Review

Inborn errors of metabolism around time of birth

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Inborn errors of metabolism commonly present around the time of birth. Although most affected babies are born healthy and subsequently deteriorate, some disorders may present at (or shortly after) birth and a few may be detected by antenatal ultrosonography. In many cases, it is important that the diagnosis is made quickly and a strategy to identify those at high risk is proposed. Treatment should not be delayed for a definitive diagnosis.

Inborn errors of metabolism are individually rare, but since many are now recognised, affected babies will present in any neonatal unit from time to time. General paediatricians and neonatologists have the crucial role of identifying which patients need to be investigated. This should be done in collaboration with a specialist unit. The true nature of the illness must be diagnosed quickly to prevent permanent neurological damage. Since the early symptoms and signs are almost always non-specific, a strategy is needed that will identify children at high risk of metabolic disorders.

Family history

In families known to have a metabolic disease, investigations and treatment should be considered before a child develops symptoms. Since some metabolic disorders are X-linked, knowledge of relatives outside the immediate family may be relevant. Even without a specific diagnosis, undiagnosed neonatal deaths or unexplained severe illness in childhood may provide useful clues. Most patients, however, have autosomal recessive disorders and have no affected relatives, but there may still be pointers in the family history, such as consanguinity, which increases the risk of rare autosomal recessive disorders.

Presentation

Inborn errors may present at almost any time in many different ways, but characteristically, they may do so before birth, at birth, or during the first 2–3 days of life, as sudden death, or as deterioration after normal birth and delivery.

During pregnancy

Women carrying a fetus with a long-chain 3-hydroxyacyl-Coenzyme A dehydrogenase deficiency (LCHAD deficiency) are at high risk of developing complications during pregnancy. The most frequent related disorder is haemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome, but acute fatty liver at pregnancy and persistent hyperemesis are also recognised.[1] In most pregnant women, these complications are not related to the inborn error.

Lancet 2000; **356:** 583–87

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At birth

Several disorders present at or soon after birth. Such presentations include early-onset seizures, severe hypotonia, ascites or hydrops fetalis, and dysmorphic syndromes. Panel 1 shows the main metabolic causes of presentations.[2–5] Perinatal asphyxia is a common misdiagnosis in babies presenting with neurological abnormalities, especially in those with congenital lactic acidoses and pyridoxine dependency. Some disorders associated with early-onset fits cause seizures in utero, but these disorders are not generally recognised at the time. By contrast, most fetuses with ascites and many with malformations are detected before birth by prenatal ultrasonography. The biochemical basis of more dysmorphic syndromes will probably be elucidated with time.

Sudden death

Sudden death at age 2–3 days is devastating for any family. Non-metabolic disorders causing sudden death at this age include sepsis and congenital heart disease. Defects of fatty-acid oxidation may also be important, especially long-chain disorders, which can lead to respiratory arrest and heart block or arrhythmias.[6] In most cases, necropsy reveals an excess of fat droplets in liver or heart tissue but samples for metabolic tests should be obtained as soon as possible after death, without waiting for necropsy (panel 2). Under these circumstances, collection of blood spots on Guthrie cards is especially important for analysis of acylcarnitines and a sample for DNA extraction and skin for fibroblast culture.

Deterioration after symptom-free period

Most babies with inborn errors are born at term and initially seem to be well but deteriorate. Since some catabolism always occurs in the first few days of life, metabolites accumulate even in babies who do not receive oral feeds. The rate of deterioration is variable and babies are frequently suspected initially as being septic. Other differential diagnoses include neurovascular disorders (especially in preterm babies), duct-dependent heart disease, drug withdrawal, and endocrine disorders such as adrenal insufficiency. Ultimately, most neonates with inborn errors presenting in this way become encephalopathic, but every effort should be made to identify patients before they are seriously ill if neurological sequelae are to be avoided. We think, therefore, that some additional investigations should be done at the same time as septic screening, especially in term babies (panel 3).

