REVIEW

Inborn errors of metabolism as a cause of neurological disease in adults: an approach to investigation

R G F Gray, M A Preece, S H Green, W Whitehouse, J Winer, A Green

In 1927 Archibald Garrod presented the Huxley Lecture at Charing Cross Hospital[1] Out of this lecture emerged the concept of an "inborn error of metabolism" whereby an inherited defect may lead to the accumulation in cells or body fluids of a metabolite which in itself may predispose to disease. The disorders cited as examples were all adult onset disorders.

Today there are over 200 known inborn errors of metabolism; however, the vast majority of cases reported are of childhood onset (<16 years of age). In part this may reflect the fact that the paediatric forms of the disease are more severe and hence more easily recognisable. However, in some cases it may be due to a lack of awareness by physicians treating adults of the possibility of inborn errors of metabolism being a cause of disease. Certainly, current experience of inborn errors of metabolism leads us to think that, potentially, every disorder has a milder form with a later onset.

In an attempt to increase awareness of adult onset inborn errors of metabolism this article reviews the disorders which can present at or older than 16 years of age with CNS or neuromuscular disease. We have included disorders in which the patient may present with mild or "soft" signs before that age, which are likely to be overlooked or mistaken for other disorders. This is not intended to be an in depth review of each disorder but rather to be a practical guide to the initial diagnosis of these disorders for neurologists outside specialist centres for the investigation of inborn errors of metabolism.

West Midlands Regional Metabolic Disease Service, Birmingham Children's Hospital NHS Trust, Steelhouse Lane, Birmingham B4 6NH, UK
R G F Gray
M A Preece
A Green

Department of Neurology, Diana, Princess of Wales Children's Hospital NHS Trust, Birmingham, UK
S H Green
W Whitehouse

Department of Neurology, University Hospital NHS Trust, Birmingham, UK
J Winer

Correspondence to:
Dr R G F Gray
George.Gray@bhamchildrens.wmids.nhs.uk

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The disorders

We have prepared two tables listing inborn errors of metabolism presenting in adulthood.

Table 1 lists the disorders reported in the literature together with the main clinical symptoms, primary defect (if known), and diagnostic tests for their detection.

Table 2 lists the disorders associated with specific symptom groups together with any specific neurological signs and characteristic non-neurological features. Diseases are categorised in a specific group based on the symptom(s) which is the major feature of the disorder, and may in some cases be the initial presenting symptom.

LYSOSOMAL STORAGE DISEASES

The lysosome is an intracellular organelle involved in the degradation of various complex lipids, glycoproteins, and mucopolysaccharides. Defects in specific enzymes lead to the accumulation of complex catabolic intermediates. Although the process occurs in utero the age of onset of clinical symptoms can vary substantially. Alleles are known which are associated with a milder, later onset phenotype. This may be related to the presence of significant residual functional enzyme activity resulting in a lower rate of accumulation of the intermediate metabolite. The clinical symptoms of the adult onset forms of these diseases can differ substantially from the childhood onset forms. This disparity between the text book description of the "classic" phenotype and the reality of the presentation in adults can cause considerable diagnostic difficulty.

Tay-Sach's and Sandhoff's diseases are gangliosidoses which present in the infantile period with seizures, blindness, hypotonia, and developmental delay. The adult onset forms present with a much wider clinical range varying from atypical forms of motor neuron disease[2] to dystonia[3] and bulbospinal neuronopathy.[4]

Metachromatic leukodystrophy presents (in its severe form) in the first 2 years of life with spastic paraparesis and developmental delay whereas in the adult form it is associated with dementia and behavioural problem.[5]

Acid maltase deficiency (glycogen storage disease type II) usually presents in the first weeks of life with hypotonia and hypertrophic cardiomyopathy. The adult onset forms may present with muscle weakness but without obvious cardiomyopathy.[6]

Some of the lysosomal enzymes show a "pseudodeficiency" state. Enzyme activity, although reduced to as little as 5% of normal, does not produce clinical symptoms. In any patient who does not show the typical phenotype but who shows a gross enzyme deficiency this state needs to be excluded by demonstration of the accumulating metabolite or by analysis of the relevant gene. This is particularly a problem with metachromatic leukodystrophy, where 1/50 -1/100 of the population are

