

REVIEW

Detection of inborn errors of metabolism in the newborn

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It is important for paediatricians and neonatologists to keep in mind inborn errors of metabolism (IEMs) as a cause of illness in the neonatal period, as many disorders are treatable and, in most cases, successful outcome is dependent on a rapid diagnosis and early instigation of therapy. Even with untreatable disorders, it is important to establish the diagnosis in the index case in order to allow prenatal diagnosis in subsequent pregnancies. In desperately sick neonates for whom no diagnosis is readily available, IEMs are near the top of the list of differential diagnoses.

IEMs can present in the newborn in a variety of ways. Typically, an IEM is suspected as a result of a suggestive combination of acute clinical symptoms without any prior warning. However, sometimes non-specific clues exist, such as a previous unexplained neonatal death and, in some families, the risk of an IEM is already highlighted by the presence of a previously affected child. IEMs may be detected through the newborn screening programme, though at present phenylketonuria is the only disorder for which mass screening is accepted in the UK. Some IEMs result in dysmorphism, and the investigation of these cases is not complete without considering metabolic causes. Finally, disorders that normally manifest in older children may sometimes cause abnormalities in the newborn period.

Pathogenesis of IEMs—"placental protection"

Like all genetic disorders, IEMs are present from conception, and most defective enzymes are active in fetal life. Nevertheless, most conditions have no adverse consequences on the fetus, as the placenta provides an effective dialysis system for the removal of toxic metabolites. Thus most babies with an IEM are born in good condition and of normal birth weight. Some IEMs, such as galactosaemia, manifest only after the substrate for the deficient enzyme becomes available in the form of feeds. There are some exceptions to this concept of "placental protection"; for example, disorders that affect energy metabolism, such as the primary lactic acidoses and glutaric aciduria type II or non-ketotic hyperglycinaemia where the primary defect is in cerebral intermediary metabolism and the substrate accumulation in body fluids represents an overflow from the brain.

Clinical presentation of IEMs

Maintaining a high index of suspicion of metabolic disease in an ill neonate is essential, and it must be borne in mind that some disorders, such as galactosaemia, can predispose to Gram negative septicaemia.

The first step in the recognition of IEMs is a careful scrutiny of the family history and the obstetric notes. The majority of metabolic disorders presenting in the neonatal period are autosomal recessive, and thus a history of parental consanguinity can be a helpful clue. A few metabolic conditions are associated with maternal problems during pregnancies carrying affected fetuses. It has recently been recognised that some fetal disorders of fatty acid oxidation can predispose the mother to developing acute fatty liver of pregnancy (AFLP) and the HELLP syndrome of haemolysis, elevated liver enzymes, and low platelet count.^{1,2} Steroid sulphatase deficiency can cause prolonged labour as a result of decreased placental oestrogen production,³ and conditions associated with renal pathology can result in oligohydramnios.

PATTERNS OF PRESENTATION

Neurological abnormalities—encephalopathy and seizures

Two general patterns of presentation can be distinguished. The first is a baby, apparently healthy at birth, who after a symptom free interval develops non-specific symptoms such as lethargy, poor feeding, vomiting, or irritability. Metabolic acidosis, altered sensorium, convulsions, and hyperammonaemic coma become apparent soon afterwards. Normal ammonia concentrations in neonates are less than 65 $\mu\text{mol/l}$,⁴ but we have frequently observed concentrations of up to 180 $\mu\text{mol/l}$ in sick newborns. Higher ammonia concentrations warrant thorough investigation for metabolic causes. The organic acidurias (propionic, methylmalonic, and isovaleric aciduria) and the urea cycle defects classically present in this manner, and in either case respiratory alkalosis may be the initial acid–base disturbance.^{5,6} Maple syrup urine disease (MSUD) is a possibility when acid–base disturbances and hyperammonaemia are not prominent features. The likelihood of a metabolic disorder is very high in the presence of ketonuria, as neonates otherwise do not readily produce ketones.

