Conference of Inborn Errors of Metabolism in Infants and Children 2002
Hong Kong Society of Neonatal Medicine, Hong Kong Society of Medical Genetics, Hong Kong Society of Clinical Chemistry, Hong Kong Society of Paediatric Endocrinology & Metabolism, Hong Kong Nutrition Association and Obstetrical and Gynaecological Society of Hong Kong

1. Dietary Treatment of Amino Acids Inborn Errors of Metabolism
A MacDONALD, A DALY, A CHAKRAPANI
The Children's Hospital, Steelhouse Lane, Birmingham, B4 6NH, United Kingdom

Introduction
Dietary treatment is essential for many amino acid disorders, particularly phenylketonuria (PKU), homocystinuria, maple syrup urine disease (MSUD) and tyrosinaemia type I, II and III. Diet may be the sole form of therapy or used in combination with other treatments e.g. betaine in homocystinuria or NTBC in tyrosinaemia type I. Although simple in principle, diet therapy is complex for patients and carers, difficult to administer, and highly restrictive. It is important to acknowledge that diet therapy can significantly impact on family lifestyle, demands self-discipline, good organisational skills, increases parental anxiety, exacerbates family conflict and may cause embarrassment and even bullying in school age children. Severe dietary restriction is usually less acceptable to patients diagnosed after infancy.

The goals of dietary management in amino acid disorders are four-fold:
1. Prevention of excessive accumulation of substrate amino acids by strict control of natural protein intake. This is in combination with the administration of an appropriate protein substitute.
2. Achievement of normal growth and nutritional status.
4. Provision of a diet that is palatable, flexible and compatible with a modern day lifestyle.

Although the principles of diet therapy are similar for all these amino acid disorders, their prevalence, presentation, symptoms, and complications are quite different.

PKU
PKU is usually caused by a deficiency of the hepatic enzyme, phenylalanine hydroxylase (phenylalanine 4-mono-oxygenase, EC 1.14.16.1). This is a mixed function oxidase which catalyses the hydroxylation of phenylalanine
to tyrosine, the rate limiting step in phenylalanine catabolism. Deficiency of this enzyme leads to an accumulation of phenylalanine, resulting in hyperphenylalaninaemia and abnormalities in the metabolism of many compounds derived from aromatic amino acids. Phenylalanine hydroxylase deficiency is heterogeneous with a continuum of metabolic phenotypes ranging from classical PKU, characterised by blood phenylalanine of 20 times the normal rate to mild hyperphenylalaninaemia with blood phenylalanine levels 3-5 times higher than normal. There are over 400 mutations with good genotype and phenotype correlation. Overall, the prevalence amongst Caucasians is approximately 1 in 10,000, corresponding to a carrier frequency of about 1 in 50. In Asian populations, PKU is rare and prevalence figures range from approximately 1:16,500 in China to 1:120,000 in Japan.

Untreated PKU leads to mental retardation, hyperactive behaviour with autistic features, and seizures. If dietary treatment is started within the first 3 weeks of life, irreversible mental retardation is prevented. However, even when patients with PKU treated continuously and carefully, following neonatal diagnosis, mildly depressed IQ is common in treated PKU, and depressive mood, anxiety, and social isolation have been reported. Even so, most early treated children who have started diet by 4 weeks of age fall within the broad normal range of general ability and there is strong evidence to indicate that outcome is closely related to the quality of early blood phenylalanine control.

A low phenylalanine diet is recommended for life. At diagnosis, dietary treatment is widely advocated when blood phenylalanine concentrations are consistently over 600 µmol/l. There is less agreement about the use of dietary treatment when presenting phenylalanine concentrations persist between 360-600 µmol/l. Although dietary treatment has been the main stay of therapy since the mid 1950's, the enzyme phenylalanine ammonia lyase may be used as an alternative therapy in the future. It converts phenylalanine to a nontoxic derivative and in a PKU rat model has been shown to lower plasma and tissue phenylalanine more effectively than diet.

**MSUD**

MSUD is caused by a deficiency in activity of the branched chain α-keto acid dehydrogenase (BCKD) complex. This metabolic block results in the accumulation of the branch chain amino acids leucine, isoleucine, and valine and the corresponding branched chain keto-acids. It was described in 1954 and dietary treatment was first used in 1959. It is named after the sweet, malt, caramel like odour produced by elevated concentrations of 2-oxo-3-methyl-N-valeric acid. There are four forms, which differ in the age of onset, biochemical findings, and responsiveness to thiamin, a cofactor for the BCKD complex. The genetic heterogeneity is explained by the various mutations that occur in the E1 alpha, E1 beta, E2, and E3 loci of the BCKD complex. Treatment involves both long term dietary management and aggressive intervention during acute metabolic decompensation. At any age, an emergency regimen must be adhered to during intercurrent infections.

Classic MSUD has a neonatal onset, with poor feeding, irritability, lethargy and encephalopathy and is the most common and severe form. Any delay in diagnosis or treatment may result in permanent neurological damage and early death. Toxic metabolites may need to be removed by haemodialysis or haemofiltration. Diagnosis before 10 days is imperative. An intermediate form presents at any age, infancy to adulthood, with failure to thrive, neurological features, and ketoacidosis. An intermittent form manifests episodic ataxia and ketoacidosis, often associated with increased protein consumption or intercurrent illness. Children are normal between attacks but there is still a chance of permanent neurological damage from acute episodes. The fourth type is a thiamin responsive form.

The concentrations of branch chain amino acids, particularly leucine are greatly increased in the plasma and urine. The presence of alloisoleucine is diagnostic of MSUD. The worldwide frequency is only approximately 1 in 185,000, but is common among the Mennonites of North America where the incidence is 1 in 176. It is found in all racial types. Long-term outcome is variable but the average intellectual ability is below normal. Approximately one third of classic MSUD patients have IQ scores greater than 90 and a further one third have IQ scores between 70 and 90.

**Homocystinuria**

Cystathionine β-synthase (CBS) deficiency is the most frequently encountered cause of homocystinuria (HCU). Homocysteine, methionine and other sulphur containing metabolites accumulate in the body or are excreted in the urine. Plasma cystine is usually low. It was first described in 1962. The worldwide incidence of HCU is approximately 1 in 335,000 but varies from 1:65,000 (Ireland) to 1:900,000 (Japan). Two clinical forms of CBS deficiency have been described on their basis to respond to pyridoxine treatment (pyridoxine responsive and non pyridoxine responsive HCU). There is considerable genetic heterogeneity.

The most frequent complications of the disease are divided into four areas: 1) dislocation of the optic lens,
myopia and glaucoma; 2) osteoporosis, scoliosis, thinning and lengthening of the long bones; 3) learning difficulties, developmental delay affecting approximately 60% of patients, psychiatric problems, EEG abnormalities and epilepsy; and 4) thromboembolism affecting large and small arteries and veins are the most common clinical features. Thrombosis is a frequent cause of death. Patients vary widely in the extent to which they manifest these abnormalities. Accumulation of homocysteine probably plays an important role in the development of many of these complications.

In non-pyridoxine responsive patients, early diagnosis together with a life-long low methionine diet can be highly successful in preventing complications. Strategies for treatment of CBS deficiency include: 1) pyridoxine and folic acid supplementation in pyridoxine responsive HCU; 2) reducing the methionine substrate load and supplementing the diet with cysteine; and 3) betaine supplementation as a homocysteine lowering agent. Betaine may be effective in vitamin B6 nonresponsive patients in whom dietary management is unsatisfactory but patient compliance may be poor. It acts as a methyl donor for the remethylation of homocysteine to methionine. Its use is often associated with an increase in plasma methionine, but not always.

Tyrosinaemia

Type I: caused by deficiency of fumarylacetoacetate hydroxylase, the last enzyme in tyrosine degradation. The fumarylacetoacetase gene is located at 15q 23-25. The condition is clinically heterogeneous, more than 30 different mutations have been identified and it presents either as an acute or chronic form. Plasma tyrosine is elevated in most patients and alpha-fetoprotein may reach high concentrations. Symptoms are variable and include acute liver failure, cirrhosis, hepatocellular carcinoma, renal Fanconi syndrome, glomerulosclerosis, and neurological crisis resembling acute intermittent porphyria. Vitamin D resistant rickets develops due to severely impaired renal function. Elevated levels of succinylacetone in plasma or urine are diagnostic for this function.

NTBC (2-[2-nitro-4-trifluoro-methylbenzoyl]-1, 3-cyclohexandione), a potent inhibitor of 4-hydroxyphenylpyruvate dioxygenase (4HPPD) prevents tyrosine degradation and production of succinylacetone. Since it was first used in the treatment of this disorder in 1991, patients have not developed acute hepatic or neurological crisis, but current data do not allow conclusions on the long-term risk of hepatocellular in NTBC treated patients.

