REVIEW ARTICLE

Metabolic Liver Diseases Presenting as Acute Liver Failure in Children

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Context*:** Suspecting metabolic liver disease in an infant or young child with acute liver failure, and a protocol-based workup for diagnosis is the need of the hour. ***Evidence acquisition: Data over the last 15 years was searched through Pubmed using the keywords "Metabolic liver disease" and "Acute liver failure" with emphasis on Indian perspective. Those published in English language where full text was retrievable were included for this review. ***Results:*** Metabolic liver diseases account for 13-43% cases of acute liver failure in infants and young children. Etiology remains indeterminate in very few cases of liver failure in studies where metabolic liver diseases were recognized in large proportion. Galactosemia, tyrosinemia and mitochondrial disorders in young children and Wilson's disease in older children are commonly implicated. A high index of suspicion for metabolic liver diseases should be kept when there is strong family history of consanguinity, recurrent abortions or sibling deaths; and history of recurrent diarrhea, vomiting, failure to thrive or developmental delay. Simple dietary modifications and/or specific management can be life-saving if instituted promptly. ***Conclusion:*** A high index of suspicion in presence of red flag symptoms and signs, and a protocol-based approach helps in timely diagnosis and prompt administration of life-saving therapy.

Keywords: *Acute liver failure, Etiology, Infants, Liver Transplantation.*

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Inborn errors of metabolism, where hepatomegaly and/or abnormal liver functions form part of the clinical disease, are collectively referred to as Metabolic liver diseases (MLD). MLD can have varied presentations in infants and children, most common of them being: (*i*) organomegaly, (*ii*) encephalopathy due to hyperammonemia and/or primary lactic acidemia, (*iii*) pediatric acute liver failure (ALF), (*iv*) cirrhosis with or without portal hypertension, and (*v*) cholestatic liver disease. A high index of suspicion for MLD is important as urgent intervention such as dietary manipulation or disease-specific treatment may be life-saving. The outcome of patients undergoing liver transplantation for MLD has improved considerably over the last decade. Moreover, it is important to establish the correct diagnosis, so that appropriate genetic counselling can be offered to the family. MLD merit special attention in differential diagnosis of pediatric ALF, especially in infants and young children in whom they constitute 13-43% of all cases **(*Web Table* I)** [1-9].

The Pediatric ALF study group definition can be used to define acute liver failure in infants and children [6]. The group enlists criteria for defining ALF as follows: (*i*) children with no known evidence of chronic liver disease (CLD), (*ii*) biochemical evidence of acute liver injury, and (iii) hepatic-based coagulopathy defined as International normalized ratio (INR) ≥1.5 not corrected by vitamin K in the presence of clinical hepatic encephalopathy or INR ≥2 regardless of the presence or absence of clinical hepatic encephalopathy. Neonatal liver failure is defined as "failure of the synthetic function of liver within 4 weeks of birth" [10]. Presence of encephalopathy is not mandatory for defining acute liver failure in infants as it is often very difficult to recognize. Moreover, encephalopathy may be a very late event in the course of the disease [1,5]. We have previously reported that average jaundice to encephalopathy interval is significantly higher in pediatric ALF due to MLD group *vis-à-vis* other etiologies [1]. Another important difference is that complete absence of evidence of CLD cannot be kept as prerequisite, especially when the etiology is a suspected MLD [4]. MLD patients may have variable degrees of liver damage before clinical presentation, and overt signs and stigmata of chronic liver disease may be present.