Table 1 Inherited metabolic disorders with adult onset forms

Disease	*Clinical symptoms*	*Tests*
	Lysosomal storage diseases	
Acid maltase deficiency	Muscle weakness, respiratory difficulty	Lymphocyte α-glucosidase
Fabry's disease	Peripheral nerve pain (±renal failure±angiokeratoma±cardiomyopathy), stroke-like episodes	Leucocyte α-galactosidase A
Gaucher's disease type III	Horizontal supranuclear gaze defect, developmental delay, hydrocephalus, skeletal abnormalities, psychosis	Leucocyte β-glucosidase, bone marrow aspirate
GM1 gangliosidosis	(i) Extra pyramidal signs, flattening of vertebral bodies, normal cognitive function. sometimes with psychosis	Leucocyte β-galactosidase, urine oligosaccharides
GM2 gangliosidosis (Tay Sach's and Sandhoff's disease)	(i) Lower motor neuron disease with onset 20–40 y, pyramidal signs, and cerebellar degeneration (ii) Atypical amyotropic lateral sclerosis	Leucocyte total, hexosaminidase, and hexosaminidase A
Krabbe's leukodystrophy	Pes cavus, hemiparesis, spastic tetraparesis, leukodystrophy	Leucocyte β-galactocerebrosidase
Metachromatic leukodystrophy	Loss of cognitive function or behavioural abnormalities, neuromuscular weakness with impaired nerve conduction, leukodystrophy	Leucocyte arylsulphatase A (the pseudodeficiency state must be excluded)
Sialidosis (mucolipidosis type I)	Type I Visual defect with lens or corneal opacity, ataxia, myoclonus, generalised seizures sometimes with nystagmus, ataxia Type II Dementia±cherry red spot Myoclonus, blindness, cherry red spot, dysmorphic features, angiokeratoma.	Urine oligosaccharides, fibroblast α-neuraminidase
Niemann-Pick's disease type C	Psychomotor retardation leading to dementia, ataxia with dystonia	Bone marrow aspirate, fibroblast cholesterol uptake and staining.
	Amino acid disorders	
Arginase deficiency	Disorientation, coma	Plasma and urine amino acids, plasma ammonia (1 h postprandial).
Citrullinaemia	Disorientation, restlessness, coma	Plasma and urine amino acids, plasma ammonia (1 h postprandial).
Hartnup's disease	Dementia, ataxia ±skin lesions.	Plasma and urine amino acids
Homocystinuria (cystathionine synthasedeficiency: classic form)	Occlusive cerebrovascular disease, dislocated lenses, osteoporosis, psychiatric disturbances	Urine homocystine, plasma homocystine and methionine
Homocystinuria (methylene tetrahydrofolatereductase deficiency remethylation defect).	Parasthaesia, hallucinations, tremor, withdrawal, mental retardation, limb weakness, memory loss	Urine homocystine, plasma homocystine and methionine
Hyperornithinaemiawith gyrate atrophy of the retina	Gyrate atrophy of choroid and retina	Plasma and urine amino acids (ornithine)
Ornithine transcarbamylase deficiency	Behavioural disturbances, comatose episodes, sleep disorders	Plasma ammonia (1 h postprandial)plasma amino acids, urine amino acids and orotic acid
	Organic acid disorders	
Fatty acid oxidation defects	Muscle weakness, easy fatigability ±liver disease ±cardiomyopathy ±hypoglycaemia	Urine organic acids (fasting)
Glutaric aciduria type 1	Dystonia±hypoglycaemia, may present with a Reye-like syndrome	Urine organic acids, blood spot acyl carnitines
Propionic acidaemia	Chorea and dementia, recurrent vomiting	Urine organic acids, blood spot acyl carnitines
	Peroxisomal disorders	
X linked adrenoleukodystrophy	(i) Onset 20–30 y in males, gait disturbance, spastic paraparesis, intellectual function usually intact, impotence±Addison's disease, occasionally cerebral symptoms may occur, eg dementia and psychosis. (ii) Onset >30 y in females, spastic paraparesis, vibratory sense loss, long tract signs, peripheral neuropathy	Plasma very long chain fatty acids.
	Lactic acidaemias	
Electron transport chain disorders (i) mtDNA encoded	NARP, MELAS, MERRF, Kearns-Sayre syndrome, LHON	Blood or tissue mtDNA analysis
(ii) Nuclear DNA encoded	Muscle weakness, multisystem disease	CSF/plasma lactate, muscle biopsy for respiratory chain assays