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The second pattern of involvement is a neonate who has overwhelming neurological illness with unconsciousness, convulsions, and apnoea in the absence of significant hyperammonaemia and acid–base disturbances, and without an apparent symptom free interval. The differential diagnosis includes non-ketotic hyperglycaemia, molybdenum cofactor deficiency, pyridoxine dependent seizures, and the primary lactic acidoses. Mitochondrial and peroxisomal disorders can also present in this manner, and often result in severe hypotonia, with or without dysmorphism and congenital anomalies.

Metabolic acidosis

Unexplained, persistent metabolic acidosis is a common feature of IEMs that present neonatally. Calculation of the anion gap can be helpful, as conditions that cause acidosis with a normal anion gap are limited to those associated with renal and intestinal bicarbonate loss. The organic acidaemias and the primary lactic acidoses cause metabolic acidosis with a raised anion gap in the early stages. Most metabolic conditions result in acidosis in the late stages as encephalopathy and circulatory disturbances progress.

Lactic acidosis—Infants with lactic acidosis present a difficult diagnostic problem. A high plasma lactate can be secondary to hypoxia, cardiac disease, infection, or convulsions, whereas primary lactic acidosis may be caused by disorders of pyruvate metabolism and respiratory chain defects. Some IEMs (fatty acid oxidation disorders, organic acidaemias, and urea cycle defects) may also be associated with a secondary lactic acidosis.⁷ As venous obstruction by tourniquet, crying, or breath holding may increase plasma lactate concentrations by two- to threefold, arterial samples are more reliable. Persistent increase of plasma lactate above 3 mmol/l in a neonate who was not asphyxiated and who has no evidence of other organ failure should lead to further investigations for an IEM. The lactic acidoses are a heterogeneous group of disorders, and many defects are tissue specific (for example, limited to muscle or the CNS). Often the infant dies without a diagnosis, and it is essential to collect the correct skin, muscle, and liver samples for enzyme and DNA analyses.

Hypoglycaemia

Inborn errors of metabolism should be considered in all patients with hypoglycaemia in the newborn period although most patients will turn out to have a different diagnosis. Samples should be collected during an episode of hypoglycaemia if possible. Fat oxidation defects, the hepatic forms of glycogen storage disease, and disorders of gluconeogenesis such as fructose-1,6 bisphosphatase deficiency can present in this way. An IEM that primarily affects liver function (see below) can also result in secondary hypoglycaemia.

Cardiac disease

Cardiac failure, particularly in the presence of hypertrophic cardiomyopathy and hypotonia, may suggest a mitochondrial respiratory chain

defect, a long chain fatty acid oxidation disorder, or Pompe's disease (GSD II). Other lysosomal disorders may also be associated with cardiac disease, but dysmorphism is usually the revealing symptom (see below). The multisystem congenital disorders of glycosylation (CDG) can present soon after birth with cardiomyopathy and/or pericardial effusion.⁸ Additional features include failure to thrive, facial dysmorphism, inverted nipples, and abnormal fat distribution.⁹ X linked dilated cardiomyopathy and neutropenia (Barth syndrome) is a recently described entity with characteristic abnormalities on urine organic acid analysis.¹⁰ Cardiac arrhythmias, with or without cardiomyopathy, have been described in most of these conditions.

Liver dysfunction

Galactosaemia is the commonest metabolic cause of liver dysfunction in the newborn period. Besides signs of liver disease, early onset cataracts are very suggestive. Other rarer IEMs such as hepatorenal tyrosinaemia, α_1 antitrypsin deficiency, neonatal haemochromatosis, and mitochondrial respiratory chain disorders must also be considered in the differential diagnosis. Niemann–Pick disease type C (NPC) is a lipid storage disorder that results from a defect of intracellular cholesterol esterification, and classically presents with neurodegenerative manifestations in childhood.¹¹ A significant proportion of patients, however, have neonatal manifestations with variable degrees of cholestasis, liver dysfunction, and hepatosplenomegaly, well before the onset of neurological illness.¹²