A low tyrosine diet was first used in 1964. Most patients show only a partial response to dietary restriction of tyrosine and phenylalanine and now diet is used in combination with NTBC treatment.

Type II: caused by L-tyrosine aminotransferase deficiency, it was first described in 1983. It causes corneal lesions and keratitis and blisterous lesions on the soles and palms but the onset of symptoms may vary. Furthermore, approximately 50% of patients suffer from neurological complications including fine co-ordination and language deficits, microcephaly, self-mutilation and severe developmental delay. Plasma tyrosine concentrations are elevated but is successfully treated with a low tyrosine diet. There is no consensus on optimal blood levels of tyrosine or what age diet should be started.

Type III: a rare disorder caused by deficiency of 4HPPD, the second enzyme in the catabolic pathway of tyrosine. Plasma tyrosine is highly elevated. Ataxia, convulsions, and a cerebral atrophy have been reported. It may be asymptomatic or is associated with neurological symptoms. All patients reported so far have normal liver and renal function and none have skin or eye abnormalities. It is not clear how beneficial dietary tyrosine restriction is but it is thought it may be important, particularly in infancy.

Dietary Management

The principles of dietary management for all these amino acid disorders are similar. There are five key elements to dietary management.

1. Restriction of substrate amino acids to maintain blood phenylalanine concentrations within desirable reference ranges. High protein foods such a meat, fish, eggs and cheese are not permitted in the diet.
2. Daily allocation of dietary substrate amino acids from measured quantities of moderate protein containing foods to provide minimum requirements. These are given in the form of an exchange system, whereby one food can be exchanged or substituted for another of equivalent content.
4. Maintenance of a normal energy intake by encouraging liberal use of foods naturally low in protein and specially manufactured low protein foods such as bread, pasta and biscuits. These are called ‘free’ foods.
5. Provision of all vitamins and minerals to meet dietary requirements. These can either be given together in the protein substitute or as separate modules.
Restrictions of Substrate Amino Acids

The tolerance of substrate amino acids is variable and dependent on:
- Severity of disorder.
- Target plasma amino acids range.
- Compliance with protein substitute.
- Energy intake.
- Age and weight of the child.

Requirements per kg body weight for amino acids are highest in early infancy and decreases with increasing age. Total daily requirements change very little after initial stabilisation of diet. Acosta et al reported in PKU that to maintain blood phenylalanine concentrations between 60-324 µmol/l in infants, mean phenylalanine requirements were 0-3 months: 55 mg/kg/day; 4-6 months: 36 mg/kg/day; 7-9 months: 31 mg/kg/day and 9-12 months: 27 mg/kg/day. Suggested leucine requirements in MSUD are 100-120 mg/kg/day in 2-3 month old infants, reducing to 40-50 mg/kg/day in 1-year-old children. In tyrosinaemia type I, natural protein requirements varies from a peak of 1.8-2.4 g/kg/day at 5 months of age to 1 g/kg/day in later infancy. Average daily tolerance of substrate amino acids is given in Table 1.

The substrate amino acid is given in the form of a daily allowance via a food exchange system. This does not take into account the small quantities of protein obtained from the very low protein foods allowed without restriction. Foods such as meat, fish, eggs, cheese, milk, nuts, ordinary bread, biscuits, cakes and chocolates are avoided because these are too high in natural protein. The exchange foods are made up from moderate protein foods like potatoes, peas, sweetcorn, rice and breakfast cereals. Examples of exchange systems from the different amino acid disorders are given in Table 2. Ideally amino acid exchanges should be spread evenly throughout the day so that a load of dietary substrate amino acids is not given at any one time.

### Table 1

<table>
<thead>
<tr>
<th>Amino acid disorder</th>
<th>Amino acid tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKU</td>
<td>200-400 mg/daily phenylalanine</td>
</tr>
<tr>
<td>MSUD</td>
<td>400-600 mg/daily leucine</td>
</tr>
<tr>
<td>Homocystinuria</td>
<td>160-900 mg/daily methionine</td>
</tr>
<tr>
<td>Tyrosinaemia Type I</td>
<td>1 g/kg/day of protein in late infancy</td>
</tr>
</tbody>
</table>

NB. This is the amount of amino acid from exchange foods. It does not take into consideration the small, additional quantities consumed from low protein free foods.

### Table 2

<table>
<thead>
<tr>
<th>Amino acid disorder</th>
<th>Exchange system</th>
<th>Examples of exchanges</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKU</td>
<td>50 mg phenylalanine</td>
<td>30 ml cow's milk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>80 g potato</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45 g chips</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 g baked beans</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25 g peas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45 g boiled rice</td>
</tr>
<tr>
<td>MSUD</td>
<td>50 mg leucine</td>
<td>15 ml cow's milk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60 g potato</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35 g chips</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 g baked beans</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 g peas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25 g boiled rice</td>
</tr>
<tr>
<td>Homocystinuria</td>
<td>20 mg methionine</td>
<td>20 ml cow's milk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>85 g potato</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35 g chips</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35 g baked beans</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45 g peas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40 g boiled rice</td>
</tr>
<tr>
<td>Tyrosinaemia Type I</td>
<td>1 g protein</td>
<td>30 ml cow's milk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>55 g potato</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25 g chips</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 g baked beans</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 g peas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45 g boiled rice</td>
</tr>
</tbody>
</table>
Protein Substitute

These are essential in the treatment of amino acids disorders for several reasons:
- Provide sufficient amino acids for normal growth.
- Helps suppress plasma precursor amino acids concentrations.
- May supply a source of energy.
- May also supply a source of vitamins and minerals.

In the UK, protein substitutes are supplied in generous quantities as L-amino acids may be inefficiently utilised. Guidelines for the total protein requirements per kg body weight (i.e. protein from amino acid exchanges and protein substitute) are given in Table 3. They should be given evenly during the day. The effect of timing of protein substitute has been extensively studied; and it is better to given protein substitute in small frequent doses, three to four times daily spread evenly throughout the day. Theoretically it is better given with some of the substrate amino acid allowance. Added carbohydrate to the protein substitute may increase net protein synthesis. There is evidence that infrequent administration of large doses of protein substitute increases nitrogen excretion as well as oxidative utilisation of amino acids; so this practice is not advocated.

The protein substitutes are available in a variety of different presentations and the range of novel presentations is increasing. They include: L-amino acids with added carbohydrate, +/- fat, vitamins and minerals designed to be administered as a drink or gel; powdered protein substitutes which contain L-amino acids only; modular protein substitutes (presented in 3 different formats i.e. tablets, power, and bar); and amino acid tablets. The latter two have been developed for PKU only.

Administration of Protein Substitute

Protein substitutes can be taken as a drink or paste. The traditional method of administering protein substitute is in the form of a drink. However, when dissolved in water it is bitter tasting and produces a hyperosmolar solution. If diluted with less water than recommended by the manufacturers, an additional drink of water should be taken at the same time.

Alternatively, protein substitute can be given as a paste or gel. A small amount of water, or concentrated fruit juice is added to each dose of protein substitute to make a thick paste. An additional drink of water should be given with each dose to dilute this hyperosmolar mixture. Protein substitutes are now being developed in a gel format for all amino acid disorders. Giving protein substitute as a paste appears an acceptable method of protein substitute delivery to young children.

Other Considerations

PKU: The inability to convert phenylalanine into tyrosine transforms tyrosine from a non-essential to an essential amino acid. Consequently, patients are dependent on a dietary source of tyrosine and so UK protein substitutes are supplemented with tyrosine to supply tyrosine requirements.

Homocystinuria: Cystine is usually deficient due to the metabolic block, so an additional source is needed. The UK methionine free protein substitutes are supplemented with cystine.

MSUD: Sometimes, additional, small amounts of valine and isoleucine must be given as the tolerance to leucine is lower than valine and isoleucine.

Low Protein Free Foods

These are essential and encouraged liberally in amino acid disorders. Their benefits include:
- Provide a good source of calories.
- Ensure normal growth.
- Enhance protein synthesis.
- Minimise catabolism. Long periods of fasting should be avoided – particularly in conditions such as MSUD.

Table 3  Total protein requirements for amino acid disorders (includes protein equivalent from amino acid supplement and natural protein)

<table>
<thead>
<tr>
<th>Age (year)</th>
<th>Total protein (g/kg/body weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>3.0</td>
</tr>
<tr>
<td>3-5</td>
<td>2.5</td>
</tr>
<tr>
<td>6-10</td>
<td>2.0</td>
</tr>
<tr>
<td>11-14</td>
<td>1.5</td>
</tr>
<tr>
<td>&gt;14</td>
<td>1.0</td>
</tr>
</tbody>
</table>
There are a number of foods naturally low in protein which are given freely in the UK low amino acid diets.

