

- to prevent decompensation before baby's status is known:
 - provide enough calories (oral/intravenous);
 - may need to restrict protein especially if index case presented very early (during first week of life).
 - protein-free formula should be given initially; small amount of protein (e.g. breast milk) is gradually introduced after 48 hours depending on baby's clinical status.
- if the index patient presented after the first week of life, the new baby should be given the minimum safe level of protein intake from birth (approximately 1.5 g/kg/day). Breast feeding should be allowed under these circumstances with top-up feeds of a low protein formula to minimise catabolism.
- get the metabolic test results as soon as possible to decide whether the baby is affected or not

INVESTIGATING INBORN ERRORS OF METABOLISM (IEM) IN A CHILD WITH CHRONIC SYMPTOMS

Introduction

IEMs may cause variable and chronic disease or organ dysfunction in a child resulting in global developmental delay, epileptic encephalopathy, movement disorders, (cardio)-myopathy or liver disease. Thus it should be considered as an important differential diagnosis in these disorders.

The first priority is to diagnose treatable conditions. However, making diagnosis of non-treatable conditions is also important for prognostication, to help the child find support and services, genetic counselling and prevention, and to provide an end to the diagnostic quest.

Problem 1: Global developmental delay (GDD)

- defined as significant delay in 2 or more developmental domains
- investigation done only after a thorough history and physical examination
- if diagnosis is not apparent after the above, then investigations as in Table 1 may be considered. Even in the absence of abnormalities on history or physical examination, basic screening investigations may identify aetiology in 10-20%.
- in the absence of any other clinical findings or abnormalities in the baseline investigations then further investigations are not indicated.

Table 1. Suggested investigations in children with global developmental delay

Basic screening investigations	
Karyotyping	Metabolic screening using Guthrie card ¹
Serum creatine kinase	Plasma Amino acids ²
Thyroid function test	Urine organic acid ²
Serum uric acid	Neuroimaging ³
Blood Lactate	Fragile X screening (in boys)
Blood ammonia	

Footnote: 1. This minimal metabolic screen should be done in all even in the absence of risk factors

2. This is particularly important if there is one or more of following risk factors: consanguinity, family history of developmental delay, unexplained sibling death, unexplained episodic illness.

3. MRI is more sensitive than CT, with increased yield. It is not a mandatory study and has a higher diagnostic yield when indications exist (e.g. macro/microcephaly; seizure; focal motor findings on neurologic examination such as hemiplegia, nystagmus, optic atrophy; and unusual facial features e.g. hypo/hypertelorism)

- if history and physical examination reveal specific clinical signs and symptoms, a number of potential further investigations for possible IEM may be available. Many of these highly specialised investigations are expensive – it is not suggested that they are all undertaken but considered. Referral to a clinical geneticist, paediatric metabolic physicians or paediatric neurologist is useful at this stage to help with test selection based on “pattern recognition”.

Table 2. Interpretation of basic screening investigations

Test Abnormality	Possible causes of abnormal results
Creatine kinase ↑	muscle injury muscular dystrophy fatty acid oxidation disorders
Lactate ↑	excessive screaming, tourniquet pressure glycogen storage disorders; gluconeogenesis disorders disorders of pyruvate metabolism mitochondrial disorders is plasma alanine also increased? <i>If yes, then it is suggestive of true elevation of lactate</i>
Ammonia ↑	sample contamination sample delayed in transport/processing specimen haemolysed urea cycle disorders liver dysfunction
Uric acids	any abnormality - high or low result is significant glycogen storage disorders (↑ uric acid) purine disorders (↑ uric acid) molybdenum cofactor deficiency (↓ uric acid)

Table 3. Metabolic/Genetic tests for specific clinical features

Developmental delay and	Disorders	Investigations
severe hypotonia	peroxisomal disorders purine/pyrimidine disorders neurotransmitters deficiencies neuropathic organic academia Pompe disease Prader Willi syndrome	very long chain fatty acids (B) purine/pyrimidine analysis (U) neurotransmitters analysis (C) organic acid analysis (U) biotinidase assay (G) lysosomal enzyme (G) methylation PCR (B)
neurological regression + organomegaly + skeletal abnormalities	mucopolysaccharidoses oligosaccharidoses	urine MPS (U) oligosaccharides (U)
neurological regression ± abnormal neuroimaging e.g. leukodystrophy	other lysosomal disorders mitochondrial disorders biotinidase deficiency peroxisomal disorders Rett syndrome (girl)	lysosomal enzyme (B) respiratory chain enzymes (M/S) biotinidase assay (G) very long chain fatty acids (B) MECP2 mutation study
progressive myopia ± lens subluxation	homocystinuria	total homocysteine (B)
abnormal hair	Menkes disease argininosuccinic aciduria trichothiodystrophy	copper (B), ceruloplasmin (B) amino acid (U/B) hair microscopy