Panel 1: **Inborn errors presenting before or soon after birth**

Seizures/apnoea	Severe hypotonia	Ascites/non-immune hydrops	Dysmorphism
Pyridoxine dependency	Peroxisomal disorders	Some lysosomal disorders*	Peroxisomal disorders
Peroxisomal disorders	Non-ketotic hyperglycinaemia	Erythrocyte enzymopathies†	Disorders of cholesterol synthesis‡
Molybdenum cofactor deficiency	Congenital lactic acidoses	Pearson syndrome and other respiratory-chain disorders[2]	Some lysosomal disorders§
Non-ketotic hyperglycinaemia	Carbohydrate deficient glycoprotein syndromes	Neonatal haemochromatosis	Carbohydrate-deficient glycoprotein syndromes
Congenital lactic acidoses		Carbohydrate-deficient glycoprotein syndromes[3]‖	Congenital lactic acidoses[5]
		Glycogen storage disease type IV[4]‖	Glutaric aciduria type II
			3-Hydroxyisobutyryl-Coenzyme A deacylase deficiency‖

Neonatal haemochromatosis is included since it may present like an inborn error, but cause is unclear. *Lysosomal storage disorders associated with hydrops fetalis include Gaucher's disease type II, infantile free-sialic-acid storage disease, sialidosis type II, galactosialidosis, G_{M1} gangliosidosis, Niemann-Pick disease type C, mucopolysaccharidosis types IV and VII, mucolipidosis type II, and Farber disease. †Erythrocyte enzymopathies associated with hydrops fetalis include glucose-6-phosphate dehydrogenase, glucose phosphate isomerase, and pyruvate kinase deficiencies. ‡Disorders of cholesterol synthesis include Smith-Lemli-Opitz and X-linked dominant Conradi-Hunermann syndromes, desmosterolosis, and mevalonic aciduria. §Lysosomal storage disorders that can be associated with dysmorphism from birth include G_{M1} gangliosidosis, galactosialidosis, sialidosis type II, infantile free-sialic-acid storage disease, mucopolysaccharidosis type VII, and mucolipidosis type II. ‖Rare causes.

Patterns of deterioration

Almost all babies with inborn errors who deteriorate after an initial period of health fall into one or more of five groups. Acute parenchymal liver disease; disorders of acid-base status; cardiac disorders: cardiomyopathy and arrhythmias; neurological deterioration; and unexplained hypoglycaemia. The disorders that may lead to these illnesses are listed in panel 4.[7] Although some babies have characteristic odour (eg, maple syrup urine disease, isovaleric acidaemia), such signs are uncommon and are seldom diagnostically useful. Other disorders may coexist with inborn errors. Thus, galactosaemia predisposes to gram-negative sepsis, and cerebral or pulmonary haemorrhage may be the terminal event in urea-cycle disorders.

Acute parenchymal liver disease

Jaundice, hepatomegaly (sometimes with splenomegaly and ascites), and clotting abnormalities are seen in these disorders. Renal tubular abnormalities commonly accompany the liver disease. The most common metabolic causes in the UK are galactosaemia and α-1-antitrypsin deficiency; other causes are summarised in panel 4. Though typical of galactosaemia, cataracts may also accompany liver disease in patients with respiratory chain disorders.[8] Hereditary fructose intolerance presents at this age only if fructose is given, and peroxisomal disorders generally present with dysmorphism or neurological disorders rather than liver disease. Crigler-Najjar syndrome, the main disorder of bilirubin metabolism seen at this age causes unconjugated hyperbilirubinaemia.

Acid-base disorders

Acid-base disorders are common in sick neonates—most commonly they have a mixed respiratory and metabolic acidosis. In babies presenting with grunting and dyspnoea, however, two findings may provide useful clues. First, a persistent metabolic acidosis with normal tissue perfusion may suggest an organic acidaemia or a congenital lactic acidosis. Second, a mild respiratory alkalosis in babies who are not being ventilated almost certainly suggests hyperammonaemia, which is frequently associated with irritability and stridor and is a valuable pointer to many inborn errors (panel 5). These acid-base changes are not specific. Babies with organic acidaemia can be alkalotic[9] and those with urea-cycle disorders may be acidotic. The latter is especially likely if the diagnosis has been delayed, since hyperammonaemia leads to vasomotor instability and collapse, which emphasises the importance of early assessment of acid-base status.

Cardiac disease

Some patients with long-chain fatty-acid oxidation disorders or respiratory-chain defects (including Sengers and Barth syndromes) present with cardiomyopathy or arrhythmias shortly after birth or later in the neonatal period.[6,10–12] Neonates with carbohydrate-deficient glycoprotein syndromes sometimes have pericardial effusions or, more rarely, cardiomyopathy.[13] Cardiomegaly is also a feature of hyperinsulinaemic hypoglycaemia. Other metabolic diseases associated with cardiomyopathy include lysosomal disorders, notably Pompe's disease, but these disorders seldom present in the neonatal period.