METABOLIC CAUSES OF ACUTE LIVER FAILURE

MLD are an important causes of pediatric ALF, especially in neonates, infants and young children. MLD account for 13-43% of acute liver failure in younger children, while accounting for only 5-20% of ALF in older children [1-9] (***Web Table* I**). Studies which focus on infants and young children have higher prevalence of MLD as compared to the studies which include older children. The proportion of cases with indeterminate etiology are higher (38-53%)[4-6] in studies, where the proportion of MLD cases is lower (13-19%). On the other

hand, the studies with higher prevalence (33-43%) of MLD among pediatric ALF [1,3,7] had much smaller proportion (13-18%) of cases remaining indeterminate. Narkewicz, *et al*. [11] retrospectively analyzed the workup of children labelled as indeterminate in pediatric ALF study group, and found that 54% of these children had not been screened for some common metabolic disorders, before assigning them as indeterminate. In an earlier Indian study, 4 children among 67 with fulminant liver failure were reported to be non A, non E, but MLD was not reported [12]. However, this series included only one infant, and the definition used for ALF was different. With advent of better diagnostic protocols, MLDs are more frequently diagnosed now [1].

Some of the authors have earlier listed neonatal hemochromatosis as a MLD. Being a gestation-associated alloimmune disorder, it has now been excluded from the list of MLDs. Galactosemia, tyrosinemia, mitochondriopathies and fatty acid oxidation defect (FAOD) are the commonest metabolic diseases presenting as ALF in infants. Wilson's disease is the commonest MLD presenting as ALF among older children, others being mitochondriopathies, FAOD and urea cycle defects.

PATHOPHYSIOLOGY

In disorders such as galactosemia, tyrosinemia and Urea cycle defects, the pathogenesis of MLD can be attributed to a defect in the intermediary metabolic pathway leading to the accumulation of toxic metabolites (formed in one of the preceding steps) which leads to liver failure. These conditions present after a symptom-free interval before clinical signs of 'intoxication' appear. Acute attacks may be preceded by catabolic states, fever, intercurrent illnesses and specific food intake. Most of these disorders are treatable and require emergency removal of the toxin by using special diets, extracorporeal procedures, drugs or vitamins [13]. Another pathogenetic mechanism is an energy deficiency state. The mitochondrial energy defects encompass the congenital lactic acidemias, respiratory chain disorders, pyruvate oxidation defects and FAOD. Cytoplasmic energy defects include disorders of glycolysis, glycogen metabolism, gluconeogenesis and the pentose phosphate pathways. The metabolic defects with energy-deficient states present early and can even have prenatal onset. In lysosomal disorders (Wolman disease and cholesteryl ester storage disorder), peroxisomal disorders (Zellweger syndrome) and congenital defect of glycosylation, liver failure occurs due to involvement of cellular organelles.

SUSPECTING MLD AS CAUSE OF ALF

***Box* 1** enumerates the important points in history that should raise the suspicion of a metabolic disorder. Children with MLD presenting as ALF tend to be younger. A strong family history of consanguinity, recurrent abortions, sibling deaths and previously affected children are strong pointers to the possible etiology of MLD. History of recurrent diarrhea and vomiting, failure to thrive and developmental delay are other indicators suggesting MLD [1,3]. Patients with MLD tend to have a longer jaundice to encephalopathy interval. Neurological involvement in form of hypotonia, myopathy, seizures, ophthalmoplegia, psychomotor dysfunction or presence of multisystem involvement should raise the suspicion of a mitochondrial depletion syndrome [14].

A meticulous dietary history can help guide the clinician. Onset of liver dysfunction on milk feeds points towards diagnosis of galactosemia, whereas onset of symptoms after introduction of complementary foods (containing fructose or sucrose) points towards hereditary fructose intolerance that can also present in those receiving fructose in form of honey, syrups or formula milk containing fructose or sorbitol. Aversion to sugars and sweet foods in older children also suggests this disorder. Some MLD have their typical age of presentation and age-appropriate differential diagnosis should be considered **(*Table* I).** Encephalopathy is difficult to diagnose in children and could be disproportionately more severe to the liver dysfunction in urea cycle defects and primary lactic acidemias. Developmental delay, cardiomyopathy, renal tubulopathy in a hypotonic child with convulsive disorder with or without treatment with valproic acid could be a setting for mitochondrial disorders.

