

Biochemical Investigation for Inborn Errors of Metabolism in Adults Presenting With Neurological Disorders



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Inborn errors of metabolism (IEM) constitute a diverse group of genetic disorders characterised by defects in biochemical pathways. Many have a predominantly neurological phenotype reflecting accumulation of neurotoxic metabolites and/or a deficiency of substrates critical for normal neurological development and function. Whilst classically presenting in childhood, late onset variants of these disorders are increasingly recognised in adults, either as a true mild phenotype which presents in later life or because the symptoms in childhood were not sufficiently severe to merit investigation. Accurate diagnosis of these disorders is of particular importance given the expanding therapeutic options available¹ and the inherent genetic implications for the patient and their family. Whilst an in depth review of specific disorders is beyond the scope of this article, we aim to provide an overview of IEM presenting with adult-onset neurological disease, focussing upon a practical approach to biochemical investigation and diagnosis.

Adult-onset IEM

Adult-onset IEM together with the broad neurological phenotypes are detailed in Table 1. In reviewing the literature we have excluded metabolic myopathies and reports where neurological disease developed during childhood or where the age of onset is not clear. We have listed the different neurological features reported in each disorder, although many patients will not have a "full house", particularly where the disorder is mild. Further information on the individual disorders is available via the website 'Online Mendelian Inheritance in Man' (www.ncbi.nlm.nih.gov/).

When to consider an IEM

Many of the biochemical tests for these disorders are complex and expensive and so extensive biochemical screening is not practical. It can be difficult to identify which patients with neurological disease need investigation; we list below some features which may be suggestive of an IEM.

- Progressive neurological disease and/or disparate neurological signs; e.g. psychiatric and cerebellar disease with cognitive decline in metachromatic leukodystrophy.
- Neurological disease together with systemic features: e.g. hepatosplenomegaly in storage disorders, disordered liver function tests in Wilson disease, adrenal insufficiency in X-linked adrenoleukodystrophy.
- Combinations of various movement disorders
- Abnormal fundus examination; e.g. cherry red spot
- Episodic illness or fluctuating symptoms; particularly where it is out of proportion to the insult

and/or precipitated by intercurrent illness, protein load, or occurring post partum.

- Aberrant response to drugs; valproate may exacerbate urea cycle disorders and multiple drugs precipitate attacks in the acute porphyrias.

The history can provide important evidence; with hindsight there may have been subtle problems in childhood and elucidating the developmental and schooling history of the patient can be fruitful. As with all genetic conditions, the family history may provide important information, although the majority of IEM are autosomal recessive and often present as sporadic cases. Evidence of familial consanguinity should be sought. X-linked conditions in which females may be affected due to skewed X-linked inactivation (lyonisation) can cause diagnostic difficulty, and are discussed in more detail below.

In addition, brain imaging and neurophysiological studies may provide useful information, but are beyond the scope of this review.

Biochemical Tests

Routine biochemistry and haematology tests may provide clues (e.g. creatine kinase in mitochondrial disorders) but must be interpreted in conjunction with the clinical picture as these tests are non-specific.

Table 2 lists the first-line biochemical tests useful in the investigation of suspected IEM. These include markers of intermediary metabolism (e.g. organic and amino acids, orotate and acylcarnitines), peroxisomal function (very long chain fatty acids, pristanate and phytanate), bile acid biosynthesis (cholestanol) and lysosomal function (enzymes and storage compounds). Further information on the clinical and technical aspects of these tests is available in biochemical textbooks.²³ It is recommended that clinicians contact their local specialist metabolic laboratory for advice on appropriate tests, sample type and timing, pitfalls and interpretation of results. Further confirmatory tests will usually be required, such as fibroblast enzyme measurement or mutation analysis.

It should be noted that in patients with episodic illness it is crucial to obtain samples for metabolic investigations during an acute attack as the biochemistry may be normal when they are asymptomatic. A negative result during an acute attack makes a diagnosis of an underlying IEM unlikely.

