Inborn errors of metabolism causing epilepsy

SHAMIMA RAHMAN | EMMA J FOOTITT | SOPHIA VARADKAR | PETER T CLAYTON

Clinical and Molecular Genetics and Neurosciences Units, University College London Institute of Child Health, London and Metabolic and Neurosciences Units, Great Ormond Street Hospital for Children NHS Trust, London, UK.

Correspondence to Shamima Rahman at Clinical and Molecular Genetics Unit, University College London Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK.
E-mail: shamima.rahman@ucl.ac.uk

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ABBREVIATIONS

CoQ_{10}	Coenzyme Q_{10}
GAMT	Guanidinoacetate methyl transferase
IEM	Inborn error of metabolism
MoCoF	Molybdenum cofactor
NCL	Neuronal ceroid lipofuscinosis
PDE	Pyridoxine-dependent epilepsy
PLP	Pyridoxal 5′-phosphate
PNPO	Pyridox(am)ine 5′-phosphate oxidase
SUOX	Sulphite oxidase

Seizures may be the first and the major presenting feature of an inborn error of metabolism (IEM), for example in a neonate with pyridoxine-dependent epilepsy. In other IEMs, seizures may be preceded by other major symptoms: by a reduced level of consciousness in a child with an organic acidaemia or urea cycle defect; or by loss of skills, progressive weakness, ataxia, and upper motor signs in a child with a lysosomal storage disorder or peroxisomal leukodystrophy. This review concentrates on those IEMs for which specific treatment is available. The common metabolic causes of seizures vary according to the age at presentation. Features from the history, examination, imaging, and first line biochemical investigations can all provide clues to an inborn error. This review attempts to delineate these and to provide a guide to the specific tests that can be used to make the diagnosis of disorders with specific treatment.

Inborn errors of metabolism (IEMs) are a relatively infrequent cause of epilepsy, but their recognition is of paramount importance because many of these conditions are treatable, particularly those presenting in the neonatal period and in early infancy. Many biochemical and genetic investigations are requested by practising clinicians because of the imperative of not missing a treatable cause of the early onset epileptic encephalopathies. This review is timely because the genetic basis of several treatable metabolic epilepsies has been established in recent years, and experimental treatments are being developed and trialled in some conditions that were previously considered to be untreatable. These treatments include vitamin supplementation, provision of alternative substrates (to bypass a block), and dietary manipulation.

An epileptic seizure has been defined by the International League Against Epilepsy and International Bureau for Epilepsy as a 'transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain'.[1] The same groups defined epilepsy as 'a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition'. Although epilepsy is common, affecting at least 0.5% of the population,[2] the precise prevalence of metabolic epilepsies is unknown, but they are likely to represent a small minority of all causes of epilepsy. However, seizures are a frequent symptom in metabolic disease, having been reported in more than 200 different IEMs, and seizures are a relatively common reason for referral to the metabolic paediatrician or biochemical geneticist. Furthermore, although IEMs are rarely the cause of epilepsy, it is important to recognize and diagnose this group of disorders, since they may be treatable, and there are significant implications for genetic counselling.

The classification of metabolic epilepsies is difficult. Seizures may be characterized by their semiology and electroencephalographic (EEG) features, although epilepsies in IEMs are associated with multiple, usually generalized, seizure types. The most recent International League Against Epilepsy Commission on Classification and Terminology proposes 'structural/metabolic' as an aetiology group for conditions or diseases that have been demonstrated to be associated with a substantially increased risk of developing epilepsy, including disorders of genetic origin.[3] A more practical way of considering the metabolic epilepsies is by age at presentation (Table I), and in this review we consider those epilepsies that present in the neonatal period and first 6 months of life; those that more often present in late infancy and early childhood; and, finally, metabolic epilepsies presenting in later childhood and adolescence. There is, of course, considerable overlap between these groups. We recently reviewed mitochondrial epilepsies in a companion article in this journal,[4] and so will not discuss them in great detail here, but will indicate which mitochondrial epilepsies may present at particular ages.

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PATHOGENESIS

The large number of IEMs associated with epilepsy may be explained by the plethora of different disease mechanisms that may trigger seizures. In some patients electrolyte disturbance may lead to seizure generation, particularly in disorders associated with hyponatraemia, hypocalcaemia, or hypomagnesaemia. In other cases seizures may occur at times of acute metabolic decompensation due to hypoglycaemia (e.g. fat oxidation disorders, glycogen storage diseases, and disorders of gluconeogenesis) or hyperammonaemia (e.g. urea cycle disorders or organic acidaemias). Other pathogenic mechanisms associated with seizure generation include deficiency of a vitamin or cofactor (such as pyridoxal phosphate, 5-methyltetrahydrofolate, biotin, or coenzyme Q_{10} [CoQ_{10}]), cerebral energy deficiency (as in glucose transporter defects, disorders of creatine biosynthesis or transport, and mitochondrial respiratory chain deficiencies), chemical disruption of neurotransmission (ion channel disorders and defects of neurotransmitter synthesis or recycling), or physical disruption of neural networks as a result of brain malformations or IEMs with cerebral accumulation of abnormal storage material. Finally, seizures may be triggered by direct neurotoxicity of accumulating intermediates, as in untreated phenylketonuria.

EPILEPTIC ENCEPHALOPATHY PRESENTING IN THE NEONATAL PERIOD AND EARLY INFANCY

Seizures occur in 1 in 1000 live births, and the most common cause is hypoxic–ischaemic encephalopathy. However, some newborn infants are in a poor condition at birth because they have an underlying inborn error of metabolism so, if seizures are persistent and difficult to treat with conventional antiepileptic drugs (AEDs), the neonatologist should consider whether hypoxic–ischaemic encephalopathy is the primary problem or whether there could be an underlying IEM. Clinically, a semiology of infantile spasms or myoclonic seizures, or, electrographically, hypsarrhythmia or burst suppression, should always suggest careful consideration of an IEM. Abnormal intrauterine movements (fluttering or hiccoughs) can also be a pointer to a metabolic disorder.

What this paper adds

- This paper provides a concise summary of the major inborn errors of metabolism (IEMs) which may present with epilepsy, categorized by age at presentation.
- An overview of key clinical, biochemical, and genetic diagnostic features to aid differential diagnosis is presented.
- Most importantly, this article emphasizes the *treatable* IEMs causing epilepsy and provides information about appropriate medications, doses, and routes of administration.

Treatable disorders

Pyridoxine-dependent epilepsy

Pyridoxine-dependent epilepsy (PDE) due to antiquitin deficiency (α-amino adipic semialdehyde [α-AASA] dehydrogenase deficiency; OMIM 266100) is an inborn error of lysine catabolism that results in a secondary deficiency of vitamin B6 due to adduct formation between Δ1-piperideine-6-carboxylate and pyridoxal 5′-phosphate (PLP), the active form of vitamin B6 in humans.[5,6] Patients with this disorder typically present in the first days of life with a severe seizure disorder that is resistant to treatment with conventional anticonvulsant medications but responsive to treatment with pyridoxine. Often the infant is in poor condition at delivery and the seizure disorder may be accompanied by multisystem symptomatology such as metabolic acidosis, electrolyte disturbance, abdominal distension, and feed intolerance, resulting in misdiagnosis as hypoxic–ischaemic encephalopathy or sepsis.[7] Frequent multifocal and generalized myoclonic jerks are observed in PDE, often intermixed with tonic symptoms, abnormal eye movement, grimacing, or irritability.[8]

Although in most instances PDE responds quickly and completely to pyridoxine, any child with a resistant epileptic encephalopathy should undergo an adequate treatment trial of vitamin B6 (see recommended doses below) accompanied