Table 1 Inherited metabolic disorders with adult onset forms (continued)

Disease	*Clinical symptoms*	*Tests*
	Disorders of the glycogenolytic and glycolytic pathway	
Glycogen storage diseases	Muscle weakness, cardiomyopathy, hepatomegaly, hypoglycaemia, myopathy	Muscle enzyme assays, but many of the glycogen storage diseases can be diagnosed by leucocyte or erythrocyte enzyme assays
Glycolytic pathway disorders	Muscle weakness (second wind phenomenon), exercise intolerance, myoglobinuria ± haemolytic anaemia	Muscle enzyme assays, but many of the glycolytic disorders can be diagnosed by erythrocyte enzyme assay
	Other disorders	
Abetalipoproteinaemia	Ataxia, retinitis pigmentosa	Plasma cholesterol, blood film (acanthocytes), lipoproteins
Acaeruloplasminaemia	Ataxia, retinal dystrophy±diabetes mellitus±presenile dementia	Plasma and urine copper, plasma iron and ferritin
Adult polyglucosan body disease	Upper and lower motor neuron signs, sensory loss, neurogenic bladder, dementia	Leucocyte glycogen brancher enzyme (some forms may show normal muscle activity).
Cerebrotendinous xanthomatosis	Spasticity, ataxia, cataracts, tendon xanthomas	Urine bile alcohols
Hereditary vitamin E deficiency	Tremor, ataxia, head titubation, loss of vibration sense.	Plasma vitamin E, plasma cholesterol and triglycerides
Homocystinuria and methylmalonic aciduria (combined defect)	Megaloblastic anaemia, dystonia	Urine organic acids and homocystine
Juvenile Batten's disease	Seizures, visual loss, dementia	Skin or rectal biopsy for histological analysis, DNA analysis for the common mutation
Kuf's disease	Type A Progressive myoclonic epilepsy Type B Motor problems, psychosis, dementia	Skin or rectal biopsy for histological analysis
Lesch-Nyhan syndrome	Some forms may present late with choreiform movements, dysarthria ± renal problems	Plasma urate and urine,urate/creatinine
Porphyrias	Limb, neck, and chest pain, muscle weakness, sensory loss, seizures,behavioural abnormalities±abdominal symptoms±photosensitivity	Urine delta amino laevulinic acid and porphobilinogen, urine and fecal porphyrins
Pyridoxine responsive seizures	Persistent seizures responsive to pyridoxine	In vivo pyridoxine response test: primary defect not known
Refsum's disease	Retinitis pigmentosa, peripheral polyneuropathy, cerebellar ataxia	Plasma phytanic acid
Segawa disease	Cyclical dystonia	Levodopa trial (some forms have a defect in biopterin metabolism)
Sjogren-Larrson syndrome	Spastic tetraplegia ±ichthyosis, mental retardation	Fibroblast fatty alcohol, oxidoreductase assay
Wilson's disease	Dysarthria, loss of coordination of voluntary movements, pseudobulbar palsy, parkinsonian features, renal failure, liver disease, Kayser-Fleischer rings, dementia	Urine copper (pre and postpenicillamine) Plasma copper and caeruloplasmin

Table 2 Symptom groups associated with adult onset inborn errors of metabolism

Disorder	*Other symptoms*	*Tests*
	Muscle weakness or exercise intolerance	
Fatty acid oxidation defects	±Cardiomyopathy±hypoglycaemia±liver disease±myoglobinuria	Urine organic acids (fasting)
Glycolytic pathway disorders	±Anaemia ±liver disease, muscle weakness ±cardiomyopathy±endocrinological disorders±ptosis	Red cells or muscle biopsy for enzyme assays
Glycogen storage diseases		
(a) Type II (acid maltase deficiency)	±Respiratory difficulties due to diaphragmatic weakness	Lymphocyte acid α-glucosidase
(b) Type III (Cori's disease)	History of early hypoglycaemia and hepatomegaly	Leucocyte glycogen debrancher enzyme assay
(c) Type V (McArdle's disease)	Myoglobinuria, exercise intolerance, cramps	Ischaemic exercise test
(d) Phosphorylase b kinase deficiency	±Cardiomyopathy ±liver disease	Erythrocyte or liver phosphorylase b kinase assay
Myoadenylate deaminase deficiency	Note: most persons are asymptomatic	Ischaemic exercise test (increased ammonia), muscle biopsy for myoadenylate deaminase assay, blood for DNA analysis for the common mutation.

