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Arch Dis Child Educ Pract Ed 2010 95: 40-46
doi: 10.1136/adc.2008.151183

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An approach to the diagnosis of inherited metabolic disease

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Inherited metabolic diseases (IMDs) pose a particular challenge to diagnosis. Although individually rare, improved diagnostics and greater awareness have shown that the incidence is much greater than previously thought. The commonest disorders such as phenylketonuria and medium chain acyl-coA dehydrogenase deficiency (MCADD) have an incidence of approximately 1 in 10,000; however, collectively, all IMDs have an incidence of <1 in 1000. It is important to make IMD diagnoses because there are many effective treatments and early diagnosis greatly enhances the chance of a better outcome. The individual rarity of the IMDs means that exposure remains limited for most paediatricians unless working in a centre specialising in these disorders, and so experience and confidence in dealing with such patients may not be well developed.

Presentations are also non-specific further increasing the chances of a diagnosis being missed. At present, a sick neonate is more likely to have multiple septic screens undertaken than a metabolic one. Infection is far commoner than an IMD presentation, but it is important to entertain the possibility of an IMD early, allowing the opportunity for effective intervention. The other difficulty is that most IMDs will not be diagnosed unless specific investigations for that disorder are undertaken. An infant with maple syrup urine disease, although very sick, will not be revealed by standard investigations. Plasma amino acids are required to reveal the diagnostic elevation of the branched chain amino acids, leucine, isoleucine and valine. Similarly, the workup of an encephalopathic child should include measurement of ammonia because this is unlikely to be picked up in any other way. It is therefore essential to develop an approach to thinking about and investigating IMDs, particularly when one considers that these patients will present initially to the local hospital rather than to the specialist centre.

HISTORY

As with all paediatric disorders, the basis of diagnosis relies on a good history and careful examination with subsequent investigations. In view of the non-specific presentation of many IMDs, it is necessary to search for metabolic clues to initiate specific IMD investigations. There are times when metabolic presentations are more likely (box 1). The neonatal period might be considered the front line because, before delivery, the neonate has the advantage of maternal support via the placenta to clear certain metabolites along with reduced flux through many pathways.

The classic IMD presentation is that of intoxication. The key to diagnosis is an initial symptom-free period shortly after birth; but then as a particular metabolite accumulates either secondary to the metabolic stress of birth and or as feeds are introduced and established, the neonate becomes increasingly drowsy with poor feeding before full decompensation. Neonatal conditions that classically present in this way include the urea cycle defects, organic acidemias and some amino acid disorders such as tyrosinaemia. They usually, but not exclusively, present in the first 2–3 days of life. The differential includes infection and duct-dependent cardiac lesions, but IMDs must not be forgotten. Some intoxications present later such as galactosaemia at the end of the first week, or indeed much later such as phenylketonuria, which is not detected in non-screening countries until 6 months or a year of age when the developmental impact is apparent.

Neonates with energy deficiencies may present from birth with lactic acidosis as their marker such as occurs in mitochondrial disorders and disorders of pyruvate metabolism, or with hypoglycaemia when there are interruptions in the fuel supply with delay in establishing or interruption of feeds. Examples include fat oxidation disorders, gluconeogenesis defects and the glycogenoses.

Blocks in the making of complex molecules are a third presentation. Such molecules are key to cell–cell signalling and embryogenesis and therefore present in the neonatal period with dysmorphic features. Such conditions include the peroxisomal disorders—for example, Zellweger syndrome and the congenital disorders of glycosylation. Failure to break complex molecules results in storage presenting with dysmorphic features. These are not obvious at birth with a few exceptions such as I-cell disease, although rarely, storage disorders can present as hydrops fetalis. The dysmorphic features becoming more pronounced and obvious with time as storage material accumulates.

