

Epilepsy in inborn errors of metabolism

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ABSTRACT – Although inborn errors of metabolism are rarely found to be the cause of epilepsy, seizures are a frequent symptom in metabolic disorders. In a few of these, epilepsy responds to specific treatment by diet or supplementation. However, in most, no such treatment is available and conventional antiepileptic drugs must be used, often with no great success. However, because uncontrolled epilepsy will hamper development and may even lead to further cerebral damage, treatment is necessary. Seizure types are rarely specific for a particular metabolic disorder, nor are EEG findings. Other symptoms and findings must be taken into account in order to achieve a diagnosis and, in some cases, specific management. We review the main characteristics of epilepsy due to inborn errors of energy metabolism, to disturbed neuronal function due to accumulation of storage products, to toxic effects and to disturbed neurotransmitter systems. We also discuss vitamin-responsive epilepsies and a number of other metabolic disorders focusing on possible pathogenetic mechanisms and their implication for diagnosis and treatment.

Key words: inborn errors of metabolism, storage disorders, neurotransmitter, vitamin-responsive epilepsy, epilepsy

Seizures are a common symptom in a great number of metabolic disorders, occurring mainly in infancy and childhood. In some, seizures may occur only until adequate treatment is initiated or as a consequence of acute metabolic decompensation, as is the case in hyperammonaemia or hypoglycaemia. In others, seizures can be the main manifestation of the disease and can lead to antiepileptic drug-resistant epilepsy, e.g. in one of the creatine deficiency syndromes, guanidinoacetate methyltransferase (GAMT) deficiency. In a few metabolic disorders, epilepsy can be prevented by early, exclusively “metabolic” treatment initiated after screening of newborns, as is the case for phenylketonuria (PKU) or biotinidase deficiency in certain countries. In some disorders, for instance glutaric aciduria type 1 (GA 1),

“metabolic therapy” has to accompany treatment with conventional antiepileptic drugs; however, in most metabolic disorders, the only way to treat seizures is by antiepileptic medication alone.

Epilepsy in inborn errors of metabolism can be classified in different ways. One useful way uses the possible pathogenetic mechanisms for classification: Seizures can be due to lack of energy, intoxication, impaired neuronal function in storage disorders, disturbances of neurotransmitter systems with excess of excitation or lack of inhibition, or associated malformations of the brain (*table 1*). Other approaches take into account the clinical presentation, with emphasis on seizure semiology, epilepsy syndrome and associated EEG findings (*table 2*) or the age of manifestation (*table 3*). A

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pragmatic way to categorise these epilepsies is according to whether they are treatable using a metabolic approach or not (*table 4*). In this review, we will focus on pathogenesis and its implication for diagnosis and treatment.

Epilepsy due to inborn errors of energy metabolism

Mitochondrial disorders

Mitochondrial disorders are frequently associated with epilepsy, although exact data about incidence are scarce, with only a few publications addressing this question specifically. In infancy and childhood, epilepsy is found in 26–60% of all mitochondrial disorders (Darin *et al.* 2001, Wolf and Smeitink 2002). In a common subgroup, Leigh syndrome, epilepsy occurs in about half of all patients (Rahman *et al.* 1996). In our experience, epilepsy is common in disease with early onset and severe psychomotor retardation, it is less frequent in milder disease and where there is predominantly white matter involvement on MRI. Clinically, all seizure types can be seen.

Decreased ATP production, the main biochemical consequence of impaired respiratory chain function, probably leads to unstable membrane potentials, making neurons prone to epileptic activity because about 40% of neuronal ATP production is needed for Na,K-ATPase and maintenance of the membrane potential (Kunz 2002). One of the mitochondrial DNA (mtDNA) mutations causing myoclonic epilepsy with ragged red fibres (MERRF) seems to impair mitochondrial calcium handling, again leading to increased seizure susceptibility (Brini *et al.* 1999). Another possible mechanism has recently been discussed after impaired importation of mitochondrial glutamate was shown to cause one form of early myoclonic encephalopathy (EME); the clinical features may be caused by a putative imbalance of this excitatory neurotransmitter (Molinari *et al.* 2004)

One of the first mitochondrial disorders to be described, MERRF, caused by mutations in the mitochondrial tRNA for lysine, presents in the second decade or later, as progressive myoclonus epilepsy with typical EEG findings of giant, somatosensory potentials and photosensitivity. Clinically, patients show prominent cortical myoclonus as well as other seizure types (So *et al.* 1989). Another mitochondrial disorder caused by mutations in the mitochondrial tRNA for leucine, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS), also frequently leads to seizures, especially during acute stroke-like episodes where focal seizures arise in the involved cortical areas (*figure 1*); sometimes leading to focal status epilepticus. This prominent epileptic activity might also be responsible for the spread of the lesion, which can be observed in some acute episodes (Iizuka *et al.* 2002, Iizuka *et al.* 2003).

In infancy- and childhood-onset mitochondrial encephalopathies, myoclonic seizures are frequent, sometimes with very discreet clinical manifestation (eyelid flutter), and there is profound mental retardation. EEG patterns range from burst suppression to irregular polyspike wave paroxysms during myoclonus. However, other seizure types can also be observed – tonic, tonic-clonic, partial, hypo- and hypermotor seizures or infantile spasms. One study found that 8% of all children with infantile spasms suffer from a mitochondrial disease (Sadleir *et al.* 2004). Status epilepticus is also seen, which is either convulsive or non-convulsive. Epilepsia partialis continua as focal status epilepticus is frequent in Alpers' disease, some cases of which are caused by mutations in mitochondrial DNA polymerase gamma, causing mitochondrial depletion (Naviaux and Nguyen 2004, Ferrari *et al.* 2005). Alpers' disease should be considered in children presenting with this symptom, as one of the differential diagnoses for Rasmussen's encephalitis. Non-convulsive status epilepticus or the development of hypersarrhythmia can lead to insidious dementia which might be mistaken for the inevitable and untreatable progression of the underlying disease; however, both can and should be treated.

Disorders of creatine metabolism

Disorders of creatine metabolism comprise three different defects: impaired creatine transport into the brain in the X-linked creatine transporter defect (Salomons *et al.* 2001); and impaired creatine synthesis in GAMT (guanidinoacetate methyltransferase) and AGAT (arginine-glycine amidinotransferase) deficiencies (Stockler *et al.* 1996, Item *et al.* 2001). Only GAMT deficiency is regularly associated with epilepsy, which is often refractory to conventional treatment (*figure 2*). Creatine supplementation alone frequently leads to improvement. However, in some patients, reducing the toxic compound guanidinoacetate by dietary reduction of arginine and supplementary ornithine has been found to achieve epilepsy control (Schulze *et al.* 2001). Whether early, presymptomatic treatment is able to prevent neurological symptoms remains to be shown. Seizure types are many and various. Infants can present with West syndrome, with atypical absences, astatic and generalised tonic-clonic seizures being common later on. Imaging findings can be normal even in untreated adults (Schulze *et al.* 2003); but in some patients, basal ganglia signal abnormalities can be found. A diagnosis of GAMT deficiency may be suspected, by demonstrating biochemically increased excretion of guanidino compounds in urine; all three defects can be assumed when the prominent creatine and creatine phosphate peak is absent on proton magnetic resonance spectroscopy (1H-MRS) of the brain or cerebrospinal fluid.

Table 1. Classification of epilepsies of metabolic origin according to their pathogenesis.

