Acute presentations of inherited metabolic disorders: investigation and initial management☆

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Abstract

Inborn errors of metabolism are individually rare but so many have now been described that the general paediatrician will encounter one from time to time. For many, early treatment is important. Unfortunately most that present acutely do so with non-specific symptoms and signs. It is therefore necessary to identify and investigate those at high risk. The most common problems are neurological (including coma, seizures and stroke-like episodes), hypoglycaemia, disorders of acid-base regulation, acute liver disease, rhabdomyolysis, cardiomyopathy and sudden collapse. Treatment should be started as soon as an inborn error is suspected.

Keywords acute liver failure; ataxia; cardiomyopathy; catabolism; encephalopathy; hyperammonaemia; hypoglycaemia; metabolic acidosis; respiratory alkalosis; rhabdomyolysis; seizures; stroke-like illness

Introduction

Inborn errors of metabolism are generally rare, although some disorders are more common in genetically isolated or inbred populations. Many inherited metabolic conditions are now well recognised and they may present at almost any age from the newborn period into adult life. New disorders continue to be elucidated, particularly involving complex molecules, but the 'classic' metabolic disorders more often present acutely. Many of these disorders are treatable and it is important to recognise the underlying disorder at the earliest possible stage to prevent permanent damage. Unfortunately, for most disorders the early symptoms and signs are not specific so it is necessary to try to identify those at high risk of having a metabolic disorder.

History

The key to identifying patients at high risk is the history, including the past history, family history and that of the present illness.

Past history

After resuscitation it is important to inquire about any previous problems, such as developmental delay, episodic vomiting and episodes of drowsiness, particularly on waking. Patients presenting with a severe acute encephalopathy may have had previous episodes, commonly much milder, precipitated by intercurrent infections or fasting. The results of newborn screening should be sought, particularly in countries that test for multiple metabolic disorders.

Family history

Similar illnesses or unexplained deaths in siblings must be followed up. More distant relatives are particularly relevant in consanguineous pedigrees or for X-linked disorders. Parental consanguinity increases the risk of autosomal recessive disorders but many patients with inborn errors are born into non-consanguineous families.

Modes of presentation

Although inborn errors may present in many different ways and at almost any age, acute presentations fall into six main categories: (1) neurological presentations including acute encephalopathy, seizures, stroke-like illness and acute ataxia (2) hypoglycaemia, (3) disorders of acid-base regulation, (4) acute liver disease, (5) rhabdomyolysis, (6) cardiomyopathy and (7) cardiac arrhythmias and sudden death. Metabolic disorders may also present at or soon after birth with a number of different problems that include ascites/hydrops, dysmorphic syndromes, seizures and severe hypotonia. Lists of the causes of these problems can be found in Leonard and Morris (2006).

Neurological presentations

Acute encephalopathy: this is a common presentation of inborn errors but there are also many non-metabolic causes of such an illness. Typically there is a gradual onset of symptoms, unless the patient has a convulsion. The early symptoms are often drowsiness, lethargy, altered behaviour and unsteady gait. These symptoms may fluctuate and, in mild cases, patients may recover spontaneously. In severe cases, patients deteriorate, often somewhat unexpectedly, becoming comatose. Treatment is urgent and basic metabolic investigations should always be done in any patient with an undiagnosed encephalopathy. Encephalopathy with fever is often attributed to 'encephalitis' when it is really caused by metabolic decompensation precipitated by an infection. The metabolic causes of encephalopathy are summarised in Table 1, with relevant investigations.

Seizures and Stroke-like episodes: the metabolic disorders that most commonly present with seizures or stroke-like episodes are listed in Tables 2 and 3 with appropriate investigations. The list is not exhaustive as seizures are a late feature in many metabolic disorders.

Investigation of the CSF is often useful but, if this is done, ensure that samples are collected correctly for all likely possibilities, to avoid the need for a repeat lumbar puncture.

Acute ataxia: occasionally patients will present with an episodic ataxia. These patients should be screened for maple syrup urine

☆ Notes: This chapter is a short introduction and cannot cover all situations. If in doubt, consult your local specialist metabolic centre. Detailed and free instructions on the management of acute illness in specific inborn errors of metabolism can be found on the British Inherited Metabolic Disease Group Website (BIMDG) http://www.bimdg.org.uk/.