The fourth main group of neonatal presentation is seizures. This expanding group has increasing significance because many of these are treatable (table 1). Increased fetal movements may represent in utero seizures. Hiccoughs with the subsequent development of apnoeas are seen in non-ketotic hyperglycaemia. Diagnosis may not be so obvious if after a difficult delivery, and distinguishing a metabolic cause from a hypoxic/ischaemic aetiology can be difficult. IMDs should always be considered in unexplained refractory seizures. Pyridoxine-dependent seizures may be missed because of an unclear response to a trial.
of pyridoxine. This is less likely if urine is specifically analysed for α-amino adipic semialdehyde, the key diagnostic marker.4 A trial of pyridoxal phosphate should be given initially because this will successfully treat both pyridoxine- and pyridoxal phosphate-dependent seizures, whereas the latter do not respond to pyridoxine because of the block in conversion to the active pyridoxal phosphate. If successful, conversion to pyridoxine allows differentiation between the two dependent on the continued cessation/modification of the seizures or their reappearance.

Further clues may be gained from the obstetric history. Previous multiple spontaneous abortions may indicate previously affected fetuses that were non-viable. Maternal symptoms may also be a clue. Hyperemesis is associated with fat oxidation disorders as is frank hepatic symptoms such as acute fatty liver of pregnancy and the more severe HELLP syndrome (haemolysis, elevated liver enzymes, low platelets).5 These are also associated particularly with the long-chain fat oxidation defects such as long-chain hydroxy acyl-CoA dehydrogenase deficiency and the very long-chain acyl-CoA dehydrogenase deficiency (VLCAD). They do, however, represent only a small proportion of all such cases but indicate that the neonate should be screened with plasma acylcarnitines to exclude these diagnoses shortly after birth.

Recessive inheritance is the commonest mode of inheritance for all IMDs and therefore consanguinity is a major flag to consider an IMD in a sick infant or child, as is a family history of a previous neonatal or sudden infant death. It is not uncommon for the diagnosis to have been missed previously. X-linked conditions have a predominance of affected males in the family, although some disorders such as ornithine transcarbamylase deficiency, Fabry disease and Danon disease commonly have symptomatic females (hemizygotes) but are often milder. Mitochondria have their own DNA (mtDNA) that is inherited exclusively from the mother. mtDNA point mutations are therefore inherited in a matrilineal fashion; that is, the trait may affect males and females, but only females pass on the trait.6 mtDNA rearrangements such as deletions and duplications tend to be sporadic with a low risk of recurrence.

The medical history for the child may include previous episodes. Admission to hospital for “a viral pneumonia” may actually have been an episode of previous acidosis with tachypnoea secondary to compensatory clearance of CO₂. Stopping feeds because the child was ill and giving intravenous dextrose are effectively promoting anabolism and reducing metabolite production and therefore the child may have recovered without the diagnosis being secured. Children may also unknowingly avoid certain foods as they feel less well and therefore self-treat to a degree. Classic examples include low-protein intake in children with urea cycle defects and the avoidance of sweets with resultant perfect dentition in hereditary fructose intolerance. Fussy/faddy eating is not uncommon in modern living, but a dietary history may be very helpful and revealing. Similarly, IMDs have associated impact on development.7 This may be only minor and therefore direct enquiry in all areas of development is important. There are exceptions such as MCADD, glutaric aciduria type I and intermittent maple syrup urine disease where the child may be completely healthy with normal development until acute decompensation for the first time.

It is important to remember that IMDs can present at any age and are not restricted to neonates and young infants.8 Like most disorders, IMDs are a continuum and therefore milder patients do exist and therefore symptoms may not develop until much older. Other presentations include the development of cardiomyopathy, liver disease,
Best practice

eye disease and indeed any organ system and therefore, all subspecialties may have primary presentations.