Panel 2: **Samples to be taken after death when metabolic disease suspected**

Plasma: heparinised, separated, and deep frozen
Blood spots: on filter paper for acylcarnitines
Urine: deep frozen in plain tube
Sample for DNA: blood anticoagulated with edetic acid and deep frozen (other samples may be suitable)
Skin: for fibroblast culture, taken with sterile precautions into medium and stored at 4–8°C **not** frozen
Liver: snap frozen for histochemistry or enzymology
Muscle and other tissues: as indicated, snap frozen for histochemistry or enzymology

Panel 3: **Additional investigations to be done at time of septic screening**

Blood or plasma	Urine
pH and blood gas	Sugars
Glucose	Ketones
Electrolytes and anion gap	
Liver-function tests	
Ammonia	
Guthrie card for aminoacids and acylcarnitines*	

*Increasing availability of tandem-mass spectrometry enables rapid analysis of aminoacids and acylcarnitines in blood spots. Guthrie cards carrying blood spots are useful and should be stored since they can also be used as a source of DNA.

Panel 4: **Metabolic disorders associated with various patterns of deterioration**

Liver disease	Acid-base disorders	Cardiac disorders	Neurological deterioration	Hypoglycaemia
Galactosaemia	Metabolic acidosis	Disorders of fatty-acid oxidation[2]	Hyperammonaemia	Endocrine disorders
α-1-antitrypsin deficiency	Organic acidaemias	Respiratory-chain disorders[5-7]	Organic acidaemias	Disorder of fatty-acid oxidation
Respiratory chain disorders[2]	Congenital lactic acidosis	Carbohydrate-deficient glycoprotein syndromes[8]	Maple syrup urine disease	Fructose 1,6-bisphosphatase deficiency
Neonatal haemochromatosis	Fructose 1,6-bisphosphatase deficiency	Congenital hyperinsulinism	Disorders of fatty-acid oxidation[2]	Glycogen storage disease type 1
Disorders of fatty-acid oxidation[2]	Ketolysis defects	Some other forms of glycogen storage disease*†	Congenital lactic acidoses	Respiratory-chain disorders[3]
Tyrosinaemia type 1	Respiratory alkalosis	Pompe's disease†	Peroxisomal disorders	Organic acidaemias
Niemann-Pick type C	Hyperammonaemia		Non-ketotic hyperglycinaemia	Hereditary fructose intolerance†
Hereditary fructose intolerance†			Molybdenum cofactor deficiency	
			Remethylation defects†	

Neonatal haemochromatosis has been included since it may present like an inborn error but cause is unclear. Endocrine causes of hypoglycaemia have been included since they are common and require urgent diagnosis and management. *Glycogen storage disease type IV and heart-specific phosphorylase-D-kinase deficiency can cause cardiomyopathy in the neonatal period. †Rare causes.

Neurological deterioration

Disorders in this group include organic acidaemias, urea-cycle defects, maple syrup urine disease, fatty-acid oxidation defects, congenital lactic acidoses, and any of those disorders that might present with fits or hypotonia at birth (panels 1 and 4). The rate of deterioration varies. Some patients may have only a brief phase in which they seem well, whereas others may seem well for several days with a more gradual deterioration. In babies that deteriorate rapidly, it can be difficult to distinguish the illness from birth asphyxia. Early signs of encephalopathy are non-specific, such as poor feeding, lethargy, vomiting, and abnormalities of tone or irritability. Vigilance and strategies for early detection of biochemical markers are especially important for these neonates to avoid diagnostic delays. Later symptoms may include drowsiness, fits, hiccups, myoclonus, apnoeic episodes, severe hypotonia, irritability with cycling movements, and coma. Cerebral oedema may lead to a bulging fontanelle, and brainstem swelling to vasomotor instability.