Energy deficiency	Hypoglycaemia, GLUT1-deficiency, respiratory chain deficiency, creatine deficiency
Toxic effect	Amino acidopathies, organic acidurias, urea cycle defects
Impaired neuronal function	Storage disorders
Disturbance of neurotransmitter systems	Non-ketotic hyperglycaemia, GABA transaminase deficiency, succinic semialdehyde dehydrogenase deficiency
Associated brain malformations	Peroxisomal disorders (Zellweger), O-glycosylation defects
Vitamin / Co-factor dependency	Biotinidase deficiency, pyridoxine-dependent and pyridoxal phosphate dependent epilepsy, folinic acid-responsive seizures, Menkes' disease
Miscellaneous	Congenital disorders of glycosylation, serine biosynthesis deficiency and inborn errors of brain excitability (ion channel disorders)

Table 2. Classification of epilepsies of metabolic origin according to age at onset.

Neonatal period	Hypoglycaemia, pyridoxine-dependency, PNPO deficiency, nonketotic hyperglycaemia, organic acidurias, urea cycle defects, neonatal adrenoleukodystrophy, Zellweger syndrome, folinic acid-responsive seizures, holocarboxylase synthase deficiency, molybdenum cofactor deficiency, sulphite oxidase deficiency
Infancy	Hypoglycaemia, GLUT1-deficiency, creatine deficiency, biotinidase deficiency, amino acidopathies, organic acidurias, congenital disorders of glycosylation, pyridoxine dependency, infantile form of neuronal ceroid lipofuscinosis (NCL1)
Toddlers	Late infantile form of neuronal ceroid lipofuscinosis (NCL2), mitochondrial disorders including Alpers' disease, lysosomal storage disorders
School age	Mitochondrial disorders, juvenile form of neuronal ceroid lipofuscinosis (NCL3), progressive myoclonus epilepsies

Table 3. Classification of epilepsies of metabolic origin according to the type of presenting seizures or epilepsy syndrome.

Infantile spasms	Biotinidase deficiency, Menkes' disease, mitochondrial disorders, organic acidurias, amino acidopathies
Epilepsy with myoclonic seizures	Non-ketotic hyperglycaemia, mitochondrial disorders, GLUT1-deficiency, storage disorders
Progressive myoclonic epilepsies	Lafora disease, MERRF, MELAS, Unverricht-Lundborg disease, sialidosis
Epilepsy with generalised tonic-clonic seizures	GLUT1-deficiency, NCL2, NCL3, other storage disorders, mitochondrial disorders
Epilepsy with myoclonic-astatic seizures	GLUT1-deficiency, NCL2
Epilepsy with (multi-)focal seizures	NCL3, GLUT1-deficiency and others
Epilepsia partialis continua	Alpers' disease, other mitochondrial disorders

Table 4. Epilepsies amenable to metabolic treatment.

GLUT1 deficiency	Ketogenic diet
Cofactor-dependent epilepsy	Pyridoxine, pyridoxal phosphate, folinic acid, biotin
GAMT deficiency	Creatine supplementation, arginine-restricted, ornithine-enriched diet
Phenylketonuria	Low-phenylalanine diet; in atypical phenylketonuria substitution of L-DOPA, 5OH-tryptophan, folinic acid
Defects of serine biosynthesis	Serine supplementation

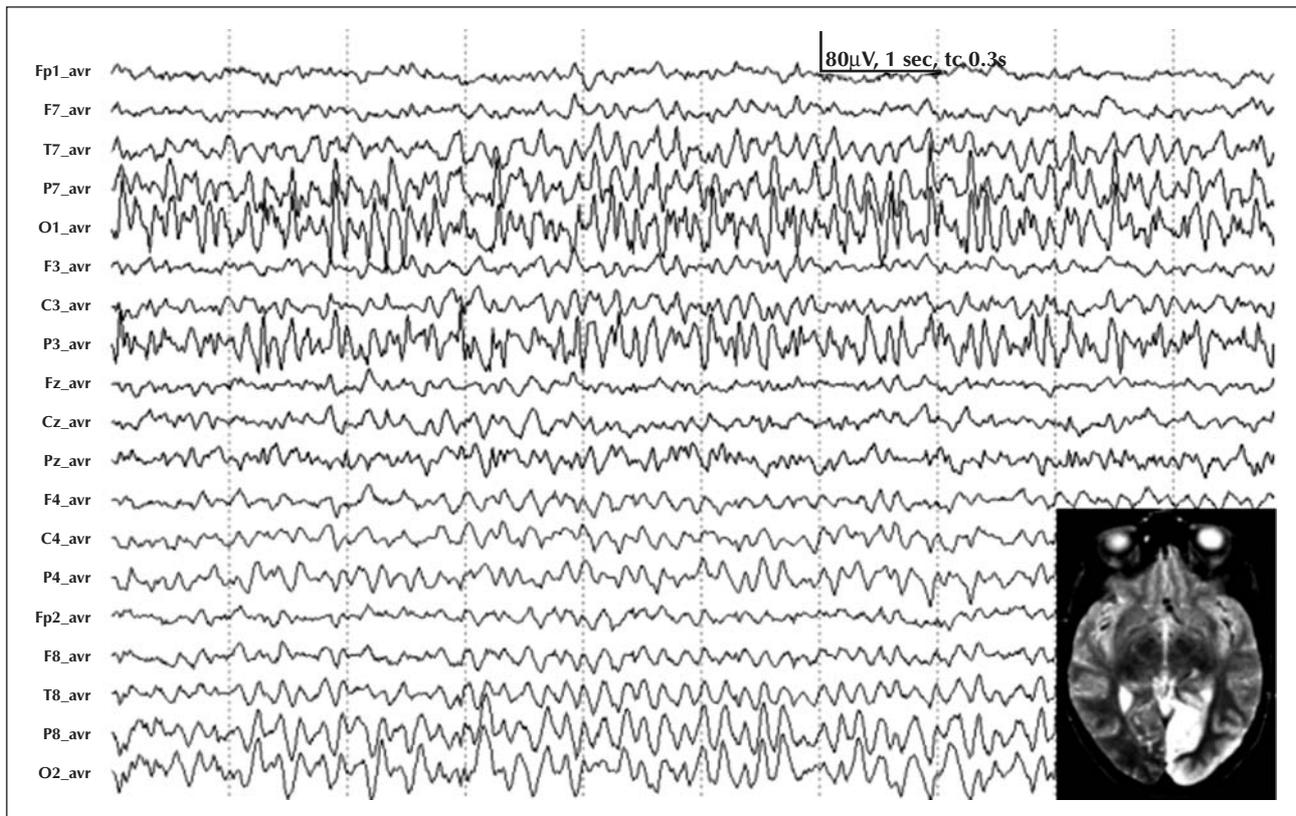


Figure 1. EEG (average reference) of a patient with MELAS syndrome in an acute, stroke-like episode demonstrating an ongoing seizure over the left parieto-occipital region corresponding to the involved brain area on T2w MRI.