EXAMINATION

Most IMDs do not have specific features to be identified on examination, presenting with generalised symptoms secondary to decompensation. There are the classic dysmorphic syndromes secondary to defects in embryogenesis that include the peroxisomal disorders such as Zellweger syndrome (large fontanelle, bulbous forehead, profound hypotonia, ptosis and jaundice), the congenital disorders of glycosylation (e.g. inverted nipples, fat pads, cerebellar dysgenesis, pericardial effusions, pleural effusions and ascites) and steroid synthesis defects (Smith-Lemli-Opitz—upturned nose, prominent forehead, syndactyly and hypotonia, genital anomalies). There are also the storage disorders that develop coarse features and hepatosplenomegaly such as the mucopolysaccharidoses—for example, Hurler and Hunter syndrome. Ophthalmic examination is very important because many disorders have eye signs. Oil-drop cataracts are present at birth in most infants with galactosaemia. They are very easy to miss as only the edge of the cataract is visible because of their transparency and therefore may not be seen unless the eyes are fully dilated. These will mature if the diagnosis is missed but will usually resolve completely with early treatment. Sphingolipidoses develop a cherry red spot due to the abnormal deposition of sphingolipids around the fovea. The relative pallor of the lipids compared to the red fovea produce the cherry red spot appearance. Pigmentary retinopathy is a feature of a number of IMDs including mitochondrial cytopathies, fat oxidation defects and peroxisomal disorders. Eye movements may also be abnormal in IMDs including external ophthalmoplegia in mitochondrial cytopathies—reduced movement of the eye in all planes of gaze. Limitation of down gaze is a feature of Gaucher disease, which is most obvious when walking down stairs manifesting as unsteadiness and also compensatory head-thrusting. In the late infantile/juvenile forms of Niemann–Pick type C, vertical supranuclear gaze palsy may also be an early feature. Ptosis is found in many conditions including peroxisomal and mitochondrial disorders.

Cardiac manifestations include cardiomyopathy and arrhythmias. The arrhythmias may be episodic such as occurs in fat oxidation defects or persistent such as heart block seen in Kearns–Sayre syndrome, a mitochondrial disorder. Cardiomyopathy may present with the features of heart failure including sweating and shortness of breath when feeding. Patients usually present with chest signs, and it is the x-ray revealing cardiomegaly that indicates the presence of cardiomyopathy. Dilated and hypertrophic cardiomyopathy is seen in IMDs, and it is important to remember that the dilated myocardium may have originally been hypertrophic. It is therefore prudent to investigate for both causes of hypertrophic and dilated cardiomyopathy. Myopathy is a common association seen in conditions such as infantile Pompe disease (glycogen storage disease type II (GSDII)): marked hypertrophic cardiomyopathy, hypotonia and myopathic facies, prominent tongue. However, sick children with cardiomyopathy tend to be floppy and therefore the distinction may not be so obvious.

The presence or absence of organomegaly may be helpful when considering an IMD. It is important to remember that glycogen is stored in the liver, muscles and kidneys. A child therefore presenting with marked hepatomegaly in the absence of splenomegaly should lead to consideration of a GSD. Splenomegaly may occur in the GSDs, particularly type IV secondary to the liver disease. Massive hepatomegaly and splenomegaly are suggestive of a storage disorder such as the mucopolysaccharidoses, and splenomegaly greater than hepatomegaly is seen in storage disorders, particularly conditions such as Gaucher.

Neurological features of IMDs are extremely varied, but in the infant it must be remembered that a sick neonate usually presents with hypotonia and therefore normal or increased tone may suggest an IMD. Odours are also often reported as being helpful when considering an IMD. Generally, this is not the case, but exceptions include maple syrup urine disease where the nappies are sweeter smelling than one might expect. Isovaleric acidemia causes pungent odour likened to sweaty feet and is obvious in the acute situation. Once treated the odour disappears.

