PAEDIATRIC METABOLIC CONDITIONS OF THE LIVER

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ABSTRACT

Paediatric metabolic disorders with the most clinical manifestations of deranged hepatic metabolism are discussed. The conditions which will be stressed are those for which effective treatment is available and early diagnosis is essential. Accurate diagnosis of other disorders for which no treatment is, as yet, available is also important as a guide to prognosis and for accurate genetic counselling. With the advancement in amniocentesis techniques there is a growing role for gene therapy. For selected metabolic disorders, paediatric liver transplantations have been successful.

Keywords: Metabolic disorders, liver, amniocentesis, paediatric, transplantation.

INTRODUCTION

Many inborn errors of metabolism (IEM) are recessive diseases. Recessive conditions are rare, as these disorders are only present when an individual is homozygous for a gene from unaffected heterozygous 'carrier' parents (1 in 4 chance). The overall incidence of autosomal recessive (AS) disorders is about 2.5 per 1,000 live births in the United Kingdom. Worldwide, diseases such as thalassaemia and sickle cell disease are very common and the frequency may be as high as 20 per 1,000 live births.[1] The clinical features of AS disorders are usually severe; patients often present in the first few years of life and have a high mortality. This is unlike dominant inheritance where some traits are 'non-penetrant'. Prenatal diagnosis is becoming possible in suspected (family history) IEM by obtaining specimens of amniotic cells for cytogenetics or enzyme studies. Carrier states can also be identified, so that sensible genetic counselling can be given.[2,3] Liver transplantation (LTx) may not only replace the diseased organ but can also potentially correct the metabolic defect. Both graft and patient survival for adults transplanted for metabolic liver disease is similar to that of other indications for liver transplant, as seen in the 80-90% 1-year survival after paediatric LTx for chronic liver disease (Tables 1 and 2). The controversy is whether LTx should be considered when the disorder is associated with severe impairment of other organ(s).[4-6]

ABNORMALITIES OF METAL METABOLISM

Wilson's Disease (WD)

WD is a very rare IEM associated with the accumulation of toxic amounts of copper in the liver, brain, kidneys, and cornea. It is inherited as an AS gene and occurs worldwide, particularly in countries where consanguinity is common. WD is caused by mutations in the *ATP7B* gene which leads to abnormal functioning copper transporting ATPase, decreased hepatocellular excretion of copper into bile, and failure to incorporate copper into caeruloplasmin.[7] Stains for copper usually show a periportal distribution associated with lipofuscin deposits. In childhood, the principal presentation is a hepatic disorder which may mimic all forms of liver disease. Neurological signs of basal ganglia involvement such as clumsiness, slurring of the speech, deteriorating school performance, or changes in personality are common in young adults.[8] There is growing evidence that genetic variation in *PRNP* encoding the prion glycoprotein may modify the neurological cause of WD.[9] Although it may be absent in young children and not specific to WD, the Kayser-Fleischer ring, which is due to copper

deposition in Descemet's membrane in the cornea, is identified frequently by slit-lamp examination.[7] Haemolytic anaemia, vitamin D resistant rickets, renal rickets, or the Fanconi syndrome (generalised renal tubular reabsorptive defects) may also be the first indications of disease. The diagnosis depends on the measurement of the amount of copper in the liver, although high levels of copper are found in other chronic cholestatic disorders such as sclerosing cholangitis. Measurement of ^{64}Cu incorporation may be helpful as the liver copper is elevated to 25-times the upper limit of normal, except in the presence of advanced cirrhosis when it may fall within the normal range.[7,10] The serum copper and caeruloplasmin are usually reduced, due to stability of apoceruloplasmin from the high liver copper level.[11] Untreated, WD is invariably fatal. Chelation therapy with D-penicillamine (20 mg/kg/day) and trientine (20 mg/kg/day) induces cupruria leading to clinical and biochemical improvement. Treatment given when fulminant hepatic failure or decompensated cirrhosis is established is rarely successful. Toxic side-effects of the drugs are unusual and include skin rashes, leukopenia, and renal damage. Inducing metallothionein and blocking intestinal absorption of copper elemental zinc (50 mg, three times per day) is useful in the initial stages. A diet low in copper should also be given. Tetrathiomolybdate is a chelator and blocker of copper absorption but still experimental.[7] Early diagnosis and effective treatment have improved the prognosis. Neurological damage is, however, permanent and death is from liver failure, bleeding varices, or intercurrent infection.[2] All siblings and children of patients should be biochemically or genetically screened. LTx is considered for fulminant WD with acute liver failure, decompensated cirrhosis, and disease progression despite medical therapy. Transplantation for neurological symptoms without severe liver disease is controversial.[4-6]

