15 Levy-Lahad E, Wijsman EM, Nemens E *et al.* A familial Alzheimer's disease locus on chromosome 1. *Science* 1995;269:970–3.

16 Campion D, Dumanchin C, Hannequin D *et al.* Early-onset autosomal dominant Alzheimer disease: prevalence, genetic heterogeneity, and mutation spectrum. *Am J Hum Genet* 1999;65:664–70.

17 Corder EH, Saunders AM, Strittmatter WJ *et al.* Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 1993;261:921–3.

18 McKeith IG, Galasko D, Kosaka K *et al.* Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology* 1996;47:1113–24.

19 Neary D, Snowden JS, Gustafson L *et al.* Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* 1998;51:1546–54.

20 Goldman JS, Farmer JM, Wood EM *et al.* Comparison of family histories in FTLD subtypes and related tauopathies. *Neurology* 2005;65:1817–9.

21 Hutton M, Lendon CL, Rizzu P *et al.* Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. *Nature* 1998;393: 702–5.

22 Baker M, Mackenzie IR, Pickering-Brown SM *et al.* Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. *Nature* 2006; 442:916–9.

23 Joutel A, Corpechot C, Ducros A *et al.* Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. *Nature* 1996;383: 707–10.

Acute presentations of inherited metabolic disease in adulthood

Philip J Lee DM FRCP, Reader in Metabolic Medicine

Robin H Lachmann PhD MRCP, Consultant in Metabolic Medicine

Charles Dent Metabolic Unit, The National Hospital for Neurology and Neurosurgery, Queen Square, London

It has been over a century since Sir Archibald Garrod first recognised the existence of inherited metabolic diseases (IMD).[1] Technological and scientific advances have gradually led to greatly increased understanding of their aetiology and pathogenesis, and have ultimately resulted in effective therapies. Treatment has dramatically altered the natural history of metabolic disorders. Examples include:

- the phenylalanine-restricted diet for phenylketonuria[2]
- uncooked cornstarch for the hepatic glycogenoses[3]
- cobalamin for vitamin B12-responsive methylmalonic acid[4]
- nitisinone for tyrosinaemia type 1[5]
- enzyme replacement therapy for Gaucher disease.[6]

Not only can more than ever before be done today for patients but, as laboratory technology improves, more individuals with IMD are being diagnosed. Thin layer chromatography, high-peformance liquid chromatography, gas chromatography-mass spectrometry and tandem mass spectrometry (TMS) have successively led to easier screening (both primary and secondary), making diagnoses that were previously missed.

Paediatric metabolic medicine has achieved its aims:

- to prevent untreatable disease with genetic counselling and antenatal testing
- the provision of effective therapy to children with IMDs so that they can survive childhood and integrate into society.

Affected individuals can also present for the first time in adulthood. It is important for clinicians working in the adult sector to be aware of these disorders, not only to manage survivors of childhood but also to recognise patients presenting in adulthood. This article describes some acute clinical scenarios in which IMDs need to be considered. As they are genetic diseases, missing the diagnosis may have implications both for the affected individuals and for their families.

Encephalopathy/coma

IMD is high in the differential diagnosis when infants present with encephalopathy, but in adult medicine the emphasis tends to be on acquired conditions such as infection or poisoning. Even though most patients will have blood glucose and arterial blood gas measured, hypoglycaemia and acidosis are often (and often rightly) thought to be secondary features and are treated but not investigated further. It is important to remember that in the unconscious patient metabolic disturbance can sometimes be the primary cause.

In any patient with metabolic acidosis, it is important to calculate the anion gap. A raised anion gap suggests the presence of an abnormal metabolite and needs further investigation. Measuring plasma lactate or detecting urinary ketones by dipstick will often be helpful. Plasma ammonia concentrations should be readily available in all acute settings but are rarely measured on the adult intensive therapy unit. They should form part of the assessment of any unconscious

patient. The precise cause of hyperammonaemia may take some time to elucidate but the treatment, which may involve haemofiltration, is standard and life-saving.

It is crucial to collect, freeze and store urine and blood in the acute stage so that specialist investigations can be performed subsequently.

The most common metabolic causes of encephalopathy in adults are urea cycle and fatty acid oxidation defects. Decompensation occurs when patients become catabolic, which is often triggered by intercurrent infection. There are often clues in the history (not always available in the acute setting). Any patient who has had previous, unexplained episodes of impaired consciousness should be investigated for a metabolic cause.

Stroke

Metabolic stroke, such as seen in mitochondrial cytopathies, organic aci-

daemias and urea cycle defects, is very rare and the diagnosis will often be suggested by clinical and imaging features. It is important to remember that metabolic disease can also be the cause of cerebrovascular events, especially in younger patients.