- **Fruits and vegetables:** many fruits and vegetables.
- **Fats:** butter, margarine, lard and vegetable oils.
- **Sugars and starches:** cornflour, custard powder, sago, tapioca, sugar, glucose, jam, honey, marmalade, golden syrup, treacle and sweets <0.3 g protein/100 g.
- **Miscellaneous:** Vegetarian jelly, agar-agar, salt, pepper, herbs, spices and vinegar. Tomato and brown sauce. Baking power, bicarbonate of soda and cream of tartar. Food essences and colouring.
- **Drinks:** Aspartame-free squash, lemonade, Coca-Cola and fruit juice. Tea, coffee, tonic water, soda water and mineral water.
- **Low protein special foods:** a selection of low protein breads, flour mixes, cake mixes, pizza bases, pasta, biscuits, egg replacers, milks, cheese, cheese sauces and chocolate are available in the UK. Most are available free of charge on the UK government prescription system so families do not need to pay for these. These are an important source of calories in the diet.

It is important to introduce a variety of low protein 'free' foods into the diet as early as possible to give variety and adequate energy to meet estimated average requirements. Families need simple and practical ideas on how to incorporate 'free' foods into the diet effectively. They need help in interpreting food labels so they can fully utilise all free foods on the market. Low protein recipe books, cookery workshops, cookery demonstrations can all help parents prepare 'free' suitable meals and dishes.

### Vitamins and Mineral Supplementation

Comprehensive vitamin and mineral supplementation is added to some protein substitutes and providing adequate quantities of protein substitute are taken no additional supplementation is necessary. Other protein substitutes contain no vitamins and minerals so complete supplementation is necessary. Reports of vitamin and mineral deficiency is common. They include selenium deficiency, low ferritin concentrations, low vitamin B<sub>12</sub> concentrations and decreased bone mineral density. Vitamin and mineral deficiency is due to four main reasons:

1. failure of a protein substitute or vitamin and mineral supplement to contain a specific micronutrient e.g. selenium deficiency has been commonly associated with lack of added selenium to the supplement;
2. low bioavailability of micronutrients added to supplements;
3. non-compliance with the protein substitute with added vitamin and mineral supplement or separate vitamin and mineral supplement; and
4. excessive use of emergency regimen without added vitamins and minerals.

### Essential Fatty Acid Status

The long chain polyunsaturated fatty acid status of patients on low protein diets with inherited metabolic disease has been the subject of much debate, particularly in PKU. Evidence suggests that children on low protein diets have reduced concentrations of arachidonic acid and docosahexanoic acid in plasma and membrane phospholipids compared to controls and may require supplementation. A strict low phenylalanine diet is high in linoleic acid, but low in alpha-linolenic acid, arachidonic acid (AA) and devoid of any sources of eicosapentanoic acid (EPA) and docosahexanoic acid (DHA). In amino acid disorders, the extent to which long chain polyunsaturated fatty acids (LCP’s) can be synthesised from the parent fatty acids (linoleic acid and alpha-linolenic acid) is debatable and some would argue that a direct source should be provided. In the UK, new protein substitutes are being developed for PKU and other amino acid disorders with added essential fatty acids. In addition, long chain polyunsaturated fatty acid capsules have improved DHA concentrations and visual function in children with PKU.

### Illness Management

During illness protein catabolism will greatly increase production of substrate amino acids. High plasma leucine concentrations in MSUD could cause rapid neurological deterioration. All parents should have a regularly updated emergency regimen, and should be carefully instructed on appropriate action during intercurrent infections.

The following measures are recommended:

- Reduce or stop intake of substrate amino acids.
- Two-three hourly administration day and night of high calorie carbohydrate drinks.
- Maintain protein substitute intake, particularly in MSUD. If a child cannot drink the recommended volume of high carbohydrate drinks or protein substitute, administration via a nasogastric tube should be considered.
- Regular monitoring of plasma amino acids.

An emergency regimen should only be used in the short term. Prolonged and frequent use of an emergency regimen for illness may lead to nutritional deficiencies.
Breast Feeding in Amino Acid Disorders

The successful use of breast-feeding in amino acid disorders has now been increasingly reported in the form of case studies. In 1981, it was first reported in PKU and more recently, Touati reported four infants with MSUD who were successfully breast fed. Breast feeding is based on the principle of giving a measured volume of infant protein substitute before breast feeds, so reducing stimulation and protection of breast milk, thus breast milk and substitute amino acid intake is reduced.

Plasma amino acid concentrations are used to determine how much infant formula to give. If substrate amino acid concentrations are high, more protein substitute is given so less breast milk is taken. If substrate amino acid concentrations are low, less infant protein substitute is given so more breast milk is taken. Motzfeldt has recently reported successfully breast feeding seventy-four out of eighty-three babies born with PKU since 1979. It took a mean of eight days to normalise phenylalanine concentrations. Breast feeding duration was anything from four weeks to sixteen months. The growth was within normal parameters.

Monitoring

Regular monitoring of plasma substrate amino acids is recommended for all amino acid disorders. An UK MRC Working Group published a set of guidelines that included monitoring of blood phenylalanine concentrations in PKU but target ranges are set by UK clinics for all the other disorders. Blood samples are taken at a standard time each day, preferably before the first dose of protein substitute in the morning when blood substrate amino acid concentrations are usually highest.

With the exception of homocystinuria, parents are taught how to collect heal or thumb prick blood samples at home by a specialist nurse. The parents then post the blood sample to the hospital. The dietitian then contacts the parents with the results to discuss their interpretation and instruct on any dietary changes.

Conclusions

Early diagnosis and subsequent metabolic control are important for successful outcome in all amino acid disorders. Diet therapy in amino acid disorders requires close supervision by an experienced dietitian, with the close support of a metabolic team. Parental and child understanding and their co-operation are also paramount in achieving satisfactory metabolic control. Improvements in nutritional therapy, dietary foods, monitoring, and management of acute infections have helped contribute to improved outcome in all these conditions.

References

15. Walter JH, Wraith JE, White FJ, Bridge C, Till J. Strategies for...


A Stepwise Clinical Approach to Inherited Metabolic Diseases

JTR Clarke
Division of Clinical & Metabolic Genetics, Department of Paediatrics, Hospital for Sick Children, University of Toronto, Toronto, Canada

Introduction

Inherited metabolic diseases, as a group, present a particular challenge for the general paediatrician. The diseases are individually rare, and most generalists have little experience with their diagnosis and management. In addition, the clinical presentation of the diseases often mimics common acquired conditions, especially infections, intoxications, and some nutritional deficiency disorders. The perception of difficulty is increased by the fact that clinicians often find thinking about the chemical physiology of inborn errors of metabolism daunting. Moreover, most textbooks dealing with inherited metabolic diseases are organised biochemically, with chapters on inborn errors of carbohydrate metabolism, on amino acidopathies, on disorders of organic acid metabolism, and on other aspects of metabolism. The clinician confronted by a patient who is acutely ill is, therefore, confronted with the challenge of deciding which chapter is going to be most useful in working out the diagnosis and prescribing appropriate treatment.

The purpose of this paper is to 'demystify' the clinical challenge by presenting a stepwise approach to diagnosis and management that facilitates the early recognition of inborn errors of metabolism and guides further investigation. Treatment is divided into 'first aid', which is primarily symptomatic and supportive, and definitive therapy, which requires a specific diagnosis. The initiation of 'first aid' is undertaken at the suspicion stage of the diagnostic process and is critically important for a good outcome.

Suspicion

Inborn errors of metabolism may affect any system of the body. Inherited metabolic diseases may, therefore, present in a myriad of ways. However, some clinical situations are particularly common among the group of diseases and provide a clue to the nature of the underlying disorder.

Exaggerated Response to Intercurrent Illness

The presence of an inborn error of metabolism often compromises the homeostatic mechanisms that are an important part of the adjustment of infants and children to the physiological stress of intercurrent illnesses, especially infections. Children with inborn errors of metabolism, which might be well compensated most of the time, often decompensate during intercurrent illness. They become sicker and stay sicker longer than their siblings with the same infection, an important clue to the inability of the patient to adjust metabolically to the stress of the disease.

Unexpectedly Poor Response to Treatment of an Illness Presumed to Be Acquired

In the same way that inborn errors of metabolism may compromise the ability of an infant or child to compensate for metabolic disturbances occurring in the course of an intercurrent illness, they may also compromise the response to therapy. For example, lactic acidosis is a common metabolic consequence of circulatory insufficiency, but it resolves rapidly when the circulatory problem, such as hypovolemic shock, is corrected. Children with primary disorders of lactic acid metabolism may also present in what appears to be shock, but the lactic acidosis persists, after normal circulation is restored.

A Condition Resembling an Infectious Disease, but No Organism Is Isolated

Infants and children respond to severe physiological challenges, including infections, with a limited repertoire of clinical signs and symptoms. The signs of metabolic decompensation in patients with inborn errors of metabolism often mimic severe systemic infections, especially in the newborn period. Pallor, stupor, respiratory distress, intractable vomiting, hypotension, and other signs are common in both situations. The absence of fever, though unreliable in the newborn, and the failure to identify a focus of infection, along with the failure to isolate a pathogenic microorganism, are all clues to the possibility of an inherited metabolic disease.

