

## CURRENT TOPIC

# Diagnosis and management of inborn errors of metabolism—an update

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Since this topic was last reviewed rapid advances have been made in our understanding of inherited metabolic disease.<sup>1</sup> Much of this increased knowledge has been stimulated by the application of molecular genetic techniques to the study of human disease. In addition clarification of the function of various subcellular organelles has led to the recognition of a number of new disease states.

An aggressive approach to diagnosis and treatment remains the correct therapeutic option. The widespread availability of accurate imaging equipment and the advances in electrophysiological techniques have improved our ability to provide an early, accurate prognosis for most affected infants.

Despite our increased understanding of the pathophysiology of inherited metabolic disease the long term prognosis for many disorders remains poor, especially in those infants where there is a significant delay between the onset of symptoms and diagnosis and treatment. Arteriovenous haemoperfusion is being increasingly used as the method of choice for removal of toxic intermediary compounds and peritoneal dialysis is reserved for those infants in whom vascular access is not possible.

It is essential that the basic 'metabolic screen' is supplemented by a sample of blood

(collected in a 5 ml EDTA tube) for subsequent DNA analysis. This is particularly important for infants suspected of having medium chain fatty acyl CoA dehydrogenase deficiency (MCAD) where analysis for the common mutation is often the quickest method of establishing the diagnosis and will detect 90% of cases within the white population.<sup>2</sup>

Management of a child with an inborn error of metabolism while awaiting results is still based on attempts to rapidly induce an anabolic state. Glucose and insulin and the use of lipid emulsions remain the major therapeutic thrust during this period, supplemented by arteriovenous haemoperfusion. The 'blunderbuss' approach to treatment using a megavitamin cocktail can no longer be routinely recommended. Specific vitamin treatment *after* diagnosis of a disorder known to be vitamin responsive is appropriate.

The necropsy remains important in those infants for whom a diagnosis has not been found. In addition to blood, urine, cerebrospinal fluid, and skin fibroblasts, a muscle biopsy specimen should be collected and snap frozen. Muscle tissue is essential if a mitochondrial cytopathy is thought to be responsible for the infant's illness.

## Appendix Metabolic disorders that may present as severe neonatal illness

### ● Carbohydrate metabolism

Galactosaemia produces cataracts and severe liver disease; the other members of this group usually present with a combination of hypoglycaemia and lactic acidosis (see also **Mitochondrial disorders**). Hereditary fructose intolerance requires a fructose load before symptoms appear.

#### Disorders

- 1 Galactosaemia ('classical')
- 2 Glycogen storage disease
  - Type Ia
  - Type Ib
- 3 Fructose
- 4 Lactic acidosis

#### Enzyme deficiencies

- Galactose-1-phosphate uridyl transferase
- Glucose-6-phosphatase  
'Translocase'
- Fructose-1-6-bisphosphatase  
Aldolase (hereditary fructose intolerance)  
Pyruvate carboxylase  
Pyruvate dehydrogenase\*  
Phosphoenolpyruvate carboxykinase

### ● Amino acid disorders

Presentation may be variable, but central nervous system dysfunction is common. In maple syrup urine disease the urine has a characteristic odour. Acute hereditary tyrosinaemia causes severe liver disease and renal tubular dysfunction.

#### Disorders

- 5 Maple syrup urine disease
- 6 Non-ketotic hyperglycinaemia
- 7 Tyrosinaemia type I

#### Enzyme deficiencies

- Branched chain ketoacid decarboxylase  
Glycine cleavage system  
Fumaryl acetoacetase

### ● Organic acid defects

Present with a combination of lethargy, seizures, ketoacidosis, neutropenia, hyperammonaemia, and hyperglycinaemia. Hypoglycaemia is common. Isovaleric acidemia and glutaric aciduria type II produce an odour of 'sweaty feet'.

#### Disorders

- 8 Methylmalonic acidemia
- 9 Propionic acidemia
- 10 Isovaleric acidemia
- 11 Glutaric aciduria type II
- 12 MCAD deficiency

#### Enzyme deficiencies

- Methylmalonyl CoA mutase (and others)  
Propionyl CoA carboxylase  
Isovaleryl CoA dehydrogenase  
Glutaryl CoA dehydrogenase  
Medium chain fatty acyl CoA dehydrogenase

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**Appendix** *continued*● **Urea cycle defects**

Clinical features are due to hyperammonaemic encephalopathy. Hiccoughs are common. The illness is more severe the more proximal the defect in the cycle.

<i>Disorders</i>	<i>Enzyme deficiencies</i>
13 Carbamyl phosphate synthetase deficiency	
14 Ornithine carbamyl transferase deficiency	
15 Citrullinaemia	Argininosuccinic acid synthetase
16 Argininosuccinic aciduria	Argininosuccinic acid lyase
17 Argininaemia	Arginase
18 Transient hyperammonaemia of prematurity	Unknown

● **Peroxisomal disorders<sup>3</sup>**

Defects of peroxisomal biogenesis and specific deficiencies of peroxisomal enzymes can be associated with profound neurological abnormalities as well as a typical dysmorphic presentation. Only the more common disorders are mentioned below.

<i>Disorders</i>	<i>Enzyme deficiencies</i>
19 Zellweger's syndrome	Peroxisomal biogenesis
20 Rhizomelic chondrodysplasia punctata	Multiple
21 Neonatal adrenoleukodystrophy	Multiple

● **Mitochondrial disorders<sup>4 5</sup>**

Mitochondrial disorders are becoming increasingly recognised as a cause of neonatal metabolic acidosis and encephalomyopathy. With some disorders multisystem disease is common, but the central nervous system and skeletal muscle seem particularly vulnerable. Lactic acidosis is a useful biochemical marker, but the ultimate diagnosis depends on a combination of clinical picture, histological findings of skeletal muscle biopsy, biochemical analysis of the respiratory transport chain in muscle tissue, and an analysis of mitochondrial DNA for deletions and other mutations.

● **Miscellaneous**

<i>Disorders</i>	<i>Enzyme deficiencies</i>
22 Pyridoxine dependent seizures	Unknown
23 Lysosomal storage disease†	Various

\*Is associated with severe abnormality in central nervous system differentiation in some patients, for example absence of corpus callosum and other defects.

†A number of lysosomal storage disorders have been reported as presenting with hydrops fetalis.

- 1 Wraith JE. Diagnosis and management of inborn errors of metabolism. *Arch Dis Child* 1989;64:1410-5.
- 2 Gregersen N, Blakemore AIF, Winter V, *et al.* Specific diagnosis of medium-chain acyl-CoA dehydrogenase (MCAD) deficiency in dried blood spots by a polymerase chain reaction (PCR) assay detecting a point-mutation (G985) in the MCAD gene. *Clin Chim Acta* 1991;203:23-34.
- 3 Thiel AC, Schutgens RBH, Wanders RJA, Heymans HSA. Clinical recognition of patients affected by a peroxisomal disorder: a retrospective study in 40 patients. *Eur J Pediatr* 1992;151:117-20.
- 4 Tulinius MH, Holme E, Kristiansson B, Larsson N-G, Oldfors A. Mitochondrial encephalomyopathies in childhood. I. Biochemical and morphological investigations. *J Pediatr* 1991;119:242-50.
- 5 Tulinius MH, Holme E, Kristiansson B, Larsson N-G, Oldfors A. Mitochondrial encephalomyopathies in childhood. II. Clinical manifestations and syndromes. *J Pediatr* 1991;119:251-9.