GLUT1 deficiency

Impaired transport of glucose across the blood-brain barrier is due to dominant mutations in the gene for the glucose transporter 1 (GLUT1, Seidner *et al.* 1998). Usually, mutations occur *de novo*, although some families have been described with several affected members and an autosomal-dominant pattern of inheritance (Brockmann *et al.* 2001). The clinical presentation is mostly that of therapy-resistant epilepsy beginning in the first year of life, acquired microcephaly and mental retardation. Ataxia is a frequent finding and movement disorders such as dystonia may also occur. Symptoms may worsen during the fasted state, and the EEG may show an increase in generalised or focal epileptiform discharges that improve after eating (Von Moers *et al.* 2002). Cerebral imaging is normal. This diagnosis may be suspected if a reduced CSF-blood glucose ratio (< 0.46) is found. The diagnosis can be confirmed by looking for reduced glucose transport across the erythrocyte membrane (which carries the same glucose transporter), and by mutation analysis of the gene. Treatment is available and consists of a ketogenic diet,

which supplies ketone bodies as an alternate energy substrate for the brain. Several anticonvulsants, in particular phenobarbital, but also chloral hydrate and diazepam, may further impair GLUT1 and should not be used in this disease (Klepper *et al.* 1999).

Hypoglycaemia

Hypoglycaemia is a frequent and easy-to-treat metabolic cause of seizures and therefore has to be ruled out in every patient presenting with seizures. Prolonged seizures due to hypoglycaemia may lead to hippocampal sclerosis and subsequently to temporal lobe epilepsy; in newborns, lesions in the occipital lobe are predominant, which also can lead to lesional epilepsy. Hypoglycaemia may be due to an underlying metabolic disease, e.g. defects of gluconeogenesis; therefore additional metabolic investigations have to be initiated. For every child presenting with hypoglycaemia, blood glucose, β -hydroxybutyrate, free fatty acids, lactate, amino acids, acyl-carnitine esters, ammonia, insulin, growth hormone and cortisol and urine ke-

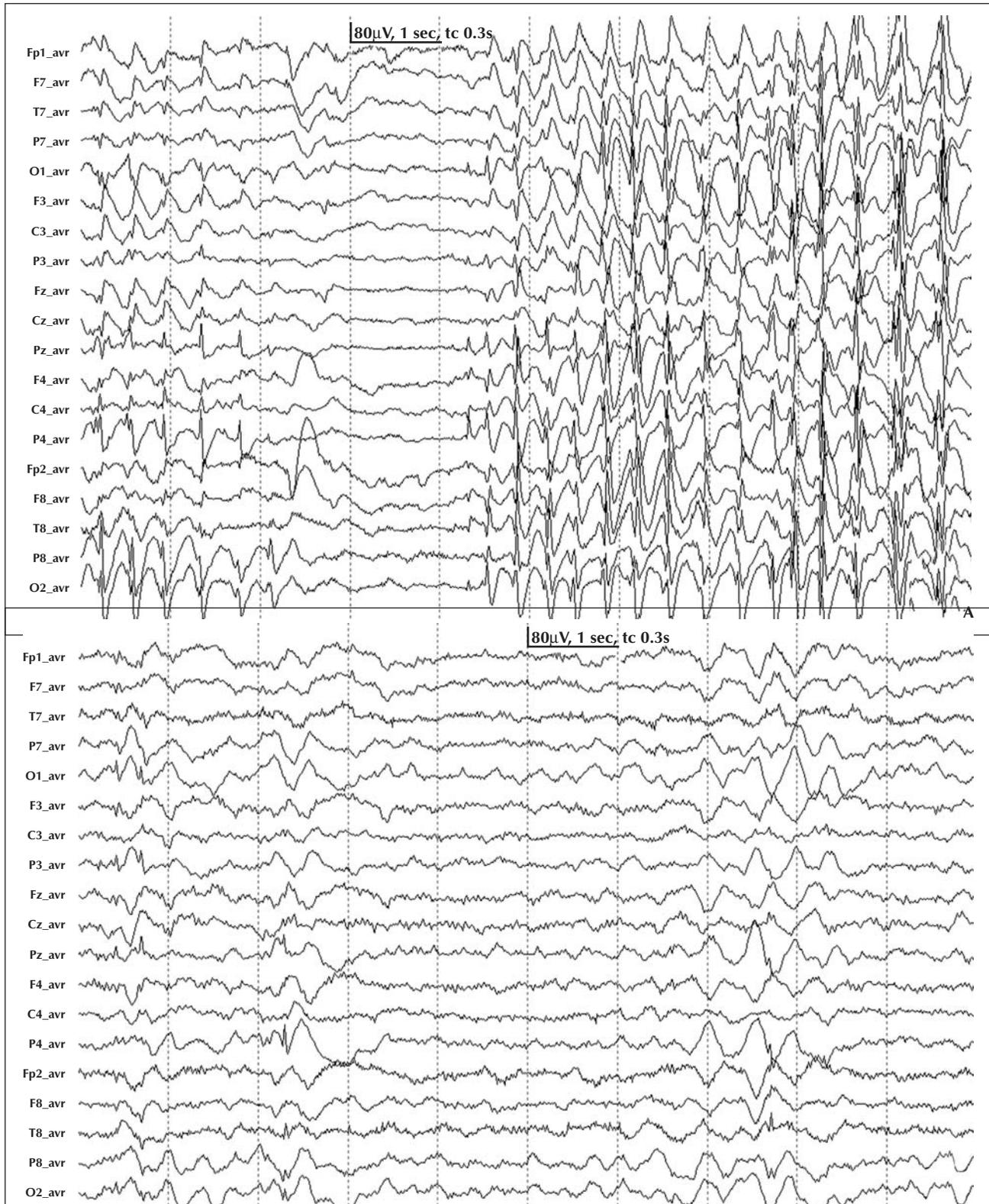


Figure 2. EEG of a child with the GAMT defect under creatine supplementation (A) and creatine supplementation plus ornithine-rich arginine-reduced diet (B). The child was in a non-convulsive status epilepticus with a nearly continuous generalised spike-wave pattern before the diet was started (A). Under diet, non-convulsive status stopped (B).

tones and organic acids are mandatory investigations at the time of the hypoglycaemia.

Disturbed neuronal function due to accumulation of storage products

Many of the storage diseases are associated with epilepsy that is often difficult to treat. Epilepsy is a prominent feature of Tay-Sachs disease, with myoclonus, atypical absences and motor seizures. Sialidosis type I leads to progressive myoclonus epilepsy, a distinguishing feature being a retinal cherry-red spot (Zupanc and Legros 2004). In the different neuronal ceroid lipofuscinoses (NCL, Batten diseases), epilepsy is a major feature (Cooper 2003). In the infantile form (NCL1), seizures start at the end of the first year of life, with myoclonus, atonic and tonic-clonic seizures. The EEG shows early and severe depression. The diagnosis should be suspected because of the rapid dementia and the development of a complex movement disorder shortly after the onset of epilepsy. MRI in NCL1 shows cortical, cerebellar and white matter atrophy, and secondary white matter signal abnormalities (*figure 3*). The electroretinogram is severely attenuated and visual-evoked potentials are absent early in the disease course.

Milder variants resemble the later-onset, juvenile form of the disease (Mitchison *et al.* 1998).

The clinical manifestation of the late-infantile form (NCL2) is usually after the second year of life. Transient, delayed language development is common, but it is the development of seizures that usually leads to further investigation. The seizures might be generalised tonic-clonic, atonic and atstatic and myoclonic; the children may present with the clinical picture of myoclonic-astatic epilepsy. The EEG shows spikes with slow, photic stimulation (*figure 4*). Giant potentials with visual-evoked and somatosensory-evoked responses are found. The seizures are often resistant to therapy. An early clinical clue to the diagnosis is the presence of action myoclonus, which can be mistaken for cerebellar ataxia.