A Condition Resembling an Intoxication, but without a History of Ingestion or Exposure

Most poisons cause illness by the effect they have on metabolic processes in the body. The observation that inborn errors of metabolism often mimic an intoxication is, therefore, no surprise. Poisons often have a general effect on metabolism, affecting more than one metabolic process; inborn errors of metabolism tend to affect only one or a small group of related metabolic processes. However, the secondary metabolic consequences of point defects in metabolism are often so prominent that the distinction between the general effect of toxins and the more restricted primary effects of inborn errors of metabolism is difficult.
to make. The inability to elicit a history of ingestion, or a negative drug screen, increases the possibility that the patient actually has an inborn error of metabolism.

**A Positive Family History**

Inherited metabolic diseases are hereditary. Most are transmitted as autosomal recessive disorders, and the possibility that siblings or cousins might be affected with the same disease is high. A history of parental consanguinity is a particularly important clue to the possibility of an inborn error of metabolism.

**Catastrophic Illness in the Newborn**

A history of acute deterioration after a period of apparent normalcy, which may be as short as a few hours, is a feature of many inborn errors of metabolism presenting in the newborn period. Prominent nonspecific signs of diffuse cerebral dysfunction, especially if they are progressive, are a strong indication of inherited metabolic disease. The onset is usually gradual, often no more than poor sucking, drowsiness, and some floppiness. Vomiting often occurs and may be severe enough to suggest mechanical bowel obstruction. Deterioration is marked by increasing somnolence, progressing to stupor and coma, associated with the development of abnormalities of tone and posturing, abnormal movements, and disturbances of breathing, bradycardia, and hypothermia. The recognition of subtle clinical discrepancies between the severity of what appears to be sepsis and the degree of acidosis in this situation is sometimes a critical clue to the true nature of the underlying disease. The presence of an unusual odour is also a clue to the possibility of an inborn error of metabolism, though unusual dietary preferences of mothers appear to be a more common cause of abnormal odours in breast-fed infants.

**Acute Encephalopathy of Any Kind, Especially Recurrent**

Inherited metabolic diseases are among the more common causes of acute encephalopathy in infants and children. In some cases, the response to supportive treatment, such as intravenous fluids and glucose, is rapid, and the incentive to pursue the underlying cause of the problem is often weak. However, encephalopathy associated with any combination of hypoglycaemia, metabolic acidosis, or hyperammonaemia is particularly common in some inborn errors of metabolism, such as urea cycle enzyme defects and the organic acidopathies. What is more, the results of treatment, when the problem is recognised early and treated aggressively, are excellent. Acute encephalopathy in an infant or child of any age is a powerful clue to the possibility of a treatable inherited metabolic disease.

**Developmental Regression**

Developmental regression is a widely recognised feature of many inherited metabolic diseases. What is less widely appreciated is that frank regression, that is the loss of previously acquired skills, usually occurs after a period varying from some weeks to several years of development deceleration and arrest. For example, a child who is normal at 12 months of age, significantly behind her peers at 2 years of age, and frankly retarded at 3 years of age, is showing developmental ‘regression’ even if she is still acquiring new skills. Failure to recognise this is one of the reasons that many couples with a child with Sanfilippo disease (MPS III) have a second affected child before the diagnosis is suspected in the older child.

**Hypoketotic Hypoglycaemia**

Hypoglycaemia is a common metabolic response to severe systemic disease in infants and children. It is undoubtedly the result of a combination of starvation and inability of the body to keep pace with increased tissue demands for energy. It is associated with ketosis, and it is relatively easy to control. Hypoketotic hypoglycaemia is the result of obligatory over-utilisation of glucose, either from hyperinsulinism or defects in fatty acid oxidation. The hypoglycaemia caused by hyperinsulinism is often severe and difficult to control. In children with defects of fatty acid oxidation, the encephalopathy is often out of proportion to the hypoglycaemia and persists after correction, and it is often associated with hyperammonaemia and evidence of hepatocellular dysfunction. One of the most useful—and inexpensive—tests to do in the investigation of hypoglycaemia in a young child is measurement of urinary ketones.

**Recurrent Reye Syndrome**

Acquired Reye syndrome (encephalopathy with fatty degeneration of the viscera) has become so uncommon that a child presenting with vomiting, lethargy progressing to stupor, hepatomegaly with hepatocellular dysfunction, and hypoglycaemia is much more likely to have an inborn error of fatty acid oxidation, such as medium-chain acyl-CoA dehydrogenase (MCAD) deficiency. Delays in recognising the significance of this combination of signs is probably why a high proportion of infants with MCAD deficiency, an easily treatable disease, die before the diagnosis is made.
Storage Syndrome

'Storage syndrome' is a selection of physical and radiological signs that occurs in a number of lysosomal storage diseases, such as Hurler disease, and some peroxisomal diseases. It consists of a triad of unusual coarse facial features, hepatosplenomegaly, and changes in the bones and joints causing dysostosis multiplex and variable but painless limitation of active and passive movement of many joints. Included in this presentation are children with isolated, asymptomatic splenomegaly, such as is seen in Gaucher disease, cholesterol ester storage disease, and Niemann-Pick disease, type B (Table 1).

A growing number of inherited metabolic diseases are being recognised in which dysmorphism is prominent. Menkes disease, congenital disorders of glycosylation (CDG) syndromes, and Smith-Lemli-Opitz (SLO) syndrome are examples. To deal adequately with the clinical approach to this group of disorders is beyond the scope of this paper.

Treatment on Suspicion

Regardless of the underlying cause, treatment of some of the metabolic abnormalities associated with inborn errors of metabolism is not only possible, but necessary, before a specific diagnosis is made.

Hypoglycaemia

Symptomatic hypoglycaemia is a medical emergency demanding immediate treatment by intravenous infusions of glucose, regardless of the cause of the problem. The dosage of glucose administered is determined by the amount that is necessary to maintain euglycemia. In the course of treatment, two measures that may turn out to be diagnostically important in the later investigation of the patient are testing the urine for ketones and keeping track of the amount of glucose (mg per kg, body weight per minute) needed to maintain euglycemia.

Metabolic Acidosis

Metabolic acidosis is a common presenting feature of several inborn errors of metabolism. Usually this is the result of accumulation of organic anions (abnormally wide anion gap; normal plasma Cl⁻); rarely, it is caused by renal tubular damage resulting in abnormal losses of bicarbonate (normal anion gap; elevated plasma Cl⁻). The treatment is virtually the same as the treatment of other causes of metabolic acidosis: intravenous fluids containing 10% glucose and intravenous bicarbonate. Collection of urine for analysis of urinary organic acids, and plasma for acylcarnitine analysis, at this time, while the child is acidotic, is often extraordinarily useful in making the diagnosis of an organic acidopathy or ruling it out as a diagnostic possibility.

Except in situations in which glucose oxidation is impaired, such as in pyruvate dehydrogenase (PDH) deficiency, glucose is oxidised to bicarbonate (each mole of glucose produces 6 moles of bicarbonate), facilitating correction of the acidosis without the sodium intake associated with the use of sodium bicarbonate. Sodium bicarbonate should be used aggressively if the child is known or suspected to have pyruvate carboxylase (PC) deficiency or the plasma bicarbonate concentration is <4 mmol/L, and measures will have to be taken to control the resulting hypernatremia (e.g. administration of furosemide, or dialysis). In other situations, bicarbonate should be used carefully in order to avoid over-treatment and resulting iatrogenic metabolic alkalosis.

Hyperammonaemia

Symptomatic hyperammonaemia is a medical emergency requiring immediate and aggressive treatment, regardless of the cause. Elimination of exogenous (dietary) sources of nitrogen, the minimisation of the production of

<table>
<thead>
<tr>
<th>Physical feature</th>
<th>Hurler disease</th>
<th>Hunter disease</th>
<th>Infantile GM1 gangliosidosis</th>
<th>Sanfilippo disease</th>
<th>Juvenile GM1 gangliosidosis</th>
<th>Gaucher disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coarse facies</td>
<td>++++</td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>0+</td>
<td>0</td>
<td>+++</td>
</tr>
<tr>
<td>Dysostosis multiplex</td>
<td>++++</td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
<td>0</td>
<td>+++++</td>
</tr>
<tr>
<td>Neurodegeneration</td>
<td>++++</td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
<td>0</td>
<td>+++++</td>
</tr>
<tr>
<td>Cardiac abnormalities</td>
<td>++++</td>
<td>++++</td>
<td>+++</td>
<td>0+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Growth retardation</td>
<td>++++</td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
endogenous nitrogen (high calorie intravenous infusions, non-absorbed gastrointestinal antibiotics, laxatives), and facilitation of the removal of waste nitrogen (water diuresis, dialysis) are the key elements of therapy. If a urea cycle enzyme defect is strongly suspected, administration of arginine, along with sodium benzoate and sodium phenylacetate or sodium phenylbutyrate is also indicated. The collection of blood for measurement of plasma amino acids, and urine for analysis of organic acids and orotic acid, is an important part of the initial management of hyperammonaemia, regardless of the age of the patient.