Table I: Classification of metabolic epilepsies according to age at presentation

Neonatal period to early infancy	Late infancy to early childhood	Late childhood to adolescence
PDE	Creatine synthesis defects	CoQ_{10} deficiency
PNPO deficiency	Infantile and late infantile NCL	Lafora body and Unverricht–Lundborg disease
Folinic acid responsive seizures	Mitochondrial disorders (Alpers syndrome and others)	MERRF
Biotinidase deficiency	Sialidosis	MELAS
GLUT1 deficiency	Gangliosidosis	*POLG*-related disease: MIRAS, SCAE, MEMSA
Non-ketotic hyperglycinaemia	Milder variants of PDE and PNPO deficiency	Juvenile NCL
Serine biosynthesis defects	Congenital disorders of glycosylation	Late onset GM2 gangliosidosis (Sandhoff, Tay–Sachs)
Molybdenum cofactor and sulphite oxidase deficiencies		Gaucher type III
Menkes disease		Niemann–Pick type C
Disorders of peroxisome biogenesis and β-oxidation		Peroxisomal disorders
Congenital disorders of glycosylation		
Cathepsin D deficiency (congenital NCL)		

PDE, pyridoxine-dependent epilepsy; CoQ_{10}, coenzyme Q_{10}; PNPO, pyridox(am)ine 5′-phosphate oxidase; MERRF, myoclonic epilepsy with ragged-red fibres; MELAS, mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes; GLUT1, glucose transporter across the blood–brain barrier; *POLG*, gene encoding catalytic subunit of DNA polymerase gamma; MIRAS, mitochondrial recessive ataxia syndrome; SCAE, spinocerebellar ataxia with epilepsy; MEMSA, myoclonus, epilepsy, myopathy, sensory ataxia; NCL, neuronal ceroid lipofuscinosis.

by EEG recording, as some patients do not show a dramatic initial response, probably because of multiple contributing pathologies. Treatment should initially be commenced in an intensive care setting as these infants are vulnerable to apnoea, profound hypotonia, and hypotension. Following a single 100mg dose of intravenous pyridoxine, seizures will usually stop, and our practice is to follow this up with a maintenance dose of 5 to 15mg/kg/day in two divided doses; however, higher doses (15–30mg/kg/d) have been recommended by an international study group.[9] Seizures, which are of multiple types in children with PDE, will respond to both pyridoxine and PLP, although pyridoxine tends to be used as the first-line treatment in the UK as there is more experience of its use and it is available in both intravenous and oral formulations. Pyridoxine treatment has been associated with peripheral neuropathy; thus, annual monitoring of nerve conduction is recommended in children who can cooperate. Clinicians should aim to reduce pyridoxine to the lowest effective dose if there is any evidence of abnormality on neurophysiological testing or clinical symptoms. Our experience suggests that, to minimize the risk of neuropathy, in most cases treatment with pyridoxine should not exceed a total daily dose of 200mg in children.

Diagnostic confirmation of PDE is by measurement of elevated α-AASA in urine and/or plasma and cerebrospinal fluid (CSF). This can be done while the child is taking vitamin B6 and thus should not delay commencement of treatment. Other investigations which may be suggestive of the diagnosis include plasma and CSF amino acids, CSF monoamine metabolites, and CSF PLP (Table II). PDE should also be considered in children who show an initial response to AEDs but subsequently become drug resistant, as they may represent the atypical later-onset group.

In the long term, treated children with PDE remain seizure-free, although some have breakthrough fits during periods of intercurrent infection and fever.[7] In some children it has proved helpful to double the regular dose of pyridoxine during the first few days of a febrile illness to prevent seizures. Mild to moderate learning difficulty is common, with speech and language development being particularly impaired.

Pyridox(am)ine 5′-phosphate oxidase deficiency

Pyridox(am)ine 5′-phosphate oxidase (PNPO) is essential for the synthesis of PLP.[6] Deficiency of this enzyme (OMIM 610090) has been described in only a small number of families worldwide and typically results in a severe neonatal seizure disorder which responds to treatment with PLP. Often infants with PNPO deficiency are born preterm and there may be a family history of infertility and recurrent miscarriage. Seizures are similar to those seen in PDE, with prolonged episodes of mixed multifocal myoclonic–tonic symptoms often associated with grimacing and abnormal eye movements.[8] Alongside clinical clues and an EEG burst suppression pattern, diagnosis of this disorder is suggested by secondary changes in plasma and CSF amino acids, together with reduced CSF PLP and monoamine metabolites (Table II). The diagnosis may be confirmed by mutation analysis of the *PNPO* gene.[10]

Outcome in the first described cases was poor, with a high mortality in the first weeks of life. However, increased awareness of the disorder and prompt diagnosis has subsequently revealed an expanded phenotype, with some children presenting with a comparatively mild seizure disorder beyond the neonatal period and some surviving into adulthood.

Treatment is with PLP, which is currently available in an oral formulation only; doses between 10 and 30mg/kg/day in divided doses have been successful in controlling seizures. As with initiation of pyridoxine treatment, the first doses of PLP should be given in an intensive care setting because of the risk of respiratory and cardiovascular collapse. In the long term it is recommended that children on PLP be monitored with liver ultrasonography and liver function tests. This is based on the observation that PLP treatment has been associated with liver damage in a single patient with PNPO deficiency (it has not been firmly established that PLP, or the specific formulation of PLP, was responsible for the patient's liver damage). Prenatal diagnosis of PNPO deficiency has been undertaken, and parents who had previously lost a child as a result of severe neonatal epileptic encephalopathy opted for termination (unpublished observation); in theory, prenatal treatment would be an alternative but there are no data on the outcome of this approach.

Folinic acid-responsive seizures

Folinic acid-responsive seizures were first described in a group of neonates with onset of seizures (myoclonic or clonic) in the first 5 days of life, associated with irritability and white matter abnormalities on brain magnetic resonance imaging (MRI). These infants also shared a characteristic unidentified 'peak' on the CSF high-performance liquid chromatogram and all responded, to a variable degree, to folinic acid. Subsequently, other infants fulfilling these criteria have been identified whose seizures responded to pyridoxine and who have been diagnosed with antiquitin deficiency, with elevated α-AASA and pathogenic mutations in the antiquitin gene. Thus, folinic acid-responsive seizures and PDE due to antiquitin deficiency are now understood to be biochemically and genetically identical. The 'peak' on high-performance liquid chromatogram remains unidentified.[9,11]

Multiple carboxylase deficiency due to biotinidase or holocarboxylase synthetase deficiency

Both inherited disorders, biotinidase deficiency (OMIM 253260) and holocarboxylase synthetase (HCS) deficiency (253270), affect the vital coenzyme function of biotin. This results in reduced activity of all four biotin-dependent carboxylases (acetyl-CoA carboxylase, pyruvate carboxylase, propionyl-CoA carboxylase, and 3-methylcrotonyl-CoA carboxylase) and a clinical picture characterized by neurological disease including seizures, often infantile spasms.[12] Other typical symptoms include ataxia, hypotonia, encephalopathy, and skin manifestations including alopecia and a generalized or perioral eczematous rash. Age at presentation is extremely variable, as is the pattern of symptoms; however, many patients present in the first months of life. Biochemical investigation in symptom-