BOX 1 CLINICAL POINTERS OF METABOLIC LIVER DISEASES

- Consanguinity, abortions and neonatal deaths
- SIDS and psychiatric illnesses
- Recurrence in times of catabolic stress (fever, exercise, prolonged fasting)
- Recurrent vomiting, diarrhea, failure to thrive , short stature, dysmorphic features, edema
- Seizures, early morning irritability, lethargy-hypoglycemic symptoms
- Developmental delay, hypotonia and seizures, cataract, unusual odours, rickets, and renal tubulopathy
- Jaundice, hepatosplenomegaly and hepatic failure, hypoglycemia, lactic acidemia, hyperammonemia and coagulopathy
- Relation to specific foods like aversion to sugars in HFI, dislike for proteins in urea cycle defects

SIDS: Sudden Infant Death Syndrome, HFI: Hereditary Fructose Intolerance.

Children with MLD have much higher bilirubin, more severe synthetic dysfunction, hypoglycemia and hyperammonemia as compared to those with ALF not related to MLD [1,3]. Children with MLD tend to have a much higher bilirubin, but lower transaminases, gamma-glutamyl transferases (GGT) and INR as compared to the viral causes of ALF [4].

APPROACH TO MLD PRESENTING AS ALF

The algorithmic diagnostic approach to an infant or young child with ALF and suspected MLD is depicted in ***Fig* 1**. For an older child, the etiological list includes only WD, HFI, mitochondrial defect and FAOD. Except WD, all others have been covered in the above mentioned algorithm. WD should be suspected in a patient with ALF who have KF ring on slit-lamp examination, Coombs negative hemolytic anemia, low serum uric acid levels (<2.5 mg/dL), low serum alkaline phosphatase (SAP) activity (SAP: bilirubin ratio <4) and increased AST:ALT ratios [15]. As per European Association for Study of Liver (EASL) guidelines, serum ceruloplasmin <10 mg/dL is contributory for definitive diagnosis of WD [16], but ceruloplasmin, being an acute phase reactant, can be falsely normal in children with acute liver failure. Hence, 24 hours urinary copper (>100 µg/day) and KF ring are important for diagnosis of WD in setting of ALF.

A careful history and examination should narrow down the differential diagnosis and establish the degree of liver dysfunction. The time of onset of the symptoms and the rapidity of progression can give a clue to diagnosis. First line metabolic screen should be done in all cases of pediatric ALF, that includes three consecutive samples of urinary non-glucose reducing substances, ketones, arterial blood gas analysis, and serum lactate, serum alpha-feto protein and blood ammonia levels. Non-glucose reducing substances in urine can be identified by testing for reducing substances in urine by Benedict test, and then demonstrating absence of glucose by dipstick method. If suspecting galactosemia, it should be ensured that the child was on galactose-containing diet when the urinary samples were examined. In liver failure, blood sugar may be low and lactate may be high due to advanced liver disease. On the basis of the metabolic screen, we can narrow down on the possible etiology of the MLD. The specific diagnostic tests for the common MLDs presenting as pediatric ALF is shown in ***Table* II**. It is important to remember that galactose-1-phosphate uridyl transferase (GALT) assay is not reliable if the child has received blood transfusion in the preceding three months. In such cases, it is advisable to continue the galactose free diet, till we can get reliable results of the GALT assay.