Indian Childhood Cirrhosis

This condition of children is seen in the Indian subcontinent and it is still not clear whether this condition has a major genetic component in which copper metabolism is abnormal in these children, or whether the copper loading of the liver results from increased dietary intake. The liver pathology in this condition is characterised by the presence of a fine, micronodular cirrhosis associated with typical hyaline bodies (Mallory's bodies) identical to those which are seen in alcoholic hepatitis.

Table 1: Paediatric liver metabolic diseases: indications for liver transplantation.

Wilson's disease	• **Fulminant Wilson's disease with acute liver failure** • **Decompensated cirrhosis** • **Disease progression despite medical therapy** • **Neurological symptoms without severe liver disease (controversial).**
Hereditary haemochromatosis	• Transplant if decompensated cirrhosis • Risks of transplantation are increased due to associated cardiomyopathy and post-transplant sepsis.
Alpha-1-antitrypsin deficiency	• 15% develop liver failure by adolescence • Transplant if decompensated cirrhosis or liver failure • 5-year post-transplant survival 80%.
Cystic fibrosis	• 15% develop cirrhosis • Risks of transplantation increased by associated cardiopulmonary disease, malnutrition, and chronic infection.
Hereditary tyrosinaemia (Type 1)	• Transplantation considered early in childhood to prevent hepatocellular carcinoma (develops in a third by 2 years).
Primary hyperoxaluria **Urea cycle defects** **Glycogen storage diseases Types 1 and 4**	• Characterised by nephrocalcinosis and renal failure • Treated by combined liver and renal transplantation.

Table 2: Prerequisites for successful paediatric liver transplantation.

• Donor and recipient should be ABO blood group compatible, but preferably ABO matched
• Donor age <50 years
• Satisfactory donor liver function
• Negative donor virology for hepatitis A, B, C, and HIV
• Appropriate size-match or surgically size reduced graft
• 80-90% 1-year survival after liver transplantation for chronic liver disease

The hepatic copper level is markedly increased but without the periorbital distribution seen in WD. Furthermore, there is insufficient evidence to determine whether removal of copper has any effect on the progression of liver damage.[1,12]

Haematochromatosis

Idiopathic haemochromatosis (IHC) is a relatively rare inherited disease characterised by excess iron deposition in various organs, leading to eventual fibrosis and functional organ failure. Iron loading of the liver cells leads to hepatocellular damage and fibrosis. It is inherited as an AS with only homozygotes manifesting the clinical features of the disease. It is associated with HLA-A3 and B14 and may be used for screening relatives of patients for the disease.[1,13] IHC is best diagnosed by liver biopsy as it defines the extent of tissue damage, assesses tissue iron, and measures the hepatic iron concentration. The pathology is similar for idiopathic or from secondary iron overloading states such as sideroblastic anaemias, thalassaemia with multiple transfusions, and alcoholic cirrhosis. Cirrhosis with nodularity is a late feature. It is becoming increasingly apparent that the liver iron content (>180 μmol/g dry weight) is the most sensitive marker of the disease as the amount of iron in the biopsy correlates well with the total body iron load.[14] It is possible to monitor therapy with repeated biopsies and quantitative iron techniques using magnetic resonance imaging.[15] The serum ferritin (SF) is elevated (usually >500 μg/l) and is evidence of excessive parenchymal deposition. Liver function tests are often normal, even with established cirrhosis.[3,14] Although most affected individuals present clinically in the fifth decade, it is important to screen all first-degree relatives with the SF test to detect early and asymptomatic disease in all cases of IHC. 30% of patients with cirrhosis will develop primary hepatocellular carcinoma (HCC) and may be the mode of presentation. There is excessive excretion of iron following administration of chelating agents and, along with long-term venesection and monitoring, cirrhosis may be prevented.[13,14] LTx is indicated for decompensated cirrhosis, but the risks are increased due to associated cardiomyopathy and post-transplant sepsis.[6]