Dysmorphism

Besides CDG, other metabolic conditions can manifest with dysmorphism; for example, disorders that affect energy metabolism directly (pyruvate dehydrogenase deficiency, glutaric aciduria type II) or indirectly (3-hydroxyisobutyric aciduria) can result in various physical malformations including facial dysmorphism, and cardiac, renal, and skeletal defects. The disorders of peroxisomal biogenesis (the “Zellweger spectrum”) can present with hypotonia associated with facial features resembling Down's syndrome. Patients with lysosomal disorders usually appear normal in early infancy, but some conditions (GM1 gangliosidosis, I-cell disease, and infantile sialic acid storage disease) can manifest in the first weeks of life with coarse facies, upper airway obstruction, and cardiac dysfunction. Severe defects in cholesterol synthesis (Smith–Lemli–Opitz syndrome, X linked chondrodysplasia punctata, and mevalonic aciduria) can also present with characteristic dysmorphic features and multiple anomalies.^{13 14}

Other suggestive abnormalities

Abnormal body odour is noted in some organic acidaemias, for example, the smell of maple syrup in maple syrup urine disease, and of sweaty feet in isovaleric aciduria and glutaric aciduria type II. Most babies who have an unusual or powerful odour, however, do not have

Table 1 Metabolic conditions associated with hydrops fetalis

| |
|----------------------------------------------|
| Lysosomal disorders |
| Mucopolysaccharidosis types IV and VII |
| Gaucher disease type II |
| GM1 gangliosidosis |
| Niemann–Pick disease type C |
| Farber disease |
| Infantile free sialic acid storage disease |
| Sialidosis |
| Galactosialidosis |
| Mucopolipidosis II (I cell disease) |
| RBC enzyme abnormalities |
| Glucose-6-phosphate dehydrogenase deficiency |
| Pyruvate kinase deficiency |
| Glucosephosphate isomerase deficiency |
| Neonatal haemochromatosis |
| Respiratory chain disorders |
| Congenital disorders of glycosylation |
| Glycogen storage disease type IV |

an IEM. Temperature instability has many common causes, but is also an early feature of Menke's syndrome. Non-immune hydrops fetalis can be associated with a number of metabolic disorders (table 1).^{15 16} Jaundice and bleeding diathesis occur in disorders that affect liver function, but may also be a late sign in other IEMs such as the urea cycle defects.

Investigation of a neonate who may have an IEM

As a wide variety of IEMs can present in the neonate, the level of clinical and biochemical experience required for their diagnosis and treatment is substantial. It is essential to discuss investigations with all the laboratories involved and to give some indication of urgency. Appropriate transportation to the metabolic laboratory must be arranged, and as much clinical information as possible must be provided on the request cards. The interpretation of many metabolic investigations can be confounded by medications and special feeds, hence a full drug and feeding history must be stated.

The approach to diagnosis varies with the nature of severity of symptoms. In some situations, it is possible to make a good guess at the diagnosis clinically and then select the tests most likely to give the answer (see table 2). In

Table 2 Investigations for the diagnosis of an IEM

| |
|-------------------------------------------------------------------------------|
| <i>First line investigations</i> |
| Full blood count |
| Urea and electrolytes |
| Anion gap |
| Blood gases |
| Glucose |
| Lactate |
| Ammonia |
| Liver function tests |
| Urine reducing substances |
| Urine ketones |
| CSF lactate |
| <i>Second line investigations</i> |
| Urine organic acids |
| Urine amino acids |
| Plasma uric acid |
| Plasma amino acids |
| Plasma carnitine and acylcarnitine profile |
| Biotinidase |
| Galactosaemia screening tests (e.g. Beutler) |
| CSF amino acids |
| <i>Third line or specialised investigations</i> |
| Enzyme assays on skin fibroblasts or blood cells |
| DNA mutation analysis |
| Special metabolite assays (e.g. VLCFA, transferrin isoelectric focusing, etc) |

most cases, however, it is necessary to perform a group of tests, as many IEMs can cause very similar symptoms.

THE "METABOLIC SCREEN"

The scope of metabolic disorders is enormous and constantly expanding. The term "metabolic screen" (which would denote a set of investigations to rule out most known metabolic causes of illness) is therefore inappropriate, and such a request to a laboratory is meaningless. Specialised metabolic investigations in a sick neonate must always be dictated by the clinical situation, and directed towards specific conditions (table 3).

