Current topic

Diagnosis and management of inborn errors of metabolism

J E WRAITH

Willink Biochemical Genetics Unit, Royal Manchester Children's Hospital

Few paediatricians will have avoided the predicament of being faced with a desperately ill neonate for whom a diagnosis is not immediately obvious. The majority of such infants will have comparatively common neonatal problems such as systemic infection, congenital heart disease, necrotising enterocolitis, or intracranial haemorrhage. An appreciable minority, however, will have a potentially treatable inborn error of metabolism, and rapid diagnosis and institution of appropriate treatment is essential if a good outcome is to be achieved.

Metabolic disease can present in several ways in the newborn period,[1] but this review will concentrate on those that present acutely and result in death or severe brain damage if not detected and treated.

Before discussing individual diseases, a number of general points must be made. Inborn errors of metabolism are rare and experience is necessary if diagnosis and treatment are to proceed rapidly. As well as expert laboratory and dietetic services, skilled interpretation by a clinician is essential and this will generally lead to transfer to a specialised unit of infants suspected of having one of these diseases. Facilities for initial metabolic investigations must be readily available in each region, and clinicians should be encouraged to use them freely. More specialised investigations—for example, assays of specific enzymes—are needed in only a small number of supraregional laboratories.

Diagnosis and treatment should be aggressive. Some paediatricians are concerned by this therapeutic approach and feel there is a risk of keeping alive a grossly handicapped infant who would otherwise have died peacefully. In practice this is not a problem as it is usually possible to assess prognosis accurately after a short period of energetic treatment. If there is no prospect of reasonably normal cerebral function one can refrain from active measures during the next acute exacerbation. In this way treatment can be assessed at regular intervals, and initially most survivors will be mentally normal or have only minor degrees of brain damage. The long term prognosis for many of the diseases remains guarded, however, even in units providing the best care. The appendix gives some examples of disorders producing severe neonatal illness; more comprehensive lists are available.[1–4]

Clues to the diagnosis of metabolic disease in the newborn

The diagnosis of a metabolic disorder in a seriously ill neonate depends largely on the awareness of the clinicians, but a number of clues can be obtained from the history, clinical examination, and simple 'bedside' tests.

CLUES FROM THE HISTORY
A history of consanguinity is important as many of the disorders are recessively inherited. In addition a previous history of stillbirth or neonatal death in the family is relevant. Ornithine carbamyl transferase deficiency is X linked, and there may be a history of male deaths on the maternal side of the family.

Most affected infants are delivered at or near full term in good condition with a normal birth weight and remain well in the early hours or days of life. The placenta effectively 'haemodialyses' the fetus by removing toxic metabolites, and the fetus has not had contact with substances in the diet (for example, protein) that can precipitate clinical symptoms.

Intense catabolism during the first few days of life together with the introduciton of feeds containing protein unmask the metabolic lesion. Further problems such as starvation, surgery, or superadded infection may all add to the catabolic stress and lead to an exacerbation of symptoms.

A change of feeds may be of importance in an infant with galactosaemia or hereditary fructose intolerance, and a full dietary history is essential. Often the infant will improve when feeds are discontinued only to relapse when milk is restarted, and this episodic pattern of improvement with deterioration should immediately indicate a possible diagnosis.

CLUES FROM THE EXAMINATION

On most occasions physical examination of the affected infant will not lead to a diagnosis. Rarely the typical odour of isovaleric acidaemia, glutaric aciduria type II, or maple syrup urine disease will be noted. Infants with galactosaemia develop cataracts within the first week of life, but otherwise signs and symptoms are non-specific and usually one is faced with a neurologically abnormal, convulsing infant who rapidly proceeds to a comatose state.

CLUES FROM 'BEDSIDE' TESTS

All severely ill neonates will have rapid biochemical and haematological tests carried out. These generally include a full blood count and blood film, estimations of bilirubin, electrolyte and blood glucose concentrations, and acid-base studies. A true metabolic acidosis can easily be missed unless acid-base testing is carried out promptly. A mixed metabolic and respiratory acidosis is common in a severely ill neonate, and the metabolic component may be further masked by mechanical ventilation.