Table II: Investigation of metabolic epilepsies

Investigation	Abnormality	Disorder
Routine clinical chemistry		
Glucose	Low	Fat oxidation disorders Glycogen storage diseases Disorders of gluconeogenesis
Calcium	Low	Disorders of calcium homeostasis Renal tubulopathy PDE
Magnesium	Low	Disorders of magnesium transport Renal tubulopathy PDE
Ammonia	High	Urea cycle disorders Organic acidaemias
Lactate	High	PDHc deficiency Mitochondrial respiratory chain defects Biotinidase deficiency Lipoic acid synthetase deficiency
Liver function	Abnormal	May suggest Alpers or another hepatocerebral mtDNA depletion syndrome Disorders of *N*-glycosylation
Creatine kinase	High	Dystroglycanopathies
Specialised investigations in blood		
Plasma amino acids	High glycine High glycine and threonine Low serine Low glutamine High phenylalanine High proline	NKH; Lipoic acid synthetase deficiency PNPO deficiency; PDE Serine biosynthesis disorders Glutamine synthase deficiency Untreated phenylketonuria Hyperprolinaemia type II
Urate	Low	MoCoF deficiency
Copper and caeruloplasmin	Low	Menkes syndrome
Plasma VLCFA	High	Zellweger syndrome Other peroxisomal disorders
Pristanic acid	High	Alpha methyl-acyl-CoA racemase deficiency
Plasma biotinidase activity	Low	Biotinidase deficiency
Serum transferrin isoelectric focusing	Abnormal transferrin glycoforms	Congenital disorders of glycosylation
White cell CoQ_{10}	Low	Disorders of CoQ_{10} biosynthesis; secondary deficiency in some mitochondrial disorders
Vacuolated lymphocytes	Present	Lysosomal storage disorders, including late infantile and juvenile NCL
Metabolic investigations in urine		
Organic acids	Vanillactate Specific organic acids Krebs cycle intermediates	PNPO deficiency Organic acidaemias, e.g. D and L-2-hydroxyglutaric acidurias, cobalamin C deficiency (form of methylmalonic aciduria); biotinidase/HCS deficiencies Krebs cycle disorders; mitochondrial respiratory chain defects
Sulphite and sulphocysteine	High	SUOX deficiency MoCoF deficiency
Guanidinoacetic acid	High Low	GAMT deficiency AGAT deficiency
Creatine	Low High	GAMT and AGAT deficiencies Creatine transporter deficiency
Alpha-aminoadipic semialdehyde	High	PDE; MoCoF and SUOX deficiencies
Purine/pyrimidine screen	Hypoxanthine Succinyladenosine	MoCoF deficiency Adenylosuccinate lyase deficiency

Table II: Continued

Investigation	Abnormality	Disorder
Investigations in CSF (with paired blood sample)		
Glucose	Low CSF: blood glucose ratio <0.4	GLUT1 defect
Lactate	High	Mitochondrial respiratory chain disorder PDHc deficiency
Amino acids	High glycine CSF: plasma glycine ratio >0.06 (normal <0.04)	NKH
	Low serine	Disorders of serine biosynthesis
	High threonine and glycine	PNPO deficiency, PDE
Pyridoxal 5′-phosphate	Low	PNPO deficiency, PDE
5-Methyltetrahydrofolate	Low	Dihydrofolate reductase deficiency Folate receptor defect Kearns–Sayre syndrome Other mitochondrial disorders May be low in serine biosynthesis disorders and methylene tetrahydrofolate reductase deficiency
Neurotransmitter amine metabolites (HVA and 5-HIAA)	Low	PNPO deficiency, PDE
3-Methoxytyrosine	High	PNPO deficiency, PDE

PDE, pyridoxine-dependent epilepsy; PDHc, pyruvate dehydrogenase complex; mtDNA, mitochondrial DNA; NKH, non-ketotic hyperglycinaemia; PNPO, pyridox(am)ine 5′-phosphate oxidase; VLCFA, very long-chain fatty acid; CoQ_{10}, coenzyme Q_{10}; NCL, neuronal ceroid lipofuscinosis; HCS, holocarboxylase synthetase; SUOX, sulphite oxidase; MoCoF, molybdenum cofactor; GAMT, guanidinoacetate methyl transferase; AGAT, arginine–glycine amidinotransferase; CSF, cerebrospinal fluid; GLUT1, glucose transporter across the blood–brain barrier; HVA, homovanillic acid; 5-HIAA 5-hydroxy indoleacetic acid.

atic patients usually shows lactic acidosis and a characteristic organic aciduria, although some patients do not have these features present.[13] Diagnosis is confirmed by measurement of serum enzyme activity in biotinidase deficiency and by mutational analysis or lymphocyte or fibroblast carboxylase activity in HCS deficiency. Screening of newborn infants for biotinidase deficiency is performed in some countries.[12]

All patients with biotinidase deficiency and most with HCS deficiency respond excellently to oral biotin. Delay in treatment will result in irreversible neurological disease; thus, a treatment trial of 5 to 10mg oral biotin daily is justified in any child with an unexplained neurological disorder including seizures, pending confirmatory diagnostic investigations. This is particularly true in unscreened populations such as in the UK.[14]

GLUT1 deficiency syndrome

GLUT1 is a membrane transporter that facilitates glucose transport across the blood–brain barrier. Defective GLUT1 (OMIM 606777) results in cerebral deficiency of glucose, the vital source of energy for brain metabolism, and a low CSF glucose concentration. The phenotype of this IEM is expanding with classical early onset seen before 2 years of age, later onset between 2 and 10 years, and a non-classical form with mental retardation* and movement disorder but no epilepsy.[15,16] Familial transmission has been reported. In classical early-onset GLUT1 deficiency the neonatal period may be normal and breastfeeding may be protective. Seizures are the main presenting symptom, with 79% of all first seizures occurring in the first 6 months of life. Semiology is often of cyanotic attacks or of eye movement seizures which may be mistaken for opsoclonus–myoclonus. The interictal EEG may be normal. The ictal EEG may show focal slowing or discharges, including 2.5 to 4 Hz spike and wave. A striking difference between pre- and postprandial EEG may be seen, with a decrease in epileptic discharges following carbohydrate intake. GLUT1 deficiency is now known to be a cause of drug-resistant childhood absence epilepsy and of adult-onset absence epilepsy with a normal CSF glucose.

A lumbar puncture, preferably while fasting, to demonstrate hypoglycorrhacia is the first step in diagnosis. CSF glucose is typically less than 2.5mmol/L, although values greater than this have been reported. The ratio of CSF to plasma glucose is particularly important, so a non-stressed (again, preferably, fasting) plasma glucose should be taken before the lumbar puncture. In the absence of central nervous system (CNS) infection, a CSF to blood ratio of less than 0.5 is diagnostic. CSF lactate is normal or low. The degree of hypoglycorrhacia and absolute 'cut-off' for a diagnosis of GLUT1 deficiency remain a source of debate, and mild clinical phenotypes have been reported with normoglycorrhacia and a normal CSF to blood glucose ratio; thus molecular genetic analysis of the *SLC2A1* gene is considered the standard criterion for diagnosis.[16] Approximately 80% of patients harbour pathogenic mutations. As GLUT1 is the predominant glucose transporter in red blood cells, reduced erythrocyte glucose uptake may also be indicative of reduced glucose transport into the CNS. However, this investigation is not routinely available and may give false-negative results in mild cases.[17]

*UK usage: learning disability

Epilepsy in GLUT1 deficiency is drug resistant and may be aggravated by fasting and by AEDs that inhibit GLUT1 (phenobarbitone, valproate, diazepam). GLUT1 deficiency is eminently treatable with the ketogenic diet, which should be commenced at the earliest opportunity and continued until at least adolescence, when the energy demands of the brain decrease. This high-fat, low-carbohydrate diet provides an alternative source of energy for the brain as ketone bodies, which are produced in the liver and which can easily penetrate the blood–brain barrier. In the vast majority of patients the ketogenic diet is successful at controlling seizures, allowing withdrawal of AEDs.[18] Seizures are controlled at lower blood levels of β-hydroxybutyrate than are needed to nourish the brain.

