National Metabolic Biochemistry Network Best Practice Guidelines
Metabolic liver disease in the older child

Introduction

Metabolic liver disease in the older child can present with;

- Acute liver failure (ALF) (defined as acute onset with no evidence of chronic liver disease and INR >2 or >1.5 with encephalopathy)
- Abnormal liver function tests with our without hepatomegaly / splenomegaly
- Cholestatic liver disease
- Chronic liver disease or cirrhosis
- Intermittent metabolic decompensation with or without developmental delay

It is important to consider the age of the child, the nature of the liver disease and any associated extrahepatic features.

Approach to investigation

This is often directed by clinical features and employs a variety of techniques including biochemical, haematological, radiological and histological. It is appropriate to perform first line investigations and proceed to more complex tests as indicated.

If metabolic liver disease is suspected, a full history and examination can provide clues to the diagnosis. A history of symptoms such as hypoglycaemia and failure to thrive, consanguinity and a family history of liver disease may be suggestive. A dietary history may reveal specific aversions or faddy eating. Clinical examination may reveal dysmorphology and peripheral stigmata of liver disease (spider naevi, palmar erythema, xanthelasma) and sometimes incidental, hepatomegaly/splenomegaly.

Routine biochemical tests may show elevated transaminases (defined as >50 IU/L) with or without jaundice (bilirubin >20 µmol/L) and/or raised gamma glutamyltransferase (>50 IU/L). Hepatic synthetic function may be disturbed (INR >1.3 or albumin <35 mmol/L), coagulopathy often being more acute and hypoalbuminaemia more chronic. Hyperammonaemia and lactic acidosis may not only reflect acute liver dysfunction but an underlying metabolic disease.

Ultrasonography may detect a homogeneous or heterogeneous liver parenchyma, the latter in keeping with chronic change or showing fatty change, often associated with metabolic disease. Liver biopsy can be helpful in making a diagnosis and often provides supportive information for the clinical picture.

First line investigations

The following should be performed when there is suspicion of metabolic liver disease:

Routine biochemical tests

~ Urea and electrolytes
~ Bone profile
~ Liver function tests
~ Glucose
~ Amylase / lipase
~ Creatine kinase
~ Urate
~ Lactate
~ Ketones

Routine haematological tests

~ Full blood count
~ Coagulation screen including fibrinogen
~ Blood film and Direct Coombs test
~ Cholesterol (total, LDL, HDL) and triglycerides

Specialist metabolic tests

~ Plasma amino acids
~ Urine organic acids
~ Bloodspot or plasma acylcarnitines
~ Plasma VLCFA

Specific disorders

Disorder	Supportive findings	Investigations
Hepatomegaly		
Wilson's disease	Can present with ALF Neurological symptoms Kayser-Fleischer rings (uncommon in children)	Plasma copper/caeruloplasmin Urinary copper pre- and post-penicillamine Liver copper content *ATP7B* gene
Alpha-1-antitrypsin deficiency	Can present with ALF	A1AT phenotype/genotype
Cystic fibrosis	Cholestasis Portal hypertension Decompensated liver disease	Sweat test *CFTR* gene
Glycogen storage disorders (types I, III, IV, VI and IX)	Symptoms of hypoglycaemia / shortened fasting tolerance Cirrhosis (type IV)	Urate, lipids, lactate, CK, ketones (Plasma/liver enzymology) Mutation analysis
Fructose-1,6-bisphosphatase deficiency	Acute crisis with ketoacidosis, hypoglycaemia and lactic acidosis	Lactate, ketones Urine organic acids (Liver enzymology) *FBP1* gene
Fanconi-Bickel syndrome (GLUT2 deficiency)	Renal tubulopathy, severe glucosuria, galactosuria hypophosphataemic rickets	Lipids, urate, lactate Urine amino acids, urine sugars (galactose) Liver histology/enzymology *GLUT2* gene
Mevalonic aciduria	Episodes of fever Gastrointestinal symptoms Hepatosplenomegaly	Urine organic acids IgD Enzymology (leukocytes or fibroblasts) *MVK* gene

Mucopolysaccharidoses	Organomegaly Coarse facies Bone dysplasia	Urine glycosaminoglycans Lysosomal enzyme screen Vacuolated lymphocytes Mutation analysis
Niemann Pick Type C*	Splenomegaly Neurological involvement	Chitotriosidase / oxysterols Filipin staining (fibroblasts) (Vacuolated lymphocytes / bone marrow aspirate) *NPC1* / 2 gene
Lysosomal acid lipase deficiency	Abnormal transaminases Elevated total cholesterol and LDL cholesterol	Liver histology Blood spot LAL activity Chitotriosidase *LIPA* gene
Cholestasis		
PFIC type 1 (PFIC1 deficiency)	Failure to thrive Low GGT	Liver histology Mutation analysis
PFIC type 2 (bile salt exporter pump (BSEP) deficiency)	Low GGT Cholestasis Association with hepatocellular carcinoma	Plasma bile acids Liver histology/immunostaining Mutation analysis
PFIC type 3 (MDR3 deficiency)	High GGT Cholestasis Pruritus Intra-hepatic gallstones (cholesterol)	Liver histology/immunostaining Mutation analysis
Peroxisomal biogenesis disorders*	Dysmorphic Hypotonia	Urine bile acids Plasma VLCFA Mutation analysis
Bile acid synthesis disorders*	Dysmorphology Often low GGT	Urine bile acids Plasma VLCFA Mutation analysis
Acute liver failure		
Galactosaemia*	Failure to thrive Cataracts Coagulopathy	Blood spot/red blood cell galactosaemia screen Blood spot galactose-1-phosphate Gal-1-PUT enzymology *GALT* gene
Tyrosinaemia type 1*	Hepatocellular carcinoma Chronic liver disease Renal tubulopathy	Urine or blood spot succinylacetone Urine organic acids Urine 5-aminolevulinate Plasma amino acids *FAH* gene
Hereditary fructose intolerance (HFI)	Hepatomegaly Aversion to fructose-containing foods	Transferrin isoforms Liver enzymology *ALDOB* gene
Mitochondrial disease*	Other organ involvement	Lactate (CSF/plasma)

	(often neurological)	Plasma amino acids Liver/muscle respiratory chain enzymology *POLG, DGUOK, MPV17, TRMU* genes
Urea cycle disorders*	Hyperammonaemia Aversion to protein containing foods Developmental delay	Plasma amino acids Urine organic acids (orotic acid) (Liver enzymology) Mutation analysis
Cirrhosis		
Transaldolase deficiency	Often associated dysmorphism, cutis laxa	Urinary polyols *TALDO* gene
Hypermanganesemia with dystonia-1 (HMNDYT1)	Extrapyramidal motor disorder Polycythemia	Elevated serum manganese *SLC39A14* gene
Arginase and argininosuccinate lyase deficiency	Episodes hyperammonaemia Neurological involvement	Plasma amino acids Urine organic acids Mutation analysis
Congenital disorders of glycosylation	Dysmorphism Neurological involvement	Transferrin isoforms Enzymology (PMM / MP1 activity) Mutation analysis

* These disorders often present in early infancy but should also be considered in the older child

References

J M Saudubray, M R Baumgartner, J Walter. Inborn Metabolic Diseases, 6th Edition, Springer.

F Suchy, R Sokol, W Ballistreri. Liver disease in children, 3rd edition, 2007. Cambridge University Press.