DISORDERS OF CARBOHYDRATE METABOLISM

Paediatric Non-Alcoholic Fatty Liver Disease (NAFLD)

NAFLD is the leading cause of chronic liver disease in children.[16,17] NAFLD has emerged to be extremely prevalent, and predicted by obesity and male gender. Both genetic and environmental factors seem to be involved in the development and progression of the disease, but its pathophysiology is not entirely clear. It is defined by hepatic fat infiltration >5% hepatocytes, in the absence of other causes of liver pathology.[16] It includes a spectrum of disease ranging from intrahepatic fat accumulation (steatosis) to various degrees of necrotic inflammation and fibrosis (non-alcoholic steatohepatatis). NAFLD is associated, in children as in adults, with severe metabolic impairments, determining an increased risk of developing the metabolic syndrome. It can evolve to cirrhosis and HCC, with the consequent need for LTx.[17]

Glycogen Storage Disease (GSD)

All mammalian cells can manufacture glycogen, but the main sites of its production are the liver and muscle. Glycogen is a high molecular weight glucose polymer, and in GSD there is either an abnormality in the molecular structure or an increase in glycogen concentration due to a specific enzyme defect. The majority are inherited

as ASs except for subtype 4 (Hers disease) which is sex-linked.[1,18] They present in infancy except for Type 5 (McArdle disease) disease affecting muscle only which presents in adults. Table 3 shows the classification and clinical features. 16 novel pathogenic mutations in the phosphorylase system (*PHKA2*, *PHKB*, *PHKG2*, and *PYGL*) genes have given rise to GSD Types 6 and 9 and close monitoring for the long-term liver and cardiac complications are important.[19] All these conditions are associated with inefficient glycogen utilisation which leads to hypoglycaemia and glycogen deposition in various tissues. Hepatocellular adenoma is associated with GSD Type 1, 3, and 4 and is a common reason for consulting the paediatric hepatologist.[20] Mortality and morbidity in the early years is high unless the risk of acute episodes of hypoglycaemia and lactic acidosis is recognised and an efficient regimen to maintain normoglycaemia throughout the whole 24-hour period is instituted. This has usually been done by 2-hourly feeds of glucose and starch, the latter as a slow release source of glucose. Nasogastric feeding with glucose at night is a major advance. As the other biochemical parameters also improve, there is catch-up growth and normal somatic development. However, it should be emphasised that the successfully treated patients lose their ability to withstand hypoglycaemia. The crisis associated with intercurrent infections and other stressful situations require intravenous glucose and sodium bicarbonate with close biochemical monitoring as well as vigorous treatment of the precipitating cause. Paediatric LTx may be indicated for chronic liver disease from Types 1 and 4 glycogenoses.[4-6] There is a need for future studies to ascertain if uncooked cornstarch and a high protein diet would be able to prevent long-term complications of GSD-6 and 9.[19]

