Metabolic disorders presenting as liver disease

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Abstract

Many Inherited Metabolic Diseases (IMDs) have hepatic manifestations due to the highly metabolically active nature of the liver. IMDs are responsible for up to a third of acute liver failure in childhood. Manifestations include cholestatic jaundice, hepatomegaly and acute and chronic liver failure. It is important to consider and identify metabolic causes of liver disease early, particularly as some may present early for example with a self-limiting period of cholestasis before presenting in later childhood with irreversible disease, and in many early intervention improves outcomes.

This review highlights features in the history and presentation which should raise suspicion for an IMD, and the specialist metabolic investigations to consider when evaluating the child with liver disease. The review also discusses the clinical course and management of specific IMDs including glycogen storage disorders, congenital disorders of glycosylation, cholesterol ester storage disease, galactosaemia, neonatal haemochromatosis, hereditary tyrosinemia, fatty acid oxidations disorders, urea cycle defects, Niemann Pick C, Wilson disease, citrin deficiency and disorders of bile acid synthesis. The role of liver transplantation is discussed briefly.

Keywords cholestasis; hepatomegaly; inherited metabolic disease; jaundice; liver failure; liver transplant

Introduction

Inherited Metabolic Diseases (IMDs) are a group of over 600 disorders resulting from gene defects affecting pathways of intermediary metabolism. They result in either build-up of toxic or unwanted substances that interfere with organ function, or deficiency of needed products. The liver is essential to many metabolic pathways, playing a significant role in carbohydrate, lipid, protein and trace element metabolism. It is therefore unsurprising that many IMDs have hepatic manifestations. Whilst acute liver failure is rare, up to one third of acute liver failure in childhood is caused by IMDs with this proportion being highest in young infants. In early childhood IMDs are among the commonest causes of liver cirrhosis. Metabolic liver diseases are responsible for approximately 10–20% of liver transplants in children.

It is important to consider the possibility of underlying IMDs in a liver presentation as treatment is sometimes possible which can significantly reduce disability and mortality. For disorders like transaldolase deficiency, a disorder of the pentose phosphate pathway, and neonatal haemochromatosis (NH) early consideration of liver transplantation before further deterioration is advised. In addition diagnosis allows genetic counselling and facilitates prenatal diagnosis for future pregnancies. However it can be difficult to distinguish metabolic liver disease presentations from other causes of liver disease such as infection.

This article gives a structured approach to the evaluation of children with liver disease and discusses new treatment options in areas such as cholesterol ester storage disorder and congenital disorders of glycosylation. The second part will discuss individual IMDs presenting with liver failure, cholestasis and hepatomegaly.

History

It is important to take a detailed history. Many IMDs are autosomal recessive single gene disorders. Therefore a family history of consanguinity, recurrent miscarriages and infant or childhood deaths should increase the suspicion of underlying IMDs.

Antenatal history

An antenatal history of hydrops fetalis may be due to liver dysfunction in diseases such as lysosomal storage disorders (LSD), peroxisomal disorders, Smith Lemli Opitz (SLO) and congenital disorders of glycosylation (CDG). Maternal Hepatomegaly, Elevated Liver enzymes, Low Platelets (HELLP) syndrome may be associated with Long Chain Fatty Acid Oxidation Disorders (FAOD).

Neonatal history

Niemann Pick C (NPC), disorders of bile acid metabolism such as cerebrotendinous xanthomatosis (CTX) and citrin deficiency may present with a self-limiting neonatal cholestasis with subsequent presentation in later childhood or adulthood with irreversible complications which could be prevented with early intervention. Aminoacidopathies and FAODs can present neonatally with unexplained encephalopathy and liver dysfunction after a period of normalcy. They may also present later in infancy and childhood with episodes of worsening liver dysfunction with encephalopathy or hypoglycaemia associated with minor illnesses.

Introduction of new substrates

Development of jaundice following weaning onto fructose or sucrose containing foods may suggest Hereditary Fructose Intolerance (HFI).

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Clinical presentation

Most metabolic liver disease in infancy presents as part of a multisystem disorder with either cholestasis (jaundice, acholic stools and dark urine) or acute liver failure (hypoglycaemia, hypoalbuminemia, ascites, coagulopathy, encephalopathy and jaundice). A few metabolic disorders, such as NH, some CDG disorders such as *MPI*-CDG and Wilson disease, may present with predominantly hepatic presentations.

In older children presentations with features of chronic liver disease and cirrhosis (poor weight gain, hepatomegaly, ascites, gastroesophageal bleeding secondary to varices) are more common. Hepatocellular carcinoma may be a late complication in hereditary tyrosinemia (HT1) and glycogen storage diseases (GSD) types I and III.