Table 2 Symptom groups associated with adult onset inborn errors of metabolism (continued)

Disorder	*Other symptoms*	*Tests*
	Motor neuron disease	
Adult polyglucosan storage disease	Dementia, neurogenic bladder, sensory loss	Leucocyte glycogen brancher assay (some forms may show normal muscle activity).
GM2 Gangliosidosis (Tay-Sach's and Sandhoff's disease)	Slow progressive disorder, pyramidal signs, cerebellar degeneration	Leucocyte total hexosaminidase and hexosaminidase A
	Chorea and/or dystonia	
Glutamic aciduria type 1	±Reye's syndrome ±Hypoglycaemia, slow progressive disorder, gait disturbance, dysarthria	Urine organic acids blood spot for acyl carnitines
GM2 Gangliosidosis (Tay-Sach's and Sandhoff's disease)	Slow progressive disorder	Leucocyte total hexosaminidase and hexosaminidase A
Lesch-Nyhan syndrome	Renal stones	Plasma urate and urine, urate/creatinine ratio
Methylmalonic aciduria with homocystinuria	±Anaemia	Urine organic acids and amino acids. urine , and plasma homocystine.
Niemann-Pick disease type C	Supranuclear ophthalmoplegia, ataxia, psychomotor retardation, dementia, splenomegaly	Bone marrow aspirate fibroblast cholesterol incorporation and staining
Segawa disease	Diurnal variation of symptoms	Levodopa trial (some forms have a defect in biopterin metabolism)
Wilson's disease	Kayser-Fleischer rings,±liver disease ±dementia ±choreoathetosis ±renal failure	Plasma copper and caeruloplasmin, urine copper (pre and postpenicillamine), liver copper
	Ataxia	
Abetalipoproteinaemia	Muscle weakness, fat malabsorption, retinitis pigmentosa	Plasma cholesterol and triglycerides, blood film (acanthocytes), lipoproteins
Acaeruloplasminaemia	±Presenile dementia ±diabetes mellitus, retinal dystrophy	Plasma and urine copper
Cerebrotendinous xanthomatosis	Spasticity, cataracts, tendon xanthomas	Urine cholestanol
GM2 Gangliosidosis (Tay-Sachs' and Sandhoff's disease)	Slow progressive disorder	Leucocyte total hexosaminidase and hexosaminidase A
Hartnup disease	±Skin lesions	Plasma and urine amino acids
Niemann-Pick disease type C	±Supranuclear ophthalmoplegia, dementia, dystonia, splenomegaly	Bone marrow aspirate
Pyruvate dehydrogenase deficiency (X linked)	Episodes in males triggered by carbohydrate feeding	Pre and postprandial blood lactate, CSF lactate, fibroblast pyruvate dehydrogenase
Refsum's disease	Retinitis pigmentosa, polyneuropathy	Plasma phytanic acid
Sialidosis (mucolipidosis type I)	Type I Visual defect with lens or corneal opacity, ataxia, myoclonus, generalised seizures sometimes with nystagmus, ataxia, dementia ± cherry red spot Type II Myoclonus, blindness, cherry red spot, dysmorphic features, angiokeratoma.	Urine oligosaccharides fibroblast α-neuraminidase
	Leukodystrophy (diagnosed radiologically)	
Krabbe's leukodystrophy	Pes cavus, hemiparesis, spastic tetraparesis	Leucocyte β-galactocerebrosidase
Metachromatic leukodystrophy	Slow progressive disorder, impaired nerve conduction ±behavioural problems	Leucocyte arylsulphatase A (common pseudodeficiency state must be excluded)
X linked adrenoleukodystrophy	Males Gait disturbance, spastic paraparesis, rarely dementia ±Addison's disease Females Onset >30 y, spastic paraparesis, vibration sense loss, long tract signs, peripheral neuropathy	Plasma very long chain fatty acids
	Strokes and stroke-like episodes:	
Fabry's disease	Angiokeratoma, renal disease, developmental delay	Leucocyte α-galactosidase A
Homocystinuria	Lens dislocation,occlusive cerebrovascular disease, osteoporosis, skeletal deformities, mental retardation	Urine homocystine
Mitochondrial myopathy, encephalopathy with lactic acidaemia and stroke-like episodes (MELAS)	Seizures, developmental delay, sensorineural hearing loss ±diabetes mellitus	Blood for mtDNA analysis
Urea cycle defects	Postprandial vomiting, coma, confusion	Blood ammonia, plasma, and urine amino acids