Fabry disease is present in about 4% of adults below the age of 55 presenting with cryptogenic stroke.[7] The prevalence of

transient ischaemic attacks or ischaemic stroke in patients with Fabry disease is about 15% and thought to relate to small vessel disease. It is an important diagnosis to make both because it can be treated with enzyme replacement therapy and because it as an X-linked disorder so other family members are at significant risk.

About 25% of patients with homocystinuria suffer from thromboembolic

Key Points

Increasing numbers of children with inherited metabolic diseases (IMDs) are surviving into adulthood

Many IMDs can present for the first time in adulthood

Specific therapy is now available for many of these diseases

Missing a diagnosis of an IMD has implications not only for the patient but also for the rest of the family

Collecting suitable laboratory specimens in the acute phase is essential in making the diagnosis in IMDs

KEY WORDS: cardiomyopathy, encephalopathy, hypoglycaemia, inborn errors of metabolism, metabolic acidosis, psychosis, rhabdomyolysis, stroke

Table 1. Summary of possible inherited metabolic diseases presenting in adulthood.

Disorder	Clinical features	Laboratory investigations	Treatment
Urea cycle defects	Encephalopathy Stroke Psychosis	Plasma ammonia Plasma amino acids	iv dextrose Sodium benzoate Sodium phenylbutyrate L-arginine Haemofiltration
Fatty acid oxidation defects	Encephalopathy Cardiomyopathy Rhabdomyolysis	Acidosis Urinary organic acids Plasma acylcarnitines Skin biopsy	iv dextrose L-carnitine Haemodialysis
Homocystinuria	Venous and arterial thrombosis and embolism Tall stature Ectopia lentis	Total plasma homocysteine Plasma amino acids	Pyridoxine Folate Vitamin B12 Betaine
Glycogen storage diseases	Cardiomyopathy Myopathy Rhabdomyolysis	Plasma creatine kinase Muscle biopsy	Dietary starch and protein Controlled exercise
Lysosomal storage diseases	Cardiomyopathy Stroke	White cell enzymes	Enzyme replacement therapy
Adrenoleucodystrophy	Psychosis Encephalopathy (adrenal failure) Paraparesis	Plasma very long-chain fatty acids Synacthen test	Adrenal replacement
Acute porphyrias	Abdominal pain Psychiatric features Neuropathy	Urine and plasma porphyrins	Haem arginate infusion Avoidance of precipitating factors

iv = intravenous.

events at some time, 32% of which are strokes,[8] either ischaemic or secondary to venous sinus thrombosis. Adequate control of plasma total homocysteine reverses the coagulopathy in these patients and normalises thromboembolic risk.

Psychosis

In adults with urea cycle disorders, hyperammonaemia not severe enough to cause frank encephalopathy can frequently present with psychiatric features. A metabolic intoxication should be suspected in patients with an acute psychiatric presentation who have an altered level of consciousness.[9] Episodes are often recurrent and can be triggered by catabolic states, notably in the puerperium.[10]

Porphyria

Acute attacks of porphyria nearly always involve cognitive and behavioural changes, usually anxiety and insomnia, in most cases accompanied by abdominal pain and the other classic symptoms of acute autonomic and sensorimotor neuropathy. Occasionally, however, psychiatric symptoms can be predominant and psychotic features such as hallucinations can occur. The diagnosis is made by measuring urinary porphobilinogen in the acute phase. This requires a urine sample to be protected from light and delivered to the laboratory as quickly as possible. It is also helpful to collect faecal and blood samples acutely.

Structural brain disease

Structural brain disease can also present as psychiatric illness. This seems to be particularly common in metabolic demyelinating disease, with both adrenoleucodystrophy and metachromatic leucodystrophy frequently demonstrating prominent psychiatric features. Careful examination will reveal abnormal neurological signs and lead to further investigation, although brain imaging can be remarkably normal in the early stages. Measuring plasma very long-chain fatty acids and white cell enzymes is important diagnostically.

Rhabdomyolysis

Exercise-induced rhabdomyolysis is frequently due to metabolic muscle disease. Exercising muscle relies initially on glycogen breakdown and then on fatty acid oxidation as a source of adenosine triphosphate. Diseases in which these processes are impaired can therefore present with muscle damage during exercise. How long the patient can exercise before the onset of pain will depend on which metabolic pathway is affected. It is important to screen for glycogen storage diseases (GSD), especially myophosphorylase (GSD type V) and phosphofructokinase (GSD type VII) deficiencies, and fatty acid oxidation defects such as carnitine-palmitoyl transferase II and long-chain defects.