INVESTIGATION

IMDs are characterised by the need for specialist investigations and are not usually picked up by standard investigations, that is, full blood count, electrolytes and liver function tests. A common request is the metabolic screen. Unfortunately, a single blood or urine test that detects all IMDs does not exist. The first-line screen is outlined in box 2 and forms the basis of a widespread metabolic trawl for non-specific presentations. Second-line investigations can then be ordered building on this foundation. Second-line tests include specific imaging, organ-specific investigations or indeed organelle-specific such as very long-chain fatty acids for peroxisomal disorders and transferrin isoelectric focusing for the congenital disorders of glycosylation. Specific clinical scenarios are considered below.

Encephalopathy

The investigation of encephalopathy of unknown cause includes tests for IMDs. Glucose and venous gas are usually standard, but it is important to remember specifically ammonia when considering the semi-conscious patient and especially the neonate. Similarly, leucine is a key marker for maple syrup urine disease that otherwise may well be mistaken for sepsis. The metabolic disturbance is not particularly marked in this particular
IMD without major acidosis, lactate, hyperammonaemia or ketosis. Many encephalopathic children appear septic, and it is not uncommon for a neonate to have had more than one septic screen before an ammonia being measured. It is also important that the ammonia is a free-flowing venous sample, or arterial, to avoid spurious elevation. Accurate assessment of the degree of hyperammonaemia is essential to determine the degree of intervention required. If levels are rising uncontrolled >300 μmol/l or if there is evidence of worsening encephalopathy, in spite of specific fluid and drug management, haemofiltration is indicated. A further clue to hyperammonaemia may be the presence of a respiratory alkalosis that is a high normal or slightly elevated pH in the presence of a low CO₂ due to the respiratory stimulant effect of ammonia on the brainstem.

**Acidosis**

Acidosis is not an uncommon finding in sick children and the key investigations relate to the presence of absence of ketones and the anion gap ((sodium + potassium) – (chloride + bicarbonate)). The presence of acidosis with a normal anion gap (10–18 mmol/l) should be considered an indicator for bicarbonate loss, either renal or gut, rather than the presence of excess acid. Ketosis is a common accompaniment to acidosis, although in the neonate, marked ketosis is unusual and may indicate an organic acidemia. Many IMDs are associated with ketosis including organic acidemias, gluconeogenesis defects, mitochondrial disorders, ketolysis defects and maple syrup urine disease. Most are associated with elevated lactate with the exception of ketolysis defects and maple syrup urine disease. Hypoglycaemia is a key feature of gluconeogenesis defects accompanied by hepatomegaly and marked lactic acidosis; the latter rapidly resolving with dextrose administration—another important diagnostic clue. Hypoglycaemia may also be a feature of mitochondrial disorders. Hypoglycaemia or hyperglycaemia may be seen in organic acidemias.

The absence of ketosis is less common with acidosis but is seen in pyruvate dehydrogenase complex deficiency (elevated lactate and normal glucose), fat oxidation defects and gluconeogenesis defects (raised lactate with hypoglycaemia). If the acidosis is associated with normal lactate and normal glucose, then a renal tubular acidosis is more likely or another bicarbonate wasting condition. Acylcarnitines for the exclusion of fat oxidation defects and organic acids for organic acidemia are important second-line investigations for acidosis.

A raised lactate is not uncommon, and its investigation is important as the differential includes significant problems such as respiratory chain disorders and pyruvate metabolism disorders along with fat oxidation defects, organic acidemias and gluconeogenesis defects. Lactate is more commonly secondary to hypoxia, hypoperfusion, and so on, and is also seen in liver failure and seizures. It is essential to have a free-flowing venous or arterial sample to avoid spurious elevations. Unless the degree of lactate rises >5 mmol/l, it is unlikely to significantly contribute to the acidosis because it is a weak acid. It is also suggested that the presence of ketones make a primary metabolic block a more likely cause than secondary elevation.