Investigation of specific disorders

Lysosomal storage diseases

In patients with suspected mucopolysaccharidoses urine glycosaminoglycans (GAGs) provide a simple first-line investigation. It is important to examine the

pattern of GAGs in the urine (GAG typing) rather than relying on quantitative screening tests. Apart from urine GAGS there are few simple biochemical tests available for the diagnosis of lysosomal storage diseases. Urine oligosaccharide screening lacks sensitivity in detection of mild late onset forms so for the majority of lysosomal storage diseases white cell enzymes are indicated. In most circumstances normal enzyme activities reliably exclude storage disease. One notable exception is the identification of females with (X-linked) Fabry disease, as normal enzyme activity does not exclude the diagnosis. Measurement of the storage compound (globotriaosylceramide) in urine also lacks sensitivity (noted particularly in the cardiac variant),⁴ making diagnosis difficult where no family mutation has been identified. 'Pseudodeficiency' of several lysosomal enzymes complicates interpretation of low results. There is a high frequency of arylsulphatase A pseudodeficiency in most ethnic groups (carrier rate ~1 in 7)⁵ complicating the diagnosis of metachromatic leukodystrophy and necessitating confirmatory mutation analysis in patients with deficient enzyme activities.

Peroxisomal disorders

The most common adult-onset peroxisomal disorders are Refsum disease and X-linked adrenoleukodystrophy, identified biochemically by raised phytanate and very long chain fatty acids respectively. However, only ~85% of female carriers of adrenoleukodystrophy have abnormal plasma concentrations. It should be borne in mind that markedly different phenotypes of adrenoleukodystrophy can occur in one family.⁶ 2-methyl-CoA racemase deficiency provides an example of a recently described adult-onset IEM.⁷ The clinical features are similar to Refsum disease and characterised biochemically by high concentrations of plasma pristanate. Clinical features reported included peripheral neuropathy, pigmentary retinopathy and seizures. Acute and subacute presentations occur precipitated by rapid weight loss, pregnancy or fever.

Mitochondrial disorders

Mitochondrial diseases are notoriously difficult to diagnose given the large number of disorders described; they are multi-system disorders presenting at any age, with any mode of inheritance. Simple biochemical tests for mitochondrial disease are limited; the measurement of lactate in plasma and CSF is useful but normal results do not exclude mitochondrial disease, although a normal CSF result in a fitting patient is reassuring. Biochemistry may reveal renal tubular dysfunction, muscle disease and/or endocrine abnormalities. However, diagnosis usually relies on muscle biopsy (histology and respiratory chain enzymes) and genetic studies.⁸

Urea cycle disorders

Urea cycle disorders may present with acute episodic illness, the diagnosis of which may be overlooked if samples (ammonia, plasma amino acids, and urine orotate) are not collected during an attack. This group of disorders highlights

the need for ammonia estimation in any adult with unexplained encephalopathy.

Organic acidurias

Organic acidurias typically present in childhood, however some disorders may not be diagnosed until adulthood, including glutaric aciduria type 1, propionic aciduria, L-2-hydroxyglutaric aciduria and 4-hydroxybutyric aciduria. Although there are reports of adult diagnoses of the latter two conditions, presentation was in childhood with symptoms including learning difficulties and ataxia. A limited number of true adult-onset organic acidurias have been reported. A recent example is 3-methylglutaconic aciduria type 1, previously described in a small number of children with a variety of phenotypes. The adult patients described presented with a cerebellar syndrome and cognitive decline,^{9,10} which may prove to represent the true phenotype. Investigation is straightforward requiring urine organic acids as the first-line test; acylcarnitines may be useful in certain conditions.

Cerebral glucose transport

Recently, adult-onset cases of GLUT1 deficiency have been reported, presenting with paroxysmal exercise-induced dyskinesia with and without epilepsy. The fasting CSF/plasma glucose ratio is subnormal but not to the extent seen in the early onset disorder.¹¹

IEM presenting in childhood with abnormal adult neurology

Although we have concentrated on disorders presenting in adults there are a number of early presenting disorders with long term survival. These may have eluded diagnosis because the patient was not investigated, the tests were not readily available or the condition has been described relatively recently. Two examples are the cerebral creatine deficiency syndromes (CCDS) and congenital disorders of glycosylation (CDG).