Although techniques will vary, most laboratories will require samples of blood (2–3 ml each in heparinised and EDTA bottles, and a dried blood spot on a screening card) and urine (5–10 ml in a sterile container with no preservatives). It is good practice to save and freeze all urine passed for future analysis, and to save a heparinised blood sample before the first blood transfusion. Occasionally more unusual investigations, such as CSF analysis for organic and amino acids may be necessary.¹⁷ It is best to discuss such tests with the laboratory to ensure that the samples are collected and preserved correctly.

In many cases these investigations will provide a definitive diagnosis or a high suspicion of a specific IEM. The complete characterisation of the particular condition usually involves more specific studies, such as enzyme assays, DNA analysis, and family studies. Most of such work is performed on cultured skin fibroblasts or transformed lymphoblast cell lines at supraregional laboratories.

Management while awaiting results

The management should be dictated by the severity of symptoms. *Very mild symptoms* may require no change to the management. As milk feeds are often the source of the toxic metabolites, these should be stopped, if the *symptoms are more than very mild*, while preliminary results are awaited. Generally, intravenous 10% dextrose with added electrolytes should be used. In more severe cases, intravenous bicarbonate may be necessary to correct metabolic acidosis. Other additives should be dictated by the blood biochemistry with the aim of maintaining glucose and electrolyte homeostasis.

The *extremely ill or rapidly deteriorating infant* will require more aggressive therapy. Care must be taken to avoid overhydration in the presence of impaired renal function. Adequate correction of acidosis often requires very large doses of sodium bicarbonate (up to 20–30 mmol/kg in some organic acidaemias) which may cause hypernatraemia, sometimes necessitating dialysis. Blood electrolytes should be checked frequently (4–6 hourly) during correction of the acidosis. If hyperammonaemia is present, treatment with sodium benzoate should be commenced (250 mg/kg loading dose, followed by an infusion of 250 mg/kg/24 hours). The long term neurological outcome of the urea

Table 3 Metabolic investigations according to patterns of presentation

| Presentation | Condition | Specific investigations |
|----------------|---------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| Encephalopathy | Urea cycle defects | Urine amino acids |
| | Organic acidaemias and MSUD | Urine organic acids Plasma amino acids Blood carnitine and acylcarnitine profile Skin biopsy for enzyme analysis |
| | Fatty acid oxidation defects | As above, plus: Blood DNA mutation analysis |
| | Primary lactic acidoses (e.g. pyruvate dehydrogenase deficiency, pyruvate carboxylase deficiency and respiratory chain defects) | CSF lactate Mitochondrial DNA—blood and muscle Muscle biopsy—histology and electron microscopy |
| | Non-ketotic hyperglycinaemia | Skin biopsy—enzymes of pyruvate metabolism Plasma and CSF amino acids |
| Hypoglycaemia | Molybdenum cofactor deficiency | Enzyme analysis on transformed lymphoblasts Urine sulphite (dipstick) Urine amino acids Plasma uric acid |
| | Pyridoxine dependent seizures | Skin biopsy for enzyme analysis Trial of pyridoxine under EEG observation |
| | Fatty acid oxidation defects | As under encephalopathy |
| | Hypopituitarism | Hormone levels (growth hormone, cortisol, ACTH, insulin, and C peptide) |
| | Adrenal dysfunction | |
| Liver disease | Hyperinsulinism | |
| | Gluconeogenic defects (e.g. fructose-1,6 bisphosphatase deficiency) | Blood gases (metabolic acidosis) Plasma lactate Urine organic acids (for glycerol) Enzyme assay—leucocytes or liver biopsy |
| | Glycogen storage disease (types I, III, VI, IX) | Plasma lactate Enzyme assay—leucocytes or liver biopsy Histology on liver biopsy |
| | Secondary to organic acidaemias or disorders affecting the liver | As stated under respective sections |
| | Galactosaemia | Beutler test Red cell galactose-1-phosphate DNA mutation analysis Ophthalmology assessment for cataracts |
| Cardiomyopathy | Tyrosinaemia type I | Plasma amino acids Urine organic acids Investigations for renal Fanconi's syndrome |
| | α_1 Antitrypsin deficiency | Serum α_1 antitrypsin Protease typing |
| | Neonatal haemochromatosis | Serum ferritin Liver biopsy |
| | Niemann–Pick C | Foam cells on bone marrow aspirate, blood film, liver biopsy Filipin staining on skin biopsy |
| | Mitochondrial (respiratory chain) defects | CSF lactate Mitochondrial DNA—blood and muscle Muscle and liver biopsy—histology and electron microscopy |
| Dysmorphism | Pompe's disease (GSD type II) | Enzyme assay on lymphocytes or skin fibroblasts |
| | Fatty acid oxidation defects | As stated under encephalopathy |
| | Mitochondrial (respiratory chain) defects | As stated under liver disease |
| | CDG 1a syndrome | Serum transferrin isoelectric focusing Enzyme assay on skin biopsy |
| | Lysosomal storage disorders | White cell enzymes Urine oligosaccharides and mucopolysaccharides Skin biopsy |
| CDG syndrome | Lysosomal storage disorders | As under cardiomyopathy |
| | Disorders of sterol synthesis | Urine organic acids Plasma 7-dehydrocholesterol Skin biopsy |
| | CDG syndrome | Serum transferrin isoelectric focusing Enzyme assay on skin biopsy |
| | Glutaric aciduria type II | Urine organic acids Blood carnitine/acylcarnitine profile Skin biopsy |