Hypoglycaemia

There are many causes of hypoglycaemia in neonates, and most neonates with low blood glucose concentrations do not have primary metabolic or endocrine disorders. Nevertheless, well-grown term babies with severe, persistent or otherwise unexplained hypoglycaemia should be investigated for an underlying metabolic or endocrine cause (panel 4). The course of the hypoglycaemia may provide important clues. Hyperinsulinism should be suspected if the child had recurrent severe hypoglycaemia. Hypoglycaemia associated with metabolic acidosis suggests an organic acidaemia or defect of gluconeogenesis (glycogen storage disease type 1 or fructose 1,6-bisphosphatase deficiency). In patients with cholestatic jaundice, hypoglycaemia raises the possibility of adrenal or pituitary insufficiency or a defect of fatty-acid oxidation.[2]

Panel 5: **Causes of neonatal hyperammonaemia**

Inherited disorders	Acquired disorders
Disorders of the urea cycle	Any severe illness
Organic acidaemias	Birth asphyxia
Disorders of fatty-acid oxidation[2]	Total parenteral nutrition
Pyruvate carboxylase deficiency*	Herpes simplex*
Hyperornithinaemia (HHH syndrome and OAT deficiency)[7]*	Transient hyperammonaemia of the neonate*
Mild hyperammonaemia is common in many other inborn errors	

HHH= hyperornithinaemia, hyperammonaemia, homocitrolinaemia; OAT=ornithine aminotransferase. *Rare causes.

Management

For some disorders, such as Zellweger syndrome, supportive care is all that can be offered. Fortunately, treatment is possible for many inborn errors and the principles are outlined in panel 6. General neonatal intensive care is important and, in some disorders, this approach may be all that is needed (eg, phototherapy with or without exchange transfusion in erythrocyte enzymopathies). In other disorders, treatment to keep catabolism to a minimum and remove toxic metabolites are required. These measures can start before a precise diagnosis is known and are vital if the outcome of inborn errors is to improve.

First, any nutrient that may have precipitated the illness, such as galactose or protein, should be stopped and an oral or intravenous high-energy intake given. In such babies, the need to provide adequate glucose may require use of concentrated solutions through a central line (or possibly relaxation of the usual fluid restrictions, with diuretics or even dialysis if necessary). Generally, just glucose is given, although fat emulsions have been used in some disorders to increase energy intake.[14] With high rates of glucose infusion, blood glucose concentrations should be monitored. If hyperglycaemia (>12 mmol/L) and glycosuria are difficult to control, insulin may be given cautiously. Some patients with metabolic disorders are insulin resistant but some neonates are sensitive to small doses. Insulin has the additional advantage of promoting anabolism.[15] Growth hormone has also been advocated to promote anabolism, although there is no evidence that outcomes improve. Acidosis, electrolyte disturbances, dehydration, and hypothermia should be corrected and vigilance is necessary for sepsis or other complications.

Sometimes metabolic derangement cannot be controlled solely by the means outlined above. Moreover, neurological damage is frequently related to the concentration and the duration of exposure to toxic metabolites such as ammonia or leucine (in maple syrup urine disease). Toxic metabolites should be removed as quickly as possible, which often requires some form of

Panel 6: **Management of suspected metabolic disorder**

- Stop any nutrient triggering disorder, eg, protein, galactose
- Give high-energy intake, generally oral or intravenous glucose
- Neonatal intensive care by correct tissue perfusion, dehydration acidosis, hypothermia, anaemia, &c
- Treat hyperammonaemia with sodium benzoate, sodium phenylbutyrate, arginine
- Dialysis by haemofiltration, haemodialysis, or peritoneal (bicarbonate based)
- Insulin to control hyperglycaemia and reduce catabolism
- Vitamins, eg, biotin, hydroxocobalamin, or pyridoxine
- Specific treatment, eg, carnitine, glycine for isovaleric acidaemia

dialysis; removal can also correct other disorders such as acidosis and fluid overload. Peritoneal dialysis was used in the past but many studies have shown that higher clearances can be achieved with extracorporeal blood purification.[16] In theory, haemodialysis can achieve the highest clearances,[11] and haemodialysis devices are now available with small extracorporeal volumes and their haemodynamic effects can be kept to a minimum by prefilling the systems with blood.[11] The choice of haemodialysis, haemofiltration, or haemodiafiltration is, however, partly dependent on local considerations. Haemodialysis only has higher clearances than other methods at high blood-flow rates, which require the placement of adequately sized catheters.[11] Ideally, the dialysis should be continuous to avoid rebound accumulation of toxic chemicals, but adequate numbers of skilled staff must be available. Rapid changes in electrolyte and metabolite concentrations might lead to excessive fluid shifts and further complications.