CCDS comprise guanidinoacetate methyltransferase (GAMT) deficiency, X-linked creatine transporter defect and arginine:glycine amidinotransferase (AGAT) deficiency, all resulting in cerebral creatine deficiency. AGAT and GAMT deficiencies may respond to treatment with creatine. The common features are mental retardation, speech delay and epilepsy which usually begin in infancy, although the condition may not be diagnosed until much later.^{12,13} Measurement of creatine and guanidinoacetate in urine and plasma aids diagnosis of these conditions without resort to magnetic resonance spectroscopy.¹⁴

CDG disorders result in multi-systemic disease and should be considered in adults with a long-standing history of retinitis pigmentosa, seizures, stable ataxia and kyphoscoliosis.¹⁵ The diagnosis may be made by analysis of transferrin glycoforms.

Summary

The possibility of an underlying IEM should be considered in any patient with unexplained neurological disease. A wide range of biochemical tests are available with the aim of reaching a

working diagnosis. Confirmation usually requires fibroblasts and/or genetic testing. Given the rarity of individual IEM, the many disorders described and the difficulties of identifying mild cases it is likely that late-onset forms are underdiagnosed. In theory mild cases of any IEM could present at a late stage and the list of adult-onset diseases will undoubtedly grow. ♦

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Table 1: Neurological features in adult onset IEM.