Legend: B=blood, C=cerebrospinal fluid, U=urine, G=Guthrie card, CGH=comparative genomic hybridization

Table 3. Metabolic/Genetic tests for specific clinical features (continued)

Developmental delay and	Disorders	Investigations
macrocephaly	glutaric aciduria type I Canavan disease vanishing white matter disease megalecephalic leukodystrophy with subcortical cysts (MLC)	organic acid (U) organic acid (U) DNA test DNA test
dysmorphism	microdeletion syndromes peroxisomal disorders Smith Lemli Opitz syndrome congenital disorders of glycosylation	FISH, CGH very long chain fatty acids (B) sterol analysis (B) transferrin isoforms (B)
dystonia	Wilson disease neurotransmitters deficiencies neuroacanthocytosis	copper (B), ceruloplasmin (B) phenylalanine loading test, neurotransmitters analysis (C) peripheral blood film, DNA test
epileptic encephalopathy	nonketotic hyperglycinemia molybdenum cofactor deficiency glucose transporter defect pyridoxine dependency PNPO deficiency congenital serine deficiency cerebral folate deficiency ring chromosome syndromes neuronal ceroid lipofuscinosis creatine biosynthesis disorders adenylosuccinate lyase deficiency cerebral dysgenesis e.g. lissencephaly Angelman syndrome	glycine measurement (B and C) sulphite (fresh urine) glucose (blood and CSF) pyridoxine challenge amino acid (C), organic acid (U) amino acid (B and C) CSF folate karyotype peripheral blood film, lysosomal enzymes (B) MR spectroscopy purine analysis (U) MRI brain methylation PCR
spastic paraparesis	arginase deficiency neuropathic organic academia Sjogren Larsson syndrome	amino acid (B) organic acid (U) detailed eye examination

Legend: B=blood, C=cerebrospinal fluid, U=urine, G=Guthrie card, CGH=comparative genomic hybridization

Problem 2: Liver disease

- a considerable number of IEM cause liver injury in infants and children, either as isolated liver disease or part of a multisystem disease
- the hepatic clinical response to IEM is often indistinguishable from acquired causes, such as infections
- while IEM should be considered in any child with liver disease, it is essential to understand many pitfalls in interpreting the results
- liver failure can produce a variety of non-specific results: hypoglycaemia, ↑ NH₃, ↑ lactate, ↑ plasma amino acids (tyrosine, phenylalanine, methionine), positive urine reducing substances (including galactose), an abnormal urine organic acid/blood acylcarnitine profiles.
- primary paediatric doctors must communicate closely with the metabolic clinician, hepatologist and laboratory

Table 4. Approach to metabolic liver disease according to clinical manifestation

A. Acute/subacute hepatocellular necrosis

(↑AST, ↑ALT jaundice, hypoglycaemia, ↑NH₃, bleeding tendency, ↓albumin, ascites)

Metabolic / genetic causes	Clues	Diagnostic tests
<i>Neonatal/ early infantile</i>		
• Neonatal haemochromatosis	↑↑↑ ferritin	liver biopsy
• Galactosaemia	+ve urine reducing sugar, cataract	GALT assay
• Long-chain fatty acid oxidation disorders	associated (cardio)myopathy	blood acylcarnitine
• mtDNA depletion syndrome	muscular hypotonia, multi-system disease, encephalopathy, nystagmus, ↑↑ lactate (blood and CSF)	liver biopsy for respiratory enzyme assay
• tyrosinaemia type I	severe coagulopathy, mild ↑AST, ↑ ALT, renal tubulopathy, ↓ phosphate, ↑↑↑AFP	urine organic acids including succinylacetone
• congenital disorders of glycosylation	multi-system disease, protein-losing enteropathy	transferrin isoform analysis
Must rule out infections: TORCHES, echovirus, parvovirus B19, enteroviruses, HIV, EBV, Hep B, Hep C		serology, urine/stool viral culture
<i>Late infancy to childhood</i>		
• above causes		
• α-1-antitrypsin deficiency	see below	α-1-antitrypsin level
• fructosaemia	symptoms after fructose intake, renal tubulopathy	
• Wilson disease	KF rings, neurological symptoms, haemolysis	serum/urine copper, caeruloplasmin
Must rule out chronic viral hepatitis & autoimmune diseases		

B. Cholestatic liver disease

(conjugated bilirubin >15%, acholic stool, yellow brown urine, pruritus, ↑↑ ALP)
GGT (gamma-glutamyltranspeptidase) may be low, normal or high - useful to differentiate various causes.