cycle defects depends on the rapidity of resolution of the initial hyperammonaemic coma. The use of medications alone is rarely sufficient in this situation, and dialysis is usually necessary. Haemodialysis and haemodiafiltration are more effective than peritoneal dialysis, and if available, should be the methods of choice in the initial treatment of urea cycle defects, MSUD, and the organic acidaemias.^{18–20} Exchange transfusion is not useful, except in desperate situations when dialysis is not immediately available.

Secondary carnitine deficiency is common in many metabolic conditions, especially the organic acidaemias and fatty acid oxidation defects. Carnitine supplementation (100 mg/kg/day in four divided doses) is therefore useful in infants with suspected metabolic disease while awaiting results.

Respiratory depression and cerebral oedema caused by direct toxic effects of accumulating metabolites are commonly present. Ventilatory support should therefore be used early and continued until the baby is breathing vigorously. Clinical recovery to a degree sufficient to withdraw ventilatory support can be delayed two to three days after correction of the metabolic abnormality. Maintenance of good hydration and tissue perfusion may necessitate the use of inotropes and colloid infusions.

As most metabolic conditions are aggravated by tissue catabolism, nutritional support in the acute phase requires careful attention. Initially, 10% dextrose is sufficient, but more concentrated solutions (up to 20%) should be used via a central line to induce mild hyperglycaemia (blood glucose 7–12 mmol/l) if feeds cannot be commenced within 24 hours. Anabolism can

Table 4 Investigations if death is inevitable and a metabolic cause is suspected

| Specimen | Sampling details |
|---------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Plasma | 3–5 ml lithium heparin sample, plasma separated and frozen |
| Whole blood for DNA analysis | 3–5 ml EDTA sample kept refrigerated (<i>should not be frozen</i>) (other whole blood samples can also be used) |
| Blood spot for acylcarnitine analysis | 2–3 spots on filter paper or Guthrie card |
| Urine | Frozen in a plain sterile container |
| Skin biopsy for fibroblast culture | Collected using aseptic technique, stored in a skin biopsy medium (if this is not available, viral culture medium or normal saline in a sterile container may be used) (<i>should not be frozen</i>) |
| Muscle biopsy | 1 cm ³ piece immediately frozen in liquid nitrogen or dry ice for enzymology, histology, and DNA analysis; one piece preserved in gluteraldehyde for electron microscopy |
| Liver biopsy | 1 cm ³ piece immediately frozen in liquid nitrogen or dry ice for enzymology, histology, and DNA analysis; one piece preserved in gluteraldehyde for electron microscopy |

be further promoted by infusing small doses of insulin (0.05 U/kg/h).