The diagnosis of both NCL1 and NCL2 is nowadays made by enzymatic studies of the activity of palmitoylprotein thioesterase (NCL1) or tripeptidylpeptidase 1 (NCL2) in dried blood spots or leukocytes, or by mutation analysis of the genes (*CLN1*, *CLN2* and in late infantile variants *CLN5*, *CLN6* and *CLN8*). The juvenile form (NCL3) also causes epilepsy, although this occurs later and is not as prominent a feature as in the earlier-onset diseases.

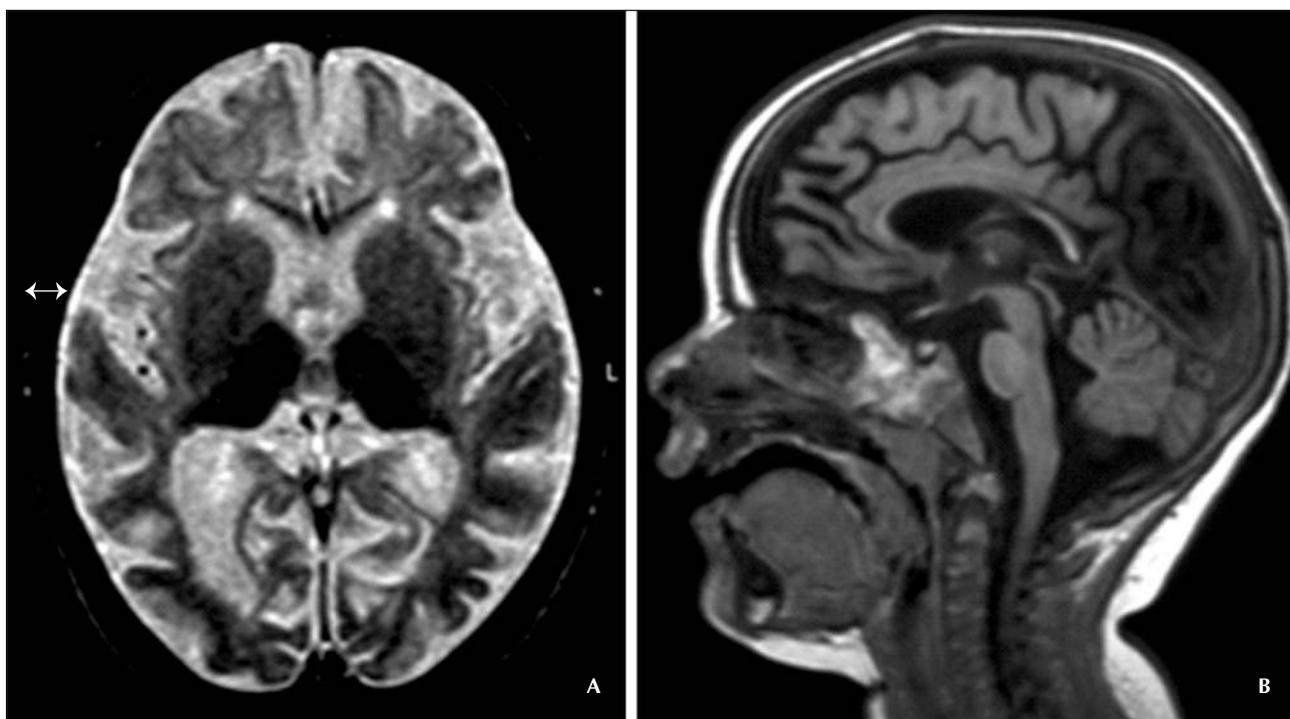


Figure 3. (A) Axial T2w image and (B) sagittal T1w image of a 12 month-old child with infantile neuronal ceroid lipofuscinosis. The supratentorial atrophy of both grey and white matter is severe, compared with a relatively intact cerebellum. Signal from both thalami is hypointense.

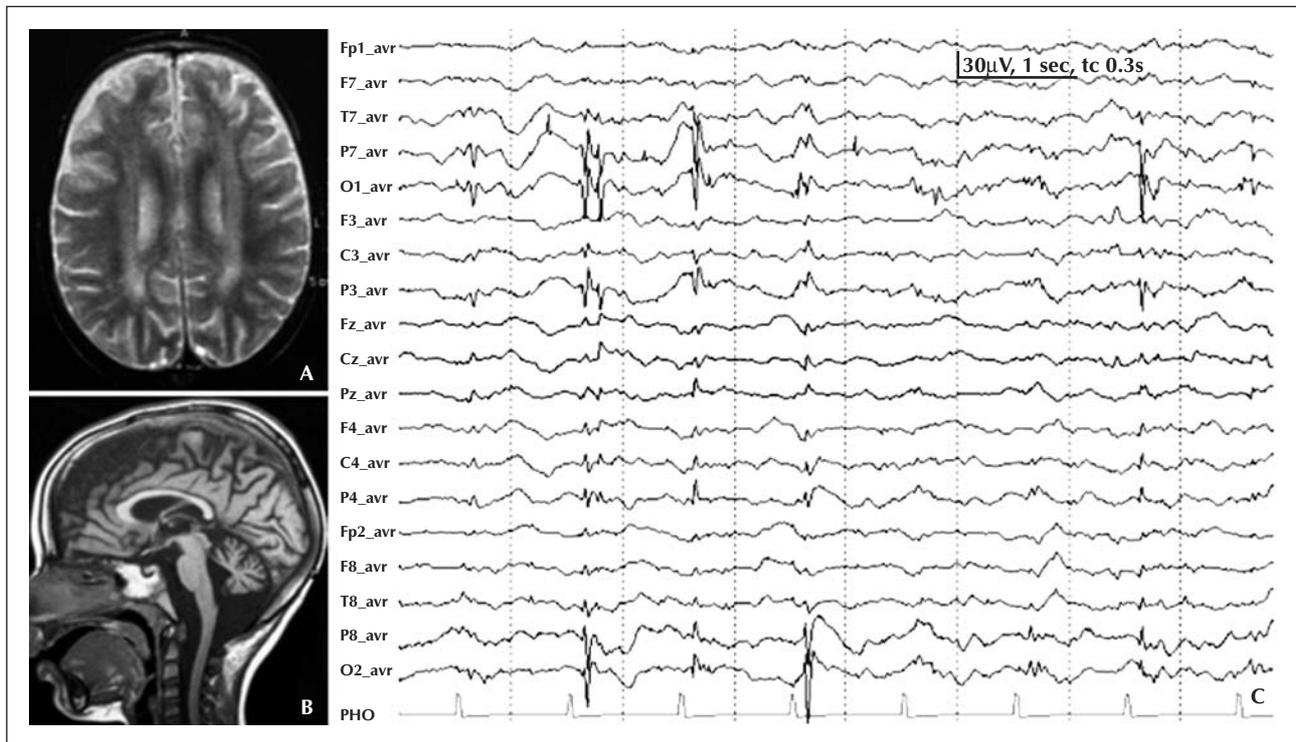


Figure 4. Late infantile neuronal ceroid lipofuscinosis. **A)** Axial T2w MRI demonstrating periventricular hyperintense white matter changes and cortical atrophy. **B)** Sagittal T1w MRI showing supra- and infratentorial atrophy. **C)** EEG (average reference) with slow photic stimulation (1 Hz) and associated spike-wave complexes over the occipital region.