Organic acidurias, aminoacidopathies, and urea cycle defects

In general, these disorders give rise to episodes of acute encephalopathy in which seizures may occur as brain intoxication progresses. There are usually associated features of systemic metabolic decompensation such as acidosis, ketonuria, and hyperammonaemia. Diagnosis is made on the basis of analysis of urine organic acids, blood spot acylcarnitine profile, and plasma and urine amino acids. A discussion of the treatment of these disorders is beyond the scope of this review, but many specific forms of treatment are available and if instituted early will prevent death and severe neurological damage.

Disorders with novel/experimental therapies

Non-ketotic hyperglycinaemia (neonatal type)

The typical neonatal form of non-ketotic hyperglycinaemia (OMIM 605899) presents within the first days of life following an apparently symptom-free period. A severe clinical picture evolves that is characterized by seizures, lethargy, encephalopathy, profound hypotonia, and hiccoughs. Respiration becomes irregular, often progressing to apnoea necessitating ventilation. EEG usually shows a burst suppression pattern which, in combination with the clinical features, is very suggestive of the diagnosis. Some patients have structural brain abnormalities on MRI, including dysgenesis of the corpus callosum and gyral abnormalities.[19]

This devastating disorder is caused by a defective glycine cleavage protein, which is a multienzyme complex that degrades glycine in the CNS. If the diagnosis is suspected, plasma and CSF amino acids should be measured and will reveal grossly elevated glycine, in particular an increased CSF to plasma ratio.[20] It should be noted that sodium valproate therapy may also lead to increased glycine levels, although usually to a far lesser degree than is observed in non-ketotic hyperglycinaemia.[20]

Untreated, the neonatal form of non-ketotic hyperglycinaemia is associated with death in the first months of life.[20] Therapy with sodium benzoate and dextromethorphan may be helpful in some milder forms of the disease, alongside AEDs and general supportive care.[21] The epilepsy remains drug resistant, infantile spasms may emerge, and the EEG evolves to hypsarrhythmia or multifocal discharges on a background without normal activity.

Serine biosynthesis defects

Seizures are a major feature of the clinical presentations of both 3-phosphoglycerate dehydrogenase deficiency (OMIM 601815) and phosphoserine aminotransferase deficiency (OMIM 610936).[22,23] Microcephaly is present at birth or acquired in early infancy. Infants are hypertonic and show severe developmental delay. The epilepsy is often characterized by infantile spasms and EEG hypsarrhythmia, and subsequent evolution to a Lennox–Gastaut syndrome has been reported.[24] CSF amino acids should be analyzed after a 6-hour fast and in affected individuals show a low concentration of serine, often with a low glycine. Concentrations of these amino acids may also be low in plasma. To control seizures and improve the outcome, treatment with serine (usually together with glycine) must be started soon after birth. The best outcome with 3-phosphoglycerate dehydrogenase deficiency has been achieved when an affected infant was treated in utero.[25] A more recent report described two siblings with a milder clinical phenotype of late childhood-onset absence epilepsy with typical EEG 3 Hz spike–wave complexes, who had learning difficulties but normal head circumference.[26]

Molybdenum cofactor and sulphite oxidase deficiencies

Molybdenum is an essential cofactor for three enzymes in humans: xanthine dehydrogenase, sulphite oxidase, and aldehyde oxidase. Patients with molybdenum cofactor (MoCoF) deficiency (OMIM 252150) are deficient in the activity of all three enzymes; the clinical phenotype is characterized by a severe seizure disorder with onset in the first days of life, with dystonia and developmental delay, and the disease usually results in death in early childhood.[27] Equally, seizures may be absent and the movement disorder mistaken for epilepsy, AEDs being symptomatically useful for either. Burst suppression may be seen on the EEG. The underlying disease process is poorly understood; however, toxic accumulation of endogenous sulphite is the most likely pathogenic mechanism. A suspected diagnosis is confirmed by finding reduced plasma urate, the presence of sulphite or sulphocysteine in the urine, and a characteristic urinary purine profile in which uric acid is replaced by xanthine.[28] Hypohomocystinaemia has also been reported in some cases.[29] Isolated sulphite oxidase (SUOX) deficiency (OMIM 272300) results in an identical clinical phenotype to MoCoF deficiency and can be differentiated on the basis of biochemical investigations which, in contrast to MoCoF deficiency, show normal plasma urate and urinary purine profile. Genetic confirmation is also possible. Elevated urinary α-AASA characteristically associated with antiquitin deficiency, has also recently been described in both MoCoF and SUOX deficiency.[30]

Up to two-thirds of patients with MoCoF deficiency have a proximal defect in the pathway of molybdenum cofactor synthesis, resulting in the failure to convert GTP to cyclic pyranopterin monophosphate. This disease type, 'type A', is potentially amenable to a new therapy and should be identified by mutation analysis of the *MOCS1* gene.[31] Treatment of 'type A' MoCoF using purified intravenous cyclic

pyranopterin monophosphate has shown early promise with a reduction in seizures and improved developmental progress, as well as correction of biochemical abnormalities.[32] However, experience with this experimental treatment is currently limited to only a few patients. This treatment is likely to be of benefit only when commenced early in life, before permanent neurological damage ensues; thus, prompt diagnosis is of utmost importance, particularly in families who are known to harbour pathogenic mutations. Furthermore, patients with MoCoF deficiency 'type B', who have a more distal defect in molybdenum cofactor synthesis (molybdopterin synthase, encoded by *MOCS2*), will not benefit from this treatment.

Unfortunately, no definitive treatment is available for SUOX deficiency, which is managed primarily with supportive treatment for epilepsy and neurodisability. Attempts at treatment with a diet restricted in sulphur-containing amino acids (methionine and cysteine) have been largely unsuccessful.[33]

Menkes disease

Menkes disease (OMIM 309400) is an X-linked recessive disorder of copper metabolism that characteristically presents with seizures and hypotonia in male infants during the first few months of life. Patients with this neurodegenerative disease may also encounter clinical problems related to collagen abnormalities such as vascular tortuosity and bladder diverticulae, which may result in infection. Clinical clues to Menkes disease include skin laxity, hypothermia, and a particular facial appearance with 'sagging' cheeks and frontal bossing. The characteristic hair abnormality 'pili torti', which is eventually present in all patients, may also be very helpful in making the diagnosis.[34,35]

Copper is essential for the normal functioning of several copper-containing enzymes, many of which have their action in the CNS. In Menkes disease, a defective ATP7A protein results in reduced copper efflux into the circulation from intestinal enterocytes and therefore reduced copper availability for dependent enzymatic processes. A reduced level of serum copper and serum caeruloplasmin is very suggestive of the diagnosis and an abnormal ratio of urinary dopamine to noradrenaline (indicative of reduced activity of the copper dependent enzyme, dopamine β-hydroxylase) further supports this. Mutational analysis of the *ATP7A* gene is required for confirmatory diagnosis.[36]

The electroclinical syndrome has been characterized as early focal status precipitated by fever with ictal runs of slow and slow spike–wave posteriorly, evolution to infantile spasms with modified hypsarrhythmia later in the first year of life and then, in early childhood, multifocal seizures, tonic spasms, and myoclonus with multifocal high-amplitude discharges mixed with slow activity.[37]