TABLE I CATEGORIZATION OF METABOLIC LIVER DISEASES BY AGE OF PRESENTATION

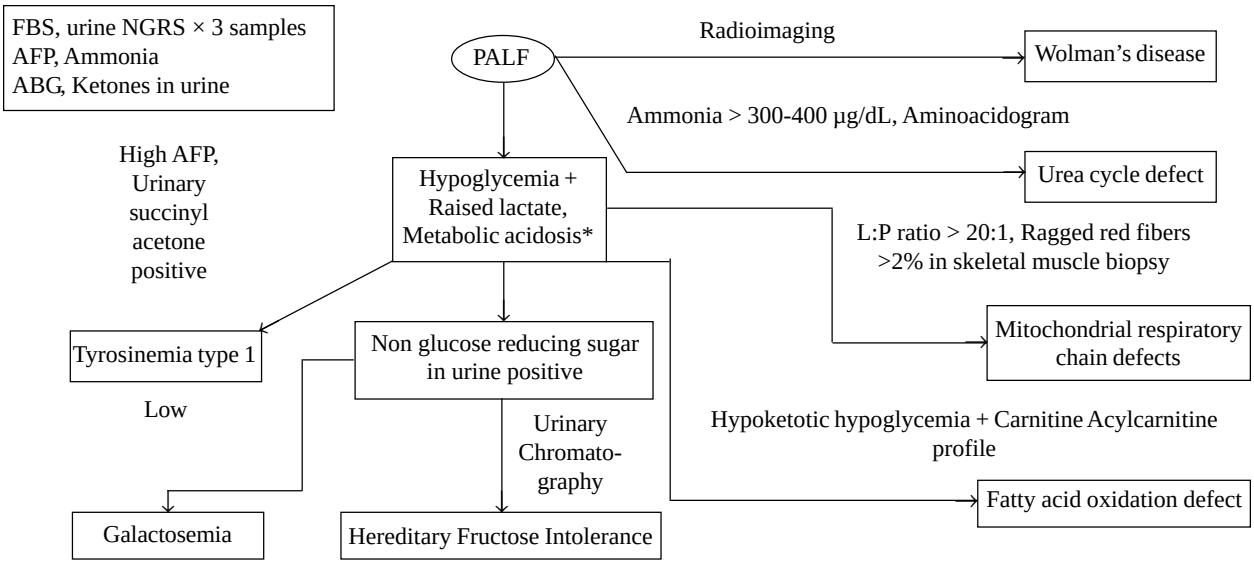
0-6 mo	Galactosemia, Tyrosinemia type 1, Mitochondrial cytopathy and Wolman's disease
6 mo - 3 y	Tyrosinemia type I, FAOD, Mitochondrial cytopathy, Galactosemia, HFI, UCD and CDG
Older children	Wilson's disease, FAOD, Mitochondrial Cytopathy, HFI, UCD and CDG

FAOD: Fatty acid oxidation defect, HFI: Hereditary fructose intolerance, UCD: Urea cycle defect, CDG: Congenital disorders of glycosylation.

MANAGEMENT

With improvement in supportive management, the outcome of pediatric ALF has improved considerably. Liver transplantation may be life-saving for children who fail to respond to conservative management. Whenever MLD is a strong possibility, all feeds should be withdrawn for 24-48 hours awaiting first line investigations. The dietary modifications can be modelled on the basis of differentials considered based on history and examination. Appropriate feeds can be introduced based on final diagnosis. The main aim of withholding feeds is to stop further accumulation of potentially toxic metabolites, but at the same time further catabolic breakdown of body stores should be avoided as it can worsen liver failure. Intravenous infusion of 10% dextrose with required electrolytes is appropriate for most cases. The exception is congenital lactic acidosis and mitochondrial disorders where a 5% dextrose-based solution should be used as high carbohydrate supply may exacerbate the lactic acidosis. Restriction of protein to 0.5 -1 g/kg/day (half in form of essential amino acids) is recommended for management of urea cycle defects. If FAOD has been excluded, then intralipid should be added at 1g/kg/day to boost energy intake.