Toxic effects

Urea cycle defects

Seizures are frequent during the early stages of hyperammonaemia, especially in newborns, before profound coma has developed. With good metabolic control of the underlying disease, epilepsy is rare in the course of these disorders.

Disorders of amino acid metabolism

In untreated phenylketonuria, epilepsy occurred in about a quarter to half of all patients, West syndrome with hypsarrhythmia and infantile spasms being the most common epileptic syndrome in infancy (Yanling *et al.* 1999). With presymptomatic treatment, this has completely disappeared. Seizures may accompany decompensation of maple syrup urine disease (MSUD) in the neonatal period, the EEG showing a “comb-like rhythm” resembling a μ rhythm in the central areas (Tharp 1992). Again, with dietary control epilepsy does not occur. In some rare disorders of amino acid metabolism, epilepsy may be an important symptom.

Disorders of organic acid metabolism

Several organic acidurias may lead to seizures during presentation or episodes of acute decompensation. The most important are methylmalonic acidemia and propionic acidemia. If treated appropriately, seizures are rare, and reflect persistent brain damage. In glutaric aciduria type I, seizures may also occur during the acute presentation, but they are rare once treatment has started. In 2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency, a recently described inborn error of branched-chain fatty acid and isoleucine metabolism (Zschocke *et al.* 2000), severe epilepsy seems to be a frequent finding (J. Zschocke, personal communication).

Disorders of purine and pyrimidine metabolism

In adenylosuccinate lyase deficiency, which affects *de novo* purine synthesis, epilepsy is frequent and starts either after the first year of life or early in the neonatal period (Van den Berghe *et al.* 1997, Castro *et al.* 2002). The patients additionally show severe psychomotor retardation and autistic features. A modified Bratton-Marshall test is used for screening of urine. There is no specific treatment available, and the prognosis is poor in most cases. Seizures also occur in half of the patients affected with

dihydropyrimidine dehydrogenase deficiency (Van Kuilenburg *et al.* 1999).

Disturbed neurotransmitter systems

Non-ketotic hyperglycinaemia

Typically, this disorder of defective glycine degradation presents early in the neonatal period with lethargy, hypotonia, hiccups (which may have been apparent before birth), ophthalmoplegia and disturbance of other vegetative functions of the brain stem. As the coma deepens, apnea and frequent, segmental, myoclonic jerks develop. Over the next few months (usually more than three), severe refractory epilepsy develops, with myoclonus as the initial major seizure type but evolving into infantile spasms or partial motor seizures. Severe mental retardation and tetraplegia also become evident. In the first days and weeks, the EEG shows no normal background activity, but bursts of epileptic sharp waves (so-called burst suppression pattern), changing to high voltage slow activity, and then to hypsarrhythmia by around three months if the infant survives (Applegarth and Toone 2004). The diagnosis is suggested by an increased glycine concentration in all body fluids and by the demonstration of an elevated CSF to plasma glycine ratio (> 0.08); it can be confirmed by a decreased activity of the hepatic glycine cleavage system and mutation analysis. MRI can be normal or show agenesis or hypoplasia of the corpus callosum. Glycine is the major inhibitory neurotransmitter in the brainstem and spinal cord. Excessive inhibition of the brainstem and cord structures is thought to produce the initial symptoms. However, glycine can also act as a co-agonist at the excitotoxic glutamate NMDA receptor (Thomson 1990). Under physiological conditions, the co-agonist site of the NMDA receptor is not fully occupied and co-agonist binding is a necessary condition (amongst others) to allow ion flow through the receptor. In NKH, it is hypothesised that the excess glycine saturates the NMDA co-agonist binding site, causing excessive excitatory neurotransmission and post-synaptic toxicity. The excitotoxic action of excessive NMDA receptor activation is thought to cause the epilepsy and to play a part in the mental retardation and tetraplegia. Specific treatment is not available although lowering of glycine by administration of sodium benzoate does improve survival. In several patients, therapeutic trials with NMDA antagonists have been reported, with some effects on EEG and seizure frequency (Hamosh *et al.* 1998). Severe epilepsy is the rule in surviving children and is treated by conventional antiepileptic drugs. Valproic acid should not be used from a theoretical point of view, as it will further inhibit the hepatic glycine cleavage system (Jaeken *et al.* 1977, MacDermot *et al.* 1980).

Defects of GABA metabolism

Deficiency of GABA transaminase is an extremely rare disease with only three patients reported (Jaeken 2002). Seizures may be present from birth. GABA levels are elevated in CSF and plasma. Growth was accelerated in two patients. There is no treatment for this disorder. Succinic semialdehyde dehydrogenase deficiency causes mild to moderate global mental retardation. Approximately half of the patients develop epilepsy and there may be other heterogeneous neurological symptoms, in particular ataxia (Pearl *et al.* 2003). The biochemical hallmark is the accumulation of 4-hydroxybutyric acid in body fluids. The antiepileptic drug vigabatrin, which inhibits GABA transaminase irreversibly, is beneficial in some patients; but can worsen symptoms in others (Gropman 2003).

Associated brain malformations

Among the disorders of peroxisome biogenesis, the severe Zellweger syndrome has the characteristic malformations of cortical development. Polymicrogyria of the frontal and opercular region is frequent, and pachygyria may also be found. Germinolytic cysts in the caudo-thalamic notch are typical (*figure 5*) (Barkovich and Peck 1997). The epilepsy that complicates Zellweger syndrome typically consists of partial motor seizures, which can be controlled by conventional antiepileptic medication and reflects the brain areas involved in the malformation (Takahashi *et al.* 1997). Disorders of O-glycosylation (Walker-Warburg syndrome, muscle-eye-brain disease, Fukuyama muscle dystrophy) lead to brain malformations including cobblestone lissencephaly (*figure 6*); patients often suffer from intractable seizures (Grewal and Hewitt 2003). EEG findings show abnormal beta-activity.

Vitamin-responsive epilepsies

Pyridoxine-dependent epilepsy and pyridox(am)ine phosphate oxygenase deficiency

The phenomenon of pyridoxine-dependent epilepsy has been known since 1954 (Hunt *et al.* 1954), but the molecular basis remains to be elucidated. A possible metabolic marker for this disorder seems to be plasma and cerebrospinal fluid pipercolic acid, which is elevated before treatment with pyridoxine and decreases during treatment, although not reaching the normal range (Plecko *et al.* 2000). In genetic studies, linkage to chromosome 5q31 has been reported in some families (Cormier-Daire *et al.* 2000).

