Inborn errors of metabolism: clinical approach and management

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Although individual metabolic disorders are rare, collectively, inborn errors of metabolism are not uncommon and paediatricians should be alert to the possibility of such disorders. The presenting symptoms are frequently non-specific and may include lethargy, poor feeding, vomiting, coma, and seizures. After investigations, appropriate therapeutic options including exchange transfusion, peritoneal- and haemo-dialysis, forced diuresis, mega-dosing of vitamin cofactors, and special dietary therapy can be instituted, depending on the diagnosis. Somatic gene therapy may offer hope of a cure for inborn errors of metabolism in the future.

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Introduction

The term inborn errors of metabolism (IEM) was coined by Garrod in 1908 to include disorders caused by a deficiency of enzyme catalysis or an enzyme that facilitates the transport of biological substances across membranes. Since then, considerable advances have been made in the diagnosis and treatment of IEM. Well over 200 of these disorders have been characterised and a significant proportion of them present in the neonatal period or in early infancy.[1] Although many IEM are rare, a paediatrician is likely to come across a patient with one of these disorders, because collectively, they are relatively common. Early diagnosis and treatment can reverse acute symptoms and prevent chronic damage. Even if the damage is irreversible, early treatment may ameliorate the long-term effects. In cases where no treatment is available, accurate diagnosis of IEM is helpful in future family planning, genetic counselling, and prenatal diagnosis in future pregnancies.

The following clues should raise the suspicion of an inherited metabolic disorder: the marriage is consanguineous; there is a history of recurrent abortion; there is a history of unexplained neonatal death in siblings especially associated with acidosis, coma, and convulsions; a sibling has been diagnosed as suffering from an IEM. In certain developed countries, neonatal screening for metabolic disorders allows diagnosis and treatment in the pre-clinical phase so that the adverse consequences of such disorders can be prevented. Metabolic disorders for which newborn screening are conducted include phenylketonuria (PKU), galactosaemia, maple syrup urine disease (MSUD), homocystinuria, and biotinidase deficiency. Although PKU has been perhaps erroneously regarded as rare in southern Chinese, the condition has been shown to be as prevalent as it is in Caucasians in northern Chinese (see related article by R-G Chen) where newborn screening for PKU is performed. Cord blood is satisfactory when screening for biotinidase deficiency, galactosaemia, and glucose-6-phosphate dehydrogenase deficiency, but is not acceptable for routine screening for other IEM such as PKU and MSUD. It is not the intention of this review to be comprehensive. Instead, the discussion will focus on the clinical manifestations and management of IEM presenting acutely in the neonatal period or early infancy.

Clinical manifestations of inborn errors of metabolism

As with all neonatal problems, the clinical manifestations of IEM are frequently non-specific.[2] Those that present in the neonatal period or in early infancy and are seen in Hong Kong, are shown on Table 1. Most of

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Table 1. Inborn errors of metabolism with presentation in the neonatal period and early infancy in Chinese patients

Disorders of carbohydrate metabolism
- Glycogen storage disease type I - IV[3,4]
- Galactosaemia[3]
- Fructose-1,6-diphosphatase deficiency[5]
- Fructose-1-phosphate aldolase deficiency[5,6]
- Pyruvate dehydrogenase complex deficiency

Disorders of aminoacid metabolism
- Maple syrup urine disease[7-9]
- Phenylketonuria[10]
- Hereditary tyrosinaemia
- Homocystinuria[11]

Organic acidaemias
- Methylmalonic acidaemia[12]
- Multiple carboxylase deficiency[9,13]
- Propionic acidaemia[9]
- Isovaleric acidaemia[9]
- Glutaric aciduria type I[14]
- Mitochondrial acetoacetyl CoA thiolase deficiency

Urea cycle defects
- Carbamyl phosphate synthetase deficiency
- Ornithine transcarbamylase deficiency[15]
- Argininosuccinate synthetase deficiency
- Argininosuccinate lyase deficiency

Lysosmal storage disorders
- Gaucher's disease[3]
- Niemann-Pick disease (sphingomyelinase deficiency)[16]
- Wolman's disease (acid lipase deficiency)[17]

Other disorders
- Congenital adrenal hyperplasia[18]
- Menke's kinky hair syndrome
- Zellweger's syndrome

these disorders are associated with protein intolerance and symptoms typically appear hours or even weeks after oral feeding commences. The initial findings are lethargy, poor feeding, vomiting, and failure to thrive. Diarrhoea is rare but has been reported in galactosaemia, Wolman's disease, and in hereditary tyrosinaemia.[2] Physical examination may reveal coarse facial and dysmorphic features, cataract or retinopathy, jaundice, and hepatomegaly.