Metabolic / genetic causes	Clues	Diagnostic tests
<i>Neonatal/ early infantile</i>		
• Alagille syndrome	eye, cardiac, vertebral anomalies	DNA study
• inborn error of bile acid synthesis	↓ or normal GGT	liver biopsy, DNA study
• Progressive familial intrahepatic cholestasis (PFIC)	↓ or normal GGT except PFIC type III	liver biopsy, DNA study
• citrin deficiency	↑ plasma citrulline, ↑ galactose, +ve urine reducing sugar	plasma amino acids, DNA study
• Niemann Pick C	hypotonia, ophthalmoplegia, hepatosplenomegaly	bone marrow examination
• peroxisomal disorders	severe hypotonia, cataract, dysmorphism, knee calcification	very long chain fatty acids
• α-1-antitrypsin deficiency	commonly presents as cholestatic jaundice, gradually subsides by 6 months age. Some develop cirrhosis	α-1-antitrypsin levels

B. Cholestatic liver disease (continued)

Metabolic / genetic cause	Clues	Diagnostic tests
<i>Late infancy to childhood</i>		
• above causes		
• Rotor syndrome	normal liver function	} diagnosis by
• Dublin-Johnson	normal liver function	} exclusion

C. Cirrhosis

(end stage of chronic hepato-cellular disease)

chronic jaundice, clubbing, spider angiomatoma, ascites, portal hypertension

Metabolic / genetic cause	Clues	Diagnostic tests
• Wilson disease	KF ring, neurological symptoms, haemolysis	serum/urine copper, ceruloplasmin
• haemochromatosis	↑↑ ferritin, cardiomyopathy, hyperpigmentation	liver biopsy, DNA study
• GSD IV	cirrhosis around 1 year, splenomegaly, muscular hypotonia/atrophy, cardiomyopathy, fatal < 4year	liver biopsy
• α-1-antitrypsin	see above	α-1-antitrypsin levels

Must rule out: chronic viral hepatitis, autoimmune diseases, vascular diseases, biliary malformation etc

Problem 3: Cardiomyopathy

- cardiomyopathy can be part of multi-systemic manifestation of many IEMs
- in isolated cardiomyopathy: actively screen for subtle extra-cardiac involvement, i.e. renal, liver function; ophthalmological and neurological examinations
- cardiomyopathy may be part of clinical features of genetic syndromes e.g. Noonan syndrome, Costello syndrome, Cardiofaciocutaneous syndrome.
- sarcomeric protein mutations may cause familial cardiomyopathy

Table 5. IEM that may present predominantly as cardiomyopathy

Disorder	Cardiac Finding	Clues
Primary carnitine deficiency	dilated cardiomyopathy	↓ serum free carnitine
Long chain fatty acid oxidation disorders	hypertrophic or dilated cardiomyopathy	myopathy, retinopathy, hypoketotic hypoglycaemia, abnormal acylcarnitine profile
Mitochondrial disorders	hypertrophic or dilated cardiomyopathy	associated with multi-system abnormalities, ↑↑ lactate Kearns– Sayre syndrome: Chronic progressive external ophthalmoplegia, complete heart block
Barth syndrome	dilated cardiomyopathy	neutropenia, myopathy, abnormal urine organic acid (↑3-methylglutaconic aciduria)
Infantile pompe disease	hypertrophic cardiomyopathy	ECG - Short PR, very large QRS; ↑ Creatine kinase, ↑ AST, ↑ ALT
Glycogen storage disease type III	hypertrophic cardiomyopathy	hepatomegaly, ↑ creatine kinase, ↑ AST, ↑ ALT, ↑ triglycerides ,

Problem 4: Haematological disorders

Table 6. Inborn errors of metabolism presenting as haematological disorders

Clinical problem	Metabolic /Genetic causes	Clues / tests
megaloblastic anaemia	<ul style="list-style-type: none"> defective transportation or metabolism of B₁₂ orotic aciduria disorders of folate metabolism 	methylmalonic aciduria, ↑ homocysteine, ↓/normal serum B ₁₂ ↑↑ urinary orotate ↓serum folate
global marrow failure	<ul style="list-style-type: none"> Pearson syndrome Fanconi anaemia dyskeratosis congenita 	exocrine pancreatic dysfunction, lactate, renal tubulopathy cafe au lait spots, hypoplastic thumbs, neurological abnormalities, increased chromosomal breakage abnormal skin pigmentation, leucoplakia and nail dystrophy, premature hair loss and/or greying