Pyridoxine-dependent epilepsy is classified into a typical, early-onset, group presenting within the first few days of life, and into an atypical, later-onset, group presenting

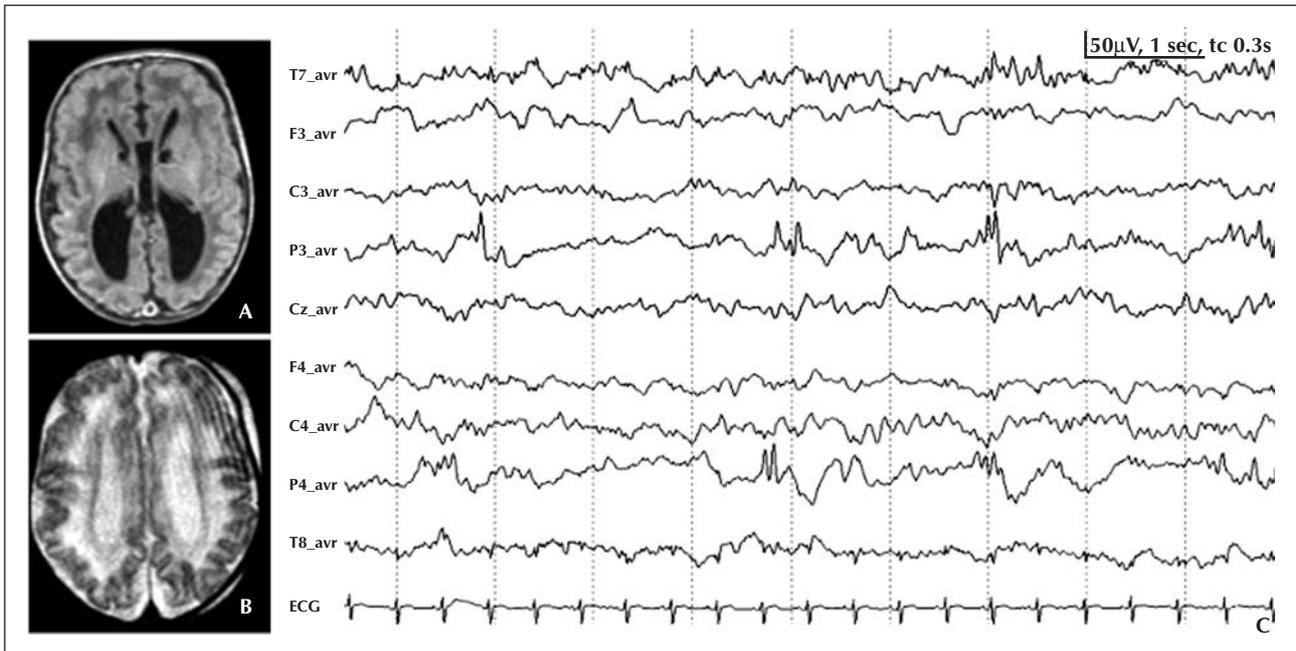


Figure 5. A) T1w and B) T2w MRI of an infant with Zellweger syndrome demonstrating polymicrogyria of the central region and bilateral cysts in the caudothalamic notch. C) EEG (average reference) of the same patient with polyspikes over both parietal regions.

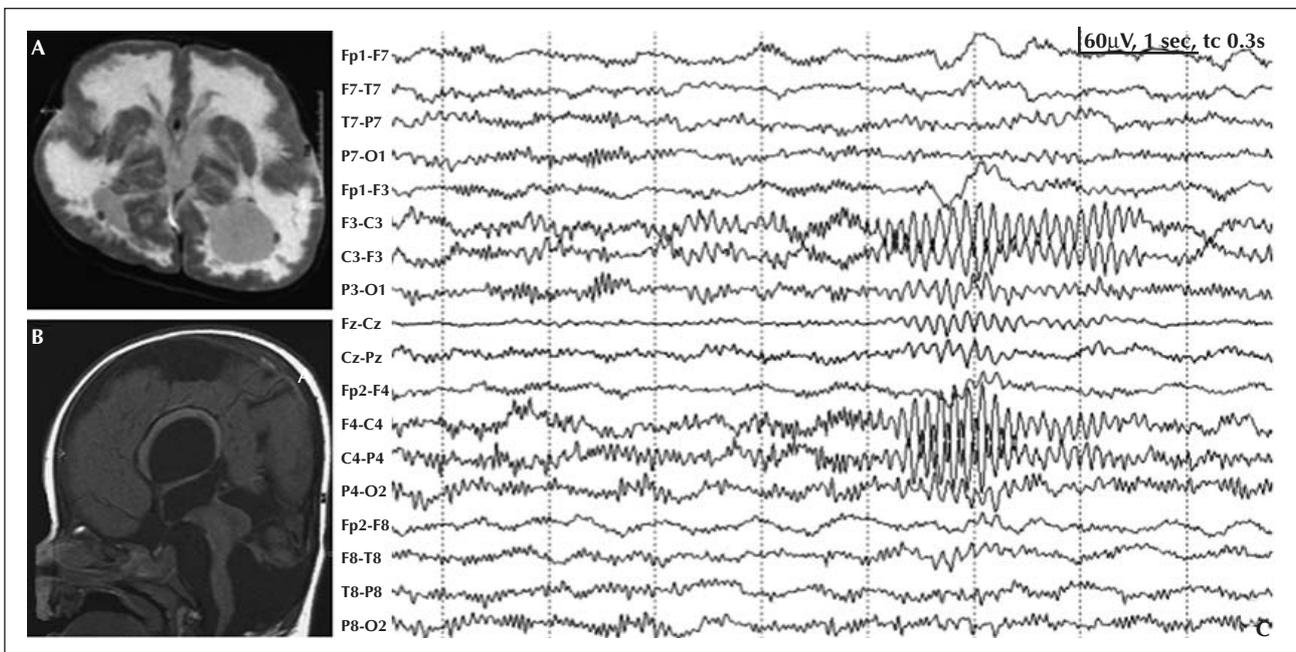


Figure 6. A) Axial T2w MRI of a patient with Walker-Warburg syndrome. Note the diffusely hyperintense abnormal signal of the entire white matter and the cobblestone lissencephaly. B) Sagittal T1w image demonstrating a small, malformed cerebellum and hypoplastic pons and brainstem. C) The EEG (bipolar longitudinal montage) shows abnormal beta activity over the posterior brain regions and a group of 8, Hz alpha activities centroparietally.

thereafter up to three years of age (Baxter 1999). In the early onset presentation, there may be prenatal seizures from around twenty weeks of gestation. There is often (in around one third) neonatal encephalopathy with hyper-alertness, irritability and a stimulus-sensitive startle and this can be accompanied by systemic features such as respiratory distress, abdominal distension and vomiting, and a metabolic acidosis. Multiple seizure types start within the first few days and these are resistant to conventional antiepileptic medication. There may be structural brain abnormalities such as hypoplasia of the posterior part of the corpus callosum, cerebellar hypoplasia or hydrocephalus and other cerebral complications such as haemorrhage or white matter abnormalities. There is a prompt (within minutes) response to pyridoxine 100 mg given intravenously, with cessation of all seizure activity. However, in about 20% of infants with pyridoxine-dependent epilepsy, the first dose of pyridoxine can also cause cerebral depression. Usually the infants become hypotonic and sleep for some hours, rarely it can involve apnea, cardiovascular instability and an isoelectric EEG. Cerebral depression with the first dose of pyridoxine is more likely if the infant is taking anticonvulsant drugs (Baxter 1999).

In contrast, late onset pyridoxine-dependent epilepsy has no encephalopathy and no brain structural abnormalities. Seizures may start at anytime up to three years of age (Baxter 1999, Goutieres and Aicardi 1985). Often these are seizures occurring in the context of a febrile illness, which may develop into status epilepticus. There is usually an initial response to conventional antiepileptic drugs, but over time, it becomes increasingly difficult to control the seizures. Pyridoxine at a daily dose of 100 mg orally, produces a response, with cessation of seizure activity within one to two days. Cerebral depression is not a complication of administration of pyridoxine in late onset, pyridoxine-dependent epilepsy.