A diffuse erythematous skin rash and alopecia are features of multiple carboxylase deficiency. In neonates with citrullinaemia, a generalised erythematous eruption with eroded patches and plaques most prominent in the peri-oral, perineum, and buttocks areas is linked to arginine deficiency. Respiratory distress and apnoea are common. Neurological manifestations include hypotonia, hypertonia, coma, and seizures. Abnormal urine and body odour have been noticed in patients with organic acidaemia. A musty odour has been described in those with PKU and hereditary tyrosinaemia, an odour of tom cat's urine in 3-methylcrotonyl CoA carboxylase deficiency, a smell of sweaty feet in isovaleric acidaemia, and of burnt sugar in MSUD.

Patients with salt-losing congenital adrenal hyperplasia present in the neonatal period with increased pigmentation, dehydration, and collapse in the neonatal period. Females will have ambiguous external genitalia, due to excessive adrenal androgen production.

Metabolic acidosis, increased anion gap and hypoglycaemia are frequent findings in patients with amino acid and organic acid disorders. Lactate is the primary metabolite that accumulates in disorders of carbohydrate metabolism. Hyperammonaemia is seen in patients with urea cycle defect and organic acidaemia. Although hypoglycaemia is seen in disorders of protein intolerance, it is more commonly observed in disorders of carbohydrate metabolism or of fatty acid oxidation. Glycogen storage disease type 1 (glucose-6-phosphatase deficiency) and type III (debrancher enzyme deficiency) presents in early life with hypoglycaemia, hepatomegaly, hyperuricaemia, hyperlipidaemia, and lactic acidaemia. Fructose 1,6 diphosphatase deficiency, which is a disorder of gluconeogenesis, presents with similar clinical findings in early infancy.

Disorders of fatty acid oxidation are due to a deficiency of long-chain, medium-chain, and short-chain acyl CoA dehydrogenases. These disorders are characterised by fasting hypoketotic hypoglycaemia, recurrent Reye's-like syndrome, cardiac hypertrophy, hepatomegaly, and muscle hypotonia.[19] The biochemical abnormalities include hyperuricaemia, hyperammonaemia, decreased total plasma carnitine, increased esterified carnitine, and dicarboxylic aciduria. Although this disorder is frequently seen in the West, no case has so far been described in Chinese. Metabolic cardiomyopathy in the neonatal period could also be due to carnitine deficiency, Pompe's disease, tyrosinaemia type 1, and carbohydrate defi-

cient glycoprotein syndrome. Cardiomyopathy due to mucopolysaccharidosis and other glycogenoses occurs at a later age.

Metabolic disorders with hepatomegaly can be divided into storage diseases and those disorders associated with liver damage or dysfunction. Isolated hepatomegaly is seen in glycogen storage disease and hepatosplenomegaly is present in GM_1 gangliosidosis type I, Gaucher's disease, Niemann-Pick disease, and in Wolman's disease. Mucopolysaccharidosis and mucolipidosis usually present later in life. Conjugated hyperbilirubinaemia, hepatomegaly, diarrhoea, and failure to thrive in the second week of life is strongly suggestive of galactosaemia due to galactose-1-phosphate uridyltransferase deficiency. The presence of a reducing sugar (Clinitest tablet-positive, Bayer Diagnostics, Mulgrave, Victoria, Australia) which is not glucose (Clinistix-negative, Bayer Diagnostics, Mulgrave, Victoria, Australia) in the urine requires confirmation of the presence of galactose and galactitol in the urine by thin layer chromatography. Hereditary fructose intolerance due to fructose-1-phosphate aldolase deficiency may occasionally present in a similar manner in the neonatal period, or in early infancy if the baby is exposed to fructose early.