Supportive management for pediatric ALF includes glucose for maintaining normoglycemia, correction of coagulopathy in case of bleeding, antibiotics for sepsis, and maintenance of fluid and electrolyte balance. Although most data is from cirrhotics, but among anti-ammonia measures, polyethylene glycol 3350 was more effective than lactulose with resolution of encephalopathy in 90% and 50% cases, respectively [17]. A systemic review states that there is insufficient evidence to support or refute the use of non-absorbable disaccharides (Lactulose and Lactitol) for hepatic encephalopathy. Antibiotics (Rifaximin and Neomycin) were superior to non-absorbable disaccharides in improving encephalopathy, but it is unclear whether this difference is clinically



*PALF: Pediatric acute liver failure, MLD: Metabolic liver disease, FBS: Fasting blood sugar, NGRS : Non glucose reducing sugar, AFP: Alphafeto protein , L: P = Lactate: Pyruvate, ABG: Arterial blood gases, GALT : Galactose-1-PO4 Uridyltransferase. *Hypoglycemia/acidosis/ raised lactate may occur in ALF with non MLD also due to liver injury/ sepsis/ hypotension.*

FIG. 1 *Approach to a child with Acute liver failure and suspected Meabolic liver disease.*

important [18]. Algorithmic approach of management of hepatic encephalopathy also mentions usage of lactulose and rifaximin [19]. In a report from US ALF study group, lactulose increased survival time but had no effect on overall outcome [20]. Sodium benzoate has been encouraged keeping in view it is as effective as lactulose but 10 times less expensive [21]. Sodium Benzoate is recommended for use in HE due to urea cycle defects [22]. Definitive management for common MLD is depicted in ***Table* II**.

LIVER ASSIST DEVICES

The role of the support device (artificial or bio-artificial) in ALF has an objective to either support the patient until the native liver recovers, or to bridge the patient to liver transplantation. Artificial support therapies (plasma exchange, hemodialysis and Molecular Adsorbents Recirculating System) provide detoxification support without the use of cellular material. Molecular Adsorbents Recirculating System has been reported to be more beneficial than combined plasma exchange and hemodialysis [24]. In another study, it was found to be beneficial in decreasing ammonia levels in adolescents but there were no benefits in infants in whom the device was poorly tolerated [25]. There is scarcity of data regarding the role of liver assist devices in management of MLD. Intermittent and continuous hemodialysis are effective modalities for the acute management of urea cycle defects and organic acidemia [26]. The pre-procedure physiological condition of the patient is the main determinant of outcome [27]. Moreover, most of the artificial liver assist devices help during hepatic encephalopathy but do not improve overall survival in ALF. Bio-artificial systems use cellular material to provide detoxification and liver's synthetic functions. A variety of such systems have been tested in non-randomized trials, but are not recommended outside clinical trials.

LIVER TRANSPLANTATION

The advent of successful liver transplantation has revolutionized management of children with MLD who fail to respond to conservative management. Galactosemia, HFI, tyrosinemia type 1 and urea cycle defects may not respond to medical therapy and dietary restrictions if diagnosed late, and in an emergency liver transplantation may prove to be life-saving. Although individually rare, when considered together, MLD represents approximately 15-25% of indications for pediatric liver transplantation [28]. MLD are the second most common indication for liver transplantation after biliary atresia [29]. UCD, alpha-1-antitrypsin deficiency, cystic fibrosis, WD and tyrosinemia type 1 are the common MLD requiring liver transplantation in children. Post-transplant survival for children with MLD is comparable to those with other diseases with a better graft survival than those with other

diseases [29]. A better outcome of liver transplantation in MLD could be attributed to the fact that many children with MLD underwent liver transplantation to correct an enzymatic defect, and did not have structural (parenchymal) liver disease.

Liver transplantation has been successfully done in many cases of tyrosinemia, galactosemia, mitochondriopathies and UCD presenting as ALF [28-30]. Liver transplantation is usually contraindicated in diseases with severe multisystemic involvement *e.g.* mitochondrial defect with severe neurological involvement/ cardiomyopathy. A rapid assessment of the severity of extrahepatic involvement in a child with mitochondriopathy and decompensating liver is mandatory, so as to take a decision about the usefulness of liver transplantation in such a case. Suitability of heterozygous parents as donors is another important issue to be resolved.