Patients may present with a Reye-like encephalopathy and hepatic dysfunction without jaundice. This presentation always warrants investigation for an underlying metabolic disorder as FAOD and aminoacidopathies are likely in a significant number of patients.

Hepatomegaly may be caused by an increase in size of hepatocytes due to storage of substances such as glycogen in GSD. Hepatomegaly may also result from inflammation, cirrhosis or tumours as seen in HT1 and citrin deficiency, or from biliary obstruction. Hepatomegaly may be intermittently seen during metabolic decompensation in urea cycle disorders (UCD), organic acidurias (OA) and FAOD.

Patients may present with symptoms due to malabsorption of fat and fat soluble vitamins with coagulopathy due to vitamin K deficiency, or rickets due to vitamin D deficiency in association with hepatomegaly (e.g. in Peroxisomal disorders (Zellweger spectrum) and bile acid synthesis disorders).

Table 1 lists clinical features indicating specific metabolic disorders.

Investigations

Liver function tests

Standard liver investigations including measures of liver synthetic function (albumin and prothrombin time) can be useful in establishing type and extent of liver disease. Transaminases are raised in hepatocellular damage with alanine transaminase (ALT) being more specific for the liver but aspartate transaminase (AST) rising earlier. Gamma glutamyl transferase (GGT) and alkaline phosphatase (ALP) tend to be raised (proportional to transaminases) in cholestasis suggesting intrahepatic cholestasis syndromes. Conjugated bilirubin can be raised in both hepatocellular damage and cholestasis. Total and conjugated bilirubin can be raised in conditions such as galactosemia and HFI. NH should be suspected in the context of severe liver dysfunction but low transaminases and raised ferritin. Cholestasis with raised conjugated bilirubin, raised ALT and raised ALP but normal GGT may be seen in disorders of bile acid synthesis and progressive familial intrahepatic cholestasis (PFIC).

More specific investigations may be directed by clinical features and age of presentation. Table 2 lists specialist tests including enzyme and molecular testing to be considered when investigating metabolic causes of liver disease. Testing and interpretation should be carried out in collaboration with the metabolic clinician and specialist biochemist as abnormalities may also be due to secondary effects of liver dysfunction (Table 3).

Management

Early intervention for several IMDs can significantly improve outcome and prevent death. Disorders like UCDs, HT1, OAs need dietary restriction of substrate, prevention of catabolism and emergency regimens in illness. Other management strategies include replacement of deficient end products, e.g. cholic acid in CTX deficiency, reduction of the stored substance, e.g. chelation therapy in NH or in Wilson disease, and substrate reduction in HT1 with NTBC (2-(2-nitro-4-fluoromethylbenzoyyl)-1,3-cyclohexaedione). For some, enzyme replacement therapy is effective such as in Pompe disease and Cholesterol ester storage disease.

The role of liver transplantation in the management of an increasing number of metabolic disorders is growing. Liver transplantation serves to cure the underlying metabolic defect or stop progression of organ dysfunction. Early consideration of bridging hepatocyte transplant followed by liver transplant can be an effective treatment for UCDs and OAs such as neonatal presentations of Ornithine transcarbamylase (OTC) deficiency. Transplantation is indicated in disorders like Wilson disease and NH when there is no or poor response to conventional treatment. Other indications include where there is a high risk of malignancy as in GSD type I, citrin deficiency and HT1.

Gene therapy studies in animal models have demonstrated encouraging short-term results in some IMDs including GSDs (Ia and Pompe), and UCDs such as OTC.

Table 4 lists IMDs with specific managements some of which are discussed in more detail below.

Glycogen storage disorders (GSDs)

GSDs are caused by deficiency of enzymes involved in the synthesis or breakdown of glycogen. The disorders are characterised predominantly by accumulation of glycogen in liver and or muscle. The cardinal manifestation of hepatic GSDs is hypoglycaemia due to the inability to metabolise glycogen.

GSD type I (a and b) is the most severe hepatic GSD with patients having extremely short fasting tolerances. Approximately 50% present between 1 and 6 months when the intervals between feeds are extended or with intercurrent infections. Infants present with episodes of fasting hypoglycaemia with or without lactic acidosis, hyperlipidaemia, hyperuricemia, hepatomegaly, growth impairment, and renal tubular dysfunction. GSD Ib is initially identical to 1a in presentation but patients may develop neutropenia, neutrophil dysfunction or inflammatory bowel disease.

Other hepatic GSDs include types III, VI and IX. Patients have a mixed picture with hepatic presentation, myopathy and cardiomyopathy, with or without hypoglycaemia. Most diagnoses are made through enzymology or next generation sequencing genetic testing. Biopsy or enzyme studies from appropriate tissue may still be useful.

Management aims to maintain normoglycaemia and limit secondary metabolic derangement through continuous supply of

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