Alpha-1-antitrypsin deficiency is another disorder associated with neonatal jaundice and hepatic dysfunction. Hereditary tyrosinaemia, which results from a deficiency of the enzyme fumarylacetoacetate fumarylhydrolase, is characterised by marked elevation of plasma tyrosine and methionine, with Fanconi's syndrome, and generalised amino aciduria, jaundice, hepatomegaly, and elevated liver transaminases. The presence of succinylacetone in the urine is a helpful diagnostic test. The enzyme deficiency can be demonstrated in lymphocytes and cultured skin fibroblasts.

Neutropaenia, thrombocytopaenia, and anaemia have been frequently described in patients with IEM. During acute decompensation in patients with amino acid or organic acid disorders, the immune system may be compromised, rendering them more susceptible to infections.[12] Babies with undiagnosed galactosaemia are more prone to *Escherichia coli* sepsis. Neutropenia and susceptibility to infection are features of glycogen storage disease type 1b due to a translocase defect.

Investigations of suspected inborn errors of metabolism

This section is necessarily brief, because this topic is covered by a related article in this issue.[20] The essential investigations are listed in Table 2. Diagnosis is usually based on the identification of accumulated or missing metabolites and protein variants by biochemical methods, and confirmation can be done by direct enzyme assay of blood cells, fresh tissue, or cultured fibroblasts (Table 3). Tissue diagnosis is usually required for glycogen storage disease, Niemann-Pick disease, Gaucher's disease, and Wolman's disease. Defects in amino acid transport can impair intestinal absorption of dietary components, renal tubular

Table 2. Investigation protocol for inborn errors of metabolism

1. Full blood count to look for cytopenia and vacuolated lymphocytes on peripheral smear.
2. Electrolytes, anion gap, renal and liver function tests, and blood sugar.
3. Acid-base status, lactic and pyruvic acid.
4. Serum calcium, phosphate, alkaline phosphatase, urate, cholesterol and triglycerides.
5. Plasma ammonia.
6. Plasma carnitine and esterified carnitine.
7. Plasma amino acids and organic acids.
8. Urine screening tests for metabolic disorders:
   ferric chloride, 2-4 dinitrophenylhydrazine, cyanide-nitroprusside and ninhydrin tests, ketones.
9. Urine tests for organic acids, dicarboxylic acids, and amino acids.
10. Urine tests for mucopolysaccharides and oligosaccharides.
11. Tissue diagnosis:
    leucocyte, fresh tissue, or skin fibroblast culture for enzyme studies; tissue for ultrastructural study, immunohistochemical staining, and biochemical analysis.
12. Analysis of the molecular defects of different IEM.

Table 3. Changes in blood and urine metabolites in common inborn errors of metabolism

Disease	Blood metabolites	Enzyme	Urine metabolites
Galactosaemia	↑ galactose-1-P	galactose-1-P uridyltransferase	galactitol
Maple syrup urine disease	↑ leucine, valine, isoleucine, branched chain ketoacids	branched chain α-keto acid dehydrogenase[1,2]	α-ketoisocaproic, α-keto-β methylvaleric, α-ketoisovaleric acids
Phenylketonuria	↑ phenylalanine	phenylalanine hydroxylase	phenylpyruvic acid
Hereditary tyrosinaemia	↑ tyrosine, methionine, succinylacetone	fumarylacetoacetate fumarylhydrolase[1,2]	sucrinylacetone, generalised aminoaciduria, parahydroxyphenylacetic and parahydroxyphenyllactic acid
Homocystinuria	↑ homocysteine, methionine	cystathionine β-synthetase	homocystine
Methylmalonic acidaemia	↑ methylmalonic acid	methylmalony CoA mutase or defective adenosylcobalamin metabolism[2]	methylmalonic acid ± homocystinuria
Multiple carboxylase deficiency		biotin dependent carboxylases,[2] biotinidase	3-methylcrotonylglycine, tiglylglycine, 3-hydroxyisovaleric acid
Propionic acidaemia	↑ propionate, glycine, valine, isoleucine, leucine	propionyl CoA carboxylase[2]	3-hydroxypropionate, methylcitrate, tiglylglycine, butanone, propionylglycine
Isovaleric acidaemia	↑ isovaleric acid, NH_3	isovaleryl CoA dehydrogenase[1,2]	isovalerylglycine, 3-hydroxyisovalerate, isovalerylcarnitine
Glutaric aciduria type 1	↑ 2-aminoadipic acid	glutaryl CoA dehydrogenase[1,2]	glutaric acid, 3-hydroxyglutaric acid, rarely generalised aminoaciduria
β-Ketothiolase deficiency		mitochondrial acetoacetyl CoA thiolase[2]	2-methyl-3-hydroxybutyrate, 2-methylacetoacetate
Ornithine transcarbamylase deficiency	↓ citrulline, ↑ NH_3	ornithine transcarbamylase[3]	orotic acid
Argininosuccinate synthetase deficiency	↑↑ citrulline, ↑ NH_3	argininosuccinate synthetase	
Argininosuccinate lyase deficiency	↑ argininosuccinate, citrulline, ↑ NH_3	argininosuccinate lyase	
21 α-Hydroxylase deficiency	↑ 17-hydroxyprogesterone, ACTH	P450c21	pregnantriol, 17 ketosteroids

