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Review Article

Metabolic liver disease in developing world with special reference to Indian children – A review

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ABSTRACT

Need and purpose of review: Metabolic liver diseases (MLD) are frequently missed and hence underreported. They are responsible for significant pediatric mortality. A fair number of these patients have a potential for favorable outcome with prompt detection and management; thus increasing the awareness regarding such disorders is important. We highlight the profile of commonly encountered pediatric MLDs and available diagnostic and therapeutic facilities in the developing countries through this review.
Methods: Articles published on pediatric metabolic liver diseases in India and other developing countries in the last 40 years were searched on PubMed and Google scholar using a defined selection criteria. Common and atypical presentation, diagnostic workup, treatment and outcome was specifically studied.
Results: Wilson disease followed by Galactosemia, Gaucher disease, Glycogen storage disorder and Organic acidemias are the commonest conditions reported from India. Alpha1 antitrypsin deficiency which is a common condition in West, seems to be rare in India. The mutational profile of Indian children in such disorders seems to vary between different parts of country and also differs from other parts of world. Definitive diagnosis is difficult on account of limited availability of genetic testing and unaffordability in most situations.
Conclusions: The phenotypic as well as the genotypic spectrum of MLD in our subcontinent seems to differ from the rest of the developed world. Setting up of a national registry for each of these problems would be important to understand the exact prevalence of such conditions.

1. Introduction

Metabolic diseases are the inherited single gene defects in the enzymatic pathways resulting in either deficiency of essential factors or accumulation of certain toxic metabolites/ substrates in body tissues resulting in organ dysfunction. They are characterized by early presentation, clinical heterogeneity, multisystem involvement and potential to progress to end stage organ damage. Hepatomegaly or deranged liver function is the usual presentation of such conditions affecting liver. Since these are genetically inherited, accurate diagnosis

Abbreviations: CBC, Complete blood count; SE, Serum electrolytes; VBG, Venous blood gas; PT, prothrombin time; aPTT, activated partial thromboplastin time; SGPT, Serum glutamic pyruvic transaminase; AG, Anion gap; RTA, Renal tubular acidosis.

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is important in not only managing the index cases but also for counseling in future pregnancies. A situation where more than one child in the consanguineous family is affected strongly suggests the diagnosis.[1] We aim to highlight the type, clinical, diagnostic and therapeutic profile of these disorders existing in India and the rest of the developing world sharing similar demographic and socioeconomic factors.

2. Methods

Articles published in last 40 years on pediatric metabolic liver disease in India and other developing countries were studied. Pubmed and Google scholar were used to identify common and atypical clinical presentations, available diagnostic and therapeutic modalities and the ultimate prognosis. Individual diseases, names of the developing countries and pediatric population were the key words used to search such conditions. Primary inherited pediatric metabolic diseases predominantly involving liver were included where as other congenital or acquired infective, inflammatory or neoplastic liver diseases were excluded. Both authors were involved in reviewing and selecting the reported cases as per the set selection criteria. Of the 120 articles reviewed, 77 articles were finally included in our review. In this review, isolated case reports unless unique in some way have not been referenced but studies reporting a case series or original articles have been quoted.

In India, 25,000 newborns are born with MLDs annually. These disorders account for 14% of childhood liver diseases in India.[2,3] They result in significant mortality and morbidity; accounting for 8% cases of fulminant hepatic failure and 24%–40 % cases of chronic liver disease.[3–6] Although a quarter of the children requiring liver transplantation have underlying metabolic liver diseases; only a minority of such cases are eventually referred for liver transplantation in our country compared to developed nations.[7] This is on account of poor awareness, delayed diagnosis, delayed referral or unaffordability. There is even scarce reporting from other developing nations; where metabolic liver diseases account for 10% of childhood liver disorders.[8–10]

Despite the non-specific nature of disease presentation; these conditions can be suspected based on age of onset; clinical picture & biochemical tests (Table 1). Galactosemia, organic acidemias, urea cycle defects & mitochondrial diseases typically manifest soon after birth; hereditary fructose intolerance & hereditary infantile tyrosinemia manifests beyond 6 months of life; glycogen storage disorders & lysosomal storage disorders manifest beyond infancy whereas Wilson disease typically presents in older children. MLDs can be categorized according to their predominant type of hepatic presentation which may give a clue to the specific etiology (Table 2). Following is the brief account of commonly encountered MLDs in the developing world.

2.1. *Galactosemia*

It results from genetic deficiencies in enzymes involved in galactose metabolism namely galactose-1-uridyl transferase (GALT) (commonest), galactokinase or uridyl diphosphogalactose-4-epimerase (least common) resulting in an inability to metabolize galactose. This condition accounts for 6–20% of MLDs in Indian children.[3,6] Exposure to milk feeds following birth results in tissue accumulation of galactose metabolites and organ dysfunction.[1] Classic variant has total enzyme deficiency or enzyme levels <10% of normal. These cases present acutely with vomiting, lethargy and diarrhea and over a period of time develop cataracts, hepatic manifestations such as cholestasis and cirrhosis, renal tubular dysfunction and ovarian failure. They are prone to gram negative & fungal sepsis on account of altered neutrophil function. Duarte variant has mild enzymatic deficiency and may present with neurodevelopmental delay, extrapyramidal signs and growth failure.[11–13] This condition may coexist with extrahepatic biliary atresia due to simultaneous involvement of GALT and inversin genes.[14] Ideally, this condition should be detected during neonatal screening with GALT assay. Non-adherence to routine neonatal screening frequently results in delayed diagnosis. Positive urine Benedict's test with presence of non glucose reducing sugar (galactose) is a typical finding. Diagnosis is possible by estimating galactose levels in blood and urine but can be affected by dietary intake. Hence, quantitative enzyme estimation is a preferred diagnostic test. Mutation testing and gene sequencing is available for prenatal detection and prognostication. In a study on 55 children with GALT deficiency, N314D (40%) was the commonest mutation and its combination with Duarte 2 allelic variant was associated with better prognosis.[11] In a South African study (17 cases; mean age at diagnosis 5.1 months); homozygous deletion of S135L was seen in black children while Q188R deletion was common in white children diagnosed with GALT deficiency.[15] Treatment involves complete elimination of galactose from diet including milk and milk products and galactose containing medications. Soy protein based (lactose free) formula should be used instead for feeding along with calcium and vitamin supplementation to maintain normal growth. Early and compliant therapy usually reverses most of the disease manifestations.[1]

2.2. *Hereditary fructose intolerance (HFI)*

Deficiency of fructose-1-phosphate aldolase disrupts fructose metabolism. It results in accumulation of fructose-1-phosphate in the liver, kidneys and small intestine which disrupts protein & ATP synthesis and results in organ dysfunction.[1] The condition is seen in 1 out of 20,000 live births per year worldwide but has been infrequently reported from India.[2] Clinical presentation described usually at the time of weaning includes intolerance to fruits with recurrent vomiting, diarrhea, hypoglycemia, cataracts, increased blood lactate, failure to thrive, renal tubular dysfunction, hepatomegaly, portal hypertension and cirrhosis in adolescent period.[16] Diagnosis is suggested by presence of positive urine non glucose reducing sugar (fructose). Fructose challenge test is tedious. Urine osazone test demonstrates characteristic needle shaped fructose crystals. Urine chromatography is available and confirms the diagnosis. Mutation analysis is not easily available in India. Although liver transplantation has been reported in treating this condition, dietary elimination of fructose is an effective therapy.[1]