Untreated, Menkes disease is life-limiting, with patients seldom surviving beyond 3 to 4 years. Therapy with subcutaneous injections of copper histidine has prolonged life expectancy in some patients in whom it was started early (first months of life), but it appears to have little impact on the neurological outcome.[36]

Other disorders

Peroxisomal disorders

Neonatal-onset epilepsy that is difficult to control with AEDs can be a major presenting feature of disorders of peroxisome biogenesis (Zellweger syndrome; OMIM 214100) and disorders of peroxisomal β-oxidation. An affected newborn infant is hypotonic, and patients with Zellweger syndrome have characteristic dysmorphic features including large fontanelle, high forehead, shallow supraorbital ridges, low-set posteriorly rotated ears, and small chin. The electroretinogram (ERG) is frequently markedly reduced or absent. Skeletal radiology may show punctate calcification of cartilage, small renal cysts may be apparent on ultrasound, and liver function tests may be abnormal, sometimes with clinical jaundice. Plasma very long chain fatty acids are elevated. Areas of polymicrogyria are often frontal or opercular, resulting in a focal EEG and seizure semiology, and there are often focal motor seizures.[38]

Neonatal-onset mitochondrial epilepsies

Neonatal-onset seizures are a relatively unusual initial presentation of mitochondrial disease. Neonatal mitochondrial epileptic encephalopathies are usually devastating diseases, often associated with multiorgan failure. In fact, involvement of multiple seemingly unrelated organs may alert the clinician to the possibility of an underlying mitochondrial disorder. These disorders are typically unresponsive to treatment, with the possible exception of CoQ_{10} deficiency (OMIM 607426).[39,40] Infants with *RARS2* mutations (OMIM 611523), causing defective mitochondrial protein synthesis,[41] may present with profound lactic acidosis on the first day of life.[42] The lactic acidosis may subsequently resolve, but the clinical course is severe, with intractable epilepsy and developmental stasis. This diagnosis should be suspected in any infant with pontocerebellar hypoplasia on MRI brain scan, particularly if there is associated lactic acidosis.[42]

Infants with mutations in *SLC25A22* (OMIM 609304), which encodes the mitochondrial glutamate transporter, present in the neonatal period with intractable myoclonic seizures with burst suppression on the EEG and low amplitude visual evoked potentials.[43] The ERG may also be abnormal. Serial MRI shows brain atrophy. Mitochondrial oxidation of glutamate is impaired but there is no readily available metabolite or enzyme test to facilitate diagnosis of this disorder. Muscle biopsy is needed to diagnose other mitochondrial epilepsies presenting in the neonatal period, as discussed by Rahman (2012).[4]

Within the past 2 years, three disorders have been described that affect the synthesis of lipoic acid or its incorporation into mitochondrial enzymes (pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, and the glycine cleavage enzyme). One of these disorders, lipoic acid synthetase deficiency presented with neonatal seizures (which were unilateral, associated with oral automatisms and initially controlled with phenobarbitone) and hypotonia, followed by progressive encephalopathy and apnoea. Blood lactate and plasma glycine were elevated. Proteins which are normally lipoylated showed reduction in incorporation of the prosthetic group.[44]

Disorders of protein O-glycosylation

The dystroglycanopathies can present in the newborn period with congenital muscular dystrophy (weakness, hypotonia, and moderately elevated creatine kinase), seizures, and ocular abnormalities. Imaging may show lissencephaly and other brain malformations. The diagnosis is usually made by muscle biopsy.

Adenylosuccinate lyase deficiency

This disorder of purine metabolism (OMIM 608222) can present in the neonatal period with severe seizures and hypotonia. An affected infant may also show signs of intrauterine growth retardation and microcephaly. Diagnosis depends on the identification of abnormal purine metabolites in the urine.

Cathepsin D deficiency

Cathepsin D deficiency (OMIM 610127) has been reported in two families with congenital neuronal ceroid lipofuscinosis (NCL), presenting with microcephaly and intractable seizures,[45] and in another child, who presented at school age.[46] Affected infants with the congenital disorder presented with microcephaly from birth (with a history of deceleration of head growth in the last trimester and abnormal fetal movements suggestive of in utero seizures), and intractable neonatal seizures leading to death by 10 days of age. Diagnosis involves demonstration of abnormal storage material, assay of cathepsin D, and mutation analysis of the *CTSD* gene. Currently there are no effective treatments for cathepsin D deficiency, or for any of the NCL disorders.

GABA transaminase deficiency

4-Aminobutyrate aminotransferase (GABA transaminase) deficiency (OMIM 613163) is a rare cause of neonatal-onset seizures and has been reported in three families to date.[47–49] Consistent clinical features are intractable seizures, severe psychomotor retardation, hypotonia, hyperreflexia, and accelerated linear growth. A spongy leukodystrophy was observed in two individuals in whom neuropathology was performed. Diagnosis can be made by demonstrating elevated levels of GABA in the CSF or on proton magnetic resonance spectroscopy of the brain; by enzyme assay in cultured lymphocytes; and by molecular analysis of the responsible gene *ABAT*. There is no effective treatment.

METABOLIC EPILEPSY PRESENTING IN LATE INFANCY AND EARLY CHILDHOOD

Treatable disorders

Disorders of creatine biosynthesis and transport

Three disorders of creatine metabolism have been described: guanidinoacetate methyl transferase (GAMT) deficiency (OMIM 612736) and arginine–glycine amidinotransferase deficiency (OMIM 612718), both of which are recessively inherited, and the X-linked cerebral creatine transporter defect (OMIM 300352). All may be associated with epilepsy, but seizures are most prominent in GAMT deficiency. This is probably because two disease mechanisms are at play in GAMT deficiency: cerebral energy deficiency (in common with arginine–glycine amidinotransferase and creatine transporter deficiencies) but also a direct neurotoxic effect of guanidinoacetate, the accumulating metabolite in GAMT deficiency.[50] Seizures occur in over 90% of patients with GAMT deficiency, and are typically of multiple types including myoclonic, generalized tonic–clonic, partial complex, head nodding, and drop attacks.[51] Diagnosis may be achieved by demonstrating low cerebral creatine levels on magnetic resonance spectroscopy; by measuring guanidinoacetate, creatine, and creatinine levels in plasma and urine; and by molecular analysis of the three responsible genes (*GAMT*, *GATM*, and *SLC6A8* for the GAMT, arginine–glycine amidinotransferase, and transporter defects respectively). Treatment with oral creatine monohydrate is sufficient to restore cerebral creatine levels, but dietary arginine restriction is additionally required in GAMT deficiency to reduce guanidinoacetate accumulation. Recent studies have indicated that ornithine supplementation, in addition to creatine supplementation and arginine restriction, improves clinical outcomes in GAMT deficiency.[52]

Cerebral folate deficiency

Several disorders of folate metabolism and transport have been reported,[53] often associated with megaloblastic anaemia and/or hyperhomocystinaemia. Recently, two defects of folate metabolism have been shown to cause prominent seizures. Mutations in the *FOLR1* gene encoding the folate receptor α (OMIM 613068), the major folate transporter across the blood–CSF barrier, have been reported in four families.[54–56] Patients presented with progressive ataxia and seizures (myoclonic epilepsy and generalized tonic–clonic seizures) in the second year of life. Deficiency of dihydrofolate reductase (OMIM 613839), the enzyme responsible for catalysing the conversion of dihydrofolate to tetrahydrofolate, causes cerebral folate deficiency with generalized tonic–clonic and focal seizures and megaloblastic anaemia or pancytopenia.[57,58] Both the folate receptor α and deficiencies of dihydrofolate reductase are associated with virtually undetectable levels of 5-methyltetrahydrofolate in CSF, and clinical and biochemical responsiveness to oral folinic acid supplementation. Cerebral folate deficiency has also been linked to the presence of autoantibodies against the folate receptor in CSF, and may occur as a secondary phenomenon in other IEMs including disorders of serine biosynthesis and mitochondrial disorders, particularly Kearns–Sayre syndrome caused by single mitochondrial DNA (mtDNA) deletions.[59]