Enzyme defects can be studied in leucocytes,[1] cultured skin fibroblasts,[2] and liver tissue.[3]

reabsorption of filtered compounds, and the deposition of compounds within the body or within the cells. Cystinuria, Hartnup's disease, and glycogen storage type 1b are examples of disorders of amino acid transport. Patients with cystinuria excrete high concentrations of cystine, ornithine, arginine, and lysine in the urine and are liable to have staghorn calculi.[21]

Management

The management of IEM requires accurate diagnosis, early intervention, and a knowledge of the biochemical and molecular basis of the disorder. Deficient function of a mutant enzyme usually leads to a disease phenotype, because of accumulation of the precursor or of an alternative metabolite produced in excessive amounts, which become toxic to the individual. Alternatively, disease phenotype is due to a deficiency in the formation of a downstream product or a combination of these mechanisms. Patients with neonatal onset of organic aciduria, amino aciduria, and urea cycle defects usually become seriously ill shortly after birth, due to accumulation of amino acids, organic acids, and ammonia. The management of the acute phase consists of the following: rapid lowering of the accumulated toxic metabolites; maintainence of an adequate caloric intake to prevent endogenous protein breakdown and promote anabolism; withdrawal of protein from the diet; treatment of metabolic disturbances such as acidosis, electrolyte imbalance, hypoglycaemia, and concurrent infections. Rapid removal of toxic metabolites can be achieved by exchange transfusion, peritoneal dialysis (PD), haemodialysis, forced diuresis, using alternative pathways for the excretion of toxic metabolites, and the use of mega-dosages of vitamin cofactors.

In neonates and young infants, the outcome of hyperammonaemic coma is related to the duration of hyperammonaemia. The goal of treatment should be a rapid correction of the metabolic disturbance. Exchange transfusion is only effective in removing toxins that are confined to the vascular space, has a short-lasting effect, and plays a minor role in the removal of ammonia and amino acids distributed through total body water. Clearance of ammonia by PD is only 10% that of clearance by haemodialysis. Although haemodialysis has advantages over PD, vascular access remains the primary technical problem[22] and PD is usually the preferred mode of treatment. Ten per cent arginine hydrochloride (6 ml/kg/day), sodium benzoate (250 mg/kg/day) and sodium phenylacetate (250 mg/kg/day) given intravenously are used to promote ammonia excretion by alternative pathways.[23] Benzoate and phenylacetate undergo conjugation with glycine and glutamine to form hippurate and phenylacetylglutamine, respectively. The conjugates are easily excreted in urine and contain more nitrogen than their precursors, thereby providing an effective means of elimination of excess nitrogen. Arginine stimulates citrulline synthesis and excretion. These substances are given in 10% dextrose, to ensure a high caloric content during the period of restricted protein intake.