Hypertrophic cardiomyopathy

Disorders affecting muscle energetics can cause a dilated cardiomyopathy in childhood but these patients more commonly present with hypertrophic cardiomyopathy (HCM) as adults. HCM can also be secondary to storage of undegraded macromolecules. In many cases, the conducting system is also affected and patients can present with arrhythmias and sometimes sudden cardiac death. Examples of IMDs that can present with HCM include Fabry disease and mucopolysaccharidoses, whilst arrhythmias are common in long-chain fatty acid oxidation defects.

Conclusions

A number of clinical situations in which IMDs need to be considered have been discussed. These disorders can present in a variety of ways at different ages, often triggered by a catabolic event such as intercurrent illness, fasting (eg preoperatively), postpartum or by the introduction of a new medication, particularly centrally acting agents such as antidepressants. Often, however, the trigger is not apparent. If IMDs are not considered, the diagnosis could be missed with potentially catastrophic consequences for the individual and their family. There are often clues in the history:

- previous similar, unexplained episodes
- unexplained deaths in the family
- parental consanguinity
- relatively young age.

Simple tests which give important clues are often not performed (eg anion gap by measuring bicarbonate and chloride with standard electrolytes, plasma ammonia). These may indicate the need for further first-line metabolic tests such as blood lactate, plasma amino acids, acylcarnitine profile (which can make the diagnosis in more than 30 different metabolic disorders) and urinary organic acids. It is essential to save samples of blood and urine in the acute phase. The diagnosis can then later be confirmed using specialised laboratory techniques such as enzymatic assays, gas-chromatography and TMS as well as molecular genetic analyses.

The specialty of adult IMD is rapidly growing as awareness of the patients' needs grows and specific treatments are increasingly available for these diseases. Giving patients access to these therapies is important as they can alter the natural history of these conditions and are potentially life-saving. When a genetic disorder has been diagnosed, patients and family members can be offered prenatal diagnosis with the aim of preventing transmission to further generations. This is of particular importance with X-linked conditions such as ornithine transcarbamylase deficiency, adrenoleucodystrophy and Fabry disease.

IMDs are individually rare but collectively common, with an overall incidence of over one in 2,000. A combination of improved diagnosis and increased longevity means that it is now likely that most adult physicians will come across a patient with an IMD at some stage in their career.

References

1 Barton NW, Brady RO, Dambroisa JM *et al*. Replacement therapy for inherited enzyme deficiency – macrophage-targeted glucocerebrosidase for Gaucher's disease. *N Engl J Med* 1991;324:1464–70.
2 Bickel H, Gerrard J, Hickmans EM. Influence of phenylalanine intake on phenylketonuria. *Lancet* 1953;ii:812–3.

3 Chen YT, Cornblath M, Sidbury JB. Cornstarch therapy in type I glycogen-storage disease. *N Engl J Med* 1984;310: 171–5.

4 Garrod AE. The incidence of alkaptonuria: a study in chemical individuality. *Lancet* 1902;ii:1616–20.

5 Hsia YE, Lilljeqvist AC, Rosenberg LE. Vitamin B12-dependent methyl-malonicaciduria: amino acid toxicity, long chain ketonuria, and protective effect of vitamin B12. *Pediatrics* 1970;46:497–507.

6 Lindstedt S, Holme E, Lock EA, Hjalmarson J, Strandvik B. Treatment of hereditary tyrosinaemia type I by inhibition of 4-hydroxyphenylpyruvate dioxygenase. *Lancet* 1992;340:813–7.

7 Mudd SH, Skovby F, Levy HL *et al.* The natural history of homocystinuria due to cystathionine beta-synthase deficiency. *Am J Hum Genet* 1985;37:1–31.

8 Rolfs A, Böttcher T, Zschiesche M *et al.* Prevalence of Fabry disease in patients with cryptogenic stroke: a prospective study. *Lancet* 2005;366:1794–6.

9 Sedel F, Baumann N, Turpin JC *et al.* Psychiatric manifestations revealing inborn errors of metabolism in adolescents and adults. *J Inherit Metab Dis* 2007;30: 631–41.

10 Arn PH, Hauser ER, Thomas GH *et al.* Hyperammonemia in women with a mutation at the ornithine carbamoyltransferase locus. A cause of postpartum coma. *N Engl J Med* 1990;322: 1652–5.

Further reading

Desnick RJ. Enzyme replacement and beyond. *J Inherit Metab Dis* 2001;24: 251–65.

Lee PJ. Pregnancy issues in inherited metabolic disorders. *J Inherit Metab Dis* 2006;29: 311–6.