Galactosaemia

As galactose is normally converted to glucose, the less common deficiency of the enzyme galactose-1-phosphate uridyl transferase results in accumulation of galactose-1-phosphate in the blood. This autosomally recessive trait results in hypoglycaemia and acidosis in the neonate.[1] Progressive hepatosplenomegaly, cataracts, renal tubular defects, and mental retardation occur.[21] Early hepatic changes include fatty infiltration and hepatic necrosis proceeding to pseudoglandular transformation of hepatocytes, hepatic fibrosis, and cirrhosis in patients who survive. Treatment is with a galactose-free diet, which if started early,

results in normal development. Untreated patients die within a few days. Prenatal diagnosis and diagnosis of the carrier state are possible by measurement of the level of galactose-1-phosphate in the blood.[3,22]

Fructosaemia

Absorbed fructose is chiefly metabolised in the liver to lactic acid or glucose. Three defects of metabolism occur and all are inherited as AS traits. Fructosuria, a benign condition, is due to a fructokinase deficiency. Fructose intolerance is due to fructose-1-phosphate aldolase deficiency caused by mutations of the *ALDOB* gene located at 9q22.3. Fructose-1-phosphate accumulates after fructose ingestion, resulting in symptoms of hypoglycaemia. Hepatomegaly and renal tubular defects occur but are reversible on a fructose-free diet.[3] Fructose 1,6-diphosphate deficiency leads to a failure of gluconeogenesis, and hepatomegaly. Steatosis and necrosis of hepatocytes in the early stages progresses to intralobular fibrosis, and ultimately cirrhosis, and its complications. Vomiting and hepatomegaly are almost always present as is a failure to thrive. In the first 2 months of life jaundice and a bleeding diathesis with deranged coagulation is found. The diagnosis is confirmed by the regression of symptoms when fructose is withdrawn from the diet and the demonstration of low activity of fructose-1-phosphate aldolase in liver or intestinal mucosa. If the patient survives, and fructose and sucrose are excluded from the diet, progress is excellent with regression of the liver damage.[1,23]

Congenital Disorder of Glycosylation Type 2A

It is a very rare inherited metabolic disorder where a GLcNAc transferase 2-enzyme defect causes defective carbohydrate compounds to be attached to glycoproteins and thus impairing their function.[24] The symptoms include dysmorphic features, psychomotor retardation, hypotonia, underdeveloped cerebellum, and seizures. Mannose supplementation may relieve the symptoms although hepatic fibrosis may persist.[25]

AMINO ACID DISORDERS

Hereditary Tyrosinaemia

This disorder is characterised by the accumulation in serum and urine of tyrosine and its metabolites. This is caused by toxic metabolites which accumulate because of deficiency of

fumarylacetoacetase, the last enzyme in the tyrosine catabolic pathway. It is associated with severe liver damage, initially in the form of fatty infiltration but proceeding to cirrhosis. Rickets and hypoglycaemia are frequent complications, and galactosaemia and fructosaemia are main differentials.[26] In its acute form the disease presents in the first 6 months of life with vomiting, diarrhoea, hepatosplenomegaly, ascites, a bleeding diathesis, and severe failure to thrive. The diagnosis is suspected on the basis of clinical features and a low urine succinyl acetone is a diagnostic marker of this disease. This test can be used as part of neonatal screening along with the grossly abnormal liver function tests, and raised serum alpha-fetoprotein levels. 2-[2-nitro-(trifluoromethyl) benzoyl]-cyclohexanedione-1,3-dione is a potent inhibitor of 4-hydroxyphenylpyruvate dioxygenase and has been shown to efficiently prevent tyrosine degradation and production of succinylacetone.[27] Treatment includes restriction of dietary tyrosine, phenylalanine, and methionine and their careful plasma monitoring, correction of hypoglycaemia and electrolyte imbalance, and large doses of vitamin D to heal the rickets. Although treatment corrects the abnormal biochemical findings, most cases die in infancy or early childhood from liver failure.[1,26] LTx should be considered early in childhood to prevent HCC, which develops in a third of patients by 2 years.[4-6]