Although Wilson disease presenting with encephalopathy is invariably fatal and can be treated only by liver transplantation, the decision to list a child with this disorder without encephalopathy is very difficult [5,31]. Revised King's score for this disorder [31] had been previously shown to be efficacious in predicting the survival with native liver [31,32]. However, doubts have been raised recently over the ability of this score to predict mortality without liver transplantation [33]. Survival is difficult to predict and continued investigations for predictors of outcome in Wilson disease are necessary.

Hepatocyte transplantation is moderately successful for MLD presenting as ALF, as a bridge to liver transplantation [34]. Hepatocyte transplantation holds promise as an alternative to organ transplantation and numerous animal studies indicate that transplants of isolated liver cells can correct metabolic deficiencies of the liver. Stem cell based technology is a new biotechnology approach to treat patients with MLD. Adult liver stem cells can differentiate into hepatocyte like cells and can be infused in the recipient's liver to activate a missing metabolic function. The percentage of liver cell replacement considered as necessary to significantly

TABLE II CONFIRMATORY TESTS AND MANAGEMENT OF COMMON METABOLIC LIVER DISEASES

Disorder	*Confirmatory Test*	*Management*
Galactosemia	Galactose-1-PO4 Uridyl-transferase assay	Galactose-free diet
Hereditary Fructose Intolerance	Fructo-aldolase B assay in liver tissue * Urine chromatography to show fructose Mutational analysis	Fructose-free diet
Tyrosinemia type 1	Urinary succinylacetone phenylalanine diet **	NTBC* + Low tyrosine and
Urea Cycle Defect (UCD)	Plasma aminoacidogram to show the levels of citrulline and arginine based on which the type of UCD can be decidedOrotic acid estimation in urine to diagnose OTC**deficiency	Ammonia scavengers, protein free diet with essential amino acids supplementation
Fatty Acid Oxidation Defect	Carnitine - acyl carnitine profile	Avoid prolonged fasting Breastfeeding in MCAD MCT rich diet in VLCAD and LCHAD Carnitine in carnitine transporter deficiency Bezafibrate* in VLCAD
Respiratory chain disorder	Analysis of oxidative phosphorylation complexes I-IV from intact mitochondria isolated from fresh skeletal muscle* Oral Coenzyme Q for CoQ10 deficiency	Normocaloric and low carbohydrate diet Avoidance of certain drugs Carnitine in carnitine deficiency
Wilson Disease	24 hour urine copper KF ring Serum CeruloplasminSAP:Bilirubin ratio < 4 AST/ALT ratio > 4	Chelation therapy with D-Penicillamine started at 10 mg/kg/d and increased to 20 mg/kg/d, Zinc & Pyridoxine

*NTBC: 2-nitro-4-trifluoro-benzoyl-cyclohexane-1,3-dione, OTC: Ornithine transcarbamylase, MCAD: Medium chain Acyl-CoA Dehydrogenase, MCT: Medium Chain Triglyceride, VLCAD: Very long chain Acyl-CoA Dehydrogenase, LCHAD: Long chain 3-hydroxyacyl-CoA Dehydrogenase, CoQ10: Coenzyme Q 10, SAP: Serum alkaline phosphatase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, KF ring: Kayser Fleischer ring. *These tests and therapeutic options are not available in India; **OTC samples are being sent outside the country by Indian laboratories; *Low Tyrosine and Phenylalanine diet is being marketed in India but not manufactured.*

improve metabolic disorders is around 5% of the total liver mass, while 10% could normalize the function [35,36].

GENETIC COUNSELING

Parents who have a child with MLD must undergo genetic couseling. The probability of the next sibling being affected from the disease should be explained, and prenatal testing and counseling should be offered where available. The parents must be explained about the nature of the illness and risk of occurrence in future pregnancies. Prenatal diagnosis of tyrosinemia is possible by analysis of succinylacetone in amniotic fluid supernatant and by assay of fumaryl acetoacetate hydrolase in cultured amniotic fluid cells or chorionic villus material [37]. Similarly, a GALT assay can be planned early for the next child of parents who already have a child suffering from galactosemia.