**Class Diagnosis**

The next step in unravelling the diagnosis of a possible inherited metabolic disease is to attempt to make a class diagnosis: Is this an 'small molecule' disease or an 'organelle' disease? This step aids in the classification of possible causes of disease, and it also facilitates the laboratory investigation, once an inherited metabolic disease is considered a possibility. The thinking process is summarised in Table 2. Inborn errors of small molecule metabolism tend to be characterised by rapid onset of symptoms and a clinical course that is characterised by remissions and relapses. Physical findings are generally nonspecific, as are the results of histopathologic studies on tissue biopsies. These disorders tend also to respond well to aggressive supportive therapy.

By contrast, organelle diseases are characterised by a gradual, often insidious, onset of symptoms and a relatively slowly progressive clinical course. Physical examination is often rewarded by finding specific clinical signs, which may be characteristic enough to make the diagnosis. Histopathologic and electron microscopic examination of tissue biopsies often reveals changes characteristic of the underlying disease. The response to supportive therapy is generally only fair or poor.

Experienced consultants will recognise that exceptions to these generalisations are common. For example, PKU, a small molecule disease, is characterised by a gradual, even insidious, onset of developmental delay, which is then slowly progressive. The response to supportive therapy is poor. However, physical findings, including imaging studies, show only nonspecific changes, and histopathologic studies of tissue biopsies is unrewarding in the investigation of the disease. Similarly, patients with disorders of the mitochondrial electron transport chain often present with Leigh disease, which is often characterised by a sudden onset of encephalopathy and a course characterised by multiple remissions and relapses. Physical examination is generally unrewarding for pin-pointing the diagnosis, and histopathologic studies are usually not particularly helpful, though abnormalities of mitochondrial morphology may be seen in electron micrographs of muscle.

**Small Molecule Disease**

The small molecule diseases include a wide range of conditions in which the inborn error is localised to a single step in the metabolism of a water-soluble metabolite, such as an amino acid or monosaccharide (Table 3). The diagnosis of most of these conditions is possible by analysis of metabolic intermediates in physiological fluids, such as blood, urine, and CSF. Table 4 shows a list of laboratory studies that might be considered the 'minimum' investigation of any child who one suspects might have an inherited metabolic disease.

**Organelle Disease**

The organelle diseases are a group of inherited metabolic diseases in which the defect is in an organelle-specific process or enzyme system. The organelle disorders that are particularly relevant are lysosomal disorders, peroxisomal disorders, mitochondrial cytopathies, and synthetic

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Clinical differentiation of organelle disease and small molecule diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Feature</strong></td>
<td><strong>Organelle disease</strong></td>
</tr>
<tr>
<td>Onset</td>
<td>Gradual</td>
</tr>
<tr>
<td>Course</td>
<td>Slowly progressive</td>
</tr>
<tr>
<td>Physical findings</td>
<td>Characteristic features</td>
</tr>
<tr>
<td>Histopathology</td>
<td>Often reveals characteristic changes</td>
</tr>
<tr>
<td>Response to supportive therapy</td>
<td>Poor</td>
</tr>
</tbody>
</table>
more difficult than for small molecule diseases. There are few so-called 'screening' tests covering a wide range of diseases, in the way that plasma amino acid analysis provides specific information on a wide variety of disorders of amino acid metabolism. The list shown in Table 5 is, therefore, incomplete, representing only a starting point.

### Definitive Diagnosis

The definitive diagnosis of specific inherited metabolic disorders generally requires access to clinical biochemistry and molecular genetics laboratories specialising in the investigation of these diseases. It may be based on:

**Analysis of specific metabolites.** The diagnosis of PKU, maple syrup urine disease, and other amino acid disorders is often possible by quantitative analysis of plasma amino acids alone. In some other classes of disorders, such as the organic acidopathies, analysis of urinary organic acids or plasma acylcarnitines makes it possible to make a strong presumptive diagnosis. By contrast, the definitive diagnosis of organelle diseases generally is not possible by metabolite analysis—it requires more sophisticated biochemical studies.

**Enzyme assay.** The definitive diagnosis of specific lysosomal storage disorders, such as the sphingolipidoses or the mucopolysaccharidoses, requires the demonstration of the deficiency of the activity of the relevant lysosomal enzyme. Although this is often possible by analysis of plasma, the results are more reliable when the assays are done on tissues, such as peripheral blood leukocytes, cultured skin fibroblasts or parenchymatous tissue obtained by biopsy, which contain lysosomes. The diagnostic laboratory procedures required for the specific diagnosis of organelle diseases are generally available only in highly specialised laboratories committed to this aspect of clinical biochemistry.

### Table 3  What is meant by 'small molecule' disease?

<table>
<thead>
<tr>
<th>Disorders of the metabolism of</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Amino acids</td>
<td></td>
</tr>
<tr>
<td>• Organic acids</td>
<td></td>
</tr>
<tr>
<td>• Carbohydrates, including glycogen</td>
<td></td>
</tr>
<tr>
<td>• Nucleotides</td>
<td></td>
</tr>
<tr>
<td>• Porphyrins</td>
<td></td>
</tr>
<tr>
<td>• Metals</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4 'Minimum' investigation of suspected 'small molecule' disease

<table>
<thead>
<tr>
<th></th>
<th>Plus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood gases and plasma electrolytes</td>
<td>Plasma amino acid analysis</td>
</tr>
<tr>
<td>Plasma glucose</td>
<td>Urinary organic acid analysis</td>
</tr>
<tr>
<td>Urinary ketones</td>
<td>Plasma acylcarnitines</td>
</tr>
<tr>
<td>Ammonium</td>
<td></td>
</tr>
<tr>
<td>Lactate</td>
<td></td>
</tr>
<tr>
<td>Urate</td>
<td></td>
</tr>
</tbody>
</table>

### Table 5 'Minimum' investigation of a possible 'organelle' disease

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Plasma lactate</td>
<td></td>
</tr>
<tr>
<td>• Urinary MPS screening test</td>
<td></td>
</tr>
<tr>
<td>• Urinary oligosaccharide screening test</td>
<td></td>
</tr>
<tr>
<td>• Bone marrow aspirate for identification of storage cells</td>
<td></td>
</tr>
<tr>
<td>• Plasma very long-chain fatty acids</td>
<td></td>
</tr>
<tr>
<td>• Imaging studies, including MRI and MRS</td>
<td></td>
</tr>
<tr>
<td>• Tissue biopsies, for histology, histochemistry, electron microscopy, and enzyme analysis</td>
<td></td>
</tr>
</tbody>
</table>
**DNA molecular testing.** As more and more genes are cloned and specific disease-causing mutations are identified, the specific diagnosis of inborn errors of metabolism is becoming increasingly possible by specific mutation analysis. This is the most specific form of diagnostic testing. When known disease-causing mutations are identified in the patient, the diagnosis of the associated inherited metabolic disease is confirmed. However, the reverse is not true. That is, the failure to demonstrate specific mutations does not rule out the diagnosis—the mutation in any particular patient may be different from any that have been described before and missed in the usual screening for known disease-causing mutations. The reliability of negative test results depends on how the mutation analysis was done.

**Specific Treatment**

Specific, rational treatment of inherited metabolic disorders is based on attempts to reverse the pathophysiological process responsible for disease (Figure 1). Disease caused by deficiency of the product of an enzyme reaction, such as occurs in inborn errors of hormone biosynthesis, generally responds well to replacement of the deficient product, C in Figure 1. Similarly, disease caused by accumulation of substrate, such as the phenylalanine accumulation in PKU, is often treatable by dietary restriction of the toxic metabolite or pharmacological inhibition of its synthesis, such as the treatment of hepatorenal tyrosinemia with NTBC. Dramatic progress has been made in the treatment of inherited metabolic diseases over the past 20 years. Improvements in the dietary therapy of PKU and other small molecule diseases have emerged from closer studies of the nutritional requirements of children with these diseases, from longitudinal and epidemiologic studies of patients on therapy for long periods of time, and from the development of a wide range of dietary supplements and more palatable semi-synthetic formulas.

Recent advances in strategies for enhancing enzyme activity have had a major effect on the treatment of lysosomal diseases, especially Gaucher disease. The treatment of Gaucher disease by long-term biweekly intravenous infusions of the deficient enzyme, glucocerebrosidase, have been shown to be safe and

![Figure 1](image-url) General scheme of inborn errors of metabolism and rationale of treatment.
highly effective in reversing the hematologic and skeletal manifestations of the disease. The results of clinical trials of the enzyme replacement therapy of other lysosomal diseases, such as Fabry disease and MPS IH/S, are promising, and these treatments are now commercially available within the next year or two.

