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 1 Some examples of varying degrees of 'storage syndrome'

Physical feature	Hurler disease	Hunter disease	Infantile GM1 gangliosidosis	Sanfilippo disease	Juvenile GM1 gangliosidosis	Gaucher disease
Coarse facies	++++	++++	+++	+-++	0	0
Hepatosplenomegaly	++	++	++	0-+	0	++-++++
Dysostosis multiplex	++++	++++	++++	+-++	0	+-+++
Neurodegeneration	++++	+++	++++	+++	+++	0
Cardiac abnormalities	+++	+++	+++	0-+	0	0
Growth retardation	++++	+++	++++	+-++	0-+	0-+

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 2   Clinical differentiation of organelle disease and small molecule diseases

Feature	Organelle disease	Small molecule disease
Onset	Gradual	Often sudden, even catastrophic
Course	Slowly progressive	Characterised by relapses and remissions
Physical findings	Characteristic features	Nonspecific
Histopathology	Often reveals characteristic changes	Generally nonspecific changes
Response to supportive therapy	Poor	Brisk

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

Disorders of the metabolism of

- Amino acids
- Organic acids
- Carbohydrates, including glycogen
- Nucleotides
- Porphyrins
- Metals

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

	Plus
Blood gases and plasma electrolytes	Plasma amino acid analysis
Plasma glucose	Urinary organic acid analysis
Urinary ketones	Plasma acylcarnitines
Ammonium	
Lactate	
Urate	

disorders, such as CDG syndrome, SLO syndrome, etc.

The physical examination is particularly important in making a diagnosis of one of these disorders. Some of the clinical signs are virtually pathognomonic of specific diseases. For example, the physical features of Zellweger disease, a severe peroxisomal disorder, are unmistakably characteristic of the disease. The angiokeratomata of Fabry disease, fucosidosis, galactosialidosis, and sialidosis are extraordinarily helpful in guiding diagnostic investigation. The combination of physical findings and imaging abnormalities in those children with 'storage syndrome' often makes a strong presumptive diagnosis possible.

Imaging studies, electrophysiological studies, and histopathologic and ultrastructural studies on tissue biopsies are often helpful in the diagnosis of organelle diseases, in part by showing the extent and severity of the pathology, as well as demonstrating the presence of disease-specific morphologic abnormalities. The storage cells in the bone marrow of patients with Gaucher disease, Niemann-Pick disease, or many other lysosomal storage diseases, are a good example. The intralysosomal inclusions in conjunctival epithelium in neuronal ceroid-lipofuscinosis are virtually pathognomonic of this group of closely related disorders.

Recommending a list of laboratory studies for the 'minimum' investigation of a possible organelle disease is

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

- Plasma lactate
- Urinary MPS screening test
- Urinary oligosaccharide screening test
- Bone marrow aspirate for identification of storage cells
- Plasma very long-chain fatty acids
- Imaging studies, including MRI and MRS
- Tissue biopsies, for histology, histochemistry, electron microscopy, and enzyme analysis

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
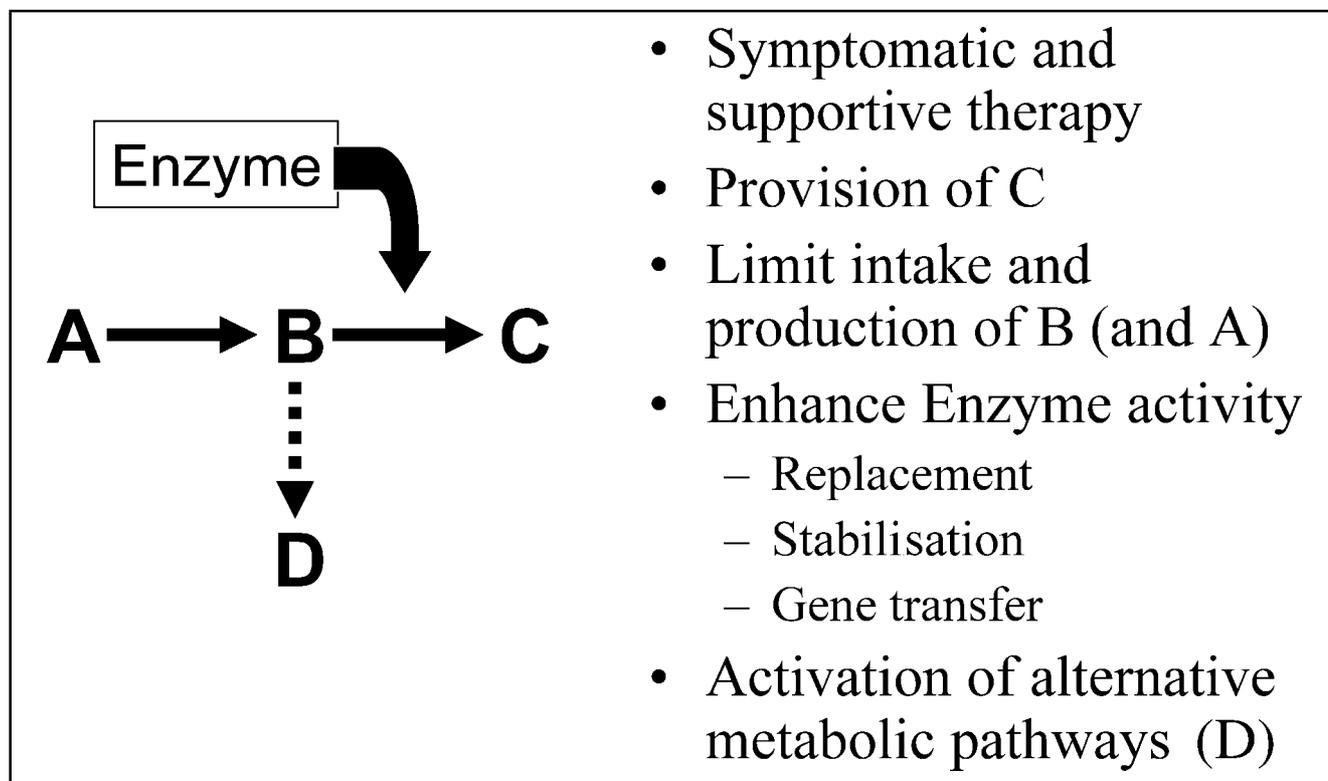

Figure 1   General scheme of inborn errors of metabolism and rationale of treatment.

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.

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