In suspected metabolic disease emphasis has been placed on 'spot' testing of the urine for various compounds. These tests have many shortcomings, are of questionable value, and should not be relied upon to make or refute a diagnosis—especially if specific metabolic screening methods are available in all regions. Urine testing for reducing substances is still often mentioned by referring clinicians who suspect galactosaemia. We have seen a number of neonates with galactosaemia whose urine did not show any reducing substances, despite their being severely ill. In others severe renal tubular disease limits the value of urine testing. A specific screening test for classical galactosaemia must be carried out as a matter of urgency on all infants suspected of having the disease, and this test must be readily available in all regions.

A urine test for ketones can be useful. Heavy ketonuria is unusual in the neonatal period and its detection should be immediately followed by organic acid analysis.

In patients with acidosis, calculation of the anion gap—the sum of the serum concentrations of sodium and potassium minus the sum of the serum concentrations of chloride and bicarbonate (mmol/l)—can be helpful. Patients with an increased anion gap, and especially those with a value greater than 25 mmol/l (normal 12–16 mmol/l), are likely to have a specific organic acidaemia. Patients with a normal anion gap and acidosis are most likely to have renal tubular acidosis or intestinal bicarbonate loss.[5][6]

The metabolic screen

Metabolic tests must be carried out urgently, at the same time as tests to detect infections and other common neonatal illnesses. One runs the risk of missing the diagnosis if a delay is caused while the results of an infection screen or echocardiogram are awaited before considering metabolic investigations. Occasionally we are asked to give advice after an infant's death, and although we are able to perform some metabolic investigations (see below) early suspicion and collection of the appropriate tissues and fluid from a living child permits a more comprehensive screen for metabolic disease.[7][8]

Although techniques vary, most laboratories will require a sample of blood (1–2 ml in a heparinised tube) and urine (5–10 ml in a sterile container with no preservatives) for a metabolic screen. If an urgent result is required it is essential that the referring clinician contacts the laboratory in advance to indicate the urgency. Full details of diet and drugs must be included, and the samples should be transported rapidly to the laboratory. Where possible blood must be taken before any blood transfusion, as this will interfere with the screening test most laboratories use to exclude galactosaemia.[9] If this is not possible the laboratory personnel must be told about the transfusion so that an alternative test can be used. It is good clinical practice to save a sample of blood from all infants who require exchange transfusion in case screening for galactosaemia is later thought to be necessary.

In our laboratory amino acids concentrations are estimated in blood and urine by one dimensional paper chromatography. Abnormal results are then characterised quantitatively. Gas liquid chromatography with mass spectrometry is used for organic acid analyses. The plasma ammonia concentration should be measured, and a portion of the urine specimen kept for orotic acid estimation if the ammonia concentration is high. Occasionally more specialised investigations will be required—for example, amino acid or organic acid analysis on cerebrospinal fluid—and if this is the case it is best to discuss the clinical problem with the laboratory to ensure that the appropriate samples are collected.

Infants with lactic acidosis present a difficult problem. It is difficult to distinguish primary lactic acidosis caused by a defect in pyruvate metabolism

from secondary lactic acidosis caused by hypoxia, cardiac disease, infection, or convulsions. It is necessary to treat possible underlying causes aggressively, while trying to separate the two groups. Plasma lactate and pyruvate are extremely sensitive to the method of collection, and venous obstruction by crying, torniquet, or restraint can cause a two to three fold increase in concentrations. The urinary lactate concentration is useful for monitoring if blood lactate is greater than 6 mmol/l. In those patients with secondary lactic acidosis, the urinary lactate concentrations fall as the underlying disorder improves, while infants with a primary defect are unresponsive to most treatments. Often the child dies before a clear distinction is made and one has to rely on formal assay of the enzymes known to cause lactic acidoses. This is an unsatisfactory approach as many patients with strong evidence of a primary defect have no biochemical abnormality on testing. Lactic acidosis is a heterogenous group of disorders and it is possible that many defects have not been fully defined.[10] With other disorders we would expect to confirm the diagnosis of a urea cycle defect, amino acid disorder, or organic acidaemia within six hours of receiving the samples (and often sooner).