**Hypoglycaemia**

Hypoglycaemia is a common problem in sick children and yet it is an area where the opportunity to take crucial samples at the time of the hypoglycaemia, to secure the diagnosis and avoid further investigation is often missed. A few simple investigations taken at the time of hypoglycaemia can rapidly limit the differential diagnosis. Various sticks and glucose meters are used in clinical practice, but it is essential that the low result given by a meter is confirmed with a laboratory sample. The definition of hypoglycaemia is 2.6 mmol/l or lower. The next essential investigation is assessing the presence or absence of ketones; most simply obtained by stick testing of the urine. The normal response to hypoglycaemia is to produce ketones that, unlike fat from which they are derived, may be used directly by the brain for fuel. Ketotic hypoglycaemia therefore has a broad differential including sepsis and hypocortisolism, whereas if ketones are absent or inappropriately low at the time of hypoglycaemia, the differential diagnosis is much more limited: hyperinsulinism, fat oxidation disorders, liver failure and, on some occasions, mitochondrial disorders.

Hyperinsulinism occurs most frequently in the neonatal period and may be in nature secondary to complications around labour including birth asphyxia and growth retardation, and can also be seen in the infant of the diabetic mother. Hyperinsulinism is suggested by the persistent increased requirement for glucose. This is
usually in excess of 8 mg/kg/min and can be very much higher.

The requirement can be calculated by the simple formula:

\[
\text{Glucose requirement (mg/kg/min)} = \frac{\text{% dextrose} \times \text{infusion rate (ml/h)}}{\text{6} \times \text{weight (kg)}}
\]

Attempts to reduce the level of glucose support results in recurrence of the hypoglycaemia. It is important to remember that high rates of dextrose and dextrose boluses can cause iatrogenic hyperinsulinism and therefore reduction in dextrose or feed supply must be gradual to avoid further swings in insulin secretion. In all neonates with hyperinsulinism, it is important to have secure venous access, usually central or if peripheral at least two cannulae in situ to prevent crashing hypoglycaemia should a single cannula fail and there be a delay in re-siting a new cannula. In neonates it is important to always measure an ammonia in such infants to exclude hyperinsulinism hyperammonaemia, which is secondary to glutamate dehydrogenase superactivity. The diagnosis is important because it is exquisitely sensitive to diazoxide and therefore effectively managed with medication. The hyperammonaemia is usually modest being <100 μmol/l and is managed with slight dietary protein reduction.

Fat oxidation is the mechanism whereby the body metabolises fat for the production of energy either by utilisation of the acetyl-coA produced by the process in the tricarboxylic acid cycle or via the production of ketones for export to the brain. Blocks in fat oxidation lead to hypoketotic hypoglycaemia due to the failure of ketone production in spite of mobilisation of fat in response to fasting. Hepatomegaly, at the time of acute presentation, is another feature due to lipid accumulation that subsequently resolves with treatment. Raised lactate is also a feature as is deranged liver function tests. Elevation of creatine kinase in long-chain fat oxidation defects is a further clue. Progression of decomposition in fat oxidation defects leads to a Reye-like syndrome with liver failure and encephalopathy. Liver failure is another recognised cause of hypoketosis in the face of hypoglycaemia secondary to the disruption of fat oxidation and ketone production that is based in the liver, but associated signs and impaired liver function and coagulopathy usually make the diagnosis obvious.

Storage disorders
Most IMDs do not have dysmorphic features; however, storage disorders are one exception. The coarsening of features with time secondary to storage build-up may suggest the diagnosis or the finding of prominent organomegaly on abdominal examination in a child. The key investigations in such cases include the assessment of the blood film for vacuolated lymphocytes. This is not simply a blood film in routine haematology but a specific histopathology investigation; the number of vacuoles, their size and staining characteristics can point to specific diagnoses. In addition, urine should be investigated for glycosaminoglycans and oligosaccharides to help diagnose the mucopolysaccharidoses and mucolipidoses. Further investigations include white cell enzymes for the specific enzyme block and chitotriosidase, which is a non-specific marker in several storage disorders. Clues can also be gained from eye examination as discussed previously looking specifically for corneal clouding as seen in the mucopolysaccharidoses or other lens abnormalities such as cornea verticillata in Fabry. Skeletal survey is also useful looking for dysostosis secondary to the build-up storage material.