Table 2 Symptom groups associated with adult onset inborn errors of metabolism (continued)

Disorder	*Other symptoms*	*Tests*
	Behavioural and/or psychiatric disorders and/or dementia	
Acaeruloplasminaemia	Ataxia, diabetes mellitus, retinal dystrophy	Plasma copper and caeruloplasmin, plasma iron and ferritin
Gaucher's disease type III	Horizontal supranuclear gaze defect, developmental delay, hydrocephalus, skeletal abnormalities psychosis	Leucocyte β-glucosidase, bone marrow aspirate
Hartnup disease	Ataxia and skin lesions	Plasma and urine amino acids
Homocystinuria (classic)	Occlusive cerebrovascular disease, dislocated lenses, osteoporosis, skeletal deformities.	Urine and plasma homocystine and methionine.
Homocystinuria (remethylation defect)	Paraesthesia, limb weakness, mental retardation	Urine and plasma homocystine and methionine.
Juvenile Batten's disease	Visual loss, seizures, retinitis pigmentosa	Skin or rectal biopsy for histological analysis, DNA for the common deletion
Kuf's disease	Dementia, psychosis, motor loss	Skin or rectal biopsy for histological analysis
Metachromatic leukodystrophy	Slow progressive disorder, impaired nerve conduction, leukodystrophy	Leucocyte arylsulphatase A (pseudodeficiency state must be excluded)
Niemann-Pick disease type C	Vertical supranuclear ophthalmoplegia, psychomotor retardation, ataxia, dystonia, splenomegaly	Bone marrow aspirate, fibroblast cholesterol incorporation and staining
Ornithine transcarbamylase deficiency	Episodic symptoms (often postprandial), sleep disorders, comatose episodes	Plasma ammonia (1h postprandial), plasma amino acids, urine amino acids and orotic acid
Porphyriria	Limb, neck, or chest pain, muscle weakness, abdominal pain, photosensitivity.	Urine and fecal porphyrins, urine delta aminolaevulinic acid and porphobilinogen
Wilson's disease	Kayser-Fleischer rings ±liver disease, dysarthria, loss of coordination, pseudobulbar palsy , parkinsonian features	Plasma copper and caeruloplasmin
X linked adrenoleukodystrophy	Gait disturbance ±Addison's disease leukodystrophy, spastic paraparesis, impotence	Plasma very long chain fatty acids
	Eye disorders	
Cerebrotendinous xanthomatosis	Spasticity, cataracts, tendon xanthomas	Urine cholestanol
Galactokinase deficiency	Cataracts	Postprandial urine sugar, chromatography
Gaucher's disease type III	Horizontal supranuclear gaze defect, developmental delay, hydrocephalus, skeletal abnormalities, psychosis	Leucocyte β-glucosidase
Homocystinuria (classic form)	Lens dislocation, occlusive cerebrovascular disease, osteoporosis, skeletal deformities, mental retardation	Urine and plasma homocystine and methionine
Hyperornithinaemia with gyrate atrophy of the retina	Optic atrophy	Plasma and urine amino acids (ornithine)
Juvenile Batten's disease	Seizures, visual loss, retinitis pigmentosa, dementia	Skin or rectal biopsy for histological analysis, blood for DNA analysis for the common mutation
Leber's hereditary optic atrophy	Bilateral optic atrophy (may be alcohol or tobacco triggered)	Blood for mtDNA analysis
Neuropathy ataxia and retinitis pigmentosa (NARP)	Retinitis pigmentosa, ataxia, neuropathy	Blood for mtDNA analysis
Niemann-Pick disease type C	Psychomotor retardation leading to dementia ataxia with dystonia, vertical supranuclear ophthalmoplegia	Bone marrow aspirate, fibroblast cholesterol uptake and staining.
Oculocutaneous albinism	Pale complexion, blue eyes	Hair follicle tyrosinase
Refsum's disease	Peripheral neuropathy, retinitis pigmentosa, cerebellar ataxia	Plasma phytanic acid
Sialidosis (mucolipidosis type I)	Type I Visual defect with lens or corneal opacityataxia, myoclonus, generalised seizures sometimes with nystagmus, ataxia, dementia ± cherry red spot Type II Myoclonus, blindness, cherry red spot, dysmorphic features, angiokeratoma.	Urine oligosaccharides Fibroblast α-neuraminidase
Tyrosinaemia type II	Cataracts, skin lesions, slight developmental delay	Plasma and urine amino acids
Wilson's disease	Cataracts, Kayser-Fleischer rings, liver disease, dementia, renal failure, parkinsonian features, dysarthria, loss of coordination of voluntary movement.	Plasma copper and caeruloplasmin