UREA-CYCLE DISORDERS

Genetically determined deficiency has been identified for five separate enzymes in the liver involved in the conversion of ammonia to urea. The diagnosis is suspected by the finding of a high blood ammonia, but established by the demonstration of deficiency of the particular enzyme involved.[3] The principal pathological change is brain damage, but the liver usually shows an increase in fat and glycogen. The clinical features include a dislike of protein-containing food and vomiting, and irritability or lethargy following ingestion of such foods. Dietary protein restriction beginning immediately after birth should therefore be the basis of their treatment. The protein requirement is highest during the first months of life and a balance has to be struck between providing sufficient protein for growth and control of hyperammonaemia.[1,28] Paediatric LTx may be indicated in these urea cycle defects.[6]

Table 3: Glycogen storage diseases

Type	Affected tissue	Enzyme defect	Clinical features	Tissue needed for diagnosis*	Outcome
1 (Von Gierke's disease)	Liver, intestine, kidney	Glucose-6-phosphatase	Hepatomegaly, hypoglycaemia, stunted growth, obesity, hypotonia	Liver	If patients survive initial hypoglycaemia, prognosis is good; hyperuricaemia is a late complication
2 (Pompe's disease)	Liver, muscle, heart	Lysosomal α-glucosidase	Heart failure, cardiomyopathy	Leukocytes, liver, muscle	Death in first 6 months; juvenile and adult variants seen
3 (Forbes' disease)	Liver, muscle (abnormal glycogen structure)	Amylo-1, 6-glucosidase	Like Type I	Leukocytes, liver, muscle	Good prognosis
4 (Andersen disease)	Liver (abnormal glycogen structure)	1,4-α-glucan branching enzyme	Failure to thrive, hepatomegaly, cirrhosis and its complications	Leukocytosis, liver, muscle	Death in first 3 years
5 (McArdle disease)	Muscle only	Phosphorylase	Muscle cramps and myoglobinuria after exercise (in adults)	Muscle	Normal lifespan; exercise must be avoided

*tissue obtained is used for the biochemical assay of the enzyme.

GLYCOPROTEIN DISORDERS

Hepatic Aspects of Alpha-1 Antitrypsin (A1AT) Deficiency

A1AT inhibits tissue damaging serine proteases and over 30 alleles of A1AT can now be distinguished by the absence of the alpha-1 band in isoelectric focusing. The gene is located on the long arm of chromosome 14 (14q 31-32). These are inherited as an AS disorder with co-dominant expression as each allele contributes 50% of the total circulating enzyme inhibitor.[1,3] In the deficient individual uninhibited action of proteases may cause progressive liver disease. A1AT deficiency was first discovered in the 1960s in a family with early-onset emphysema. Liver disease occurs in individuals who are homozygous for the variant (ZZ) (incidence 1:3,400 in the UK), or who do not have glycoprotein in their serum (Pi null phenotype). Antenatal diagnosis is possible by foetal blood sampling at 17-week gestation, at which time termination of the pregnancy is possible. Genetic counselling poses particular difficulties because not all ZZ foetuses will develop liver or lung disease.[29] Liver disease is usually first detected in infancy by the appearance of a conjugated hyperbilirubinaemia with pale stools, dark urine, hepatomegaly, splenomegaly, and failure to thrive. 25% of jaundiced infants die of cirrhosis in early childhood, while 40-50% have chronic persisting liver disease with features of compensated cirrhosis.[30] At present, no treatment has been shown to modify liver disease associated with A1AT deficiency but recent data suggest the autophagy (process that removes abnormal proteins in cells) - enhancing drug, carbamazepine, to be beneficial.[31] Hepatoma may occur as a complication of the cirrhosis and LTx is indicated in the 10-15% with PiZZ phenotype who develop features of decompensation in late childhood or early adolescence. The 5-year post-transplant survival is 80%.[4-6]

Hepatic Aspects of Cystic Fibrosis (CF)