Liver failure
In liver failure, most metabolic investigations are abnormal; however, the thrust of investigation is to diagnose the treatable causes of liver failure. These include galactosemia, tyrosinaemia, hereditary fructose intolerance, fat oxidation disorders and the congenital disorder of glycosylation 1b. All patients should therefore have galactose-1-phosphate uridyltransferase examined or if transfused undertaken in both parents to detect galactosaemia, urine organic acids for the presence of succinylacetone for tyrosinaemia type 1, very careful history to determine if there has been exposure to fructose and elimination from the diet, acylcarnitines for fat oxidation disorders and transferrin isoelectric focusing and phosphomannose isomerase enzymology for CDG 1b. It is also important to consider conditions where one might be cautious about transplantation where extrahepatic manifestations may be marked and not corrected by liver transplant—for example, mitochondrial disorders. However, there is a growing literature of successful liver transplants in such patients and certainly one would not discount liver transplant in a proven mitochondrial patient in whom signs and symptoms were restricted to the liver.

Perimortem investigations
There has been much interest and debate as to the appropriate investigation of children who have died unexpectedly to exclude a potential metabolic cause, particularly in relation to certain high-profile cases where the differential diagnoses have included non-accidental injury. The key investigations are seen in box 3. It is important to remember that enzymes degrade rapidly secondary to autolysis postdeath and therefore useful interpretation of samples taken some hours after death is impossible. One would therefore
recommend that muscle and liver biopsies, if indicated, are snap frozen in liquid nitrogen within an hour of death. Skin biopsies can be taken up to 48 h after death, but the earlier these are taken the more likely they are to be successfully cultured. Specialist culture medium does not need to be readily at hand and a skin biopsy will sit happily in sterile saline in a fridge over a weekend until appropriate handling on the Monday morning. Postmortem is essential if the cause of death is unknown.17

**Tandem mass spectrometry**

Tandem mass spectrometry has revolutionised the investigation of inherited metabolic disorders. The simplest investigation is acylcarnitines, whereby the various lengths of fatty acid conjugates with carnitine are detected. During fat oxidation, the fatty acid is reduced in length by two carbon atoms each turn of the cycle, thereby gradually shortening the chain until it is all utilised. If there is a block in fat oxidation, the length of the predominant acylcarnitine indicates the level of the block in the process—for example, MCADD (octanoylcarnitine C8), very long-chain acyl-coA dehydrogenase deficiency (tetradecenoylcarnitine C14:1). Acylcarnitines can therefore be used to diagnose where the block in fat oxidation has occurred, and this ability forms the basis of MCADD newborn screening.

Tandem mass spectrometry has wider applications, and the development of the acute patient’s screen has major benefits for rapid diagnosis and earlier and more specific interventions. On a single 0.5-ml sample, it is possible to diagnose fat oxidation defects as described above: the three main organic acidemias propionic, methylnalonic and isovaleric acidemia, the majority of urea cycle defects and some amino acidopathies including maple syrup urine disease that cannot be diagnosed without specifically measuring leucine in the blood, the main cause of the encephalopathy.18

**Box 3 Perimortem samples to store when an inherited metabolic disease (IMD) is considered**

- Blood (10 ml)
  - Red cells (refrigerate 4°C)
  - Plasma (freeze –20°C)
  - Four blood spots on Guthrie card
- Urine (10–20 ml)
  - Freeze –20°C
- Skin biopsy
  - Culture medium or saline (refrigerate 4°C if out of hours)
- Peri-mortem biopsies
  - Muscle and liver biopsy if specific IMDs considered that requires these tissues for diagnosis—formalin for histology, liquid nitrogen for enzymology
  - Samples for enzymology must be frozen within 1 h of death
- Postmortem