Table 2 Symptom groups associated with adult onset inborn errors of metabolism (continued)

Disorder	*Other symptoms*	*Tests*
	Epilepsy	
Electron transport chain disorders	Any combination of symptoms	CSF and blood lactate, blood mtDNA analysis, muscle biopsy for enzyme assay.
Juvenile Batten's disease	Visual loss	Skin or rectal biopsy for histological analysis, DNA for the common mutation
Kuf's disease	Progressive myoclonic epilepsy	Skin or rectal biopsy for histological analysis
Myoclonic epilepsy with ragged red fibres	Myoclonus	Blood for mtDNA analysis.
Pyridoxine dependent seizures	Persistent seizures responsive to pyridoxine	Pyridoxine response trial (primary defect not known)
Sialidosis (mucolipidosis type I)	Type I Visual defect with lens or corneal opacityataxia, myoclonus, generalised seizures sometimes with nystagmus, ataxia, dementia±cherry red spot Type II Myoclonus, blindness, cherry red spot, dysmorphic features, angiokeratoma	Urine oligosaccharides Fibroblast α-neuraminidase

homozygous for a common pseudodeficiency mutation in the arylsulphatase A gene.[5]

AMINO ACID AND ORGANIC ACID DISORDERS

Because environmental factors such as diet and stress (for example, infection and surgery) influence the metabolism of patients with amino acid and organic acid disorders they may not present with symptoms in childhood because they may not have been exposed to these factors. The stress of dieting, increased dietary intake, prolonged exercise (as in sport or training), or pregnancy may trigger the first recognised attack.

Defects in the urea cycle such as ornithine transcarbamylase deficiency, argininosuccinic aciduria, or citrullinaemia can cause hyperammonaemia often associated with a metabolic alkalosis. In adults this may present with intermittent episodes of coma or behavioural disturbance, which may be confused with a psychiatric disorder.[7–9]

The fatty acid oxidation defects generally present with hypoglycaemia, which can be so severe as to cause coma or, if not managed promptly, sudden death. Although adults are more resistant to fasting than children (a fast of over 24 hours is usually required to produce hypoglycaemia and fat mobilisation) they may become hypoglycaemic.[10] Often detailed questioning about the clinical history will disclose what were probably mild hypoglycaemic attacks during childhood. The long chain fatty acid defects can also present with myoglobinuria and rhabdomyolysis after extreme exercise due to the inability of the skeletal muscle to utilise fatty acids for energy production.[11]

The carnitine transporter defect can result in very low cardiac muscle carnitine concentrations causing sudden death with a hypertrophic cardiomyopathy.[12] As most of the fatty acid oxidation defects are treatable disorders, it is very important that they are promptly diagnosed.

Homocystinuria can occur in some disorders due to defects in different enzymes involved in the degradation of homocystine. The "classic" form of the disease is due to a deficiency of cystathionine synthase. This disorder may present in adulthood as late as 40 years of age with myopia, a history of thrombotic episodes, Marfanoid features, and mental retardation.[13] The presence of ectopia lentis is a useful diagnostic sign. As some show a favourable response to vitamin B6 administration it is important to diagnose this disorder at an early stage.