CF is the commonest recessively inherited disorder (abnormality of chromosome 7) in Caucasians, with a carrier frequency of 1 in 20-25. In America, Western Europe, and Australia, 1 in 2,000 births are homozygous for the CF gene, but the carrier frequency in mongoloid races is considerably less and CF is unknown in blacks.[1,3] It is a genetically determined disorder of exocrine secretory glands which causes them to produce tenacious viscoid secretions. The abnormal mucus stagnates in small ducts, causing destruction of cells draining into or associated with them, a process aggravated by infection. The respiratory system and pancreas are principally involved, with a high sweat sodium concentration over 60 mmol/l, but other organs with mucus-producing glands in their duct systems, such as the biliary system, are also affected.[32] The main cause of chronic liver disease is thought to be inspissated biliary secretions causing focal biliary obstruction and fibrosis, and in 20% of cases, the gall bladder is small with an inability to concentrate bile. Drugs, infection, and abnormal immune mechanisms have all been implicated in causing chronic liver damage. A biliary type of cirrhosis may appear in the first year of life, but more often becomes evident in late childhood or early adolescence. Obstructive jaundice is rare and only a minority of patients die of liver disease in the first few years of life. Decompensated cirrhosis with ascites is rare except when *cor pulmonale* develops.[3,32] No treatment which influences the underlying process is available. Symptomatic treatment with ursodeoxycholic acid is useful in the short term. There may be genetic modifiers of CF-associated liver disease in the future.[33] LTx is indicated for the 15% who develop cirrhosis, but the risks are increased by associated cardiopulmonary disease, malnutrition, and chronic infection.[6]

LYSOSOMAL STORAGE DISEASES (LSDS) (SPHINGOLIPIDOSES)

LSDs are due to IEM which are inherited in a sex-linked recessive manner. Sphingolipids are degraded by a series of lysosomal enzymes, and accumulate when there is a deficiency of these enzymes. Many of the sphingolipidoses can be diagnosed by demonstrating the enzyme deficiency in the appropriate tissue. Enzyme replacement therapy for lysosomal acid lipase deficiency, although not a cure, can allow improved metabolism and partially prevent disease progression, as well as potentially reverse some symptoms.[34]

Fabry's Disease (FD)

FD is a rare genetic lysosomal storage disease, inherited in an X-linked manner, involving dysfunctional metabolism of sphingolipids due to an alpha-galactosidase A deficiency causing a wide range of systemic symptoms. It causes glycolipid, and globotriaosylceramide (Gb3, GL-3) to accumulate within the blood vessels, other tissues,

and organs, leading to an impairment of their functions. There is potential replacement therapy with Fabrazyme (agalsidase beta), although most patients eventually develop renal problems in early adult life.[35]

Gaucher's Disease (GD)

In GD there is an accumulation of glucocerebroside in the reticuloendothelial system, particularly the liver, bone marrow, and spleen. There is a high incidence in Ashkenazi Jews (1 in 3,000 births). Acute GD presents in infancy or childhood with rapid onset of hepatosplenomegaly with neurological involvement, due to Gaucher's cells in the brain. The outlook is poor but treatment with recombinant glucocerebrosidase may be beneficial.[36]

Niemann-Pick Disease

Nieman-Pick Type 2 is the second most common genetic cause of liver disease in infancy in the UK after A1AT deficiency. This is due to the accumulation of sphingomyelin and foam cells in reticuloendothelial macrophages in many organs particularly the liver, spleen, bone marrow, and lymph nodes. Over 50% of cases present with hepatitis in infancy or intrauterine ascites. A third of these die by 6 months, while the survivors unfortunately develop features of progressive, ultimately fatal, neurological involvement from 2 years of age. LTx does not arrest the disease but diagnosis is essential for genetic counselling. Prenatal diagnosis by amniocentesis is possible and success derived in the experimental use of (2-hydroxypropyl)-β-cyclodextrin.[37]

CONCLUSIONS

Paediatric metabolic disorders arise invariably from IEM, which are mostly inherited in an AS manner. The implications are that they are rare but lethal as it is manifested in the homozygote form. For selected metabolic disorders, paediatric LTx have proved successful. With the advancement in amniocentesis techniques, there is a growing role for gene therapy.

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