Management while awaiting results

For most infants with severe symptoms in the newborn period active treatment is required, and at this point consideration of transfer to a specialised unit should be made. General measures will include correcting electrolyte imbalance and treating acidosis with sodium bicarbonate; often large doses of bicarbonate are necessary and we prefer to give it in a steady intravenous infusion over 24 hours. There is always a risk of inducing hypernatraemia, but with acidosis so resistant to treatment dialysis should be considered early. Mechanical ventilation is usually required for severely affected infants.

The key to treatment is to try and induce an anabolic state as quickly as possible. A high energy intake, using 15–20% dextrose infusions together with insulin (1U/3 g glucose, or approximately 0·05 U/kg/hour) and lipid solutions may help to initiate anabolism. It is prudent to insert a central venous line as this regimen rapidly damages peripheral veins and adequate venous access is of vital importance. Though this regimen is suitable for most disorders, patients with a primary lactic acidosis may be made worse by a carbohydrate load and for these patients the next phase of treatment (removal of toxic metabolites) becomes of paramount importance. A number of studies have compared the efficacy of exchange transfusion, haemodialysis, and peritoneal dialysis in the acute management of inborn errors.[11] We prefer to use peritoneal dialysis, withholding exchange transfusion for the rare case in which immediate access to peritoneal dialysis is not possible. The beneficial effects of exchange transfusion are transient. In most infants with organic acid disorders, dialysis is likely to be needed for at least seven days and once established we introduce protein cautiously, starting at 0·5 g/kg/day and increasing daily as tolerated, up to 1·2–1·5 g/kg/day. In addition, at least 0·502 MJ/kg/day are supplied and this combination is usually sufficient to achieve anabolism and promote growth.

Children with hyperammonaemia respond rapidly to treatment with sodium benzoate, ammonia nitrogen being diverted away from the defective urea cycle by being conjugated with glycine to form hippurate. Sodium benzoate should be used in conjunction with dialysis in those infants with hyperammonaemia of greater than 600 μmol/l, or alone in those infants with a more moderate increase. The effect is transient, and a loading dose of 250 mg/kg should be followed by a constant infusion of 250 mg/kg/day, depending on response. In experimental animals sodium benzoate potentiates ammonia toxicity, although this may be prevented by giving L-carnitine first. We have not noted any adverse effect on our patients.[12] [13]

The megavitamin 'cocktail'

Several inborn errors of metabolism have vitamin responsive forms, and often a combination of vitamins in pharmacological doses are given intravenously to sick infants while awaiting results. A typical 'cocktail' is shown in the table. It is important that this therapeutic approach be considered only after the appropriate specimens have been collected for metabolic investigations. It is reasonable to try the 'cocktail' in infants in whom no diagnosis has been established, but in our experience this approach is rarely effective. When a diagnosis is made of an inborn error known to have a vitamin

Table *Megavitamin 'cocktail'*

Ingredient	Mg/day
Vitamin B_{12}	1·0
Biotin	100
Thiamine	50
Riboflavine	50
Nicotinamide	600
Pyridoxine	100

responsive form, that vitamin should be given in a dose about 100 times the daily requirement until the cofactor responsiveness has been assessed.[14]

Specific management after diagnosis

UREA CYCLE DEFECTS

After dialysis has been used to reduce plasma ammonia concentrations rapidly, protein restriction with supplementary essential amino acids forms the basis of treatment. Long term oral sodium benzoate is often necessary and, in all the disorders except arginase deficiency, arginine supplementation becomes essential if chronic hyperammonaemia is to be avoided.[15-17]

ORGANIC ACID DISORDERS

Acute management includes dialysis and protein restriction. In addition there is a direct toxic effect on the tissues from a build up of acyl coenzyme A esters within the cell as a result of the metabolic block. Carnitine plays an important part by conjugating with these compounds to form acylcarnitine esters, which are excreted through the kidney. This leads to a secondary carnitine deficiency and has led to the use of carnitine supplementation in both the acute and chronic management of organic acidaemia.[18]

In isovaleric acidaemia, isovaleryl coenzyme A accumulates and the isovaleryl groups can effectively be conjugated to glycine. Glycine supplementation can therefore increase the excretion of isovaleryl glycine leading to metabolic correction.[19]

Antimicrobials (for example, metronidazole) have been used to sterilise the gut in an attempt to reduce substrate production from gut organisms in some organic acid disorders.[20]