CONCLUSION

Metabolic liver diseases account for 13-43% of cases of ALF in infants and young children. Many of these conditions are potentially curable with dietary modifications or medications if recognized early. A high index of suspicion in presence of red flag symptoms and signs is need of the hour. A protocol-based approach will identify the etiology in most of the patients. Liver transplantation has markedly improved the outcome of MLD in children.

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WEB TABLE I STUDIES EVALUATING PREVALENCE AND SPECTRUM OF METABOLIC LIVER DISEASES AMONG PATIENTS WITH PEDIATRIC ACUTE LIVER FAILURE

Study (Place) : Age (No.)	*Infants/Young children*	*Older children*
Alam, *et al.* [1] (India); 0-3 years (*n* = 40); > 3 years (*n* = 57)	MLD-13, 33% - Galactosemia: 4 - Tyrosinemia: 3 - HFI: 2 - UCD: 2 - Respiratory Chain defect: 1 - Gluconeogenetic defect: 1 Indeterminate- 4, 10%	MLD-6, 10% - Wilson's disease: 6 Indeterminate- 7, 12%
Rajanayagam, *et al*. [2](Australia); Infants (*n* = 24); >1 year (*n* = 30)	MLD-1, 4.1% - Mitochondriopathy:1 Indeterminate- 8, 33%	MLD-6, 20% - Wilson's disease:5 - Mitochondriopathy:1 Indeterminate- 9, 30%
Brett, *et al*. [3](Portugal); <2 years (*n* = 28);	MLD-12, 43% - Respiratory Chain Defect: 3 - Tyrosinemia: 2 - CDG: 2 - Galactosemia: 2 - UCD: 1 - FAOD: 1 - HFI: 1 Indeterminate- 5, 18%	NA
Sundaram, *et al*. PALF Study Group [4] (USA/UK/Canada); <3 months (*n* = 148);	MLD-28, 18.9% - Galactosemia: 12 - Respiratory Chain Defect: 5 - Tyrosinemia: 3 - Niemann Pick Type C: 3 - Mitochondriopathy: 3 - UCD: 2 Indeterminate- 56, 38%	NA
Dhawan, *et al*. [5] (UK); Neonates (*n* = 31); Older children (*n* = 100)	MLD- 4, 13% - Galactosemia - Tyrosinemia - Mitochondriopathy	MLD-18, 18%
PALF Study Group [6]; 0-3 years (*n* = 127); >3 years (*n* = 221)	MLD-23, 18% - Respiratory Chain defect: 7 - FAOD: 4 - Tyrosinemia: 4 - Galactosemia: 2 - Alpha-1 antitrypsin deficiency: 1 - HFI: 1- Niemann Pick C: 1- UCD: 1 Indeterminate- 68, 53%	MLD-13, 6% - Wilson's disease: 9 - Mitochondriopathy: 2 - UCD: 1 - Reye's Syndrome: 1 Indeterminate- 101, 46%
Durand, *et al*. [7](France); Infants (*n* = 80)	MLD-34, 42.5 % - Respiratory Chain Defects: 17 - Tyrosinemia: 2 - UCD: 2 - Galactosemia: 2 - HFI: 2 Indeterminate- 13, 16%	NA
Kaur, *et al*. [8](India); Children 0-18 years (*n* = 43)	NA	MLD-4, 9.2 % - Galactosemia: 4.6 % - Wilson's disease: 4.6% Indeterminate- 4, 9.3%
Lee, *et al*. [9](UK) 0-17 years (*n* = 97)	NA	MLD 15, 15.4 % - Mitochondriopathy: 4 - Tyrosinemia: 2 - Wilson's Disease: 2 - Other MLD: 7

MLD=Metabolic Liver Disease, HFI=Hereditary fructose intolerance, UCD=Urea cycle defect, CDG=Congenital disorders of glycosylation, FAOD=Fatty acid oxidation defect.