Bone marrow transplantation, as a form of 'gene transfer therapy', has been shown to be highly effective in the treatment of Hurler disease (MPS IH) and some cases of X-linked adrenoleukodystrophy. 'Gene transfer therapy' by solid organ transplantation has also been shown to be highly beneficial in the treatment of some of the organic acidopathies and urea cycle enzyme defects. Specific gene transfer therapy is still in the investigative stages of development. It has not been demonstrated to provide safe, long-term correction of any disease-causing inborn errors of metabolism in humans.

Concluding Remarks

The main obstacle to making a correct diagnosis in children with inherited metabolic diseases is failure to think of the possibility. The initial investigation and management of children with inborn errors of metabolism does not require a detailed knowledge of biochemistry. Appropriate 'first aid' is often life-saving, and it provides time for the physician to consult colleagues and the library for help with further investigation. Trying to establish a class diagnosis is helpful in guiding further laboratory investigation and treatment. Definitive, long-term treatment usually requires that a specific diagnosis be made.

Selected Reading

Future Challenges in the Management of Inborn Errors of Metabolism

JTR Clarke
Division of Clinical & Metabolic Genetics, Department of Paediatrics, Hospital for Sick Children, University of Toronto, Toronto, Canada

Introduction

Thirty years ago, when the third edition of Stanbury’s *The Metabolic Basis of Inherited Disease*, the encyclopedic textbook on inherited metabolic diseases was published, it consisted of a single, relatively modest volume. The eighth edition, renamed *The Metabolic and Molecular Bases of Inherited Disease*, edited by Scriver and colleagues and published in 2001, was over 4 times bigger and contained information on a vast number of new diseases, as well as new information on previously described inborn errors of metabolism. The virtual exponential expansion of the textbook is an accurate reflection of the expansion of the field of inherited metabolic diseases in general.

Not only has knowledge expanded at a formidable rate, as a result of research in laboratories and clinics around the world, advances in technology have made early diagnosis easier and the outcomes of treatment better. New treatments are emerging that are having a profound impact on outcomes. Children with diseases that were formerly invariably fatal are now surviving and thriving into adulthood, as healthy productive citizens. Despite these advances, significant barriers continue to exist to the optimum detection, diagnosis, and treatment of these disorders.

Expansion of Scope

One of the immediate challenges posed by advances in our understanding of inborn errors of metabolism is the rapid and massive increase in the scope of the field created by the identification of new diseases. The list of disorders of transport and intracellular compartmentation has been expanded by the discovery of conditions, such as cerebral creatine deficiency, occurring as a result of mutations in membrane transporters. The discovery of congenital disorders of glycosylation has sensitised us to the existence of an entire class of inherited disorders of biosynthesis. Advances in laboratory and imaging technology have also provided us with the tools to identify and diagnose an enormous number of defects in mitochondrial respiration, adding another entire class of diseases to the catalogue of inborn errors of metabolism causing disease in humans.

The discovery of new variants of previously described diseases has added further to the scope of inherited metabolic diseases. Late-onset variants of diseases formerly thought to occur only in infancy are an example of this phenomenon. Often the clinical features of the disease in older children or adults is dramatically different from that presenting in infancy. For example, classical infantile Tay-Sachs disease is a rapidly progressive disease characterised by severe psychomotor retardation, intractable seizures, blindness, the appearance of cherry-red spots in the retina, and early death. Individuals with some residual β-hexosaminidase A activity generally present later, in early adulthood, often with ataxia, suggesting a spinocerebellar syndrome, but without seizures, visual impairment, or dementia.

Some diseases, formerly regarded to be non-metabolic syndromes, have had to be re-classified as a result of the discovery that the underlying lesion is deficiency of a specific enzyme, receptor, or transport protein. Smith-Lemli-Opitz syndrome, which is characterised by multiple malformations, including dysmorphic facies, micrencephaly, cleft palate (in some), synacthy, cryptorchidism and hypospadias, is now known to be caused by deficiency of the enzyme, 7-dehydrocholesterol reductase, an enzyme involved in cholesterol biosynthesis. The possibility that the psychomotor retardation that is a prominent feature of the disease is the result of cholesterol deficiency has prompted a number of attempts to treat the disease by supplementing the diet with large amounts of cholesterol.

The identification of adults with late-onset variants of inherited metabolic diseases occurring more commonly in infants, along with the improved survival of children with treatable inborn errors of metabolism, has created a rapidly expanding cohort of ‘new’ adult patients, requiring a different approach to management than that employed in children.

Advances in Diagnosis

One of the most important recent advances in the management of inherited metabolic diseases has been the burgeoning application of molecular genetics to the specific diagnosis of disease and especially to the identification of carriers of recessive mutant genes in relatives of patients with inborn errors of metabolism. This has been facilitated by the development of laboratory techniques for rapidly and relatively inexpensively screening entire genes for disease-
causing mutations. Molecular genetic information must be interpreted with care, however. Not all sequence variations cause disease. Whether a specific sequence change is responsible for disease generally requires consultation with a specialist in clinical or molecular genetics.

The specific diagnosis of mitochondrial electron transport chain (ETC) defects, especially those caused by nuclear gene mutations, is still a formidable challenge, both for the clinician and for the diagnostic laboratory. Although the clinical course of the disease in a patient, along with some routine biochemistry, such as measurements of lactate in plasma and CSF, and neuro-imaging changes, may strongly support a diagnosis of a mitochondrial disorder, such as Leigh disease, biochemical confirmation of the diagnosis is still very difficult. Studies on cultured skin fibroblasts, and even on fresh muscle obtained by biopsy, are cumbersome and often inconclusive. When mutation analysis of known mtDNA mutations is also inconclusive, only a presumptive diagnosis is possible. And, of course, carrier detection and prenatal diagnosis are not feasible.

Screening

The introduction of tandem mass spectrometry (MS) for the analysis of amino acids and acylcarnitines in blood has revolutionised the approach to newborn screening for inherited metabolic disorders. Although the technique is extraordinarily sensitive, it does present some challenges. The laboratory operating costs of screening by tandem MS are comparable to the costs of many other screening procedures. However, the capital costs of the required equipment are high. The technology has also generated information on many newborns that is difficult to interpret, adding to the cost of follow-up diagnostic investigation of infants who turn out to be normal.

Treatment

Major advances in treatment of inherited metabolic diseases have emerged over the past 20 years, especially enzyme replacement therapy (ERT) of lysosomal storage diseases. On the other hand, treatment is very expensive, well beyond the resources of individual families, and alternative ways of paying for it are not uniformly available. Although ERT of diseases, such as Gaucher disease is safe and has been dramatically effective in the treatment of non-neurological disease, the application to neurodegenerative lysosomal diseases continues to be severely limited by the relative inaccessibility of the CNS to intravenously infused enzyme. How to breach the blood brain barrier is one of the most urgent challenges in the management of inherited metabolic disorders.

Although many would argue that the most effective and lasting approach to the treatment of inborn errors of metabolism would, theoretically, be by gene replacement or gene transfer therapy, this continues to be an elusive goal and one of the most challenging problems for the next generation of clinical scientists committed to discovering better ways to treat these diseases. So far, despite enormous investments in research and significant advances in molecular biology and gene transfer technology, no unambiguously successful gene transfer treatment for an inborn error of metabolism has been reported.

Barriers to Access

Despite the major advances in technology and knowledge that have been made over the past several years, the management of patients with inborn errors of metabolism continues to be compromised by serious barriers to access to care. One of these is directly within our own power to change—that is awareness among physicians of the presence of these disorders among our patients. Conferences like the International Workshop on Inborn Errors of Metabolism in Children held in Hong Kong in October 2002 are one way to raise awareness of inherited metabolic diseases in children and how to deal with them.

The cost of care and the necessary support systems to provide optimum care for children with inborn errors of metabolism also pose important barriers to access. These barriers are not likely to be overcome unless the public accepts the care of children in general, and those with inherited metabolic diseases in particular, as a high priority for public support. The first challenge in dealing with the health policy problem is to mobilise public opinion and focus on those values that make the care of children a public policy imperative. What must follow is the development of mechanisms for evaluating new technologies, especially those relating to screening and to the treatment of inherited metabolic diseases, to achieve the re-allocation of resources necessary to make them available to the people.

The assessment of the merits of a new technology or treatment often focuses, at least initially, on whether a
particular technology or treatment works—can it be done? This type of assessment usually involves major input by technical experts, including physicians, and rests on the ability to evaluate objectively specific expectations of a new laboratory test or a new therapy. It has become codified in 'evidence-based medicine', and it has become critically important in decision-making regarding health care resource allocation. However, public values also play a central role in the process—should it be done? This is a much more difficult area of public policy development, and it requires input from a much wider group of stakeholders, including the general public.

