproteinemia Type 1	1 (2.13)
Progressive familial intrahepatic cholestasis	1 (2.13)
Total	47 (100)

Table 5: Characteristic facial changes among children with MLDs

Diseases	Facial changes
Wilson disease with neurologic manifestations	Expressionless masked face, persistent protruded tongue, Drooling of saliva
Glycogen storage disease	Doll-like rounded face
Mucopolysaccharidosis	Large head, large tongue, hypertelorism

were seen in all cases of neurologic WD with slit lamp biomicroscopy, in some of them even with naked eyes (Figures 1 and 2). Direct ophthalmoscopy revealed optic atrophy in Gaucher disease and lipemia retinalis in familial hyperlipoproteinemia type I (Table 6).

Table 6: Characteristic eye findings among children with MLDs

Diseases	Eye findings
Wilson disease with neurologic manifestations	K-F ring, sunflower cataract
Galactosemia	Cataract
Gaucher disease	Ophthalmoplegia, Optic atrophy, Oculogyric crisis
Familial hyperlipoproteinemia type I	Lipemia retinalis

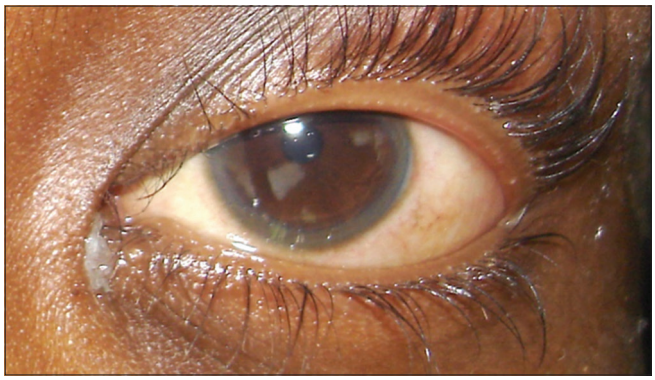

Figure 1: KF ring

Figure 2: Complicated cataract in Wilson disease

DISCUSSION

Majority of cases (39.22%) were below 2 years, mostly having galactosemia and GSD. The next age group with the highest frequency of cases (31.37%) was between 6 and 10 years and WD was predominant in this group.

WD constitutes the largest number of cases (27.66%) closely followed by GSD (23.40%), galactosemia (21.28%), and NAFLDs (12.77%). This is in contrast to North Indian studies[5] where Alpha-1-antitrypsin deficiency comes second to WD while GSD and galactosemia cases were much less. Galactosemia was the most common MLD in

neonates in our study which was also found in a combined study from 8 tertiary care centers across India.[6] Jaundice (53.19%) and progressive abdominal distension (25.53%) were the main concern among parents. Large percentage of failure to thrive and short stature were obvious outcomes of chronic liver diseases.[7]

The study reflects the huge burden of WD among all liver diseases. WD has an estimated occurrence of 1 in 500,000–1 in 100,000 in Western countries.[8] However, in Southeast Asia, the prevalence is much higher (approximately 1 in 30,000–50,000) and is the leading causes of chronic liver disease in Indian children.[9] Among 13 cases, 6 presented with features of only liver disease such as jaundice, ascites, prolonged prothrombin time, hepatomegaly, and splenomegaly. Six patients presented with neurological manifestations along with liver disease or past history of jaundice. 1 case had jaundice with hemolysis evident by hematuria. Hence, about 50% of WD cases presented with liver diseases similar to a study in Italy by Giacchino et al.[10] Western literature has mentioned that neurologic features of Wilson's disease appear after 1st decade[11] but we found cases well within 1st decade. The features were deterioration of school performances, regression of milestones, slurring of speech and later on dystonia, drooling of saliva, and involuntary movements like tremor and athetosis (Figure 3). All neurologic cases had KF ring and 1 patient had complicated sunflower cataract from copper deposition in lens.

GSD was next to WD in frequency. Among 11 cases, 7 were Type Ia or Von Gierke Disease, 1 Type IB and 3 Type IV or Anderson's disease. Majority of them presented with hepatomegaly, failure to thrive, hypotonia, and doll-like rounded face (Figure 4). Voracious appetite, craving for food on waking up, and diarrhea were present in 9 cases. Type Ib in addition had history of recurrent skin infections and mucosal ulcers. Type IV cases presented with features of chronic liver disease, i.e., hepatosplenomegaly and jaundice. One asymptomatic child with normal growth curves was referred only because of hepatomegaly found on routine checkup. On workup, it came out as Von Gierke disease. Two cases had seizure and clavicular fracture, respectively, due to osteoporosis complicating GSD. One Type I case who was readmitted with respiratory distress and acidosis later died probable due to renal tubular acidosis leading to renal failure, though uncommon but can occur in GSD.[12]

Among 10 cases of galactosemia, 7 were neonates with low birth weight and 1 neonate with very low birth weight. Remaining 2 cases were presented to us beyond the neonatal period. All cases presented with jaundice or neonatal cholestasis and 5 of them had features of neonatal sepsis.