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Causes of acute metabolic encephalopathy

Causes	Investigations
• Hypoglycaemia	• Blood gases
• Hyperammonaemia	• Blood glucose
• Disorders of fatty acid oxidation	• Blood lactate
• Amino acids disorders including maple syrup urine disease	• Plasma electrolytes & anion gap
• Organic acidaemias and biotinidase deficiency	• Plasma ammonia
• Mitochondrial respiratory chain disorders	• Plasma amino acids
	• Blood spot acylcarnitines
	• Liver function tests
	• Plasma biotinidase
	• Urine organic acids

Biotinidase deficiency is very rare but responds dramatically to treatment if started early.

Table 1

disease, hyperammonaemia, GLUT1 deficiency and organic acidaemias.

Hypoglycaemia

The blood glucose should be measured in any patient with acute encephalopathy (including coma) or seizures, except in known epileptics when they follow the usual course. The metabolic causes and investigations of hypoglycaemia are listed in Table 4. Although galactosaemia and tyrosinaemia type 1 may cause hypoglycaemia it is rarely a presenting feature. If possible, samples should be taken during hypoglycaemia; as a minimum, take some plasma and store deep frozen.

Hyperammonaemia

Plasma ammonia should be measured in every undiagnosed encephalopathic patient since early intervention is essential. Reference values are less than 50 μmol/l but any difficulty with the venepuncture, including a child struggling or a haemolysed sample, may increase the plasma ammonia concentration. Values more than 100 μmol/l suggest an inborn error although in the newborn the threshold is usually taken to be 200 μmol/l. However it must be emphasised that the interpretation of plasma ammonia concentrations requires careful assessment of the conditions under which the blood was collected as well as the effect of any treatment, such as intravenous glucose. The metabolic causes of hyperammonaemia and investigations are listed in Table 5.

Disorders of acid-base regulation

Metabolic acidosis is a common complication of almost any illness and is usually secondary to tissue hypoxia. However, if the history suggests previous episodes, there is marked ketosis or the acidosis persists after tissue perfusion is corrected, the patient should be investigated for a metabolic problem. The major causes and the investigations are listed in the Table 6.

Respiratory alkalosis is uncommon in patients who are not on a ventilator and they should be investigated for hyperammonaemia.

Acute liver disease

There are many causes of acute liver disease and the most common metabolic ones are listed with investigations in Table 7. Most of these have parenchymal disease with synthetic dysfunction including hypoalbuminaemia and clotting abnormalities but some will present with a more obstructive picture with conjugated hyperbilirubinaemia and secondary abnormalities caused by the failure of absorption of fat soluble vitamins.

Rhabdomyolysis

This presents with acute muscle pain, dark brown discolouration of the urine (myoglobinuria) and often acute renal failure. The

Metabolic disorders that may present with seizures

Causes	Investigations
Hypoglycaemia	see Table 4
Hyperammonaemia	see Table 5
Maple syrup urine disease	Plasma or urine amino acids
Non-ketotic hyperglycinaemia	Plasma and CSF aminoacids
GLUT1 deficiency	Blood and CSF glucose
Disorders of pyridoxine metabolism	Trial of treatment, urine α-aminoadipic semialdehyde, CSF neurotransmitters
Biotinidase deficiency	Plasma biotinidase
Organic acidurias (e.g. L-2-hydroxyglutaric)	Urine organic acids
Disorders or creatine metabolism	Cranial MRS or urine creatine & guanidinoacetate
Molybdenum co-factor deficiency	Urine sulphite and sulphocysteine, plasma urate
Menkes disease	Plasma copper
Peroxisomal disorders	Plasma VLCFA, red cell plasmalogens
Mitochondrial disorders, esp. Alpers syndrome	Blood and CSF lactate, mitochondrial studies on muscle, POLG sequencing
Infantile and late infantile NCL [Battens]	Electron microscopy of lymphocytes or skin, leukocyte PPT1 or TPP1 assays
Krabbe disease	Leukocyte lysosomal enzyme screen

VLCFA = very long chain fatty acids, NCL = Neuronal ceroid lipofuscinosis, PPT1 = palmitoyl protein thioesterase 1, TPP1 = Tripeptidyl peptidase 1.

Table 2