Management when death seems inevitable or the child dies despite treatment

Even if no diagnosis is established, aggressive treatment is justified as some defects are transient—for example, transient hyperammonaemia of prematurity. If death seems inevitable it is important to gather as much information about the child as possible. Necropsy is essential and careful thought is needed to ensure that the correct samples are collected. The necropsy must be carried out as soon as possible after death so that biochemical studies can be made on tissues that have not yet undergone enzymatic self digestion. The need for necropsy should be discussed with the parents before death

and permission obtained at this time. Indeed, many couples find it easier to discuss this matter before rather than after death. If possible before death 1 ml of serum or plasma should be collected and frozen together with as much urine as can be collected (even a few drops can be useful). If metabolic investigations are considered for the first time after death one can try and retrieve samples, taken during life, from routine pathology laboratories. Blood from cardiac puncture can be collected, separated, and stored. Cerebrospinal fluid is usually easy to obtain after death by cisternal puncture and can be used for amino acid and organic acid analyses. It is essential to set up a fibroblast culture, as many enzyme assays can be performed if an inborn error is suggested by necropsy findings. The results of the enzyme tests are not affected by enzymatic self digestion and, in addition, the fibroblasts can be used as a source of DNA. If permission to carry out a full necropsy is not obtained (perhaps for religious reasons) it is important to ask the parents to agree to limited biopsy study—for example, liver and muscle. Many (but not all) enzymes can be accurately assayed many hours after death, and even if more than 12 hours has elapsed it is still worth collecting samples for measurement of metabolites resistant to rapid change after death—for example, for diagnosis of fatty acid oxidation defects. Biopsy samples should be shared with the pathologist who will require material for essential histology, histochemistry, and electron microscopy. Samples for biochemical studies should be snap frozen (in dry ice or liquid nitrogen) and stored at −70°C until assayed.[21]

Conclusions

Inborn errors of metabolism are an important cause of neonatal morbidity and mortality. In many infants they are not diagnosed, and the children die without the benefit of available treatment. In addition, the parents of these children do not receive the appropriate genetic advice and often have the additional problems of further affected infants before the underlying disorder is detected.

It is important to consider an inborn error as a potential cause of any severe neonatal illness and to have a systematic approach to diagnosis and management.

Each region should have facilities to screen the sick newborn rapidly for metabolic disease, as well as a clinician whose main interest is in the management of inborn errors of metabolism.

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. Hereditary fructose intolerance requires a fructose load before symptoms appear.

Disorders	*Enzyme deficiencies*
1 Galactosaemia ('classical')	Galactose-1-phosphate uridyl transferase
Epimerase	Uridine diphosphate-galactose-4-epimerase
2 Glycogen storage disease	
Type Ia	Glucose-6-phosphatase
Type Ib	'Translocase'
3 Fructose	Fructose-1-6-diphosphatase
	Fructose-1-phosphate aldolase
	(Hereditary fructose intolerance)
4 Lactic acidosis	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	*Enzyme deficiencies*
5 Maple syrup urine disease	Branched chain ketoacid decarboxylase
6 Non-ketotic hyperglycinaemia	Glycine cleavage system
7 Tyrosinaemia type I	Fumryl acetoacetase

● **Organic acid defects**

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

Disoders	*Enzyme deficiencies*
8 Methylmalonic acidaemia	Methylmalonyl coenzyme A mutase (and others)
9 Propionic acidaemia	Propionyl coenzyme A carboxylase
10 Isovaleric acidaemia	Isovaleryl coenzyme A dehydrogenase
11 Glutaric aciduria type II	Glutaryl coenzyme A dehydrogenase
12 Dicarboxylic aciduria	Various acyl coenzyme A dehydrogenases

● **Urea cycle defects and hyperammonaemia**

Disorders	*Enzyme deficiencies*
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

● **Miscellaneous**

Disorders	*Enzyme deficiencies*
19 Pyridoxine dependent seizures	Unknown
20 Lysosomal storage disease*	Various
21 Peroxisomal disorders†	Various

*A number of lysosomal storage disorders have been reported as presenting with hydrops fetalis.[3] †Can produce profound neurological dysfunction in the newborn period.[4]

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Correspondence to Dr JE Wraith, Willink Biochemical Genetics Unit, Royal Manchester Children's Hospital, Manchester M27 1HA.