**ACUTE MANAGEMENT**

The principles of the acute management of IMD in the first instance are generally the same in all cases. The main concern is to stop further decomposition and the build-up of potential toxic metabolites and therefore feeds are stopped but anabolism must be promoted to avoid further catabolic breakdown of body stores that further add to the build-up of toxicity. This is managed by giving 10% dextrose as a basic fluid with appropriate electrolyte additives. The exception is congenital lactic acidosis and mitochondrial disorders where a 5% dextrose-based solution is used as high carbohydrate supply may exacerbate the lactic acidosis. If a fat oxidation defect has been excluded, then intralipid should be added at 1 g/kg/day to boost calories. If hyperglycaemia with glycosuria develops, it is preferable to commence an insulin infusion rather than cut the dextrose supply. In acidosis, it is essential to monitor potassium very carefully as this may fall precipitously as the acidosis corrects.

Protein free calories are inappropriate long term as one will become catabolic with regards to protein needs. The longest time of complete protein cessation should not be longer than 36–48 h; and therefore even if the cause has not been fully determined, a small amount of protein (0.5 g/kg/day) should be started after 1–2 days as even the most severe block will be able to tolerate this. Protein levels should therefore be increased readily once the diagnosis has been made or indeed a metabolic cause excluded. There are still infants who present with multiple symptoms and severe skin rashes that resolve completely on feeding due to prolonged starvation while awaiting results. It is important to liaise with the local metabolic service early, which will help speed up results but will also reduce the number of investigations undertaken.

The next principle of management is to remove toxic metabolites. This can be simply achieved with the use of carnitine in the case of organic acidemias to conjugate with the organic acid increasing solubility and therefore renal clearance. Glycine is used in a similar fashion in isovaleric acidemia. In the urea cycle defects, alternate pathway medicines, sodium benzoate and sodium phenylbutyrate, conjugate with glycine and glutamine, respectively, allowing them to be directly excreted via the kidney. This therefore reduces the nitrogen load on the liver and helps reduce hyperammonaemia. In newborns, liver immaturity may limit their effectiveness, but rapid maturation of the liver increases their potency in the first week or so.

Toxic metabolites may also be cleared using filtration and dialysis. Continuous venovenous haemofiltration is preferred because this has less systemic upset, but one is mindful of the potential complications of filtration and large central lines in infants and children. In neonates weighing <2.5 kg, peritoneal dialysis is preferred. Filtration is used for clearance of leucine in maple
syrup urine disease, organic acids, lactate and ammonia.

Most enzyme blocks do not produce symptoms and disease until activity is markedly reduced, that is, <5% or absent. All enzymes have cofactors, and the supplementation of the specific cofactor, having secured the diagnosis, may improve enzyme activity by a few percent that may be sufficient to markedly improve the clinical situation. Examples include thiamine in pyruvate dehydrogenase complex deficiency, riboflavin in juvenile glutaric aciduria type II and cobalamin in methylmalonic aciduria.

CONCLUSION
The awareness of IMDs continues to rise as does the ability to diagnose and treat such patients. Therapeutic interventions continue to expand with the advent of enzyme replacement therapy in some storage disorders, substrate deprivation therapy to reduce storage by matching storage material production to the rate of clearance, chaperonin therapy to stabilise the misfolded protein to use its residual enzyme activity, product replacement therapy such as DOPA in neurotransmitter disorders and, ultimately, in the future, gene therapy. Knowledge of these disorders and the importance of specific investigations to secure diagnosis is therefore increasingly important, and the evolution of tandem mass spectrometry and other diagnostic modalities means that the elusive metabolic screen is drawing nearer.

Provenance and peer review
Commissioned; externally peer reviewed.

Competing Interests
None

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