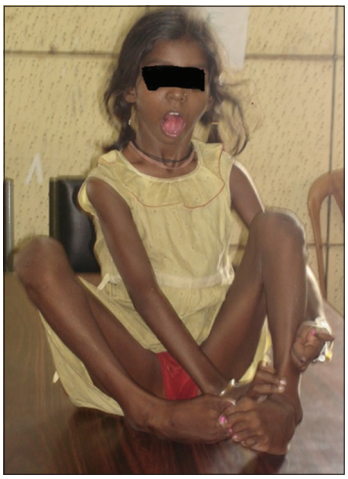

Figure 3: Dystonia in Wilson disease

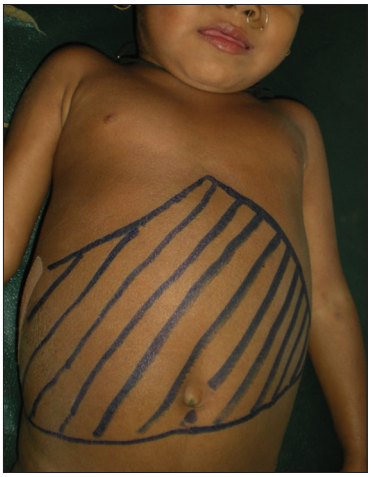

Figure 4: Massive hepatomegaly in Glycogen storage disease

Complications such as congenital cataracts were found in 1 case, seizure in 2 cases, and necrotizing ulcer of foot in 1 case. Neonatal sepsis by *Escherichia coli* is common in galactosemia.[13,14] In contrast to that, among our 5 cases of neonatal sepsis, the organisms found were *Pseudomonas aeruginosa* in 2 cases and *Citrobacter*, *Enterobacter*, *Klebsiella pneumoniae* 1 in each of rest 3 cases.

NAFLD is now a rising problem. Six patients of NAFLD were all from affluent families. Their mean age was prepubertal 6.33±1.03. Four patients were obese (body mass index >95th percentile) and rest 2 overweight (BMI >85th percentile). Pre-hypertension and stage-I hyptertension were present in 2 cases, respectively. All cases had hepatomegaly.

Three cases of Gaucher disease were detected. All of them presented with splenohepatomegaly, pallor, ophthalmoplegia, and delayed developmental milestones. One child also had optic atrophy. Two of them were previously diagnosed clinically with hemolytic anemia and

were transfused. Of the three cases, two were of Type-I (non-neuronopathic) and one of Type-II (neuronopathic) Gaucher disease.

Two mucopolysaccharidosis cases presented with growth failure, delayed development, dysmorphic face, macrocephaly, hepatosplenomegaly, and clear cornea. Clinical diagnosis in both cases was most likely Hunter disease.

A 5-month-old female child was referred with a history of irritability, recurrent cough and cold, failure to thrive, excessive vomiting, whitish plaque over the face and arm, and hepatomegaly. The white lesions were found to be eruptive xanthoma. Fundoscopic examination showed lipemia retinalis. Possibility of lipid metabolism disorder was considered as both parents were hyperlipidemic. Serology proved the case to be familial hyperlipoproteinemia type I. Studies have shown that its manifestations are common during infancy.[15]

Another female child with past history of neonatal sepsis and exchange transfusion presented with recurrent jaundice, ascites, intractable pruritus, failure to thrive, hepatosplenomegaly, and palmar erythema. Upper gastrointestinal endoscopy revealed Grade I esophageal varix. Apparently, it was like extrahepatic portal hypertension but the recurrent jaundice and intractable pruritus could not be explained. Hence, liver biopsy was done which showed intracanalicular bile stasis and mild bile duct proliferation. In addition, there was persistently raised gamma-glutamyl transpeptidase. Hence, considering all parameters, the case was diagnosed as progressive familial intrahepatic cholestasis, most probably Type 3 as the γ-GT was raised. Although type 3 manifests in early adulthood,[16,17] our case was only 6 years of age.

Limitations of the study

In the current study, the size of the sample is rather small to declare a generalized recommendation, further, a multicentric study with adequate follow-up may improve the sensitivity and specificity.

CONCLUSION

Advances in diagnostic approach have contributed to the increased incidence of MLDs in children for the last few years. High index of suspicion should be prevalent among physicians for early diagnosis of cases. Early screening along with timely proper management can definitely reduce the mortality and morbidity from MLD.

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ETHICAL APPROVAL

The study was approved by the institutional ethics committee.

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Authors Contribution:
AR- Involved in the diagnosis and management of the cases. **SM-** Did the literature search. **KKP and KPM-** Help in writing manuscript.

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