After the acute phase, the diet should contain 0.7 g/kg/day of food protein, and 0.7 g/kg/day of an essential amino acid mixture, and the rest of the calories should be made up with a glucose polymer (Polycal, Nutritia, The Netherlands) and medium-chain triglycerides to ensure adequate caloric content to promote anabolism. The essential amino acid mixture ensures a high quality nitrogen intake and contains only 12% nitrogen, compared to 16% nitrogen in whole protein. In carbamyl phosphate synthetase (CPS) and ornithine transcarbamylase (OTC) deficiency, sodium phenylacetate (550 mg/kg/day) and citrulline (0.17 g/kg/day) should also be given orally. In argininosuccinate synthase deficiency (ASD) and argininosuccinate lyase deficiency (ALD), arginine supplement is given in a dose of 3 mmol/kg/day and sodium phenylacetate should also be given in ASD.[24]

In the treatment of ALD, oral citrate supplement (2-8 mmol/kg/day) has been shown to be an effective addition to arginine therapy in further reducing the ammonia level. The addition of citrate increases the production of oxaloacetate, thereby increasing the cytosolic aspartate level which is required for the formation of readily excretable argininosuccinate by argininosuccinate synthetase in the cytosol.[25] The treatment should be adjusted, based on the plasma ammonia level being checked at regular intervals during follow up. Poor neurological outcome has been observed in patients resuscitated from hyperammonaemic coma. A more favourable outcome has been demonstrated if prospective treatment is carried out in at-risk neonates, when parents have refused prenatal diagnosis or refused abortion after diagnosis of an affected foetus prenatally.[22]

In amino acid and organic acid disorders, the accumulated toxic metabolites can be removed by two-volume exchange, or continuous exchange transfusion over 15 to 20 hours, which may be practically difficult, PD, and forced diuresis with intravenous fluids. Peritoneal dialysis has been used effectively in the management of acute presentations of MSUD, propionic acidaemia, isovaleric acidaemia, and

mitochondrial acetoacetyl CoA thiolase deficiency.[26,27] The use of bicarbonate in the dialysate may be helpful. Exchange transfusion before and after PD is effective in MSUD, propionic acidaemia, and isovaleric acidaemia. As the clearance of methylmalonic acid by PD is less than the renal clearance, exchange transfusion and forced diuresis with intravenous volume loads of 200 ml/kg/day of 10% dextrose with adequate sodium and calcium supplement with or without diuretic administration would be the treatment of choice in acute metabolic deterioration of methylmalonic acidaemia.

Isovaleric acidaemia has been effectively managed with exchange transfusion or PD. Glycine (250 mg/kg/day) given by nasogastric tube to patients with isovaleric acidaemia results in normalisation of plasma isovalerate within three days, a concomitant increase in urine isovalerylglycine excretion, and neurological and haematological improvement after two weeks.[26] During the acute phase, protein restriction and provision of adequate calories to suppress endogenous protein breakdown are important aspects of the management.

In certain IEM, enhancement of the activity of a mutant enzyme can be achieved by giving mega–doses of a vitamin cofactor required for the enzyme's action. One-third of the cases of homocystinuria due to cystathionine β-synthetase are pyridoxine responsive. Pyridoxine dependency is an autosomal recessive condition of possible disorder of gamma aminobutyric acid metabolism presenting in early infancy with intractable seizures that respond to 10 to 100 mg of pyridoxine per day given orally. Some patients with MSUD may respond to 10 to 20 mg thiamine per day together with a protein-restricted diet. Some patients also benefit from thiamine administration and a ketogenic diet in pyruvate dehydrogenase deficiency. Deficiency of multiple biotin-dependent carboxylases (acetyl CoA carboxylase, propionyl CoA carboxylase, 3-methylcrotonyl CoA carboxylase, and pyruvate carboxylase) appears in two forms, one resulting from deficiency of holocarboxylase synthetase and the other from biotinidase deficiency. This disorder will respond to 10 mg of biotin given daily with clinical and biochemical response.[14]