	Leukoencephalopathy	Spastic paraparesis	Cerebellar Disease	Cognitive decline	Movement disorder	Epilepsy	Acute encephalopathy	Stroke & Stroke-like episodes	Peripheral neuropathy	Psychiatric disease	Other features
Lysosomal Disorders											
Fabry disease							X	X	X		Angiokeratomas, cardiomyopathy, renal disease. X-linked: females affected. Stroke may be the presenting feature
Galactosialidosis			X	X	X	X					Cherry red spot may be present, corneal clouding, angiokeratomas, short stature
Gaucher disease (type III)		X	X		X	X					Horizontal supranuclear ophthalmoplegia, hepatosplenomegaly, bone pain, thrombocytopenia, anaemia
GM1 Gangliosidosis	X	X	X	X	X						Cherry red spot may be present
GM2 Gangliosidosis (Tay Sachs & Sandhoff)	X	X	X		X			X	X		Cherry red spot may be present. May mimic motor neurone disease
Krabbe disease	X	X	X	X				X			
β-Mannosidosis				X				X	X		Angiokeratomas, deafness, dysmorphic features
Metachromatic leukodystrophy	X	X	X	X	X	X		X	X		Optic atrophy
Neuronal ceroid lipofuscinosis type 1			X	X	X				X		Progress to cerebral ataxia, visual loss. Other types described, but not diagnosed biochemically
Niemann-Pick type C		X	X	X	X				X		Vertical supranuclear ophthalmoplegia, hepatosplenomegaly
Sanfilippo syndrome (mucopolysaccharidosis type III)				X					X		Mild dysmorphic features (facial coarsening)
Sialidosis type I			X		X	X					Cherry red spot, visual loss
Peroxisomal disorders											
Adrenoleukodystrophy / Adrenomyeloneuropathy	X	X		X		X		X	X		X-linked. Adults mostly present with adrenomyeloneuropathy. Males may have adrenal insufficiency
2-Methyl-CoA racemase deficiency		X		X	X	X			X		Retinitis pigmentosa
Refsum disease			X	X					X		Retinitis pigmentosa
Steinert carrier protein X deficiency	X				X						Phenotype uncertain (n = 1)
Mitochondrial disorders											
Mitochondrial disorders	X		X		X	X		X	X		Variable phenotypes, often multi-system disease, e.g. sensorineural hearing loss, optic atrophy, retinitis pigmentosa, myopathy
Coenzyme Q10 deficiency			X								Phenotype in adult-onset unclear
Pyruvate dehydrogenase deficiency			X		X				X		Phenotype in adult-onset unclear
Amino Acid Disorders											
Cobalamin C defect	X	X							X	X	Combined degeneration of spinal cord, retinitis pigmentosa, optic atrophy, thromboembolic events
Classical homocystinuria					X	X		X	X		Osteoporosis, thromboembolic events, lens dislocation, marfanoid habitus
Hartnup disorder			X							X	Pellagra-like photosensitive dermatosis
Maple syrup urine disease			X				X				Episodic attacks precipitated by metabolic stress eg catabolism (fasting, intercurrent illness)
Methylene tetrahydrofolate reductase deficiency	X	X	X				X	X	X	X	Subacute degeneration of spinal cord, thromboembolic events
Urea cycle disorders: OTC, citrullinaemia I & II, NAGS, CPS, LPI, HHH						X	X	X		X	Acute attacks triggered by protein load eg catabolism (intercurrent illness), diet. OTC is X-linked
Urea cycle disorders: arginase deficiency		X	X		X	X					Often diagnosed with cerebral palsy
Organic Acid Disorders											
Glutaric aciduria type 1	X		X	X	X	X					Macrocephaly, subdural haematomas
3-Methylglutaconic aciduria type 1	X			X							
Multiple acyl-CoA dehydrogenase deficiency							X				Episodic attacks precipitated by metabolic stress eg catabolism (fasting, intercurrent illness), myopathy
Fatty Acid Oxidation Disorders											
Medium chain acyl-CoA dehydrogenase deficiency							X				Hypoketotic hypoglycaemia. Episodic attacks precipitated by metabolic stress eg catabolism (fasting, intercurrent illness)
Carbohydrate Disorders											
GLUT1					X	X					Confusion/lethargy triggered by fasting
Purine Disorders											
Lesch-Nyhan neurological variant		X			X						X-linked, gout and/or renal calculi, attention deficit, variable mental retardation
Lipid Disorders											
Ataxia with vitamin E deficiency		X	X								Retinitis pigmentosa
Cerebrotendinous xanthomatosis	X	X	X		X	X			X	X	Juvenile cataracts, xanthomas, diarrhoea, mental retardation
Neurotransmitter defects											
GTP cyclohydrolase deficiency					X						Autosomal dominant dopamine-responsive dystonia with diurnal fluctuations in symptoms
Porphyria											
Acute intermittent porphyria						X	X		X	X	Abdominal pain, dysautonomia, hyponatraemia
Metal Disorders											
Haemochromatosis			X		X					X	Hepatic & endocrine disease, arthritis
Neuroferritinopathy		X		X	X						
Wilson disease				X	X	X	X		X	X	Kayser-Fleischer rings, hepatic disease

Abbreviations: CPS – carbamoylphosphate synthetase, HHH – hyperornithinaemia-hyperammonaemia-homocitrullinuria syndrome, LPI – lysinuric protein intolerance, NAGS – N-acetylglutamate synthetase, OTC – ornithine transcarbamoylase

Table 2: Metabolic biochemical investigation for IEM.

