Diagnosis and management of inborn errors of metabolism—an update

J E Wraith

Since this topic was last reviewed rapid advances have been made in our understanding of inherited metabolic disease. 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.

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 cytopathology is thought to be responsible for the infant's illness.

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

- **Carbohydrate metabolism**
  
  Galactosemia 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
  3. Type Ib
  4. Fructose
  5. Lactic acidosis

  **Enzyme deficiencies**
  - Galactose-1-phosphate uridyl transferase
  - Glucose-6-phosphatase
  - Transaldolase
  - Fructose-1-6-bisphosphatase
  - Aldolase (hereditary fructose intolerance)
  - Pyruvate carboxylase
  - Pyruvate dehydrogenase* (Phosphoenoxypropyruvate 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**
  1. Maple syrup urine disease
  2. Non-ketotic hyperglycaemia
  3. Tyrosinaemia type I

  **Enzyme deficiencies**
  - Branched chain ketoacid decarboxylase
  - Glucose cleavage system
  - Fumaryl acetoacetase

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

  **Disorders**
  1. Methylmalonic acidemia
  2. Propionic academia
  3. Isovaleric acidemia
  4. Glutaric aciduria type II
  5. 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.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Enzyme deficiencies</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 Carbamyl phosphate synthetase deficiency</td>
<td>Argininosuccinic acid synthetase</td>
</tr>
<tr>
<td>14 Ornithine carbamyl transferase deficiency</td>
<td>Argininosuccinic acid lyase</td>
</tr>
<tr>
<td>15 Citrullinaemia</td>
<td>Arginase</td>
</tr>
<tr>
<td>16 Argininosuccinic aciduria</td>
<td>Unknown</td>
</tr>
<tr>
<td>17 Argininaemia</td>
<td></td>
</tr>
<tr>
<td>18 Transient hyperammonaemia of prematurity</td>
<td></td>
</tr>
</tbody>
</table>

#### Peroxisomal disorders

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.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Enzyme deficiencies</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 Zellweger’s syndrome</td>
<td>Peroxisomal biogenesis</td>
</tr>
<tr>
<td>20 Rhizomelic chondrodysplasia punctata</td>
<td>Multiple</td>
</tr>
<tr>
<td>21 Neonatal adrenoleukodystrophy</td>
<td>Multiple</td>
</tr>
</tbody>
</table>

#### Mitochondrial disorders

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

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Enzyme deficiencies</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 Pyridoxine dependent seizures</td>
<td>Unknown</td>
</tr>
<tr>
<td>23 Lysosomal storage disease†</td>
<td>Various</td>
</tr>
</tbody>
</table>

*†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.

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