Methylmalonyl CoA mutase is a cobalamin-dependent enzyme and some cases of methylmalonic acidaemia respond to pharmacological supplementation of intramuscular hydroxycobalamin in a dose of 1 mg per day with a fall in methylmonate accumulation and is therefore a useful treatment adjunct to dietary protein restrictions.[12] A diet low in fat and protein together with a trial of oral riboflavin (200-300 mg per day) and carnitine may be helpful in some patients with glutaric aciduria type I and II. Oral riboflavin may lead to significant clinical improvement in some patients with fatty acid oxidation disorders and the response may reflect a role for riboflavin in stabilising a mutant flavin-dependent enzyme.[19] Carnitine levels may be low in other organic acidurias and oral carnitine (25-50 mg/kg/day) may improve metabolic control, especially in isovaleric acidaemia and 3-methylglutaconic aciduria. Carnitine supplementation has also been recommended for fatty acid oxidation disorders.[19] Oral antibiotic therapy has been advocated in propionic and methylmalonic acidaemia to reduce the bacterial production of these toxic organic acids in the gut.[12]

Simple restriction of certain dietary components such as galactose and fructose form the basis of treatment in galactosaemia and fructose intolerance.[6] A galactose-free diet will quickly reverse the clinical symptoms and prevent mental retardation, cataract, and liver damage. However, recent reports have indicated that despite early diagnosis and treatment, most cases have lower intelligence quotients, speech and motor dysfunction, and growth and ovarian failure.[28] Neonates with PKU should be given a protein substitute which is phenylalanine-free (Lofenalac Powder, Mead Johnson, US) but otherwise nutritionally complete, with a composition sufficient to provide 100 to 120 mg/kg/day of tyrosine and a total amino acid intake of 3 g/kg/day in children under two years of age. Phenylalanine intake in the form of normal protein should be adjusted to maintain a plasma level of between 120 to 360 μmol/L. Special formulae are available for tyrosinaemia (low tyrosine and phenylalanine, product 3200AB, Mead Johnson, US) and MSUD (MSUD Diet Powder, Mead Johnson, US).

Clinicians must be aware that the special formulae are incomplete and one should seek the assistance of a dietitian experienced in the care of infants and children with IEM, to ensure adequate intake of essential amino acids and fatty acids, minerals, and vitamins. Indiscriminate use of special formulae without appropriate supplementation or strict protein restriction can result in an acrodermatitis enteropathica-like syndrome, which may be secondary to deficiencies of a trace metal such as zinc, essential amino acids, and essential fatty acids.[29] Regular monitoring of plasma metabolite concentrations would be informative regarding dietary compliance, and is essential for dietary adjustment.

Another aspect in the management of IEM is the replacement of a product due to an enzyme defect. In patients with glycogen storage disease, deficient hepatic glucose output leads to hypoglycaemia. Hypoglycaemia can be prevented by frequent feeds during the day and continuous nasogastric feeding at night, in infancy and early childhood. Raw cornstarch (2 g/kg every six hours) has been shown to be effective in preventing hypoglycaemia in older children with glycogen storage disease type I as well as decreasing the hyperlipidaemia, hyperuricaemia, and lactic acidaemia.[30] Cornstarch therapy has also been used to manage the hypoglycaemic episodes in patients with fatty acid oxidation disorders. Infants with inborn errors of hormone biosynthesis should be supplemented with the deficient hormones. Examples include thyroxine in thyroid dyshormonogenesis, hydrocortisone, and fludrocortisone in 21 α-hydroxylase deficiency, and biotin in biotinidase deficiency.

Conclusion

Despite recent medical advances, no specific treatment or cure is available for most IEM. After the diagnosis of IEM is made, the parents should be referred for genetic counselling and be offered prenatal diagnosis for future pregnancies.[31] In a recent survey of treatment of more than 300 monogenic disorders, available therapy normalised life span in 15% of the patients, reproductive capability in 11%, and social adaptation in just 6%.[32] Correction of genetic diseases by transplantation is a form of treatment lying between treatment at the level of the dysfunctional protein and somatic gene therapy. Displacement bone marrow transplantation has been successful in the treatment of certain otherwise fatal metabolic diseases early in life before onset of damage. These include Gaucher's disease, Wolman's disease, mucopolysaccharidosis, adrenoleukodystrophy, and metachromatic leukodystrophy.[33] Liver transplants have been used in the treatment of hereditary tyrosinaemia, glycogen storage disease, and familial hypercholesterolaemia. In the next two decades, patients with IEM will hopefully be successfully treated using somatic gene therapy.

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