Hyperammonaemia

The interpretation of plasma ammonia concentrations can lead to difficulties. Normal values in neonates are less than 65 μmol/L,[17] but any sick neonate may have values of up to 180 μmol/L. Values higher than 200 μmol/L are probably caused by metabolic disorders (AAMM, JVL, unpublished observations) and should be investigated urgently. Severe hyperammonaemia (>500 μmol/L) is a serious complication of many inborn errors and the outcome is poor even with aggressive treatment. Before proceeding, parents must be told about the risk of neurological impairment, the likelihood of further hyperammonaemic episodes and the need for complex treatment throughout life.

Haemodialysis or haemofiltration should be started as soon as possible in patients with severe hyperammonaemia or rapidly rising concentrations. In addition, arginine, sodium benzoate, and sodium phenylbutyrate are generally administered. The latter two drugs are conjugated to glycine and glutamine, respectively, and the products are excreted, which creates an alternative pathway for nitrogen excretion. Few data are available, however, on the conjugation of these compounds in neonates and the effects are probably less than maximum (C Bachmann, personal communication). Virtually all studies have involved patients with urea-cycle defects, but it may be difficult to distinguish patients with organic acidaemias at the time of presentation. Some researchers have advocated more conservative regimens until the diagnosis is known but the evidence suggests that the drugs are safe and effective in organic acidaemias.[9]

Specific treatment

Once the diagnosis is known, any specific treatment should be given in collaboration with a specialist centre. Organic acids are excreted partly bound to carnitine. Carnitine concentrations are generally low in organic acidaemias, especially during episodes of neonatal decompensation. Carnitine supplementation increases the excretion of carnitine esters and, therefore, carnitine is widely used in organic acidaemias, despite there being no firm evidence that this treatment improves outcomes. In isovaleric acidaemia, glycine plays an important part in promoting metabolite excretion and supplements should be given in combination with carnitine. Use of carnitine in fatty-acid-oxidation defects is controversial, since long-chain acylcarnitines may accumulate. Branched chain-free aminoacid mixtures should be given as early as possible in maple syrup urine disease.[18] Tyrosinaemia type 1 sometimes presents with acute liver failure in the neonatal period, and the use of nitisinone (NTBC) may be life saving.[19]

Megavitamin treatment

Many enzymes require coenzymes derived from vitamins for enzyme activity, and disorders are well recognised in which pharmacological doses of precursor vitamins will increase the enzyme activity. Large doses of many vitamins or cofactor precursors are, therefore, commonly administered. Teatment with pyridoxine, vitamin B12, and biotin is justified since pyridoxine-dependent seizures, vitamin-responsive methylmalonic acidaemia, holocarboxylase synthetase, and, rarely, biotinidase deficiency can present in neonates. The justification for many other vitamins is doubtful, especially since vitamin-responsive forms of inborn errors are generally milder than other forms and, therefore, seldom present in the neonatal period.

Continuing management

Emergency treatment is nutritionally incomplete and, if used long-term, may increase catabolism, leading to poor metabolic control and frank malnutrition. Ideally, some protein should be introduced in the first 48 h of treatment and balanced feeds should be restarted as soon as possible.

Postmortem diagnosis

Some patients die despite aggressive therapy, whereas in others metabolic disease is considered only after a baby has died. Appropriate samples must be taken immediately before or after death (panel 2), otherwise it may not be possible to make a diagnosis. A conventional necropsy seldom provides many clues. Prenatal diagnosis is possible for many inborn errors but this requires precise diagnoses in index cases.

Conclusions

Progress in the treatment of inborn errors has been slower than progress in their biochemical and molecular bases. Nevertheless, outcomes are improving with the use of dialysis and drugs to promote the removal of toxic metabolites and measures to keep catabolism to a minimum. Early intervention is crucial if neurological sequelae are to be avoided, which requires constant vigilance and routine measurement of biochemical markers in suspected cases.

The management plan we have outlined is based largely on personal experience rather than published evidence. Researchers in no clinical trial have documented prospectively the presentation and outcome of inborn errors presenting neonatally. Some information is available from highly inbred communities such as the old-order Amish, but for the general population, studies would require large numbers (more than 1 million babies) to obtain meaningful results.

In the UK, neonatal screening will probably be extended in the future to a wider range of inborn errors, with use of tandem mass spectrometry. Evidence will, therefore, become available on management. One conclusion will probably be that, to have maximum benefit, screening will have to be done earlier than the current age of 6–14 days.

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