Disorders of coenzyme Q_{10} biosynthesis

Disorders of CoQ_{10} biosynthesis represent the most treatable mitochondrial disorders. Many present in infancy with a multisystem syndrome including epilepsy, frequently associated with sensorineural hearing loss and a prominent steroid-resistant nephropathy. Other neurological features in these patients include nystagmus, ataxia, spasticity, and dystonia. Mutations in five genes (*COQ2*, *PDSS1*, *PDSS2*, *COQ9*, and *COQ6*) have so far been reported to cause infantile onset of CoQ_{10} deficiency.[60] Treatment is with oral CoQ_{10} supple-

mentation; 10 to 30 mg/kg/day in three divided doses is usually sufficient. The best outcome in this disorder was reported in a female who was diagnosed early because of an affected older sibling, and in whom treatment was initiated at the first manifestation of disease.[61]

Pyruvate dehydrogenase deficiency

Males with the X-linked form of pyruvate dehydrogenase complex (PDHc) deficiency usually present with Leigh syndrome (OMIM 308930), but females who are heterozygous for a severe mutation in the *PDHA1* gene can present in the first 6 months of life with infantile spasms, an EEG showing hypsarrhythmia, and developmental regression (West syndrome), or just with severe myoclonic seizures (OMIM 312170). MRI may show periventricular multicystic leukoencephalopathy and agenesis of the corpus callosum. CSF lactate is often elevated, usually with an elevation of blood lactate, and fibroblast studies show reduced pyruvate dehydrogenase complex activity. Some cases of pyruvate dehydrogenase complex deficiency respond well to treatment with thiamine and/or a ketogenic diet, and this response can include a reduction in seizure severity.[62]

Peroxisomal disorders

In males with X-linked adrenoleukodystrophy (OMIM 300100), other problems usually become evident before epilepsy: changes in behaviour, perceptive, and intellectual difficulties, expressive and motor difficulties, and visual disturbances. However, in one large series, 20 out of 485 individuals presented with seizures: focal seizures in six males and generalized in the remainder, with four having status epilepticus.[63] A careful history may identify symptoms attributable to adrenal insufficiency such as weakness and tiredness, anorexia, vomiting with diarrhoea or constipation, and crises with abdominal pain, vomiting, and dehydration, and examination may reveal pigmentation of mucous membranes. The disorder is caused by mutations in the *ABCD1* gene, which impair peroxisomal β-oxidation, resulting in the accumulation of very long-chain fatty acids in plasma. It has been suggested that presymptomatic patients may benefit from early intake of oleic and erucic acids (combined in a 4:1 ratio in Lorenzo's oil) in addition to very long-chain fatty acid restriction,[64] but this has not been confirmed in other studies. Adrenal hormone replacement is necessary in all patients with adrenal insufficiency. Haematopoietic stem cell transplantation should be considered in males who develop MRI abnormalities, since this treatment can arrest the cerebral demyelination.[65] Haematopoietic stem cell transplantation is not carried out routinely in all presymptomatic cases, since some affected individuals may never develop progressive cerebral disease. Serial brain MRI is therefore extremely important in determining the need for and optimal timing of haematopoietic stem cell transplantation.

Hyperprolinaemia type II

This disorder (OMIM 239510) results from a deficiency of Δ1-pyrroline 5-carboxylate dehydrogenase and is characterized by elevated plasma proline and increased urinary excretion of proline, hydroxyproline, and glycine. It is the accumulation of pyrroline 5-carboxylate which adducts with PLP that is thought to lead to vitamin B6 deficiency,[66] a mechanism analogous to that of PLP with Δ1-piperideine-6-carboxylate in antiquitin deficiency (see above). Clinically, hyperprolinaemia type II is characterized by seizures that are usually precipitated by infection and fever. In at least one reported case, seizures have shown a good response to pyridoxine.[67]

Phenylketonuria

Seizures used to occur in infants with phenylketonuria (OMIM 261600) before diagnosis by neonatal screening and early institution of a low-phenylalanine diet. In children from developing countries who have not been part of a comprehensive newborn screening programme, phenylketonuria should still be considered as a possible cause of seizures, particularly if accompanied by developmental delay.

Cerebral organic acidurias

There are some disorders that can be diagnosed by analysis of urine organic acids and/or blood spot acylcarnitines in which seizures can occur without preceding signs of acute encephalopathy and without evidence of acidosis, hyperammonaemia, and so on. These include methylmalonic aciduria due to cobalamin defects (e.g. cobalamin C disorder; OMIM 277400) for which there are specific treatments, such as a high dose of vitamin B12 and betaine, that may be able to help with seizure control; 4-hydroxybutyric aciduria (succinic semialdehyde dehydrogenase deficiency; OMIM 271980), for which vigabatrin may be beneficial; L-2-hydroxyglutaric aciduria (OMIM 600721), for which treatment with riboflavin (with or without L-carnitine) has been shown to improve cognitive and motor performance;[68,69] D-2-hydroxyglutaric aciduria (OMIM 236792) for which no successful treatment has been described; and 3-hydoxyisobutyryl-CoA hydrolase deficiency (OMIM 250620), which can be suspected on the basis of increased hydroxy-C4 carnitine in the blood spot and in which progression of neurological disease has been arrested by treatment with L-carnitine, dietary valine restriction, *N*-acetylcysteine, and antioxidants (unpublished observation).

Other disorders

Infantile and late infantile neuronal ceroid lipofuscinosis

NCLs are a group of autosomal recessive progressive neurodegenerative disorders clinically characterized by the triad of epilepsy, developmental regression/dementia, and pigmentary retinopathy. More than 10 genetic defects have been linked to the NCLs, most with characteristic ages at onset.[50] All except infantile NCL (NCL type 1) are characterized by progressive myoclonus. Neuronal ceroid lipofuscinosis type 1 presents with developmental delay or arrest towards the end of the first year of life. Seizures are infrequent and myoclonus may be seen as only isolated jerks. By contrast, in the late infantile form (NCL type 2), myoclonus and tonic–clonic seizures are early

and frequent with onset from 2 to 4 years. Neurophysiology features can be very helpful in indicating the diagnoses in NCLs, including progressive loss of EEG activity and ERG in NCL type 1 and abnormal enlarged visual and somatosensory evoked potentials and posterior paroxysms triggered by photic stimulation in NCL type 2.

Diagnosis rests on assay of enzyme activity (palmitoyl protein thioesterase and tripeptidyl thioesterase) in dried blood spots, followed by molecular analysis of the *CLN1* and *CLN2* genes. Rare cases are not caused by mutations in these two genes, and further investigation will necessitate electron microscopic examination of skin or rectal biopsies to search for characteristic inclusion bodies. If these are demonstrated, sequence analysis of the *CLN5*, *-6*, *-7*, and *-8* genes should be performed.