Concluding Remarks

Paediatricians are faced with a number of challenges directly related to the management of inborn errors of metabolism. Staying abreast of the rapid expansion of knowledge in this area, along with the emergence of new diagnostic and screening technologies, is a familiar, though daunting, task. Despite the advances in knowledge, however, there is a pressing need for the development of new and effective treatments for many inherited metabolic diseases, especially those affecting the brain. One of the most formidable and difficult challenges is the removal of barriers to access to existing diagnostic and treatment services. Facing the public policy challenge is generally unfamiliar territory for practicing paediatricians. However, it is one in which we must be prepared to participate in a more active way than in the past if the advances in medicine that are occurring now are to reach our patients in the future.

Public Health Approach of Inborn Errors of Metabolism in Hong Kong

STS Lam
Chairman, The Hong Kong Society of Medical Genetics

The commonest inherited metabolic disease in Hong Kong is glucose-6-phosphate dehydrogenase (G6PD) deficiency. When a disease is of significant incidence and severity, the public health approach would be considered for its prevention and management. In Hong Kong, G6PD deficiency was recognised as one such condition that required massive screening and early intervention. A combined neonatal screening programme for G6PD deficiency and congenital hypothyroidism (CHT) was started in Hong Kong by the Department of Health (DH) since 1984. The screening system included activities in public education, sampling, laboratory assays, follow up intervention and evaluation. As a public health programme, it was provided free of charge on a totally voluntary basis. Although all newborns in Hong Kong were entitled to this service, only about 70% of life birth had their blood samples directed to the central neonatal screening laboratory under this programme, the remaining 30% received screening from laboratories in private hospitals. Overall, more than 99% of all newborns in Hong Kong received screening for these disorders. Cord blood was used universally as the screening sample for both conditions. The decision of employing cord blood, instead of filter paper blood spot, was based on two reasons. Firstly, it was considered important that any deficiency of this enzyme in a newborn need be notified within the first couple of days for effective counselling and intervention. The use of cord blood certainly offered distinct advantage. Secondly, transport of these samples was not a problem in a geographically compact place like Hong Kong. Screening for G6PD enzyme activity was performed by colorimetric assay. Up to the end of December 2001, a total of 679,241 neonates had been screened in the public hospitals. It was found that 4.53% of the males and 0.32% of the females were affected. Compared with 1970s, there was a tremendous decrease in the morbidity and mortality resulting from hyperbilirubinaemia due to G6PD deficiency. There are occasional cases of mishap as a result of failure to inform individual families of G6PD deficiency during the long holidays. Counselling for this condition was normally conducted by phone by genetic counselors, and this method had been shown to be effective.
The Paediatric Perspective of Inborn Errors of Metabolism in Hong Kong

RKN Yuen
Department of Paediatrics, Kwong Wah Hospital

Inborn errors of metabolism (IEM) are disorders caused by a deficiency of enzyme catalysis or an enzyme that facilitates the transport of biological substances across membranes. More than 500 inherited metabolic diseases have been identified so far. Although individually rare, inborn errors of metabolism are relatively common collectively and early diagnosis and treatment may reverse acute symptoms and prevent chronic damage. Accurate diagnosis can help in future family planning, genetic counselling and prenatal diagnosis.

Chinese children with glycogen storage disease, Gaucher disease and galactosemia were first reported in Hong Kong in 1966. Since then, homocystinuria, hereditary fructose intolerance, mitochondrial disease, Leigh's disease, methymalonic acidaemia, maple syrup urine disease and urea cycle defect have been reported in Chinese children in Hong Kong.

Some children with inborn errors of metabolism present in the neonatal period. Clinical clues to IEM in neonate include unexplained deterioration in an infant well at birth, persistent vomiting with no anatomical cause, major organ failure e.g. liver, heart, encephalopathy, intractable convulsion and congenital anomalies e.g. cataract. Metabolic conditions such as mucopolysaccharidosis, Gaucher disease, mucolipidosis, mitochondrial disease and glycogen storage disease can present as hydrop foetalis in newborn. History of consanguinous marriage, recurrent abortion, unexplained neonatal death and positive family history are suggestive of the diagnosis of inherited metabolic disease in neonates. First line investigations for IEM include full blood count, urea, electrolytes, glucose, blood gas, anion gap, ammonia, fasting lactate, pyruvate, liver functions tests, uric acid and urine for reducing substance, ketones and sulphite. Second line investigations such as urine for organic acid and orotic acid, plasma and urea for amino acid pattern, plasma carnitine and acylcarnitine profile and CSF lactate, glycine and amino acid should be considered in selected cases. Third line investigations include enzyme assay on skin fibroblast or blood cell. DNA mutation analysis and special metabolic studies e.g. very long chain fatty acid profile are required to confirm suspected cases.

With the support of hospital paediatricians of regional public hospitals, a Hong Kong Paediatric Metabolic Registry was set up in 2002. Over 40 patients with lysosomal diseases e.g. mucopolysaccharidosis, oligosaccharidosis, sphingolipidosis, mucolipidosis and gangliosidosis have been registered. Over thirty patients with organic acidaemia including glutaric aciduria type I, methymalonic aciduria, multiple carboxylase deficiency, propionic aciduria have been seen. Disorders in carbohydrate metabolism including glycogen storage disease, galactosaemia and fructose intolerance were diagnosed in over thirty patients. Mitochondrial disease including mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELA) was diagnosed in over twenty patients. Amino acid disorders such as cystinuria, tyrosinaemia, maple syrup urine disease, phenyketonuria, non-ketotic hyperglycinaemia, homocystinuria have been diagnosed as well. The diagnosis of fatty acid oxidation disorders including carnitine cycle defect, multiple acyl-CoA dehydrogenase deficiency was made in nearly twenty children. Urea cycle disorders was diagnosed in 17 children. Peroxisomal disorders namely X-linked adrenoleukodystrophy and Zellweger syndrome were diagnosed in over ten patients.
The presentation of lysosomal storage disorders are quite variable. The common presentations include hepatosplenomegaly, neurological deterioration, coarse facies, dysostosis, cardiomyopathy, angiokeratoma, etc. Less well appreciated presentations include non-immune hydrops fetalis and psychiatric symptoms meriting elaboration in the following lists:

Non-immune hydrops:
Mucopolysaccharidosis (MPS) VII, Sialidosis, Niemann-Pick A, Niemann-Pick C, Galactosialidosis, MPS I, Wolman's disease, MPS IV, Salla and sialic acid storage disease, Farber's disease.

Psychiatric symptoms:
MPS III, Adult onset MLD

Currently, antenatal diagnosis is possible for lysosomal storage disorders and is an important aspect of management to be noted. Treatment modalities include conventional supportive therapy, enzyme replacement therapy and bone marrow transplant. Cervical spine fusion in MPS IV is an example of useful treatment that could be offered. Currently enzyme replacement therapy is available for Fabry disease and Gaucher disease. There are clinical trials going on for mucopolysaccharidosis I, Niemann-Pick B and glycogen storage disease II.

Bone marrow transplant as a form of treatment for lysosomal storage diseases offers hope for amelioration of the course of the disease. However, it carries high morbidity and/or mortality. This is an important modality of treatment when there is no alternative therapy available.

In lysosomal storage diseases, enzyme deficiency results in accumulation of substrate. Bone marrow transplant works by repopulating the marrow with enzyme-producing cells, which then disseminate into the reticulo-endothelial systems in different parts of the body. There is also evidence that enzyme is transferred from these cells to other enzyme-deficient cells. Enzyme-producing marrow stem cells also turn into microglial cells in the brain and potentially prevent neurological deterioration in some transplanted patients.

The experience of bone marrow transplant is most abundant in mucopolysaccharidosis I (MPS-I). There is adequate response in central nervous system, heart, respiratory system and hearing. However, the response in the eyes, bone and cartilage remains inadequate. With accumulation of experience, it is generally agreed that bone marrow transplant in MPS-I should be done if the following criteria are satisfied:
1. Age <18 months and preferably <12 months.
2. Absence of significant hydrocephalus.
3. Parental understanding of limitation of bone marrow transplant.

Cardiomyopathy is not a contraindication for transplant although the mortality of transplant in its presence is increased. The genotype and residual enzyme activity need to be studied as these offer some prediction as to the severity of the disease progression.

In mucopolysaccharidosis II (MPS-II), the value of bone marrow transplant is less clear. Unlike MPS-I, the diagnosis of MPS-II tends to be delayed. Outcome of some previously transplanted cases is not impressive. In mucopolysaccharidosis III, bone marrow transplant is incapable of altering its course. Bone marrow transplant has a definite role in the treatment of adrenoleukodystrophy preventing progressive deterioration.