IEM	Biochemical Investigations	Notes
Lysosomal Disorders		
Fabry disease, GM ₁ gangliosidosis, Krabbe disease, β-mannosidosis, metachromatic leukodystrophy, neuronal ceroid lipofuscinosis type 1, Sandhoff, Tay Sachs	Lysosomal enzymes	Usually requires white cells (whole blood), some available on plasma/dried blood spots. Check with local laboratory for details
Galactosialidosis	White cell enzyme & urine sialic acid	
Gaucher disease	Chitotriosidase & white cell enzyme	Chitotriosidase markedly elevated (benign chitotriosidase deficiency occurs in ~6%)
Niemann-Pick type C	Chitotriosidase & fibroblast studies	Fibroblast filipin staining & cholesterol esterification. Chitotriosidase mildly elevated
Sanfilippo syndrome (MPS III)	Urine glycosaminoglycans (including typing)	Enzyme analysis required to distinguish subtypes
Sialidosis type 1	Urine sialic acid	
Peroxisomal disorders		
X-ALD, AMN, 2-methyl-CoA racemase deficiency, Refsum disease, sterol carrier protein X deficiency	Plasma VLCFA, phytanate and pristanate	~15% female carriers of X-ALD have normal VLCFA
Mitochondrial disorders		
Mitochondrial disorders	CSF & plasma lactate, respiratory chain enzyme activities in muscle	Lactate & respiratory chain enzymes may be normal
MERRF, MELAS, NARP	Common mitochondrial point mutations	
Pyruvate dehydrogenase deficiency	Enzyme in muscle / fibroblasts	
Coenzyme Q10 deficiency	White cell coenzyme Q10	Consider if abnormal respiratory chain enzymes
Amino Acid Disorders		
Urea cycle disorders (OTC, citrullinaemia I & II, NAGS, CPS, LPI, arginase, HHH)	Plasma ammonia & amino acids, urine amino acids & orotate	Allopurinol loading tests to identify carriers of OTC are not particularly sensitive or specific. ¹⁶
Hartnup disorder	Urine amino acids	
Homocysteine defects (CblC defect, classical homocystinuria, MTHFR deficiency)	Plasma total homocysteine & amino acids (methionine), & urine methylmalonate	MTHFR thermolabile variant is not a cause. B12 & folate usually normal in classical homocystinuria & CblC defect
Maple syrup urine disease	Plasma amino acids & urine organic acids	May be normal between acute attacks
Organic Acid Disorders		
Glutaric aciduria type 1	Urine organic acids & acylcarnitines	Normal results described in the literature – consider fibroblast enzyme assay
Multiple acyl-CoA dehydrogenase deficiency	Urine organic acids & acylcarnitines	Results may be normal between attacks
3-Methylglutaconic aciduria type 1	Urine organic acids	Beware various subtypes of 3-methylglutaconic aciduria
Fatty Acid Oxidation Disorders		
Medium chain acyl-CoA dehydrogenase deficiency	Acylcarnitines & urine organic acids	Positive dipstick for ketones does not exclude
Carbohydrate Disorders		
GLUT1	Paired fasting CSF & plasma glucose	Collect blood prior to lumbar puncture. In adult onset cases ratio may not be <0.4
Purine Disorders		
Lesch-Nyhan neurologic variant	Serum & urine urate, red cell / fibroblast HPRT	HPRT activity very variable (0-50%)
Lipid Disorders		
Cerebrotendinous xanthomatosis	Plasma cholestanol	Serum cholesterol may be normal
Ataxia with vitamin E deficiency	Plasma vitamin E	Protect sample from light
Neurotransmitter defects		
GTP cyclohydrolase deficiency	CSF neurotransmitters	Special collection tubes and snap freeze
Porphyria		
Acute intermittent porphyria	Urine porphobilinogen	Protect sample from light. To exclude collect urine during an acute attack
Metal Disorders		
Haemochromatosis	Transferrin saturation	C282Y common mutation, low penetrance
Neuroferritinopathy	Serum ferritin	Increased by acute phase response
Wilson disease	24 h urine copper	Consider penicillamine challenge

Abbreviations: AMN – adrenomyeloneuropathy, CblC – cobalamin C, CPS – carbamoylphosphate synthetase, HHH – hyperornithinaemia-hyperammonaemia-homocitrullinuria syndrome, HPRT – hypoxanthine guanine phosphoribosyl transferase, LPI – lysinuric protein intolerance, MPS – mucopolysaccharidosis, MTHFR – methylene tetrahydrofolate reductase, NAGS – N-acetylglutamate synthetase, OTC – ornithine transcarbamoylase, X-ALD – X-linked adrenoleukodystrophy, VLCFA – very long chain fatty acids.