At present, the only way to confirm a diagnosis of pyridoxine-dependent epilepsy is to withdraw pyridoxine and demonstrate the recurrence of seizures that again show a prompt response to pyridoxine. Treatment is lifelong, and the usual dose of pyridoxine is around 15 mg/kg/d up to 500 mg/d. Learning difficulties, particularly language, seem to be a common complication of early-onset pyridoxine-dependent epilepsy (Baxter *et al.* 1996). Delay in treatment over months or years causes a severe motor disorder, with learning difficulties and sensory impairment. Every neonate with seizures, even if the suspected diagnosis is perinatal asphyxia or sepsis, should therefore undergo a trial with oral or intravenous pyridoxine. Similarly, every child with the onset of epilepsy under three years of age should also undergo a trial with pyridoxine.

Pyridox(am)ine phosphate oxidase (PNPO) catalyses the conversion of pyridoxine phosphate to the active co-factor pyridoxal phosphate. Deficiency of PNPO is thought to

cause a neonatal seizure disorder similar to early onset, pyridoxine-dependent epilepsy, but one that does not respond to pyridoxine but does to pyridoxal phosphate at a dose of 10-50 mg/kg/day (Clayton *et al.* 2003, Bräutigam *et al.* 2002, Kuo and Wang 2002) (*figure 7*). Pyridoxal phosphate is a cofactor for different enzymes in the synthesis of neurotransmitters and also the degradation of threonine and glycine. Biochemical markers for this disorder are, decreased concentrations of homovanillic acid and 5-hydroxyindoleacetic acid (stable breakdown products of dopamine and serotonin), and increased concentrations of 3-methoxytyrosine, glycine and threonine in cerebrospinal fluid. The prognosis of treated PNPO deficiency is not known, untreated it is believed to be fatal.

Folinic acid responsive seizures

This is a rare disorder, and treatment response to folinic acid was discovered by serendipity (Torres *et al.* 1999). The molecular basis is not clear. In all cases a hitherto undefined compound has been found to be raised in the CSF. Newborns with therapy-resistant seizures should undergo a trial with folinic acid after pyridoxine and pyridoxal phosphate have failed.

Biotinidase deficiency and holocarboxylase synthase deficiency

Biotinidase is a cofactor for different carboxylases. Different metabolites accumulate in urine, and lactic acidosis is frequent. In biotinidase deficiency, the endogenous recycling of biotin is impaired. Epilepsy is frequent, often starting after the first 3 or 4 months of life, and often as infantile spasms; optic atrophy and hearing loss are also often seen (Collins *et al.* 1994, Salbert *et al.* 1993). Clues to the diagnosis are alopecia and dermatitis. The refractory seizures respond promptly to small doses of biotin, usually 5-20 mg/d. In holocarboxylase synthase deficiency, symptoms start during the neonatal period. Seizures are less frequent, occurring in 25-50% of all children. Biotin controls symptoms and is effective at similar doses as in biotinidase deficiency, although in some children the dose needed is higher.

Miscellaneous disorders

Molybdenum cofactor deficiency and sulphite oxidase deficiency

These rare, inborn errors of metabolism usually present in the neonatal period with encephalopathy, intractable seizures (often myoclonic) and lens dislocation. Cerebral MRI shows cystic degeneration of white matter and severe atrophy. An easy screening test is a simple dipstick test for sulphite in fresh urine; the different enzyme deficiencies can be proven in fibroblasts. There is no treatment for these disorders.

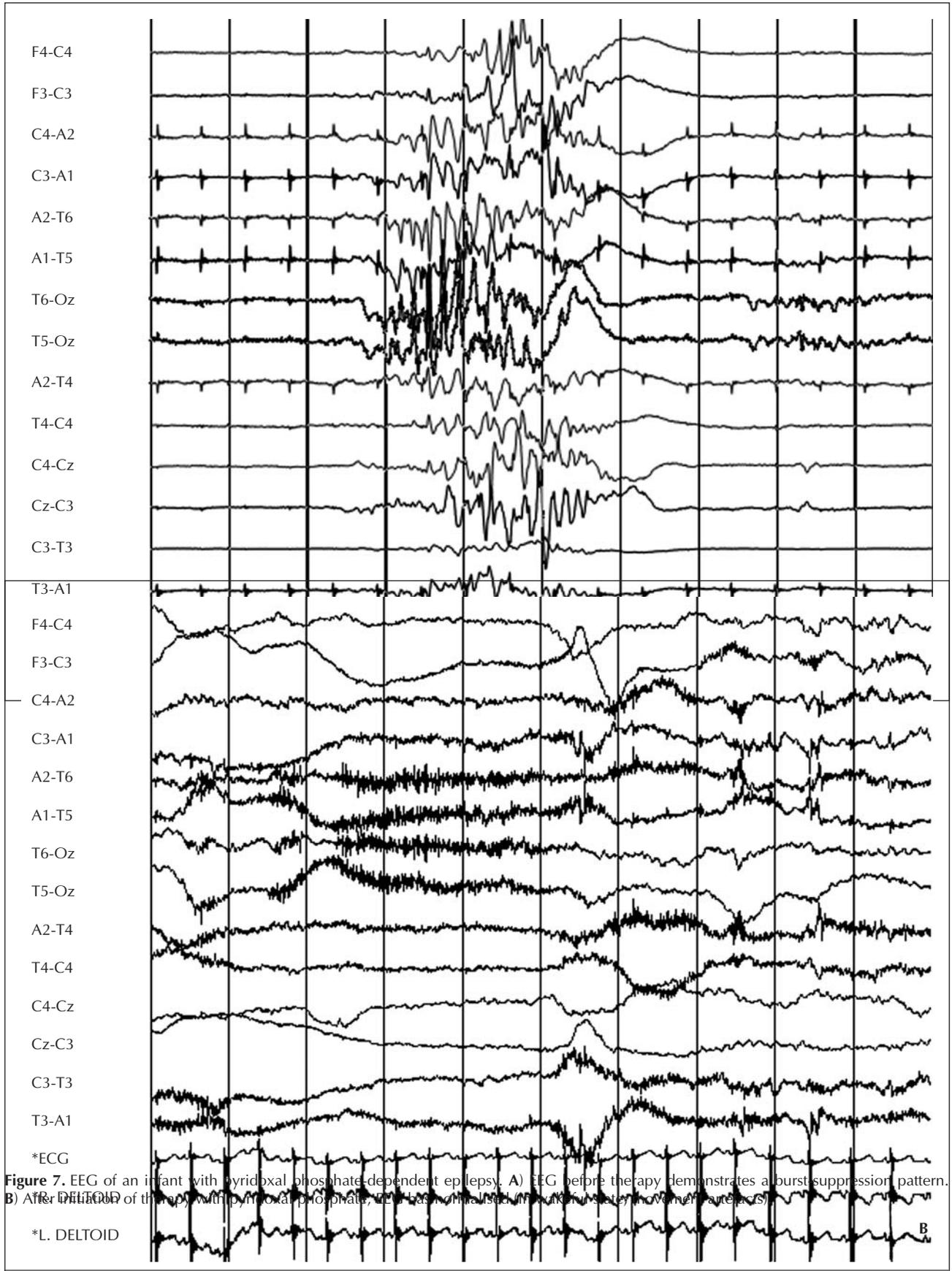


Figure 7. EEG of an infant with pyridoxal phosphate-dependent epilepsy. A) EEG before therapy demonstrates a burst suppression pattern. B) After initiation of therapy with pyridoxal phosphate, EEG has normal background (low voltage state) however artefacts.