Gangliosidoses

Infants with infantile GM1 gangliosidosis (OMIM 230500) are often hypotonic from birth and stop making developmental progress at 3 to 6 months of age. Examination will reveal coarsening of facial features, and usually hepato(spleno) megaly. Many have a cherry-red spot at the macula, and radiology often shows dysostosis. Seizures are a major part of the progressive neurological dysfunction. GM2 gangliosidosis (Tay–Sachs disease; OMIM 272800) presents at 4 to 6 months with motor weakness, hypotonia, and a typical startle response to sound (auditory myoclonus). Progressive loss of milestones, hypotonia, and visual inattentiveness follow. A cherry-red spot is almost always present. Seizures and spasticity characterize the final phase of the illness. Myoclonic seizures are common, and can be massive and multiple. Focal, generalized, and occasionally gelastic seizures also occur.

Alpers syndrome and other infantile-onset mitochondrial disorders

Alpers syndrome (progressive neuronal degeneration of childhood with liver disease; OMIM 203700) typically presents in late infancy with intractable seizures, which may initially be focal and subsequently generalize.[70] Epilepsia partialis continua and convulsive status epilepticus are common. A characteristic and unusual EEG pattern of large-amplitude slow activity with superimposed smaller multispike discharges may be seen early on and then disappear as the disease progresses. There may be an antecedent history of developmental delay and associated liver dysfunction. The disorder is caused by progressive depletion of the mtDNA, as a result of an underlying recessively inherited defect of mtDNA replication, most often because of defective DNA polymerase gamma function resulting from *POLG* mutations, although occasionally the responsible mutations may be in the *PEO1* gene encoding the Twinkle DNA helicase.[71] The course is usually rapidly progressive; most affected infants die before the age of 3 years. Treatment is supportive. Other mitochondrial disorders presenting with epilepsy in infancy, including maternally inherited Leigh syndrome, have been discussed in detail in a recent review.[4]

Congenital disorders of protein N*-glycosylation*

More than 13 disorders affecting *N*-glycosylation have been described, and the majority affect the CNS. They can present with failure to thrive and multisystem disease in early infancy; hypotonia and seizures can be part of the clinical picture. Seizures can be a major presenting feature in an older infant. They can be associated with hypotonia and/or ataxia, suggesting a diagnosis of cerebral palsy, but additional clinical features can point the astute paediatrician to the correct diagnosis; these include dysmorphic features such as unusual fat pads on the buttocks, inverted nipples, long fingers and toes, and craniofacial dysmorphic features. Diagnosis of most of the disorders of protein *N*-glycosylation can be made by isoelectric focusing of serum transferrin. There is no specific form of treatment for the seizures associated with the disorders of *N*-glycosylation.

METABOLIC EPILEPSIES OF LATE CHILDHOOD AND ADOLESCENCE

Treatable disorders

Coenzyme Q_{10} deficiency

Very few metabolic epilepsies presenting in late childhood and adolescence are treatable; CoQ_{10} deficiency (OMIM 607426) is a notable exception.[60] Late-onset CoQ_{10} deficiency syndromes are frequently associated with epilepsy, particularly those caused by mutations in the *ADCK3* (*CABC1*) gene. Patients with *ADCK3* mutations have a relatively homogeneous phenotype, with cerebellar ataxia and seizures, and a favourable response to exogenous CoQ_{10} supplementation.[72,73] Other patients with CoQ_{10} deficiency present with recurrent rhabdomyolysis and an encephalomyopathy including seizures,[74] but the genetic basis of this variant of CoQ_{10} deficiency remains unknown.

Other disorders

Progressive myoclonic epilepsy

Progressive myoclonic epilepsies presenting in this age group include Unverricht–Lundborg disease (Baltic myoclonus; OMIM 254800), Lafora body disease (OMIM 254780), and mitochondrial diseases such as MERRF (myoclonic epilepsy with ragged-red fibres; OMIM 545000) syndrome, and disorders related to mutations in the DNA polymerase gamma. Unverricht–Lundborg disease is a Finnish heritage disorder and occurs in approximately 1 in 20 000 of the Finnish population. It has also been reported in other ethnic groups in northern Europe and North America. Affected children are normal in early childhood, and usually present with clonic or tonic–clonic seizures followed by stimulus-sensitive, action-triggered myoclonus between the ages of 6 and 16 years. Associated clinical problems include ataxia and mild learning difficulties. The diagnosis is confirmed by finding mutations in the *EPM1* gene encoding cystatin B.[75] Severity and disease progression vary between and within families. The disease is associated with severe disability but is not usually life-limiting. Phenytoin is contraindicated in this condition since it may exacerbate the seizures.

Lafora body disease presents in the same age group (6–18y) but is more rapidly progressive. Affected individuals are often bed bound and require almost constant rest, exhibit action-triggered myoclonus, and develop severe dementia within 5 to 10 years of disease onset. Visual seizures may be a feature. Convulsive status epilepticus often precipitates death. The diagnosis may be suspected by the identification of Lafora bodies (polyglucosan inclusion bodies) in neurons in a full-thickness skin biopsy. Eighty per cent of affected individuals have mutations in the *EPM2A* gene encoding laforin, whereas approximately 20% have mutations in *NHLRC1*, encoding malin. No genetic defect is identified in a minority of cases.[75]

Mitochondrial epilepsies

Several mitochondrial disorders may present with seizures in late childhood and adolescence.[4] MERRF syndrome is usually caused by a maternally inherited mtDNA mutation, most often the m.8344A>G mutation in the gene encoding the transfer RNA for lysine. Recessive *POLG* mutations typically cause Alpers syndrome (see above) or other infantile-onset mtDNA depletion syndromes, but may also present in adolescence with progressive epilepsy mimicking MERRF syndrome. Several acronyms have been coined for these late-onset recessive *POLG* disorders associated with epilepsy, including MIRAS (mitochondrial recessive ataxia syndrome), SCAE (spinocerebellar ataxia with epilepsy; OMIM 607459), and MEMSA (myoclonus, epilepsy, myopathy, sensory ataxia), but these probably represent a disease continuum. Patients with MELAS (mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes; OMIM 540000) syndrome typically present towards the end of the first decade of life with a stroke-like episode which may be heralded by focal seizures, migrainous headache, and vomiting. Eighty per cent of patients with MELAS have the same genetic cause: the m.3243A>G mutation in the gene encoding the transfer RNA for leucine^{UUR}.

Lysosomal storage disorders

In juvenile NCL (Batten's disease; OMIM 204200), retinopathy is usually the presenting symptom, whilst epilepsy and dementia typically occur late in the disease course. The triad of clinical features (retinopathy, epilepsy, and dementia), together with the presence of vacuolated lymphocytes in the peripheral blood film, may suggest the diagnosis, which is confirmed by mutation analysis of the *CLN3* gene. Absence seizures may be more frequent than tonic–clonic seizures. Myoclonus particularly affects the face.

In subacute/chronic neuronopathic Gaucher disease (Gaucher type III; OMIM 231000) neurological symptoms with evidence of systemic disease (e.g. splenomegaly) typically occur at a mean age of 10 years. One neurological phenotype is characterized by progressive myoclonic encephalopathy with seizures and dementia. In some cases this is preceded by supranuclear gaze palsy, and there may be an extrapyramidal movement disorder. As in juvenile NCL, facial myoclonus is a feature.

Type I sialidosis (neuraminidase deficiency; OMIM 256550) often presents in the second or third decade with progressive visual handicap with impaired colour vision and/or night blindness; a cherry-red spot is typically present at the macula. Severe myoclonic epilepsy follows in almost 50% of cases, leading to the name 'cherry-red spot myoclonus syndrome'. Seizures are often difficult to control.