In conclusion, bone marrow transplant does not result in normality. It works better in slowly progressive disorders. Alternative therapy like enzyme replacement therapy may complement BMT in the management of lysosomal storage disorders.
**Disorders of Amino Acids, Organic Acids and Fatty Acids**

**XP Luo**
Department of Pediatrics, Tongji Hospital, Center for the Diagnosis of Genetic Metabolic Diseases, Tongji Medical College, Huazhong University of Sciences and Technology, China

**Introduction**

With the recent advances in laboratory investigations and molecular genetics, the number of known hereditary diseases has increased tremendously in the past decade. Currently, there are nearly 14,000 entries in *Mendelian Inheritance in Man*, of which about 10,000 have established gene loci. Eighty percent of them are inherited in an autosomal recessive manner.

Inborn errors of metabolism (IEM) are a group of genetic disorders with enzymatic, membranous or receptor defects. These result in accumulation of intermediate products, lack of essential metabolites, or deficiency in energy supply. The molecular property of the substrate determines the dimension of the pathological lesion. The diagnosis is often difficult, as the clinical manifestations are nonspecific in most cases. However, some of them are treatable if diagnosed early. Laboratory diagnosis frequently relies on the identification of quantitative/qualitative alteration of particular substances. The major types of IEM include amino acidopathy, organic academia or aciduria, fatty acid oxidation defects, peroxisomal disorders, glycometabolic disorders, nucleic acid metabolic disorders, and lysosomal disorders.

**Clinical Features**

The family history may reveal parental consanguinity, siblings with unexplained diseases ("encephalopathy", "sepsis", SIDS), familial disorders (such as progressive neurological disease, maternal phenylketonuria, multiple miscarriages), or malnutrition. In the neonatal period, IEM may present as neurological symptoms such as feeding problems, abnormal breathing, hypotonia, lethargy, coma, or seizures. The other manifestations include vomiting, diarrrhoea, jaundice, growth retardation, hepatomegaly, hypoglycaemia, liver failure, cardiomyopathy, arrhythmia, hyperammonaemia, and metabolic acidosis. One third of the cases may have asymptomatic intervals or of late-onset, with the disease triggered by fever, infection, or protein intake. The clinical course is characterised by periodic metabolic acidosis, ataxia or come; preceded by vomiting, lethargy, hypotonia, or seizure. These may ultimately result in severe CNS injury or death. Specific triggers of metabolic decompensation are summarised in Table 1.

Some of the IEM may present with chronic progressive symptoms, including anorexia, feeding problems, vomiting, diarrhoea, progressive developmental retardation, seizures, ataxia, language delay, autism, mental retardation, hypotonia, or progressive myopathy. The other manifestations include congenital brain malformation, spinal cord symptom, peripheral neuropathy, failure to thrive, chronic liver/ kidney/heart diseases, and immunodeficiency. The presentations of specific groups of disorders are summarised as follows:

**Disorders in Amino Acid Metabolism**

In general, the brain, liver and kidneys are the organs most frequently affected in this group of disorders. The clinical manifestations depend on the specific toxicity of the accumulating metabolites, concurrent product deficiency, severity of the enzyme deficiency, extent of protein intake, and endogenous amino acid release in catabolism. They may present in the neonatal period, late infancy, or puberty. The clinical features are diversified, including acute coma/ataxia/encephalopathy, acute

<table>
<thead>
<tr>
<th>Triggers</th>
<th>Groups of disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting, infections, fever, vaccination, operations, accidents</td>
<td>Disorders of protein, energy, and carbohydrate metabolism</td>
</tr>
<tr>
<td>High protein intake and/or protein catabolism</td>
<td>Protein metabolism: aminoacidaemias, organic acidurias, urea cycle defects</td>
</tr>
<tr>
<td>Major alterations in carbohydrate intake</td>
<td>Mitochondriopathies</td>
</tr>
<tr>
<td>Rapidly absorbed carbohydrates</td>
<td>Hyperinsulinsim, mitochondrialopathies</td>
</tr>
<tr>
<td>Fruit, table sugar (sucrose)</td>
<td>Fructose intolerance</td>
</tr>
<tr>
<td>Lactose, milk protein</td>
<td>Galactosaemia</td>
</tr>
<tr>
<td>High fat intake</td>
<td>FAOD, lipoprotein lipase deficiency, glycerol kinase deficiency</td>
</tr>
<tr>
<td>Drugs</td>
<td>Porphyrias, G6PD, FAOD</td>
</tr>
</tbody>
</table>
deterioration or prolonged disease course of a non-specific infection, progressive symptoms, multi-system disorders, metabolic acidosis, ketonuria, and hypoglycaemia. In a suspected case of amino acid disorder, we should collect blood and urine sample for blood count, electrolytes, sugar, liver and renal functions, ammonia, lactate, plasma amino acids, and urine organic acids before therapy.

**Organic Aciduria**

The clinical presentations are variable. In the neonatal period, the features are that of “intoxication type” metabolic encephalopathy. Some patients have a chronic intermittent presentation characterised by recurrent episodes of ketoacidotic coma, lethargy, ataxia, focal neurological signs, and Reye syndrome. The chronic progressive form may present as failure to thrive, chronic vomiting, anorexia, osteoporosis, hypotonia, developmental retardation, and recurrent infections. Secondary organic aciduria may result from certain drugs and food intake, bacteria in the gut, prematurity, renal failure, and asphyxia.

**Disorders of Fatty Acid Oxidation**

This group of disorders include carnitine transporter deficiency, carnitine palmitoyltransferase I deficiency, carnitine translocase deficiency, carnitine palmitoyltransferase II deficiency, short-chain acyl-CoA dehydrogenase (SCAD), medium-chain acyl-CoA dehydrogenase (MCAD), long-chain acyl-CoA dehydrogenase (LCAD), long-chain hydroxyacyl-CoA dehydrogenase (LCHAD), and multiple acyl-CoA dehydrogenase (glutaric aciduria II). They typically present in late infancy or early childhood as hypoketotic hypoglycaemic coma during catabolic states (e.g. prolonged fasting, operations or infections). The other features include signs of liver failure with hyperammonaemia, myopathy and cardiomyopathy. The pathogenesis is related to insufficient energy production during fasting, deficiency of mitochondrial free CoA, and accumulation of toxic long-chain acylcarnitines. A useful screening test is the detection of dicarboxylic aciduria during decompensation.

**Sudden Infant Death Syndrome (SIDS/SUDS)**

It is not uncommon for infants with IEM to present as SIDS. In a review involving 7058 cases of SIDS, 66 were found to have IEM, including 55 cases of fatty acid oxidation disorders and 11 cases of organic aciduria.¹

**Laboratory Investigations**

The initial investigations should include assessment for abnormal urine colour/odor, and screening tests such as reducing substance. We should check the complete blood count, blood gases, acid base status, electrolytes, glucose, liver function, ketones, ammonia, lactate, and pyruvate. Qualitative urine amino acid analysis may be performed by thin layer chromatography (TLC) and high voltage electrophoresis (HVE/TLC). Quantitative amino acid analysis may be performed by amino acid analyzer, high performance liquid chromatography (HPLC), and tandem MS. Organic acid and acylcarnitine analysis may be done by gas chromatography, gas chromatography/mass spectrometry (GC/MS), and tandem MS. GC/MS was first utilised by Tanaka in 1966 for the diagnosis of isovaleric academia. Since then, over 70 different types of organic academia has been identified. Many of these disorders are treatable if diagnosed early. The investigation protocols for neonatal hyperammonaemia and metabolic acidosis with increased anion gap are summarised in Figures 1 and 2.²

**Principles of Treatment for IEM**

a) Decrease the production of toxic substance by diet restriction, energy substitution, NTBC, and antibiotics.
b) Clearance of intermediate metabolites by diuretics, dialysis, haemofiltration, and medications such as sodium benzoate.
c) Replacement of essential products, such arginine; or via gene transfer.
d) Appropriate symptomatic management, such as fluid and electrolyte replacement and correction of acidosis.

**Acknowledgement**

Supported by the National Science Fund for Distinguished Young Scholars from the Natural Science Foundation of China (30125019) and the Clinical Key Subject Fund from the Ministry of Health (97070240).

**References**

Symptoms in first 24 h of life
- Premature
  - THAN INBORN ERRORS OF METABOLISM (i.e. organic acidaemia or PC deficiency)
  - Absent citrulline
    - Urine orotic acid
      - Low: CPS deficiency
      - Elevated: OTC deficiency

Symptoms after 24 h of age
- Full-term
  - INBORN ERRORS OF METABOLISM (i.e. organic acidaemia or PC deficiency)
  - Citrulline moderately elevated; ASA present
    - Argininosuccinic aciduria
  - Citrulline markedly elevated; no ASA
    - Citrullinemia

Acidosis
- No acidosis

ORGANIC ACIDAEMIAS
- UREA CYCLE DEFECTS
  - PLASMA AMINO ACIDS

Figure 1  Differentiation of conditions associated with neonatal hyperammonaemia.
Proceedings

Figure 2  Evaluation of metabolic acidosis in the young infant.