Menkes' disease

Children with this X-chromosomal, recessive disorder almost always suffer from epilepsy, often presenting with infantile spasms resistant to treatment (Sfaello *et al.* 2000). The characteristic hair abnormalities point to the diagnosis, which can be confirmed by low serum copper and caeruloplasmin. Administration of subcutaneous copper histidinate may stop seizures and improve development.

Deficiency of serine biosynthesis

Serine biosynthesis is impaired in two enzyme defects: 3-phosphoglycerate dehydrogenase deficiency and 3-phosphoserine phosphatase deficiency (Jaeken 2002). For the latter defect, only one patient has been described. 3-phosphoglycerate dehydrogenase deficiency is also rare. Affected children are born microcephalic and suffer from seizures with onset usually in the first year of life, often as West syndrome. Seizures respond to oral supplementation of serine (De Koning and Klomp 2004). Decreased CSF serine is the clue for diagnosis. MRI shows atrophy due to lack of white matter and hypomyelination.

Congenital disorders of glycosylation (CDG)

Epilepsy is one of the less prominent symptoms seen in children with CDG type Ia (phosphomannomutase deficiency), sometimes only during the acute, stroke-like episodes (Jaeken 2003). It is an important symptom in CDG Ic (Grunewald *et al.* 2000) and has been described in single patients with other subtypes of CDG type I. Seizure semiology also varies within one subgroup. Treatment is with conventional antiepileptic drugs, according to seizure semiology. Diagnosis is made by isoelectric focussing of transferrin, which should be part of the workup of children with unexplained epilepsy and mental retardation.

Inborn errors of brain excitability

One concept of inborn errors of metabolism is that the name implies interruption of flow. This flow can be along metabolic pathways as above, but also transport and flow across intracellular and cellular membranes. Neuronal excitability is determined by the membrane potential, which is maintained by energy-dependant, ionic pumps (Na/K-ATPases and the K/Cl co-transporter in particular), and modulated by ion flow through protein channels. These channels can be gated, with the gate opening (and thereby allowing ionic flow across the membrane) in response to ligands (such as neurotransmitters) or changes in membrane potential. Genetic defects of ion channels can cause defined epilepsy syndromes in a number of cases. Thus, in some cases, primary epilepsy might be thought of as an inborn error of metabolism.

Genetic defects of the $\alpha 2$ subunit of Na/K-ATPase 1 are one cause of the allelic disorders familial hemiplegic migraine and alternating hemiplegia of childhood (Van-

molkot *et al.* 2003, Swoboda *et al.* 2004). In both of these conditions there is a high incidence of epilepsy. In one family (Vanmolkot *et al.* 2003), benign familial infantile convulsions were also reported, either as an isolated phenomenon or preceding the development of hemiplegic migraine. Genetic defects of the K/Cl co-transporter 3 are one cause of Andermann syndrome (Charlevoix disease or agenesis of the corpus callosum with peripheral neuropathy) (Howard *et al.* 2002). This disorder too has a high incidence of epilepsy (Dupre *et al.* 2003).

Ligand-gated, ion channel disorders can also cause epilepsy. Genetic defects of the neuronal nicotinic acetylcholine receptor (either the $\alpha 4$ or the $\beta 2$ subunit), are one cause of autosomal dominant frontal lobe epilepsy (Steinlein *et al.* 1995, De Fusco *et al.* 2000). Inherited defects of the $\alpha 1$ subunit of the GABA A receptor are one cause of juvenile myoclonic epilepsy (Cossette *et al.* 2002); mutations in the gene coding for the $\gamma 2$ subunit of this receptor cause generalised epilepsy, febrile seizures plus (GEFS+), severe myoclonic epilepsy of infancy (SMEI) and childhood absence epilepsy (Wallace *et al.* 2001, Harkin *et al.* 2002).

Other inherited ion channel disorders (channelopathies), can also cause epilepsy syndromes. Defects in the voltage-gated potassium channel (KQT-like subgroup) are one cause of benign familial neonatal convulsions (Singh *et al.* 1998, Charlier *et al.* 1998). Defects in the voltage-gated chloride channel are one cause of childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy and generalised epilepsy with *grand mal* seizures (Haug *et al.* 2003). Mutations in the genes encoding different α -subunits of the voltage-gated, brain sodium channel can cause benign neonatal-infantile seizures (type II α -subunit, Berkovic *et al.* 2004), and both GEFS+ and SMEI (type I α -subunit, Escayg *et al.* 2000, Claes *et al.* 2003, Claes *et al.* 2001). Because GEFS+ and SMEI are allelic disorders at two different loci (*GABRG2* chromosome 5q31.1-q31 and *SCN1A* chromosome 2q24), and because both forms of epilepsy have occurred within the same family, SMEI has been regarded as the most severe phenotype within the GEFS+ spectrum of epilepsy, an observation which had already been made before the discovery of the genetic basis (Singh *et al.* 2001).

Conclusions

Inborn errors of metabolism are rarely found to be the cause of epilepsy. However, epilepsy is a common symptom in many metabolic disorders. Which patients should be screened for which metabolic disease? The answer is certainly not easy. An underlying metabolic disease should be sought if seizures are resistant to therapy, and also if there are additional symptoms such as mental retardation or a movement disorder. Sometimes, during the workup of a patient with epilepsy, results are found

suggestive of a metabolic disorder, e.g. MRI abnormalities typical of mitochondrial or storage disease. If seizures start in adulthood, the spectrum of metabolic disorders is certainly much smaller than in children; mitochondrial disorders are the main diagnosis to consider.

In children, the diagnostic approach also depends on the age group. Neonates should all undergo a therapeutic trial with pyridoxine and pyridoxal phosphate, even if seizures are thought to be due to sepsis or perinatal asphyxia; if seizures are resistant to conventional antiepileptic drugs, folinic acid should be tried as well. In infants, early myoclonic encephalopathy (EME) is often thought to be due to an inborn error of metabolism, although the precise defect can often not be pinpointed. Clues for further metabolic workup can be worsening of seizures or EEG abnormalities before meals (GLUT1 deficiency), movement disorder (creatine deficiency), abnormalities of hair and skin (Menkes' disease and biotinidase deficiency), characteristic dysmorphism (Zellweger syndrome) or involvement of additional systems (mitochondrial disorders). Epilepsia partialis continua, if not due to Rasmussen's syndrome, and status epilepticus resistant to therapy, should prompt investigation for a mitochondrial disease, especially for mtDNA depletion often found in Alpers' disease. The basic metabolic workup should comprise simple parameters such as serum and CSF glucose and lactate levels, but also ammonia, amino acids in blood and CSF and urinary organic acids.

The diagnosis of a metabolic disorder in a patient with seizures sometimes raises the possibility of a specific treatment, which often improves epilepsy and also other symptoms. Often, treatment with antiepileptic drugs has to be continued nevertheless. If no specific treatment is available, antiepileptic treatment should be directed, as in other patients with epilepsy, according to seizure phenotype and epilepsy syndrome, with the exception of valproic acid, which should not be used in mitochondrial disorders and urea cycle disorders and used with caution in many other inborn errors of metabolism. A precise diagnosis might not only influence treatment, but also allow counselling of the family, an important goal even if there are no direct therapeutic consequences. □

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