Niemann–Pick type C (NPC; OMIM 257220) is a disorder of lysosomal cholesterol export with secondary accumulation of sphingomyelin. Although the disease most often presents in the first 2 years of life, late-onset forms presenting with epilepsy (partial, generalized tonic–clonic, and atonic seizures) are recognized. Hepatosplenomegaly and vertical supranuclear gaze palsy may provide clues to the underlying diagnosis, which may be tricky to establish. Abnormal storage cells (sea-blue histiocytes) may be observed in the bone marrow and filipin staining of cultured skin fibroblasts may demonstrate lipid accumulation. Approximately 95% of cases have mutations in the *NPC1* gene and 5% in *NPC2*. There is no curative treatment for Niemann–Pick type C but recently a glycosphingolipid synthesis (glucosylceramide synthase) inhibitor was approved for the treatment of this condition, based on evidence from a randomized controlled trial that showed stabilization/slowing of neurological progression.[76]

Peroxisomal disorders

Alpha methyl-acyl-CoA racemase deficiency can produce a wide range of neurological problems with onset in childhood or adult life. These include developmental delay, epilepsy, acute encephalopathy, tremor, pigmentary retinopathy, hemiparesis, spastic paraparesis, peripheral neuropathy, depression, headache, and cognitive decline. One female presented at age 13 with epilepsy and a postictal confusional state and had no further symptoms for 5 years.[77] Elevation of plasma pristanic acid is a diagnostic clue.

APPROACH TO DIAGNOSIS

The differential diagnosis of seizure disorders is extremely wide and includes ion channel disorders (e.g. *SCN1A* mutations), malformations of cortical development, neurocutaneous syndromes, chromosomal disorders, hypoxic–ischaemic encephalopathy, congenital infection, sepsis, and tumours. However, certain features in the history and clinical examination may lead to suspicion of an underlying inborn error of metabolism. These include parental consanguinity, a similarly affected sibling, and a history of in utero 'hiccoughs' or 'fluttering' movements, which might represent antenatal seizures. Seizures occurring after fasting are suggestive of hypoglycaemia or neuroglycopaenia.

The combination of particular facial features (large fontanelle, high forehead, flat occiput, and shallow supraorbital ridges) with seizures may raise suspicion of a peroxisomal disorder, particularly Zellweger syndrome. A macular cherry-red spot on fundoscopy, or vacuolated lymphocytes in the peripheral blood film, indicate a lysosomal storage disorder. In other patients there may be characteristic abnormalities of the skin

Table III: Treatment of metabolic epilepsies

Disorder	Treatment
Established therapies	
Pyridoxine-dependent epilepsy	Pyridoxine 100mg i.v. initial dose followed by 5–10mg/kg/d p.o., maximum 200mg per day
PNPO deficiency	Pyridoxal 5′-phosphate 10–30mg/kg/d p.o.
Biotinidase deficiency	Biotin 5–10mg/d p.o.
Holocarboxylase synthetase deficiency	Biotin 10–20(40)mg/d p.o.
GLUT1 defect	Ketogenic diet
Disorders of creatine biosynthesis and transport	Creatine 350–500mg/kg/d p.o. Arginine restriction in GAMT deficiency (15–25mg/kg/d; corresponds to 0.4–0.7 g/kg/d protein intake)
Dihydrofolate reductase deficiency	Folinic acid 30mg/d p.o.
Folate receptor defect	Folinic acid 5mg/kg/d p.o.[54]
Disorders of serine biosynthesis	L-Serine 200–600mg/kg/d p.o.; if seizures continue add glycine 200mg/kg/d p.o.
Disorders of CoQ_{10} biosynthesis	CoQ_{10} 10–30mg/kg/d p.o. in children; 1200–3000mg/d in adults
Experimental therapies	
Menkes syndrome	Copper injections (early diagnosed cases only)
Molybdenum cofactor deficiency (MOCS1)	Cyclic pyranopterin
Non-ketotic hyperglycinaemia	Benzoate, dextromethorphan, folinic acid
GAMT deficiency	Ornithine supplementation

i.v., intravenous; p.o., per os; PNPO, pyridox(am)ine 5′-phosphate oxidase; GLUT1, glucose transporter across the blood–brain barrier; GAMT, guanidinoacetate methyl transferase; CoQ_{10}, coenzyme Q_{10}; MOCS1, molybdenum cofactor synthesis gene 1.

and/or hair. For example, in Menkes syndrome defective keratinization of the hair leads to sparseness and a 'kinky' appearance caused by the formation of pili torti. Patients with Menkes syndrome also have typical facies and may have connective tissue and bone abnormalities, as well as severe developmental delay and epilepsy. Children with biotinidase deficiency may present with an eczematous rash, particularly affecting the periorbital and perioral areas, together with alopecia. They may also have optic atrophy and sensorineural hearing loss, particularly if diagnosed late. Multisystem disease features may raise suspicion of a mitochondrial disorder. For example, the combination of steroid-resistant nephrotic syndrome, sensorineural hearing loss, ataxia, and seizures is suggestive of CoQ_{10} deficiency.[60]

Although neither seizure type nor EEG appearance is specific for particular IEMs, an underlying metabolic disorder should be considered in children with myoclonic seizures, intractable seizures resistant to multiple AEDs, epileptic encephalopathy, and those with a burst suppression EEG pattern. Burst suppression is typically seen early in the disease course in several early-onset metabolic epilepsy syndromes, including non-ketotic hyperglycinaemia, pyridoxine-dependent epilepsy, PNPO deficiency, defects of the mitochondrial glutamate transporter SLC25A22, and SUOX and MoCoF deficiencies, but is also a feature of many non-metabolic epilepsy syndromes. In Alpers syndrome there may initially be characteristic EEG changes (rhythmic high-amplitude delta waves with superimposed [poly]spikes over parieto-occipital regions), but later in the disease course EEG abnormalities tend to generalize.[70]

Brain MRI usually reveals non-specific changes only. However, in occasional cases, brain MRI may be diagnostic: for example, children with pontocerebellar hypoplasia visible on MRI that is associated with intractable seizures and developmental stasis may have *RARS2* mutations, a disorder of mitochondrial translation.[42] In other conditions MRI may be suggestive but not diagnostic; for example, cystic degeneration may be observed in SUOX and MoCoF deficiencies. Magnetic resonance spectroscopy is essential for the diagnosis of the creatine transporter disorder, since urinary levels of creatine metabolites may be normal in this condition.

The mainstay of diagnosis of IEMs is of course biochemical investigation. Metabolites may be assayed in blood, urine, or CSF (Table II). Where specific enzyme assays are available, these have been described in the appropriate sections above. Genetic diagnosis is increasingly available for IEMs, and constitutes the first line of investigation in rare instances where there are no characteristic metabolites or diagnostic enzyme assay, such as mutation analysis of *SLC25A22* for mitochondrial glutamate transporter deficiency. Increased availability and ease of genetic testing is leading to expansion of the epileptic phenotypes of many of the genetic and indeed the metabolic epilepsies, with GLUT1 and serine disorders being more recent examples.

TREATMENT

Specific treatments, where available, have been described in the main text above, and are summarized in Table III.

CONCLUSIONS

IEMs are a relatively rare cause of epilepsy, but their recognition and diagnosis is important because several disorders are treatable, often with simple therapies such as vitamins. Prompt treatment can affect long-term neurological outcome, therefore diagnosis should not be delayed. Associated clinical, biochemical, and imaging features may provide clues to the underlying diagnosis.

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ONLINE RESOURCES

It has not been possible to provide a detailed discussion of all the metabolic epilepsies mentioned in this review, owing to space constraints; the reader is referred to the database Online Mendelian Inheritance in Man (http://www.omim.org) for further information. OMIM numbers have been indicated throughout the text. Further information may also be found in The Online Metabolic and Molecular Bases of Inherited Diseases (http://www.ommbid.com).

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