After stabilisation, subsequent dietary management will vary depending on the specific diagnosis, and should be supervised by a dietician with experience in managing metabolic disease.

Some metabolic disorders have vitamin responsive forms and in the past, a combination of vitamins and cofactors were administered to sick newborns while results were awaited. Nowadays, this blind vitamin treatment is not justified, as most metabolic conditions can be diagnosed fairly rapidly. Once the diagnosis is made, appropriate cofactor therapy can be used in therapeutic doses (approximately 100 times the daily requirement).

Management when no diagnosis can be made

Occasionally no clear diagnosis can be made on the initial investigations. Every effort must be made to keep such neonates alive until all investigations are completed. A sick neonate with hyperammonaemia merits full biochemical correction by dialysis, even if the initial biochemical tests are negative, as transient hyperammonaemia of the newborn (THAN) may be the underlying diagnosis. The majority of patients with THAN have been preterm infants who have mild respiratory distress syndrome.²¹ Plasma ammonia concentrations may be greatly increased, but the plasma and urine amino acid analyses are not characteristic of any of the urea cycle defects. If treated aggressively, THAN is compatible with a good long term neurological outcome, and hyperammonaemia does not recur even on a normal protein diet.²² The aetiology of this condition is unknown.

Management when death is inevitable

Some patients will not survive, despite intensive treatment. In such cases, establishing a diagnosis is very important for genetic counselling and for later prenatal diagnosis. A full autopsy is preferable for internal anomalies, but it is uncommon to arrive at a metabolic diagnosis based on routine autopsy findings alone. It is therefore essential to collect the relevant specimens and biopsy specimens before or shortly after death. It is useful to discuss the infant's poor prognosis frankly with the parents

and to obtain their permission for autopsy and biopsies before the infant dies. In our experience, it is unusual not to obtain at least the minimum specimens required for a metabolic diagnosis, even if full autopsy is refused. These include a blood spot on a screening card, a lithium heparin, and an EDTA blood sample (3–5 ml each), all possible urine frozen in plain sterile containers, and a skin biopsy refrigerated in culture medium (table 4). If possible, muscle and liver biopsy specimens should also be obtained. Open liver biopsy is preferable, but needle biopsy is also of use if an open biopsy cannot be performed. One piece of each should be immediately frozen in liquid nitrogen or dry ice for enzyme analysis, and another stored in an appropriate medium (for example, gluteraldehyde) for electron microscopy.

Management when an IEM is anticipated

Sometimes the diagnosis of an IEM can be known or suspected in advance: there may be a previously affected sibling, specific antenatal testing may have established the diagnosis, or a mother may be a proven carrier of an X linked condition. The optimal management should be established prior to delivery. The choice is whether to treat the baby as affected while awaiting tests, or to investigate promptly and commence appropriate treatment when results are available. The decision will vary depending on the disorder in question, but should be made in collaboration with the paediatrician, obstetrician, and metabolic specialist.

Many disorders (such as fatty acid oxidation defects and organic acidaemias) can be readily diagnosed by analysis of cord blood specimens using tandem mass spectrometry, and discussion with a metabolic laboratory before delivery should enable a rapid diagnosis.

Withdrawal of treatment

If clinical improvement does not occur within a few days, the infant is unlikely to recover near normal cerebral function. In such a situation, it is reasonable to discuss withdrawal of intensive life support measures with the parents. This is not difficult if the diagnosis is known and the prognosis can be explained with some certainty. Even if the exact diagnosis is not known, it is often possible to give the parents some idea of the likely group of conditions (for example, disorders of pyruvate metabolism or respiratory chain defects) that their child might have. Occasionally, a gravely ill neonate may survive withdrawal of intensive care against all expectations. Such infants are likely to have frequent acute episodes of deterioration, and depending on the degree of brain damage and the underlying condition, a decision to not undertake extraordinary measures to prolong life during the next episode may be made in discussion with the parents.

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