PEROXISOMAL DISORDERS

For many years the role of the peroxisome in mammalian biochemistry remained unknown. The discovery, in the 1970s, that some neurogenetic syndromes were due to defects in metabolic pathways within this organelle led to the recognition of this group of disorders as significant causes of paediatric mortality and morbidity.[14]

Milder forms of disorders such as Zellweger's syndrome and rhizomelic chondrodysplasia punctata exist, but adult onset forms of these disorders have not yet been reported. The most commonly encountered adult onset disease within this group is X linked adrenoleukodystrophy (X linked adrenomyelopathy).[15] The disorder is due to a defect in a peroxisomal membrane protein involved in the first step in the degradation of very long chain fatty acids (VLCFAs)—fatty acids with a chain length>24 carbons. These fatty acids are important components of brain lipids and their accumulation leads to demyelination which, in the childhood onset form, affects the brain, spinal cord, and peripheral nerves. In the adult onset form the brain is spared, the symptoms primarily reflecting demyelination of the spinal cord and peripheral nerves. The affected hemizygous males usually have a more severe presentation than the heterozygous females and the females may often present as "atypical multiple sclerosis".[16]

One important consequence of the accumulation of VLCFAs in the adrenal cortex is the development of adrenal dysfunction. This can present without overt neurological symptoms and if present in a relative of a patient with a demyelinating disease should raise the possibility of X linked adrenoleukodystrophy.[15] All male patients with Addison's disease in whom there is no established cause should be tested

for this disease by measurement of plasma VLCFAs.

LACTIC ACIDAEMIAS

Increased blood lactate occurs in a wide range of acquired and genetic conditions and lacks specificity. In CNS disease often a more specific indicator of inherited disturbances in lactate metabolism is the finding of increased CSF lactate.[17] Increased CSF lactate (>2.2 mmol/l) in the presence of a normal or only marginally increased blood lactate is suggestive of defective lactate metabolism within the CNS.

A useful aid to differential diagnosis is the presence or absence of hypoglycaemia. Hypoglycaemia suggests a defect in glycogen metabolism, gluconeogenesis, or fatty acid oxidation. The absence of hypoglycaemia suggests a defect in the electron transport chain, Kreb's cycle, or pyruvate dehydrogenase[18] although mtDNA depletion disorders may present with hypoglycaemia.[19]

Although to date no patients with adult onset symptoms with pyruvate dehydrogenase deficiency or a Kreb's cycle defect have been reported, many patients have been described with adult onset electron transport chain defects. Classically these present as myopathies with muscle weakness and ophthalmoplegia. However, it is now clear that patients can have a much wider range of clinical symptoms including endocrinological problems (diabetes mellitus, pseudohypoparathyroidism),[20] cardiomyopathy (hypertrophic cardiomyopathy and the Wolf-Parkinson-White conduction defect),[21] Fanconi syndrome,[22] and liver disease.[23] Any patient with multisystem disease, in whom the multiple abnormalities are not explicable as a "domino effect" or sequelae from primary organ dysfunction, should be investigated for an electron transport chain defect. This would require as a minimum the measurement of blood lactate and a blood sample for mitochondrial DNA analysis.

Some of the subunits of the electron transport chain are encoded by the mitochondrial DNA and some point mutations have been clearly associated with certain clinical groups with adult onset. These include Leber's hereditary optic atrophy (LHON), neuropathy ataxia and retinitis pigmentosa (NARP), mitochondrial encephalopathy with lactic acidaemia and stroke-like episodes (MELAS), and myoclonic epilepsy with ragged red fibres (MERRF).[23] Also a large proportion of patients with Kearns-Sayre syndrome and chronic progressive ophthalmoplegia (CPEO) have deletions in the mitochondrial DNA.[24] However, to diagnose these disorders a muscle biopsy is usually required, as the mutated DNA may not be present in an unaffected tissue such as blood or fibroblasts.[25] To detect defects in nuclear encoded electron transport chain subunits a muscle biopsy for enzyme assay is usually required.

DISORDERS OF THE GLYCOGENOLYTIC AND GLYCOLYTIC PATHWAYS

Glycogen catabolism to pyruvate generates ATP, which is used for biosynthetic reactions and for muscle contraction. It is an anaerobic pathway that predominates in type IIb muscle fibres but is also a major pathway in type IIa fibres. A defect in this pathway results in impaired ATP production in muscle manifesting as exercise intolerance and in excess glycogen storage. If the liver pathway is also affected hypoglycaemia or liver disease may also result.

The most commonly recognised adult onset disorder within this group is glycogen storage disease type V (McArdle's disease) which is due to a deficiency of a muscle specific glycogen phosphorylase.[26] It is often associated with a "second wind" phenomenon wherein the pain associated with moderate exercise progressively disappears even if exercise is prolonged. The mechanism for this is not as yet clearly defined; however, it is thought to be related to increased blood flow after ischaemic exercise and to fat mobilisation to provide fatty acids for energy production in muscle. Defects in the enzymes responsible for the activator system for glycogen phosphorylase (for example, phosphorylase b kinase) may also present with muscle weakness although liver disease or cardiomyopathy may also have been noted at some time.[27]

There is an atypical presentation of a glycogen brancher enzyme deficiency called adult polyglucosan body disease. Although in children this disorder presents with liver or muscle disease it presents in these adults with purely neurological symptoms[28] with progressive upper and lower motor neuron disease, sensory loss, neurogenic bladder, and dementia. The CNS has a functional pathway for glycogen catabolism (although glucose cannot be released extracellularly) and these abnormalities may reflect the importance of this pathway in normal CNS function.

There is a range of disorders due to deficiencies in the enzymes of the glycolytic pathway. They present with muscle weakness and exercise intolerance. In some cases, as the gene involved also codes for an erythrocyte enzyme, they may present with haemolytic anaemia.[26]

Phosphofructokinase deficiency (Tauri's disease) overlaps both groups in that whereas the enzyme is part of the glycolytic pathway there is moderate glycogen storage. However, there are no hepatological symptoms and hypoglycaemia is not a feature.

These disorders are usually diagnosed on muscle biopsy by enzyme analysis in a specialist centre. There is a common mutation for McArdle's disease, which may obviate the need for a biopsy if it is detected by DNA analysis of blood.[29] Disorders of the glycolytic pathway which affect erythrocyte as well as muscle function may also be detectable by assays in red cells.

OTHER DISORDERS

Disorders such as Wilson's disease[30] and porphyrias[31] are well established as adult inborn errors of metabolism. However, it is not

always appreciated that Lesch-Nyhan syndrome (hypoxanthine: guanine phosphoribosyl transferase deficiency) may sometimes present with neurological symptoms in adulthood. In these patients the main presenting feature is athetosis without cognitive impairment or behavioural abnormalities.[32] Renal stones may occur due to the insolubility of uric acid.

Cerebrotendinous xanthomatosis is a disorder of bile acid metabolism due to a deficiency of mitochondrial sterol 27-hydroxylase. In the later onset forms the key diagnostic clue is tendon xanthomas.[33]

Diagnosing inborn errors of metabolism in adults

When presented with a patient it is most important to "think metabolic." A history of intermittent attacks triggered by feeding or fasting or some stress factor may suggest a disorder of the urea cycle, amino acid catabolism, or fatty acid oxidation. A slow progressive course may suggest a lysosomal storage disease or a peroxisomal disorder. Often detailed questioning may disclose evidence of problems in childhood or adolescence. A family history may at first not seem revealing; however, the occurrence in members of apparently different symptoms may indicate an inborn error of metabolism the expression of which is modified by environmental or other genetic factors.

Many adults with inborn errors of metabolism have shown mild clinical symptoms at an early age. These often remain unrecognised, particularly if they are relatively "soft" or are intermittent in nature. Even patients with an early onset of progressive diseases may, with appropriate care, plateau out and survive well into adulthood.

Specific neurological signs such as vertical supranuclear ophthalmoplegia or a cherry red spot may suggest a particular metabolic disease. Alternatively there may be abnormalities affecting other organ systems, such as hypertrophic cardiomyopathy, liver disease, or dysmorphic features.

The baseline investigations performed will depend on the clinical features and most can be done in local district general hospital clinical chemistry laboratories. More specialised tests should be sent to the Regional Metabolic Disease Service. The local clinical chemistry laboratory should know the address of the nearest centre and will help with information and specimens requiring shipment. Most specialist centres usually perform analyses for amino acids, organic acids, very long chain fatty acids, some lysosomal enzyme assays, and there is a network of laboratories involved in inborn errors of metabolism that can supply details of addresses for those performing more specialised tests.[34]

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